Annex 8 : Evidence tables

This annex includes the evidence tables for the PICO questions included in the guideline.

Q 3 How should information on fertility preservation options be provided to patients?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Allingham, *et al.*, 2018)	cross-sectional study	34 parents of patients with cancer, who discussed fertility, and 11 clinicians at a tertiary children's hospital	Web-based decision aid developed according to the International Patient Decision Aid Standards	acceptability, usability, and feasibility of a Web-based FP decision aid (DA) in parents of children and adolescents with cancer and clinicians. (pre-post survey design) Measures included the validated Decision Regret Scale and open-ended responses for additional feedback. Clinicians involved in FP were also invited to review the DA.	Participants who reviewed the DA (15 parents and 11 clinicians) expressed satisfaction with its content and functionality. Parents reported an improved understanding of cancer treatments, infertility, and FP procedures and did not report greater decision regret after DA review. Most parents (13/15, 86%) would recommend the DA to other parents. All clinicians had a consensus that this was a valid and relevant information source for all involved in fertility care.	This is the first fertility DA for parents of children and adolescents with cancer and is found to be relevant and acceptable by parents and clinicians.	
(Anazodo, *et al.*, 2019)	Review	147 out of 846 were included. Date published 2007-2016. 42 papers women data, 12 paper male data and 32 male and female data. Decision aid: 9 studies	DECISION AID: Studies on decision trees (1 study), web based and electronic educational tools (3 studies) brochures and booklets (4 studies)	not reported	Overall, decision aids were found to be highly useful and lead to more discussions about FP and less decisional regret, and therefore the use of these tools should be encouraged.		
(Borgmann-Staudt, *et al.*, 2019)	questionnaire survey at 3 and 6 months after diagnosis	patients (n = 113 and n = 101 in the control and intervention groups, resp.) Parents (n = 111 and n = 99 in the control and intervention groups, resp.)	Educational intervention	knowledge and empowerment + Treating physicians were surveyed on their medical consultation regarding fertility.	Educational intervention increased knowledge in both patients and parents, but the difference did not achieve statistical significance (knowledge difference patients. Parents of older patients (OR = 1.3, 95%CI = 1.1-1.7) and higher educational groups (OR = 6.2, 95%CI = 2.1-18.3) in the intervention group (OR = 1.9, 95%CI = 1.03-3.7) achieved higher knowledge levels. Empowerment was significantly improved in both patients (p = 0.046, d = 0.27) and parents (p = 0.046, d = 0.48) in the intervention group.	In our study, the use of specifically prepared flyers and brochures successfully raised the level of fertility preservation knowledge in parents of older patients as well as parents with higher educational levels. Overall, the intervention improved patient and parent empowerment. Subsequent projects will include simpler information and digital material to particularly reach out to younger and less educated individuals.	whether specially designed educational materials regarding fertility preservation increase knowledge and empowerment of patients and parents.
(Ehrbar, *et al.*, 2016)	Other	12 cancer patients (4 focus groups) aged 21-45 y	NO intrvention, no comparison	viwes of patients	Patients wished: 1) seprarate consultation with an experienced expert to discuss FP. 2) Written information would have been	Standardized decision aids will be helpful	

					considered as helpful, to get informed properly, precisely, and prevented them from forgetting important information. A checklist or brochure about the options was mentioned most often as a convenient and helpful tool to provide information. According to the participants, a guide should be offered either as booklet or via internet Internet clock available method to provide up-to-date information about cancer and FP.		
(Ehrbar, *et al.*, 2018)		N=40; Female patients with cancer , 18-40 years old (Mean age 29,23, SD 5,79). 77.5% (31) of all participants stated to have already made a decision for or against FP.	20 control group (fertility counselling) and 20 intervention group (fertility counselling and DA. Data was collected after the counselling session. Only cross sectional data was analysed in this paper.	Knowledge of FP; decisional conflict, satisfaction with online decision AID (interventiomn group only). .	No significant diffference between groups except for nationality. No significant differences between groups regarding information, excep for information on freezing oocytes (p=0,047). No significant differences between groups regarding decisional conflict. In a 1-5 likert scale, patiens of intervention group reported satisfaction (M= 3.45, SD=1.09) with DA, that it was helpful (M= 3.20, SD=1.36) and would recommend it to other women in their situation (M= 3.95, SD=1.09)	The DA seems to serve as additional and well-accepted support tool in decision-making for patients. RCT with Prospective study with three time points: 1) T1: imediatly after counselling; t2: 1 month after (expedtec time for decision); T3 12 months after counselling. In this study only T1 is presented.	
(Ehrbar, *et al.*, 2019)	RCT	59 female cancer patients who were referred by their treating oncologist to a specialist in reproductive medicine for fertility counselling	27 in control group (counselling only) 24 in intervention group (counselling and additional use of the online DA immediately after counselling)	questionnaire at three time points: - T1, after counselling and/or DA use, - T2, 1 month later - T3, 12 months later questions about fertility-related knowledge, attitude towards FP, willingness to undergo FP and socio-demographic data, as well as the decisional conflict and decisional regret scales	intervention group showed a significantly lower total score on the Decisional Conflict Scale (DCS) vs control group at T1 (P = 0.008; M = 12.15, SD = 4.38; 95% CI, 3.35-20.95) and at T2 (P = 0.043; M = 9.35, SD = 4.48; 95% CI, 0.31-18.38). At T3, the mean total score of the DCS was still lower in the intervention group (no longer significant) The majority of participants had already made a decision regarding FP (yes or no) at T1 (72.5%): 91.7% in the intervention vs 55.6% in the control group (P = 0.014). Those who had decided already at T1 showed significantly lower decisional conflict (P = 0.007; M = 13.69, SD = 4.89; 95% CI, 3.86-		

					23.52). The average number of DA sessions per user was 2.23, and 80.8% of the participants completed the DA's value clarification exercises. Participants in the intervention group were satisfied with the DA and would recommend it to other patients.		
(Garvelink, et al., 2015)	observational	33 women who received FP counselling. Time since counselling about 24 months (SD 13)	No intervention.	Decision about FP,	Receiving information was mentioned to empower women decision making, It was suggested that women should be provided with some information, after which they could decide for themselves whether they would like more information. Three women, who did not receive the information face to face, mentioned providing face-to-face information as an improvement. Many others preferred to receive information they could take home, either before the consultation with the fertility specialist to prepare themselves for it or after the consultation to be able to read it again. Brochures, websites and checklists (both for patients and clinicians) were mentioned.	Women recommended standardization of the information provision, improvement of communication among clinicians and medical centres, and availability of FP-specific patient information materials to improve future information provision processes.	
(Garvelink, et al., 2013)	Survey - report on development of the DA	The study population consisted of 185 participants: 20 patients, 17 physicians and 148 healthy volunteers.	Development consisted of four stages: (I) development of a draft DA, (II) acceptability of the draft DA to patients, (III) understanding (knowledge) in healthy populations, (IV) acceptability of the revised DA among patients and physicians.	acceptability	The draft DA was considered to be relevant and understandable by patients, physicians and healthy volunteers. The values clarification exercise needed adaptation in explanation and navigation, which was done after stage II. Knowledge scores improved by 18% for lower educated women (from 4.1 (41%) to 5.9 (59%) correct answers), and by 34% for higher educated women after viewing the website (from 3.9 (39%) to 7.3 (73%) correct answers). Design of the DA was evaluated to be clear, but not always very appealing.	The DA was regarded as a relevant source of information that seemed coherent and understandable.	
(Garvelink, et al., 2012)	Other	10 Breast cancer patients (survivors). 17 clinicians (Bc nurses, oncologists and FP specialists), Patients: mean age 34.4	No comparison, no intervention. Online questions and online Focus groups	Consensus on FP care	1) The availability of the DA-website was regarded as important to inform patients, and to enable patients to talk about FP more easily. 2) Handing	The DA-website was thought to decrease the load for patients (e.g. in travel expenses), to enable patients and clinicians to	10 Breast cancer patients (survivors). 17 clinicians (Bc nurses,

Study	Study type	Sample	Design	Outcomes	Results		
		(SD 2.8). 8 patients underwent FP			out information (e.g. a DA-website) after the consultation with the oncologist, and before the consultation with the fertility specialist was thought to save time in both these consultations. Experts thought the DA-website would decrease the load on patients, and would enable clinicians to talk about FP. Questions about FP should be addressed to a fertility specialist. 3) Many patients were in favor of using the DA-website in the consultation with the fertility specialist. 4) Seventy-eight percent of the experts agreed that guidelines are needed to structure the procedure for informing patients.	talk about FP, and to save time in the consultation with the oncologist as well as with the fertility specialist	oncologists and FP specialists), Patients: mean age 34.4 (SD 2.8). 8 patients underwent FP
(Garvelink, et al., 2017)	RCT	N=26 women with breast cancer aged 18-40 (26 women completed baseline)	RCT. Group :1 Randomized brochures (n=13) Group 2 brochures + Decision aid (n=13). Three time points	Primary outcomes: Feasibility; Use; Secondary outcomes: Decisional conflict, Knowledge; Reproductive concerns. Design: 3 time points: T0 (baseline); T1 (6 weeks after baseline - time of decision) and T2 (six months after T0).	Feasibility: about 42% of eligible women were recruited. USE: 87% read de brochures, 54% logged in the DA; PREFERENCES: No differences in choices between the two groups; DECISIONAL CONFLICT: Women in G1 had lower decisional conflict; KNOWLEDGE: higher between baseline and T1/T2, no differences between groups; REGRET/CONCERNS: No differences between groups	Recruitment is difficult; DA may increase difficulties in decision due to more information	
(Goossens, et al., 2014)	review	M=27 papers		Preferences about provision of information	Written information on fertility was judged as supplementary to oral information. Patients had different opinions on whether written information was useful or not. Some patients were over-whelmed by the amount of written information and 'added it to the pile'. Others judged it as useful, especially for revisit or as a prompt which could lead in discussing fertility		
(Hand, et al., 2018)	Other	N= 39 health care professionals (10 nurses, 22 doctors, 7 supportive staff; 31 female, 8 male;	No comparison, no intervention	Acceptability			
(Johnson, et al., 2016)	Other	N= 12 healthcare providers of a multidisciplinary group - Gender and sex diversity fertility working group	Cross sectional. No comparison, no intervention	Self administered survey with close and open questions assessing participant and team characteristics and	75% (9/12) expressed preference for developing either a Decision aid or a provider assessment tool. 3/12 (25%) felt both were equally important. 6/9 (67%)	A development of a DA tool would be important and it is preferred over a provider assessment tool because it allows for the discussion in	(Suggestion of telemedicine as a way to allow for a

		from 8 different institutions.		preferences on tools to help FP decision.	preferred Decision aid; 3/9 (33%) preferred provider assessment tool.	the clinic, provides neutral source of information, and helps to manage a large amount of information and to go back to the tool later, for review in a different time.	multidisciplinary team)
(Jones, et al., 2017b)	Study protocol	women of reproductive age (16 years +) with a new diagnosis of any cancer				Development and evaluation of a fertility preservation patient decision: Cancer, Fertility & Me in 3 stages	
(Jones, et al., 2017a)	Review	N= 46 studies Women with cancer patients > 16 years old at recruitment. Any cancer, any stage of cancer trajectory	No intervention	Mains outcomes/findings 1) fertility information provision (lack of information, timing of the information and patient provider communication); 2) fears concerning the perceived risks associated with pursuing FP (delaying cancer treatment, aggravating a hormone positive cancer and consequences of a future pregnancy); (2) non-referral from oncology (due to personal situation, having a hormone positive cancer, FP not being a priority and transition between service issues); 4) difficulties in deciding /dilemma); (5) personal status (parity and relationship status) and 6) costs (financial concerns).	women needed to be given written FP information on multiple occasions, to enable them to re-visit information at different treatment stages (Tschudin et al., 2010; Hill et al., 2012; Corney and Swinglehurst, 2014; Perz et al., 2014).	Women would benefit from the provision of more evidence-based FP information, ideally received at cancer diagnosis, in advance of seeing a fertility specialist, for example through the implementation of patient decision aids.	Low quality studies, retrospective, etc
(Kelvin, et al., 2016)	observational	N= 270 male cancer patients; 591 female cancer patients;	Cohort study. Cohort 1 (before cancer program: 150 male, 271 female); Cohort 2 (after cancer program with fertility consultation: 120 male, 320 female)	Satisfaction with information received, with consultation.	CONSULTATION: In all but one of the topics queried females who had an FCNS consultation were more likely to report satisfaction than those who did not. WRITTEN INFORMATION: Among males, of the 77% (51 of 66) who reported having read. USING FP Females who received FCNS counselling were 6.1 times more likely (95% CI, 3.2 to 11.5) to undergo FP than those who did not the material, 96% found it helpful. Among females, of the 78% (71 of 91) who reported	Improvements in patient satisfaction with information received demonstrate the potential for fertility programs in cancer care settings to improve the quality of clinician-patient discussions about fertility.	

					having read the material, 99% found it helpful. Higher satisfaction with information at C2 compared to C1 in both men and women.		
(Kemertzis, et al., 2018)	Other	Phase 1 & 2. N=59 (41 nurses, 13 doctors, 5 allied health). No comparison group. Phase 3. N=38 (10 nurses, 22 medical staff, 6 allied health)	3 phases: 1) Usual discussion; 2) Toolkit implementation; 3) impact of toolkit after 2 years of use	Satisfaction and confidence with the use of the toolkit and with the FP discussion. Change in provision of information with the use of the toolkit.	Phase 1. 66% reported dissatisfaction with existing FP system. 56.7% were not confident in providing up-to-date information. only 34.5% often or always provided verbal (oral) information; 14% often or always provided written information. Phase 2. The professionals were satisfied with the toolkit in 63.6% of discussions (7/11), and extremely satisfied or satisfied with the FP discussion in 100% of cases (11/11). Comparison between phase 1 and phase 3 showed no significant difference in satisfaction with discussion (p=0,06) and an improvement in confidence (p=0.005). There was a significant change in provision of verbal (p=0.003) and written (p=0.02) information.	The use of the toolkit provided significant perceived and actual benefits.	
(Muller, et al., 2017)	survey	155 women with former or current cancer (mean age at diagnosis 31.27, SD 6,94)	No intervention. No comparison	Decisional conflict. Use of other sources for information and support and helpfulness.	Lower Decisional conflict was associated with being informed about HCP about infertility after cancer (.001). Websites and leaflets were important sources of information (Weighted helpfulness .99 and .87.	Young female cancer patients' DC with regard to fertility preservation is very	155 women with former or current cancer (mean age at diagnosis 31.27, SD 6,94)
(Peate, et al., 2012)	Observational	120 newly diagnosed early stage breast cancer patients, aged 18-40, mean age 33,23 (SD =4,3), 69.3% childless	N=70 Control group (TAU; N=44 Intervention group (Decision aid). recruited 2006-2009. Baseline, 1 month and 12 months. No differences at baseline	Decisional conflict, knowledge, decision regret, satisfaction about fertility related treatment decisions.	DA had greater reduction in decisional conflict; greater improvement in knowledge, after adjusting for education, desire for children and baseline uncertainty. No differences in anxiety or depression between groups. 12 months later decisional regret was lower in DA.	This DA should be used shortly after diagnosis (before chemotherapy) among younger breast cancer patients who have not completed their families	
(Peate, et al., 2011)	Questionnaire	111 young women with breast cancer		fertility-related knowledge, decision-making preferences, and treatment intentions	From a potential fertility-related knowledge score of 10, the mean was 5.2 (standard deviation = 2.3; range, 0 to 10). Decreased knowledge was associated with increased decisional conflict about pursuing fertility preserving interventions (odds ratio [OR] = 0.57; 95% CI, 0.44 to 0.73; P < .001). Thirty-one		

				percent of women reported that they would consider undertaking in vitro fertilization (IVF) as a method to conserve their fertility, whereas 38% were uncertain. Consideration of IVF was not related to whether subjects were in a committed relationship (OR = 1.20; P = .716) or a definite desire for more children (OR = 1.54; P = .513).		
(Peate, _et al._, 2009)	Review	N=12 studies Fertility information needs and preferences for provision of information	1) Attitudes to, and actual decisions made by women regarding, pregnancy, breastfeeding, and contraception, 2) Fertility related information needs; 3) Preferences for fertility-related information provision;	1) dissatisfaction with information provided: Women also reported that it was difficult to know what questions to ask and expressed frustration with the uncertainty or lack of clarity in the answers they received. 2) preferred method of obtaining information: with breast cancer was consultation with a fertility or menopause specialist followed by a decision aid (an information booklet designed to assist with decision-making)	Lack of studies, namely prospective and at the beginning of treatment. A pathway for information provision and referral could be implemented to ensure fertility-related needs and concerns are addressed effectively.	
(Shen_, et al.,_ 2019)	Review				Although discussions about fertility concerns in the context of cancer between physicians and patients are occurring more frequently, there are inconsistent findings regarding satisfaction with these discussions. Recent research has found that the timing, type of information given, and level of openness of the HCP can impact how patients perceive communications regarding the risks of cancer treatment on fertility preservation options and future family planning. Age, sex, and HCP's knowledge of fertility risks and fertility preservation services are also notable factors associated with whether and how extensively discussions about fertility take place. More women than men report having a fertility discussion with an HCP. However, men are more likely to report satisfaction with the fertility discussion than women.	
(Speller, _et al._, 2019a)	development and alpha testing of a fertility tool	The "Begin Exploring Fertility Options, Risks and Expectations" (BEFORE) decision aid for premenopausal breast cancer patients	Development of a DA: Our team used integrated knowledge translation by collaborating with multiple stakeholders throughout the development process including breast cancer survivors, multi-		Our team developed an 18-page paper prototype containing information deemed valuable by stakeholders for fertility decision-making. The engagement meeting brought together 28 stakeholders to finalize the prototype. Alpha testing of the paper and online	The BEFORE DA is a new tool for premenopausal breast cancer patients and HCPs to assist with fertility discussions and decision-making. The BEFORE DA helps to fill the information gap as it is a tool that HCPs can refer patients to for

			disciplinary health care providers (HCPs), advocates, and cancer organization representatives. Based on previously conducted literature reviews and a needs assessment by our team - we developed a paper prototype. The paper prototype was finalized at an engagement meeting with stakeholders and created into a graphically designed paper and mirrored online decision aid. Alpha testing was conducted through a questionnaire, telephone interviews, or focus group. Iterative reviews followed each step in the development process to ensure a wide range of stakeholder input.		BEFORE DA occurred with 17 participants. Participants found the BEFORE DA usable, acceptable, and most provided enthusiastic support for its use with premenopausal breast cancer patients facing a fertility decision. Participants also identified areas for improvement including clarifying content/messages and modifying the design/photos. The final BEFORE DA is a 32-page paper and mirrored online decision aid (https://fertilityaid.rethinkbreastcancer.com). The BEFORE DA includes information on fertility, fertility options before/after treatment, values clarification, question list, next steps, glossary and reference list, and tailored information on the cost of fertility preservation and additional resources by geographic location.	supplementary information surrounding fertility.	
(Speller, et al., 2019c)	evaluation of oncofertility decision support resources	breast cancer patients and health care providers	We conducted 30 to 90-min interviews that included a survey questionnaire and open-ended questions with patients and providers between March and June 2016. Interviews were transcribed verbatim. Analysis involved descriptive statistics for survey responses and thematic analysis of qualitative data.		A total of 16 participants completed interviews. Key information perceived by most participants as necessary for fertility decision-making included tailored post-treatment pregnancy rates, cost ranges and financial assistance for the fertility options based on patients' situation. However, patient and provider participants expressed differing opinions on the inclusion of all before and after treatment fertility options and the amount of fertility information required at diagnosis.	The evaluation identified fertility information needs among patients in addition to providers' views on patient needs. While existing oncofertility resources contain information perceived as necessary for decision-making there is an opportunity to use these findings to create or enhance resources to better meet the needs of patients. Additionally, patients and providers differing views on information needs highlight the opportunity for provider training to ensure better communication using resources in clinic to understand specific patient needs.	
(Speller, et al., 2019b)	Systematic Review		Systematic review and grey literature search 1994-2018.	characterize Web-based oncofertility decision aids and health education materials accessible for women of reproductive	31 open access resources including 4 decision aids and 27 health educational materials. The most common fertility preservation options listed in the	More focus is required to improve the awareness and the access of existing resources among patients and providers. Providers can	

					resources included embryo (31/31, 100%), egg (31, 100%), and ovarian tissue freezing (30, 97%). Notably, approximately one-third (11, 35%) contained references and 5 (16%) had a reading level of grade 8 or below. Resources were of varying quality; two decision aids from Australia and the Netherlands, two booklets from Australia and the UK, and three websites from Canada and USA rated as the highest quality.	address patient information needs by leveraging or adapting existing resources to support clinical discussions and their specific patient population.	
				age with a diagnosis of any cancer.			
(Srikanthan, *et al.*, 2019)	A qualitative study	consecutive, female breast cancer survivors, 39 years of age or younger at diagnosis and within 2 years of diagnosis, who attended routine outpatient follow-up: 50 women with a median age of 34.5 years (range 25-39 years): 39 (78%) had completed university education, 33 (66%) recalled having fertility preservation discussions at diagnosis.	Interviews lasted 30 minutes and were transcribed verbatim. Thematic analysis was conducted to explore experiences around fertility discussions.	patient experiences with fertility discussions at diagnosis to identify barriers and preferences to patient-centered delivery of care.	The most common themes identified include: (i) the requirement for more patient support, (ii) improving information, (iii) integration of patient values, (iv) creating options for patients, (v) financial limitations, and (vi) the need to look beyond the immediate impact.	In this contemporary cohort of young adult breast cancer survivors, fertility discussion experiences at diagnosis remain suboptimal. Improved information and a focus on individual patient desires can improve experiences.	
(Tam, *et al.*, 2018)	Cross sectional questionnaire	N= 56 cancer patients (n=48) or patients partners (n=8) aged 15-49, 46% male.	No intervention: Cross sectional; Survey	Preferences of receiving information	Pamphlets rated as effective (82% men and 79% women). 52% increased knowledge after reding men's pamphlet and 63% after reading women's pamphlet.	Cross sectional questionnaire	
(Vindrola-Padros, *et al.*, 2017)	Review	N=16 Papers (14 Studies). Sample were children (0-15) and young people (16-24) with cancer. Studies published before 2014	No intervention.	healthcare professionals' beliefs, attitudes, or practices regarding fertility issues in cancer patients,	factors affecting the discussion of FP: (a) knowledge, (b) sense of comfort, (c) patient factors, (d) parent factors, and (e) availability of educational materials.	Importance of training HCP in communication and providing them with kowledge and materials do discuss FP	
(Vogt, *et al.*, 2018)	prospective, mixed-methods design (questionnaires, in-depth interviews).	58 Women of childbearing age with new cancer diagnoses	Interviews were analysed using thematic analysis. Comparisons were made between women who declined FP referral in oncology (Group1) and women who chose referral (Group2). Group 2 was further split into those who had some FP (2A) and those who did not (2B). Questionnaires and PROMs were	explore this FP decision-making process and its impact on patient-reported outcomes (PROMs) and health-related quality of life (HRQoL).	HRQoL was negatively affected, particularly depression. Women's lack of understanding about the relationship between CT and fertility were evident. Five themes emerged from the interviews as barriers and facilitators to the FP decision-making process.	- better information and support resources aimed at women to support their decision making - the need for psychological support in the FP care-pathway - research exploring the contributions of depression and hopelessness to the decision-making process.	

			administered prior to and after the fertility consultation, before the start of CT and 3 months post CT.				
(Wang, et al., 2019a)	review	12 papers detailing 11 studies od DA. N=772 participants, 9 Das. Cancer patients were men and women aged 18-43 y	DA's were developed for patients.		A total of 12 papers, detailing 11 studies with a total of 772 participants, evaluating nine decision aids, were included within the review. PtDAs were shown to significantly increase fertility preservation knowledge and decrease decisional conflict. Overall satisfaction with decision aids was high. Currently, only two reviewed decision aids are available for cancer patients. Another tool has been integrated into a web page, and one implementation study has been completed.		to be completed
(Woodard, et al., 2018)	Other	Field testing N=20 cancer survivors, 23-42 years old, highly educated. N=9 clinicians	No comparison group. Pre and post assessment of the total group. Prospective study in filed testing, but no pre and post comparison	PRE: sociodemographic and clinical data; Tool use: Decision making values, preferences; post decision: FP knowledge, tool usability and acceptability.	High acceptability of the tool (usefulness, Easy to use, visually attractive: 100%; clarity, length, navigability (95%), 100% of the participants would recommend the tool. Clinicians: tool is helpful	The decision aid is a usable and acceptable tool to help women learn about fertility preservation.	

INCLUDED FOR NARRATIVE QUESTION 2
(Baram, et al., 2019, Greenwood, et al., 2018, Hickman, et al., 2018, Silva, et al., 2018)

INCLUDED AS BACKGROUND INFORMATION
(Chen, et al., 2019, Crawshaw, et al., 2009, Fritz, et al., 2018, Kim, et al., 2013, Logan, et al., 2019, Patel, et al., 2020)

Q 4 Is there a benefit of psychological support and counseling, and are there particular groups that would benefit?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Anazodo, et al., 2019)	Review	147 out of 846 were included. Date published 2007-2016. 42 papers women data, 12 paper male data and 32 male and female data. Decision aid: 9 studies			DECISION AID: Studies on decision trees (1 study), web based and electronic educational tools (3 studies) brochures and booklets (4 studies)	Overall, decision aids were found to be highly useful and lead to more discussions about FP and less decisional regret, and therefore the use of these tools should be encouraged.	
(Chiavari, et al., 2015)	54 patients	54 cancer patients	Prospective study (T1 - Intervention -T2). No comparison group. Intervention - Decision counselling (DeCo).	Decision making, decisional conflict and anxiety. Value based decisions.	improvement in Stage of decision making (p=0.01) and decrease in decision conflict with intervention.	There is no control group. Fertility counselling included two phases: information provision and help regarding decision making with a counsellor (trained health professional). Limitations are absence of a control group and heterogeneity of fertility related decisions.	
(Greenwood, et al., 2018)	other	201 women undergoing FP for social reasons.	retrospective cohort study	Decisional regret, attitudes regarding decision satisfaction.	On average, perceiving adequate emotional support was associated with a reduction in regret score (95% CI 4.3 to 0.0, P=.05).		
(Lawson, et al., 2014)	prospective observational study	47 women with cancer (FP patients) and 91 matched infertile patients	No intervention. Just group Comparison. Pre assessment Registration day for COH-T1) and post assessment (before oocyte retrieval-T2)	Depression (CES-D), state and trait anxiety (STAI), Coping strategies (WOC-R), Infertility stress (FPI).	FP patients reported more anxiety and depression than infertile patients at enrolment in treatment. 44% of FP patients reported clinically relevant depression scores (vs 14% of controls). 62% of FP patients reported clinically relevant anxiety scores (vs 27% controls). There was a great discrepancy between self reported and psychometrically assessed depression and anxiety scores.	There was no intervention It is an observational study on psychological outcomes in FP patients	
(Logan and Anazodo, 2019)	Review	33 published fertility preservation guidelines, guideline updates or clinical recommendation documents based on expert opinion and review			These documents represent the views of 19 differing organizations and two expert meetings, from 12 separate countries worldwide, across Europe, with all but two documents published in English (one in Swedish29 and one in	Fertility counselling, as information provision and psychosocial support, is an important component of fertility care that should be available to cancer patients undertaking fertility preservation at the time of	The psychological importance of fertility preservation counselling and support for cancer patients.

					Japanese30). Differences in health-care systems, availability of resources, provision of information and supportive care practices may all differ based on region where guidelines are utilized. These factors may influence the degree to which fertility counselling is prioritized and available, and the consequent evidence basis to inform on a clinical recommendation.	cancer diagnosis, and at later time-points of family planning.	
(Logan, *et al.*, 2019)	systematic review	47 papers	systematic review of the literature was conducted in January 2018 utilising electronic databases Medline, EMBASE, PSYCH Info, Web of Science, and SCOPUS.	Fertility-related psychological distress persists from diagnosis through to survivorship, with cancer patients reporting a range of negative emotional experiences brought about by threatened infertility. In survivorship, reproductive concerns, unfulfilled desire for a child, nulliparous status, and early menopause were linked to higher rates of mental health disorders and psychological distress.	Fertility-related psychological distress is prevalent and persistent in cancer patients and survivors. As such, patients and survivors would greatly benefit from fertility-related psychological support implemented into standard practice from diagnosis through to survivorship. A revised model of care is proposed.		
(O'Hea, *et al.*, 2016)	Observational	836 cancer patients (part of RCT)	Multivariate regressions examined predictors of distress and interest in mental health services. Baseline Mental Health Assessment and Dynamic Referral for Oncology (MHADRO) assessment Of the 836 participants enrolled in the study, 415 were in the intervention group and therefore eligible to receive dynamic referral.	Multiple linear regression modelling revealed that participants who had never taken medication for emotional problems and those who had but currently were not taking medications had lower psychological distress scores on the BHS than those who were currently taking medications, respectively. Ever having seen a therapist for emotional problems, and reported mental health diagnoses, were associated with higher psychological distress. Heavier smokers also had significantly higher psychological distress than non-smokers, as did	Ccertain psychosocial variables may increase the risk psychological distress: younger at diagnosis, having a history of mental illness, high levels of tobacco addiction, experiencing low levels of social support, or reported high levels of pain and fatigue.

Patients who had a history of therapy, who were experiencing high levels of physical symptoms and side effects, or who were from a Latino/Hispanic or Black/African American background, were more interested in counselling than patients with other characteristics. | | |

					participants with more pain and fatigue in the past 2 weeks		
(Shah, _et al._, 2016)	OBS	356 female cancer survivors (18-49) who received fertility compromising treatments	No comparison. Retrospective study. No psychological intervention	Reproductive health counselling history, reproductive concerns (RCS), Quality of life).	Reproductive concerns higher among a)younger women at diagnosis, b) treated for leukaemia, c) treated with chemoradiation or bone marrow transplant, d) nulliparous (never been pregnant), e) desiring future children at the time of diagnosis, f) infertile after treatment, or g) with lower income. reported annual household incomes of less than $100,000 at the time of diagnosis. As quality of counselling increased (as more of the 10 counselling items mentioned above were addressed), total RCS scores decreased significantly.	Low quality study. There was no psychological intervention. Identification of predictors of higher reproductive concerns.	
(Witcomb, _et al._, 2018)	Comparative study	Transgender individuals	measure of depression, measures which predict psychopathology (self-esteem, victimization, social support, interpersonal problems), and information regarding cross-sex hormone treatment (CHT)use.	Rate of depression	Transgender individuals not on CHT had a nearly four-fold increased risk of probable depressive disorder, compared to controls. Older age, lower self-esteem, poorer interpersonal function and less social support predicted depressive disorder. Use of CHT was associated with less depression.	untreated transgender people had higher prevalence rates of possible or probable depressive disorder than controls and trans people already on cross-sex hormones. Higher age, lower self-esteem, lower social support and poorer interpersonal functioning all predicted depressive disorders.	

INCLUDED AS BACKGROUND INFORMATION
(La Rosa, _et al._, 2019, Logan, _et al._, 2018, Takeuchi, _et al._, 2019, Vogt, _et al._, 2018)

Q7. Which factors should be taken into account when estimating the individual risk of gonadotoxicity of a certain treatment?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
BREAST CANCER							
(Abusief, *et al.*, 2012)	retrospective CS	431 breast cancer patients	Different anticancer treatments	Association between patient characteristics at diagnosis of premenopausal breast cancer, including gravidity, parity, age at menarche, age at first birth, alcohol use, smoking history, weight, height, and body mass index, with the development of persistent chemotherapy-related amenorrhea	Women with older (>13 years) vs. younger (12–13 years) age at menarche were more than twice as likely to remain amenorrheic. Current smokers had 2.4 greater odds of chemotherapy-related amenorrhea vs. never smokers, although this association was not statistically significant (95% CI 0.86–6.75).	Few identifiable factors contribute to the variability in chemotherapy-related amenorrhea among premenopausal women after adjuvant chemotherapy for breast cancer. Further research to improve the prediction of chemotherapy-related amenorrhea, premature menopause, and infertility in young breast cancer survivors is warranted	
(Anderson and Cameron, 2011)	prospective CS	42 breast cancer patients	Different anticancer treatments	Association between markers of ovarian reserve and age as predictors of ovarian function after chemotherapy	Only AMH was predictive in a multivariate logistic regression (odds ratio = 13.0; 95% confidence interval = 2.5-66.7); 0.71 ng/ml gave peak likelihood ratio of 7.0 with 54% sensitivity and 92% specificity.	Measurement of AMH at cancer diagnosis predicts long-term ovarian function after chemotherapy. Use of this in clinical practice may allow better prediction of chemotherapy-related risk to future fertility.	
(Anderson, *et al.*, 2017c)	RCT	101 patiens	Different chemotherapy regimens (with or without concurrent GnRH analogs)	AMH levels before and after different anticancer treatments	AMH concentrations at both 12 and 24 months were unaffected by tamoxifen administration (at 24 months: 2.5 with tamoxifen vs. 2.1 pmol/l). In women aged >40 at diagnosis who did not receive GnRH analog, AMH measured at end of chemotherapy also gave good prediction of POI at 24 months (area under the curve 0.89 95% CI 0.75-1.0 with sensitivity 0.91, specificity 0.82, diagnostic odds ratio 42.8). FSH gave slightly lower AUC, and specificity was low at 0.55. Age but not tamoxifen impacted on AMH levels	Using this sensitive AMH assay, the finding of an undetectable AMH level in women aged > 40 at the end of chemotherapy for eBC gave a good prediction that ovarian function would not return	
(Anderson, *et al.*, 2006)	prospective CS	50 breast cancer patients	Different anticancer treatments	AMH levels before and after different anticancer treatments	AMH concentration showed a rapid and marked fall during chemotherapy, with undetectable concentrations in many women (P<0.0001). Inhibin B concentration showed a lesser fall (P<0.0001), whereas estradiol (E2) concentrations were maintained. Both antral follicle count (AFC) and ovarian volume fell (P<0.0001 and P<0.05	These data confirm the value of AMH concentration as an early indicator of ovarian ageing including assessment of chemotherapy-induced ovarian follicle loss. FSH and AMH concentration	

					respectively). Regimens containing taxanes in addition to cyclophosphamide showed increased gonadotoxicity. Gonadotrophin suppression resulted in expected falls in E2 (P<0.05) and inhibin B (P<0.001) levels, but also resulted in a delayed fall in AMH level after 6 months (P<0.0001).	measurements may be useful for the comparison of ovarian toxicity of different chemotherapy regimens.	
(Bernhard, *et al.*, 2007)	RCT	874 pre- and peri-menopausal patients	CMF vs. GnRHa vs. CMF-->GnRHa	Treatment-induced amenorrhea (POI defined only based on menstrual function following the end of treatment)	For younger patients (< 40 years), GnRHa induced amenorrhea within 2 months of study entry for 90% of the patients and within 3 months for virtually all patients. Amenorrhea continued until the end of GnRHa treatment, when menses resumed in all but a few patients. In contrast, chemotherapy-induced amenorrhea was achieved more slowly and was observed in approximately 50% of patients by the end of six courses of CMF. Among patients in whom GnRHa was not given after CMF, menses resumed in approximately 15%, but amenorrhea continued in approximately 35% to 40% of such patients throughout the 36-month period of observation. Among patients who received GnRHa after CMF, virtually all reported amenorrhea during the 18-month goserelin treatment period. Resumption of menses after cessation of GnRHa was slower in patients who had received initial CMF than in those who did not. The pattern of incidence of amenorrhea over time was different for patients age > 40. Chemotherapy-induced amenorrhea was observed sooner and in a larger proportion of patients than was observed in the younger cohort. More than 90% of these patients who received six courses of CMF reported amenorrhea by the end of chemotherapy. Although menses resumed in a few patients who did not receive GnRHa after chemotherapy, nearly all cases had amenorrhea during the entire 36-month follow-up period, regardless of whether goserelin was used	Both CMF and GnRHa induce amenorrhea. However, while it is reversible in the majority of patients after cessation of GnRHa, it is often permanent after CMF	
(Burstein, *et al.*, 2016)		ASCO adjuvant endocrine therapy guideline			The Panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not. Women with stage II or III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression with endocrine therapy. The panel recommends that some women with stage I or II breast cancers at higher risk of recurrence who might consider chemotherapy may also be offered ovarian suppression with endocrine therapy. Women with stage I breast cancers not warranting chemotherapy should not receive ovarian suppression, nor should women with node-negative cancers 1 cm or less. Ovarian		

					suppression may be administered with either tamoxifen or an aromatase inhibitor.		
(Cardoso, et al., 2019)		Recent guideline of ESMO on diagnosis and treatment of breast cancer, including recommendations on endocrine treatment			Recommendations: For premenopausal women, tamoxifen for 5–10 years is a standard of care [I, A]. In patients becoming postmenopausal during the first 5 years of tamoxifen, a switch to letrozole should be considered, depending on predicted risk of late recurrence [II, A]. In patients requiring ChT and who recover menses (in particular in the first year but acceptable within the first 2 years), addition of OFS to ET should be strongly considered [I, A]. The role of replacing tamoxifen with an AI can be considered in high-risk patients; if used, it mandates effective OFS, with regular biochemical control of oestrogen levels [I, A]. The role of OFS in patients <35 years not requiring ChT is not clear, but inferior outcomes of young luminal early breast cancer patients suggest the use of the most effective ET (i.e. combination with OFS) [III, A]. OFS during ChT provides some protection of ovarian function and has no negative impact on oncological outcomes; thus, it should be proposed to patients [I, A]. It should not, however, be the sole fertility preservation method used, in case of desired pregnancy [I, A].		
(Dezellus, et al., 2017a)	prospective CS	250 patients	Different chemotherapy regimens	AMH levels before and after different anticancer treatments	Mean basal AMH level was 4.19 ng/mL, and was negatively correlated with age. Serum AMH level rapidly decreased in all patients after each chemotherapy cycle to undetectable levels in most of them, and slowly increased in 45% of the patients during the 24-month follow-up. AMH decrease was significantly associated with age and basal AMH level, but not with cyclophosphamide dose and tamoxifen use. The prevalence of chemotherapyrelated amenorrhoea was 92.4% at the end of chemotherapy; women with amenorrhoea being significantly older and having lower basal AMH than women who resumed menses	This study confirms rapid and deep ovarian reserve alteration in young women receiving chemotherapy for breast cancer, and shows moderate AMH recovery in some patients	
(Ejlertsen, et al., 2017)	RCT	1,045 premenopausal women were included in this RCT, but 42 that did not provide information about their menstrual periods	DC vs. EC-->D	Treatment-induced amenorrhea (POI defined only based on menstrual function following the end of treatment)	Among included premenopausal women, 8% in the EC-D group and 9% in the DC group reported menstruating regularly throughout chemotherapy, 12% in EC-D group and 10% in the DC group reported irregular menstruating, and 80% in the EC-D group and 81% in the DC group reported cessation of menses for 3 months or more after initiation of chemotherapy	Amenorrhea was equally frequent after DC and EC-D, but in the absence of biochemical monitoring of ovarian function, an endocrine effect may not be completely excluded.	

(Freour, *et al.*, 2017)	SR	17 studies including 1,038 patients	Different chemotherapy regimens	AMH levels before and after different anticancer treatments	AMH levels rapidly fall down to undetectable levels in most women during chemotherapy and generally persist at very low levels in most women after the treatment. AMH is a predictor of the occurrence of chemotherapy-related amenorrhea and is the most relevant hormonal marker of ovarian reserve	Serum AMH is a relevant tool for ovarian reserve assessment and follow-up during treatment in premenopausal women with breast cancer. Further large prospective studies are necessary to determine its predictive interest for post-treatment residual fertility, and eventually use it in fertility preservation counseling before treatment initiation	
(Lambertini, *et al.*, 2019a)	Cohort study	2862 premenopausal HER2-positive early breast cancer patients	randomized to receive one year of trastuzumab, lapatinib, their sequence, or their combination	treatment-related amenorrhea (TRA) rates and whether TRA in patients with hormone receptor-positive and -negative tumors would impact disease-free survival (DFS) and overall survival (OS). Landmark and time-dependent modeling were used to account for guarantee-time bias.	1679 (58.7%) had hormone receptor-positive disease. Median age was 43 (IQR = 38-47) years. Similar TRA rates were observed in the trastuzumab (72.6%), lapatinib (74.0%), trastuzumab-->lapatinib (72.1%), and trastuzumab+lapatinib (74.8%) arms (P = .64). The association between TRA and survival outcomes differed according to hormone-receptor status (P interaction for DFS = .007; P interaction for OS = .003). For hormone receptor-positive patients, the TRA cohort had statistically significantly better DFS (adjusted hazard ratio [aHR] = 0.58, 95% CI = 0.45 to 0.76) and OS (aHR = 0.63, 95% CI = 0.40 to 0.99) than the no TRA cohort. No difference was observed in hormone receptor-negative patients.	no association between TRA rate and type of anti-HER2 treatment was observed. TRA was associated with statistically significant survival benefits in premenopausal hormone receptor-positive/HER2-positive early breast cancer patients.	(part of the In the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (BIG 2-06) phase III trial)
(Lambertini, *et al.*, 2017a)	RCT	1,396 patients included in the amenorrhea analysis (out of 1,549 included in the study)	FEC or (F)EC followed by Paclitaxel every 2 weeks (dose-dense) vs. every 3 weeks (standard-interval)	Treatment-induced amenorrhea (POI defined only based on menstrual function at different timepoints following the end of treatment)	Risk of treatment-induced amenorrhea with dose-dense vs. standard interval chemotherapy: OR 1.00, 95 % CI 0.80–1.25, P = 0.989	Dose-dense adjuvant chemotherapy does not increase risk of treatment-induced amenorrhoea in premenopausal breast cancer patients	
(Lambertini, *et al.*, 2016)	international recommendations from an expert meeting	physicians with expertise in the field of fertility preservation in cancer patients from several European countries were invited in Genova (Italy) to participate in a workshop on the topic of "cancer and fertility preservation".			10 recommendations were discussed and prepared with the aim to help physicians in counseling their young patients interested in fertility preservation. Overview included on "Risk of treatment-related infertility with the main anticancer therapies"		
(Lambertini, *et al.*, 2019c)		patients with HER2-positive		Pregnancy outcomes	92 patients (12 in the exposed group and 80 in the unexposed group) had a pregnancy. Seven patients (58.3%) in the exposed group and 10	For patients with HER2-positive early breast cancer, having a pregnancy after	Part of the : The Neoadjuvant

		early breast cancer : unintentionally exposed to trastuzumab and/or lapatinib during gestation (the exposed group) those who became pregnant after trastuzumab and/or lapatinib completion (the unexposed group).		patients (12.5%) in the unexposed group opted for an induced abortion; in the unexposed group, 10 patients (12.5%) had a spontaneous abortion. No pregnancy/delivery complications were reported for the remaining cases, who successfully completed their pregnancy, with the exception of 1 fetus with trisomy 21 (Down syndrome). No significant difference in DFS (adjusted hazard ratio, 1.12; 95% CI, 0.52-2.42) was observed between young patients with a pregnancy (n = 85) and young patients without a pregnancy (n = 1307).	treatment completion appears to be safe without compromising fetal outcome	Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) trial and the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial
(Lambertini, et al., 2018a)	RCT	2862 premenopausal patients with HER2-positive breast cancer	chemotherapy plus trastuzumab vs. lapatinib vs. lapatinib-->trastuzumab vs. lapatinib + trastuzumab	Treatment-induced amenorrhea (POI defined only based on menstrual function following the end of treatment)	Rates of treatment-induced amenorrhea were 72.6%, 74.0%, 72.1%, and 74.8% in the trastuzumab, lapatinib, trastuzumab --> lapatinib, and trastuzumab + lapatinib arms, respectively (P = 0.64). As compared with trastuzumab alone, no difference in treatment-induced amenorrhea risk was observed with lapatinib (OR 1.13, 95% CI 0.90-1.43, P = 0.29), trastuzumab-->lapatinib (OR 0.99, 95% CI 0.79-1.24, P = 0.91), and trastuzumab+lapatinib (OR 1.19, 95% CI 0.94-1.51, P = 0.14). In the multivariable analysis, the only factors that remained statistically significantly associated with higher risk of treatment-related amenorrhea were older age at diagnosis (adjusted OR 2.84, 95% CI 1.93-4.17, P < .001), addition of taxanes to anthracycline-based chemotherapy (adjusted OR 1.92, 95% CI 1.44-2.56, P < .001), administration of TCH (design 2B) regimen (adjusted OR 2.24, 95% CI 1.18-4.27, P = 0.01), and use of adjuvant endocrine therapy (adjusted OR 2.84, 95% CI 1.85-4.35, P < 0.001).	There was no association between rates of treatment-induced amenorrhea and type of anti-HER2 treatment in premenopausal patients with HER2-positive early breast cancer	
(Lambertini, et al., 2019d)	retrospective CS	148 patients	FEC vs. FEC-->D / tam yes vs. tam no / BRCA mutated vs. BRCA non-mutated	AMH levels before and after different anticancer treatments	One year after diagnosis, patients treated with FEC only had higher median AMH levels than those who received FEC-D (0.22 vs. 0.04 µg/L, p = 0.0006); no difference was observed at 3 years (0.06 and 0.18 µg/L, p = 0.47). Patients under endocrine therapy had significantly higher AMH levels than those who did not receive this treatment 1 year after diagnosis (0.12 vs. 0.02 µg/L; p = 0.008), with no difference at 3 years (0.11 and 0.20 µg/L, p = 0.22). AMH levels were similar between BRCA-mutated and	In breast cancer patients receiving FEC chemotherapy, adding D appeared to negatively impact on their ovarian reserve in the short-term; no further detrimental effect was observed for endocrine therapy use and presence of a deleterious germline BRCA mutation	

				BRCA-negative patients at baseline (1.94 vs. 1.66 µg/L, p = 0.53), 1 year (0.09 vs. 0.06 µg/L, p = 0.39) and 3 years (0.25 vs. 0.16 µg/L; p = 0.43) after diagnosis.		
(Lee, et al., 2006a)			American Society of Clinical Oncology Recommendations on Fertility Preservation in Cancer Patients			Guideline
(Ruddy, et al., 2015)	Single-arm phase II trial	64 premenopasual patients with HER2-positive breast cancer	weekly paclitaxel + trastuzumab	Treatment-induced amenorrhea (POI defined only based on menstrual function following the end of treatment)	A total of 18 of 64 women (28%, 95% CI 18-41%) developed treatment-induced amenorrhea	Amenorrhea rates among premenopausal women treated with adjuvant paclitaxel and trastuzumab for early stage breast cancer appear lower than those seen historically with standard alkylator-based breast cancer regimens
(Ruddy, et al., 2019)	RCT	1,168 breast cancer patients	Different anticancer treatments	Association between single-nucleotide polymorphisms and post-chemotherapy menstruation	Older age, tamoxifen use, and node-negative disease were associated with increased risk of chemotherapy-related amenorrhea. Adjusting for these, rs147451859, in an intron of PPCDC (phosphopantothenoylcysteine decarboxylase), and rs17587029, located 5' upstream of RPS20P11 (ribosomal protein S20 pseudogene 11), were associated with post-chemotherapy menstruation.	Genetic variation may contribute to risk of chemotherapy-related amenorrhea. Better prediction of who will experience chemotherapy-related amenorrhea may inform reproductive and treatment decision making in young women with cancer
(Silva, et al., 2016)	SR	15 articles included	Different chemotherapy regimens (with or without concurrent GnRH analogs)	Treatment-induced amenorrhea (POI defined only based on menstrual function at different timepoints following the end of treatment) and AMH levels before and after different anticancer treatments	Younger age and baseline AMH levels (patient-related factors), co-administration of GnRHa, addition of taxanes to anthracycline-based chemotherapy and addition of endocrine therapy to chemotherapy (treatment-related factors) were assessed. Menses recovery was the most used marker. Younger age (≤40 years) and exposure to GnRHa were positively associated with menses recovery (OR 6.07 and 2.03, respectively) but exposure to taxanes adversely affected recovery (OR 0.49).	Younger age and GnRH agonist (GnRHa) administration during chemotherapy were significantly associated with menses recovery, but this recovery was less likely in patients exposed to taxanes
(Su, et al., 2014)	prospective cohort study	109 participants (median age, 39 years; age range, 23-45 years) before chemotherapy		association between prechemotherapy AMH, FSH, and inhB levels and the time to return of ovarian function?	After a median follow-up of 163 days (range, 4-1009 days) after chemotherapy, 62 participants (57%) experienced return of ovarian function. In adjusted analyses, AMH levels >0.7 ng/mL (HR, 2.9; 95% CI 1.5-5.6) and FSH levels </=10 IU/L (HR, 4.7; 95% CI, 1.3-16.8) were associated with a shorter time to ovarian recovery, whereas inhB levels were not related. A prognostic score based on age <40 years, AMH >0.7 ng/mL, and BMI >/=25 kg/m(2) was used to estimate the timing of recovery.	prechemotherapy AMH and FSH levels were associated with the return of ovarian function, independent of age. A novel prognostic score incorporating AMH, age, and body size was capable of estimating the time to ovarian recovery.
(Titus, et al., 2013)	Experimental study				ovarian reserve was impaired in young women with germline BRCA1 mutations compared to controls as determined by serum concentrations of AMH.	underlying mechanism behind age-induced wastage of the human ovarian follicle reserve

(Turan, _et al._, 2018)	secondary analysis of a prospective database	145 females diagnosed with cancer who underwent embryo or oocyte cryopreservation for FP	stimulated with an antagonist protocol either using letrozole combined with recombinant follicle-stimulating hormone (rFSH; LF, n = 118) or rFSH alone (FA, n = 24).	mean number of total and mature oocytes	The mean number of total (15.6 [7.9] vs 10.2 [7.8]; P = .004) and mature oocytes (10.4 [5.1] vs 7.8 [3.5]; P = .044) and embryos frozen (7.7 [5.3] vs 5.3 [2.7]; P = .043) were significantly higher after LF stimulation versus FA. In the LF group, women with BRCA mutations produced significantly fewer oocytes (11.0 [8.0] vs 16.4 [7.7], P = .015) and embryos (5.1 [4.4] vs 8.2 [4.7], P = .013), compared to those who were mutation negative. After adjusting for age, BMI, baseline FSH level, and BRCA status, LF protocol still resulted in higher number of total oocytes (95% CI: 1.9 to 3.6; P = .002) mature oocyte (95% CI: 0.3 to 1.4; P = .028), and embryo yield (95% CI: 0.7 to 1.4; P = .015).	letrozole appears to enhance response to ovarian stimulation while the presence of BRCA mutations is associated with lower oocyte and embryo yield.	
(Valentini, _et al._, 2013)	retrospective CS	1,954 BRCA-mutated breast cancer patients	Different anticancer treatments (type of chemotherapy not specified)	Treatment-induced amenorrhea (POI defined only based on menstrual function at different timepoints following the end of treatment)	Of the 1,426 women who received chemotherapy, 35% experienced long-term amenorrhea. Of the 528 women who did not receive chemotherapy, 5.3% developed long-term amenorrhea. The probabilities of chemotherapy-induced amenorrhea were 7.2% for women diagnosed before age 30 years, 33% for women age 31 to 44 years, and 79% for women diagnosed after age 45 years (P trend < 0.001). The probability of induced amenorrhea was higher for women who received tamoxifen than for those who did not (52% v 29%; P < 0.001). The age-specific probabilities of induced amenorrhea was compared between chemotherapy-treated patients with (n=1,426) or without (n=100) BRCA mutations; no significant difference in probabilities of chemotherapy-induced amenorrhea was observed for the two groups (P = 0.18).	Age at treatment and use of tamoxifen are important predictors of chemotherapy-induced amenorrhea in women who carry a BRCA1 or BRCA2 mutation. The risk of induced long-term amenorrhea does not seem to be greater among mutation carriers than among women who do not carry a mutation	
(van Hellemond, _et al._, 2017)	nested case-control	329 patients (median age of 50.0 years (range = 45-57 years)). with chemotherapy-induced ovarian function failure. Women who underwent a bilateral ovariectomy or used luteinizing hormone-releasing hormone agonists before random	Plasma estradiol and follicle-stimulating hormone levels were monitored until 30 months after random assignment	determine the ovarian function recovery (OFR) rate during AI use	39 patients developed OFR, corresponding with a 30-month recovery rate of 12.4%. Of these, 11 (28.2%) were age 50 years or older at AI initiation. The estradiol level decreased statistically significantly by 37.8% (95% CI = 27.4% to 46.7%) over the initial 30 months of AI treatment in both groups. However, the estradiol levels in the women who experienced OFR remained statistically significantly higher (difference = 20.6%, 95% CI = 2.0% to 42.7%) prior to OFR diagnosis compared with those who did not experience OFR.	: The risk of OFR during AI treatment in breast cancer patients with chemotherapy-induced ovarian function failure is relevant, even beyond 45 years. Furthermore, women experiencing OFR had statistically significant higher estradiol levels during AI treatment (before OFR) than those without, with potential consequences regarding efficacy.	

		assignment were excluded.					
(Zhao, et al., 2014)	SR	15,916 premenopausal breast cancer patients from 46 studies	Cyclophosphamide-based regimens vs. no cyclophosphamide; anthracycline-based regimens vs. no anthracycline; taxane-based regimens vs. no taxane; tamoxifen vs. no tamoxifen	Treatment-induced amenorrhea (POI defined only based on menstrual function at different timepoints following the end of treatment)	Risk of treatment-induced amenorrhea with: 1) Cyclophosphamide-based regimens (OR 2.25; 95% CI 1.26–4.03, P = 0.006); 2) anthracycline-based regimens (OR 1.39; 95% CI 1.15–1.70, P = 0.0008); 3) taxane-based regimens (OR 1.24, 95 % CI 1.03–1.50, P = 0.02); 4) tamoxifen (OR 1.48; 95 % CI 1.28–1.70, P < 0.001).	The current meta-analysis has demonstrated that anthracyclines, taxanes, cyclophosphamide, and tamoxifen all contributed to elevated rates of treatment-induced amenorrhea.	
Hematological cancer							
(Akhtar, et al., 2015)	retrospective CS	176 females underwent single auto-SCT. 89 were eligible for menstrual cycles and pregnancy analysis.	Gonadal function after high-dose chemotherapy for SCT	Gonadal function after high-dose chemotherapy and auto-SCT for NHL and HL	Regular menstrual-cycles resumed in 56/89 patients (63%). Increasing age (P = 0.02) and number of prior chemotherapy cycles (P = 0.02) are associated with higher risk of amenorrhea. 40 patients tried to get pregnant, 26 (65%) became pregnant 50 times: 43 (86%) live birth, 7 (14%) miscarriage and 2/50 had birth defects.	These data highlight significantly higher than perceived incidence of menstrual cycle resumption, successful pregnancies after HDC auto-SCT.	
(Anderson, et al., 2018b)	Biomarker study within RCT	67 female	ABVD or AVD vs. BEACOPP	Ovarian reserve before treatment, during chemotherapy, and then annually for 3 years by use of serum AMH and FSH	AMH decreased during both chemotherapy regimens. At 1 year after chemotherapy, antimüllerian hormone concentrations recovered to a median of 10.5 pmol/L (IQR 4.3–17.3) in the ABVD-AVD group, but little recovery was seen after BEACOPP (median 0.11 pmol/L [0.07–0.20]). Age also affected the extent of ovarian function recovery, with AMH recovery in participants aged 35 years or older in the ABVD-AVD group to 37% (SD 10) of their before treatment concentrations, compared with full recovery to 127% (SD 12) in those younger than 35 years (p<0.0001). FSH recovery to less than 25 IU/L occurred for 95% of women younger than 35 years in the ABVD-AVD group by 2 years and was also dependent on age (hazard ratio 0.49, 95% CI 0.37–0.65; p<0.0001).	Reduced recovery of ovarian function observed in women older than 35 years treated with ABVD or AVD compared with younger women indicates that treatment could reduce their reproductive lifespan and supports discussion of fertility preservation before treatment. Women treated with BEACOPP should be informed of its potential high gonadotoxicity. These findings warrant further investigation in large, prospective studies with fertility and reproductive lifespan as outcomes.	
(Behringer, et al., 2013)	Survey within RCTs	1,323 survivors of HL: 562 women (and 761 men)	Different chemotherapy agents (ABVD and/or BEACOPP)	Menstrual activity, time to resumption of menstrual activity, hormone values (FSH, LH, estradiol, and testosterone; AMH and inhibin B), symptoms of hypogonadism and pregnancies after therapy.	Follicle-stimulating hormone, anti-Mullerian hormone, and inhibin B levels correlated significantly with therapy intensity (P < 0.001). Regular menstrual cycle was reported by more than 90% of female survivors of early-stage HL (recovery time mostly ≤ 12 months). After six to eight cycles of BEACOPP, menstrual activity was strongly related to age (< 30 years vs. ≥ 30 years: 82% vs. 45%, respectively; P .001; prolonged recovery time). Thirty-four percent of women age ≥ 30 years suffered severe menopausal symptoms.	The present analysis in a large group of survivors of HL provides well-grounded information on gonadal toxicity of currently used treatment regimens and allows risk-adapted fertility preservation and comprehensive support during therapy and follow-up.	

(Di Paola, et al., 2013)	Case-control	63 female treated with hematological malignancies + 64 controls	Different chemotherapy regimens and/or radiotherapy vs. age-matched controls	Gonadal function: complete clinical history, transvaginal ultrasound examination for antral follicle count (AFC), and measurement of hormone values (inhibin-B, FSH, and AMH).	Patients treated with low gonadotoxic therapies, while being similar to age-matched controls in their ovarian reserve when evaluated within a few years from the end of the therapy, show a clear impairment over longer times (cases and controls were significantly different for AFC and hormone values (mean AFC: 9.8 vs. 16.0 [p = 0.0001]; mean AMH: 2.02 vs. 2.97 ng/mL [p = 0.02]; mean FSH:16.9 vs. 8.1 /mL [p =0.03]; inhibin-B: 33.7 vs. 69.4 ng/L [p = 0.0001])). In the case of low and medium toxicity, AMH values were similar to controls in the small- and medium-gap groups (p = 0.45 and p = 0.60, respectively) but were significantly reduced in the large-gap group (p = 0.01). In the case of high toxicity, AMH values were significantly different from controls in all of the groups (p < 0.0001, p < 0.001, and p = 0.004 in the large-, medium-, and small-gap groups, respectively).	AMH is the most sensitive hormonal parameter in detecting changes in ovarian reserve when compared with FSH or inhibin-B. This study stresses the importance of accurate counseling at the time of diagnosis of cancer and emphasizes the risks of infertility with low gonadotoxic therapies that may reduce the reproductive window of survivors.	
(Gharwan, et al., 2016)	Case series	28 patients with primary mediastinal B-cell lymphoma (PMBL)	Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) chemotherapy regimen	Gonadal function: menstrual function, measurement of hormone values (LH, FSH, AMH, estradiol and testosterone) and pregnancy outcomes	Amenorrhea developed in 12 patients during chemotherapy. At > 1-year follow-up, 14/19 (74%) patients were menstruating, all < 35 years old, and six (43%) of these patients delivered healthy children. Hormonal assays showed ovarian dysfunction during chemotherapy in all patients with varying recovery at 4–18 months after treatment. Fertility was preserved in most women with ovarian failure confined to patients > 40 years old.	These results suggest that DA-EPOCH-R induces less ovarian damage than more dose intense regimens.	
(Hammond, et al., 2007)	Prospective CS	120 patients (60 male + 60 female) who received myeloablative SCT + 120 controls	High-dose chemotherapy for SCT vs. controls	Questionnaire on perceived fertility status, conception efforts, and infertility concern 10 years after SCT	A total of 22% of survivors compared with 9% of controls reported that they had looked into family-building options because of infertility (P = 0.009). Fourteen survivors (12%) compared with eight controls (7%) indicated that they had tried unsuccessfully to have children in the previous 10 years (P = not significant). A total of 25% of survivors had moderate to high levels of concern about infertility, compared with 7% of controls. A majority of survivors younger than age 40 years (54%) expressed elevated infertility concern. Survivors without children before transplant had greater risk of elevated concern after 10 years (odds ratio, 3.41; 95% CI, 1.93 to 11.30; P = 0.05). Although female controls were more likely to express elevated infertility concern (P = 0.007), sex did not discriminate concern among survivors.	The prevalence of infertility and related concerns is higher among long-term SCT survivors than among age-, sex-, and education-matched controls. Younger SCT recipients and those without children have persistent fertility-related needs even 10 years after treatment.	Previous publication: Syrjala KL, Langer SL, Abrams JR, et al: Late effects of stem cell transplant among 10-year adult survivors compared with case-matched controls. J Clin Oncol 23:6596-6606, 2005
(Lawrenz, et al., 2012)	Comparative study	64 female lymphoma patients aged <40 years (84 breast cancer)	Measurement of antimullerian-hormone (AMH) levels. Ovarian hormonal stimulation to retrieve oocytes	ovarian reserve before the start of chemotherapy	Female lymphoma patients have significantly lower AMH levels than healthy age-matched controls: mean value of AMH was 2.06 ng/mL in the study group versus 3.20 ng/mL in the control group. Analysis of the stimulation results showed that in significantly younger patients with	Ovarian reserve is reduced in female patients affected by lymphoma even before the start of chemotherapy	

		age-matched healthy volunteers (control group)			lymphoma, significantly fewer oocytes could be retrieved in comparison to those with breast cancer.		
(Lekovich, et al., 2016)	Retrospective study	64 newly diagnosed lymphoma patients undergoing COH for FP 365 healthy controls (elective oocyte cryo) 128 patients with other types of malignancy prompting fertility preservation		Primary outcomes included serum anti-Mullerian hormone (AMH) levels (ng/mL) and antral follicle count (AFC).	Patients in the lymphoma group demonstrated significantly lower AMH levels and AFC and had less oocytes harvested and cryopreserved when compared to healthy controls as well as patients with other malignancies.	: Patients with lymphoma demonstrate diminished ovarian reserve when compared with healthy controls and patients with other malignancies. This should be taken into consideration when deciding on the dose for COH.	
(Meissner, et al., 2015)	Survey within RCTs	46 women with aggressive non-Hodgkin lymphoma (NHL) vs general population	CHOP-like regimens	Long-term ovarian function and ovarian reserve: questionnaire and blood samples (AMH).	Last menstrual bleeding occurred significantly earlier in patients compared with the general population (47 vs. 51 years, P < 0.0001). In comparison to the distribution of menopausal symptoms in the general population, the percentage of women with moderate or severe menopausal symptoms was increased. In 23 patients who agreed to participate in laboratory analyses, AMH as a marker of ovarian reserve was decreased when compared with correspondent age groups of the general population.	Although most female patients regain fertility after CHOP-like chemotherapy, late ovarian impairment occurs frequently. Therefore, awareness of such delayed side-effects at the time of counselling is of importance.	Data on the age at menopause in the general population were derived from the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition
(Peigne and Decanter, 2014)	SR	15 articles (434 patients with different cancers including hematological malignancies)	Exposure to different chemotherapy regimens	AMH levels before and after chemotherapy (all cancers)	Cancer patients have significantly lower AMH after chemotherapy than age-matched controls. Longitudinal studies of AMH variations before, during and after chemotherapy provide information about the degree of follicle loss for each patient according to different chemotherapy regimens. Different patterns of AMH levels during the ovarian recovery phase make it possible to discriminate between high and low gonadotoxic chemotherapy protocols. In addition, pretreatment AMH levels are shown to predict the long-term ovarian function after the end of treatment.	These results may help to better understand the ovarian toxicity mechanisms of chemotherapy and to predict the degree of the ovarian follicle loss. Therefore, it can be useful for fertility preservation strategies, fertility counseling and future family planning.	

(Tauchmano va, et al., 2003)	Prospective CS	Stem cell transplantation (SCT): 23 allogeneic SCT + 22 autologous SCT + 45 controls	High-dose chemotherapy for SCT	Ovarian morphology and function: recovery of menstrual cycles; endocrine parameters (FSH, LH, prolactin, 17b-estradiol, testosterone and D4-androstenedione, DHEAS). Pelvic ultrasonography	Menstrual cycles recovered in two and four women in the allo- and auto-SCT groups respectively, being associated with younger age and longer period elapsed from transplant. There was no difference in previous use of alkylating agents between allo- and auto-transplantation. Significantly higher gonadotrophin levels and lower estradiol were seen in the combined group of patients than in controls. In allo-transplanted women, androgens were also significantly lower than in controls. Ovarian and uterine volumes were lower in patients than in controls, and in the allo- than in the auto-transplanted women. Within the allo-SCT group, endocrine function and ovarian and uterine volumes were significantly lower in the patients suffering from cGVHD.	Ovarian failure in SCT recipients is likely to be caused principally by myelo-ablative treatments, but the condition of gonadal and androgen insufficiency can be worsened by an altered immunomodulation in allogeneic setting	
(van der Kaaij, et al., 2012)	Survey within RCTs	1,700 women treated for Hodgkin lymphoma (HL) between 1964 and 2004: 460 selected for analysis of POF	Different chemotherapy agents (alkylating vs nonalkylating)	POI (POI was defined as menopause before age 40 years) and motherhood	Cumulative risk of POF after alkylating chemotherapy was 60% and only 3% after nonalkylating chemotherapy. POF risk increased by 23% per year of age at treatment. In women treated without alkylating chemotherapy at age younger than 32 years and age 32 years or older, cumulative POF risks were 3% (95% CI, 1% to 16%) and 9% (95% CI, 4% to 18%), respectively. If menstruation returned after treatment, cumulative POF risk was independent of age at treatment. Among women who ultimately developed POF, 22% had one or more children after treatment, compared with 41% of women without POF	Nonalkylating chemotherapy carries little to no excess risk of POF. Dose-response relationships for alkylating chemotherapy and age at treatment are both linear. Timely family planning is important for women at risk of POF	POI was defined as menopause before age 40 years. Menopause was defined as cessation of menstruation at least 1 year before the date of the survey
Gynecologic al cancer						
(Ceppi, et al., 2019)	Retrospectiv e and prospective CS	198 patients with epithelial ovarian cancer (EOC) and 350 patients with nonepithelial ovarian cancer (no-EOC)	Gonadotoxicity of chemotherapy in patients undergoing fertility-sparing treatment	Menstrual and reproductive outcomes, and menopausal age	A total of 44% of the patients received chemotherapy, with a median follow-up of 15.9 years. In no-EOC patients, chemotherapy exposure conferred a higher risk for Outcomes 1 (adjusted OR [aOR] 27; 95% CI 12 to 61; P < .0001) and 2 (aOR 5.42; 95% CI 1 to 24; P = .0256) and was associated with a younger menopausal age (adjusted β−5.52; 95% CI−10.53 to −0.52; P = .0313). Overall, 57% of patients attempted pregnancy, with a conception rate of 89%. In EOC patients, no association between chemotherapy exposure and a decreased fertility was demonstrated (aOR, 3.05; 95% CI 0.72 to 12.88; P = .1298).	Chemotherapy exposure in no-EOC was associated with an increased risk of during treatment amenorrhea, posttreatment amenorrhea, and earlier spontaneous menopausal age; chemotherapy exposure in EOC was not associated with any item at study. Patients undergoing fertility-sparing treatment had reassuringly high conception rates and low premature ovarian failure rates; however, in pretreatment counseling, the risks of this approach in such young population should be discussed.	

(Chan and Wang, 2017)	Review	Female patients with gynecologic malignancies	Gonadotoxicity of different treatments including surgery, radiotherapy and chemotherapy	1) The effects of radiation and chemotherapy on fertility; 2) Fertility-sparing surgeries and the role of assisted reproductive technology; 3) Fertility preservation in adolescent girls and women with BRCA germline mutations.	1) RT: in the Childhood Cancer Survivor Study (CCCS), a large retrospective cohort study, ovarian failure was associated with older age at the time of diagnosis (OR 1.8, p < 0.001) and treatment with abdominal or pelvic radiation (OR 25.4, p < 0.001), especially with doses ≥10 Gy. CT: Alkylating agents are associated with the highest risk for infertility and ovarian insufficiency. Platinum agents, taxanes, and anthracyclines are in an intermediate risk group for gonadotoxicity. Drugs in the anti-metabolite category, such as gemcitabine and 5-fluorouracil, are generally thought to be less gonadotoxic than alkylating agents. 2) Cervical cancer: Conization, Radical trachelectomy, Ovarian transposition prior to radiation treatment, Uterine sparing radiation, Oocyte/embryo cryopreservation. Endometrial cancer: Medical management with progestins, Hysteroscopic resection, Hysterectomy with ovarianconservation, Oocyte/embryo cryopreservation. Ovarian cancer: Unilateral oophorectomy, Oocyte/embryo cryopreservation. 3) BRCA: bilateral salpingectomy with delayed oophorectomy may be the more optimal prophylactic strategy in premenopausal BRCA mutation carriers. Randomized controlled trials are needed to determine the validity of this approach to prevent ovarian cancer	Oncofertility addresses fertility and the reproductive health needs for cancer patients, a key topic in cancer survivorship. Given that the standard treatment for gynecologic malignancies involves removal of reproductive organs, pelvic radiation, or chemotherapy, the effect of such treatment on fertility and options for fertility preservation are even more relevant than for other malignancies. In reproductive-age women with new diagnoses of cervical, endometrial, or ovarian cancers, viable strategies for fertility preservation exist and should be considered. Patients should be carefully counseled about fertility preservation and be informed about the options provided by assisted reproductive technology.	
(Gershenson, et al., 2007)	Case-control study	132 patients + 137 controls	Malignant ovarian germ cell tumor survivors (exposed to surgery plus platinum-based chemotherapy) compared with matched control group (acquaintances recommended by survivors and matched for age, race and education)	Menstrual and reproductive outcomes, sexual functioning, and dyadic adjustment.	Of 132 survivors, 71 (53.8%) had fertility-sparing surgery. Of fertile survivors, 62 (87.3%) reported still having menstrual periods. Twenty-four survivors reported 37 offspring after cancer treatment. Compared with controls, survivors had significantly greater reproductive concerns (P < 0.0001), less sexual pleasure (P = 0.003), and lower scores on the total Sexual Activity Scale Score (P = 0.001). However, survivors had better dyadic consensus (P = 0.004), dyadic satisfaction (P = 0.005), and dyadic cohesion (P = 0.014)	Women who had fertility-sparing surgery were very likely to retain menstrual function and fertility after chemotherapy. Although there is some increase in gynecologic symptoms and diminution in sexual pleasure, survivors tended to have stronger, more positive relationships with significant others.	
Other cancer						
(Anderson, et al., 2017b)	retrospective CS	2,360 women with a differentiated thyroid cancer diagnosis, 53% received radioactive iodine (RAI)	RAI vs non-RAI exposure	Associations between RAI and post-treatment live birth rates	The cumulative incidence of birth at the end of follow-up (maximum 14.5 years) was 30.0% and 29.3% among those who were and were not treated with RAI, respectively. Overall, first birth rates did not significantly differ between groups (HR 1.00; 95% CI 0.82-1.23).	In this observational cohort, treatment with RAI was not associated with a reduced birth rate. These findings add to the evidence available for counseling thyroid cancer patients with concerns about future fertility.	
(Anderson, et al., 2018a)	retrospective cohort study	female cancer patients aged < 39 years at		Incidence of pregnancy	Cancer survivors achieved fewer pregnancies: SIR 0.62 (95% CI: 0.60, 0.63). Reduced SIR was observed for all cancer types. The chance of achieving a first pregnancy was also lower,	Cancer survivors achieved fewer pregnancies across all cancer types, and the chance	impact of cancer in females aged </=39 years

	CS	diagnosis (n=23 201). Females from the exposed group not pregnant before cancer diagnosis (n = 10 271) were compared with matched general population controls			adjusted hazard ratio = 0.57 (95% CI: 0.53, 0.61) for women >5 years after diagnosis, with marked reductions in women with breast, cervical and brain/CNS tumours, and leukaemia. The effect was reduced with more recent treatment period overall and in cervical cancer, breast cancer and Hodgkin lymphoma, but was unchanged for leukaemia or brain/CNS cancers. The proportion of pregnancies that ended in termination was lower after a cancer diagnosis, and the proportion ending in live birth was higher (78.7 vs 75.6%, CI of difference: 1.1, 5.0).	of achieving a first pregnancy was also lower.	on subsequent chance of pregnancy?
(Cathcart-Rake, *et al.*, 2019)	Retrospective CS	182 premenopausal women with lung cancer	Chemotherapy exposure	Amenorrhea post-treatment	Average age at lung cancer diagnosis was 43 years (SD 6). Among the 85 patients who received chemotherapy, 64% self-reported that they had become menopausal within a year of diagnosis. Platinum salts were universally included in these chemotherapy regimens, and the majority of these women also received taxanes within 1 year of diagnosis. Only 15% of the 94 patients who did not receive systemic therapy within 1 year of diagnosis experienced self-reported menopause. Three patients received targeted therapy alone, two of whom remained premenopausal at the final qualifying survey, completed a median of 3 years after diagnosis.	Chemotherapy for lung cancer patients appears to increase risk of early loss of menses in survivors	
(Cercek, *et al.*, 2013)	retrospective CS	73 female patients with colorectal cancers of whom 49 included in the analysis	FOLFOX	Menstrual function during and after chemotherapy	In total, 41% experienced amenorrhea during chemotherapy, and 16% had persistent amenorrhea 1 year after completion of chemotherapy. The incidence of amenorrhea during chemotherapy trended higher in patients aged older than 40 compared with patients aged 40 and younger (59% vs. 31%; P = 0.075). There was no statistically significant difference in persistent amenorrhea between the 2 age groups (24% vs. 13%; P = 0.42)	In this retrospective series, there appears to be a trend toward FOLFOX induced amenorrhea during chemotherapy increasing with age. Twenty-four percent of women older than the age of 40 were found to have persistent amenorrhea after FOLFOX therapy. Because of the small sample size, the study is underpowered to detect a statistically significant difference between older and younger patients. Prospective studies are planned to further characterize the effect of FOLFOX on early menopause and fertility.	
(Cioffi, *et al.*, 2018)	retrospective CS	75 female with gestational trophoblastic neoplasia	Single agent chemotherapy (group A) vs combination chemotherapy (group B)	Menstrual and reproductive outcomes	Temporary amenorrhea occurred in 33% of group A patients and 66.7% of group B (P = 0.01). Premature menopause occurred in 3 patients in group B (0% vs 9%, P = 0.02). Ten patients in group B underwent salvage hysterectomy. Pregnancy	Except for the risk of premature ovarian failure, a rare adverse effect of combined treatments, both single-agent and multiagent	Group A= methotrexate. Group B: etoposide, actinomycin

Study	Type	Population	Exposure	Outcomes	Results	Conclusions	Notes
					desire did not differ between the 2 groups (P = 0.555). In group A, 57.1% became pregnant; in group B, 36.4% did (P = 0.060). Instead, pregnancy rate was 52.2% among high-risk patients not undergoing hysterectomy (57.1% vs 52.2%, P = 0.449). There was no difference in miscarriage (P = 0.479) and premature birth (P = 0.615) rates. In a multivariate analysis that included age, International Federation of Gynecology and Obstetrics score, chemotherapy type, use of assisted reproductive technologies, previous pregnancies, and pregnancy desire, only age (P = 0.006) and pregnancy desire (P = 0.002) had a significant impact on the probability to have subsequent pregnancies.	chemotherapy can be safely administered to patients with a desire for childbearing. High-risk patients have worse reproductive outcomes because they undergo hysterectomy more frequently than low- risk patients.	D, methotrexate, cyclophosphamide, vincristine
(Clement, et al., 2015)	systematic review	37 articles of patients with differentiated thyroid carcinoma (DTC); 4 studies (n = 405 patients) assessed gonadal function in women, 5 studies (n = 12,583 patients) assessed reproductive outcomes	Intermediate and long-term adverse effects of radioiodine therapy	Post-treatment menstrual function, markers of ovarian function (FSH, LH estrogen and progesterone), age at menopause and reproductive outcomes	Patients experienced significantly more frequently transient female gonadal dysfunction (prevalence: 28%) compared to unexposed patients. I-131 therapy seems to have no deleterious effects on female reproductive outcomes.	Treatment with I-131 for DTC may have significant adverse effects, which seem to be dose dependent. These adverse effects of treatment must be balanced when choosing for I-131 therapy in patients with DTC.	
(Evranos, et al., 2018)	Prospective CS	33 patients with differentiated thyroid cancer (DTC)	RAI exposure	AMH levels before and after RAI treatment	The median AMH levels were 3.25 (0.32–17.42), 1 (0.01–3.93), 1.13 (0.08–6.12), and 1.37 (0.09–6.1) ng/mL before and at 3, 6, and 12 months after RAI therapy, respectively. The AMH levels were higher before than after RAI therapy (P = 0.001). The AMH levels did not differ significantly between the three time points (P > 0.05).	AMH is considered an important marker of ovarian reserve. Ovarian reserve decreased after RAI therapy. More attention may be needed when considering RAI therapy for patients with reduced ovarian reserve.	
(Giusti, et al., 2018)	Prospective CS	34 patients with differentiated thyroid cancer (DTC)	RAI exposure	AMH levels before and after RAI treatment	Pregnancy (RAI group 62%; control group 61%) and miscarriage rates (18% and 26%) were similar. AMH levels were similar in the RAI (10.7 ± 1.7 pmol/l) and control (17.5 ± 4.7 pmol/l) groups. Regular menses were reported in 41% and 52% of RAI and control subjects, respectively. Non-ovulatory cycles were noted in 26% and 35% of RAI and control women, respectively. AMH levels were found to be negatively correlated with age (RAI group P = 0.0003; control group P = 0.0001) and FSH, and positively correlated with progesterone, but not with the other hormonal parameters.	AMH should replace FSH in the evaluation of gonadal reserve in pre-menopausal thyroid cancer women. At present, age is the only predictor of AMH levels. About one out of two women with a history of thyroid cancer suffers from menstrual dysregulation, but infertility must be considered a low risk	

(Longhi, et al., 2012)	Retrospective analysis within prospective studies	Total of 883 patients with osteosarcoma (207 female patients evaluated for infertility) and 543 patients with Ewing sarcoma (99 female patients evaluated for infertility)	Different chemotherapy regimens (mostly including anthracycline and cyclophosphamide-based therapy) with or without radiotherapy	Effects of anticancer treatments on the incidence of amenorrhea and infertility	Among patients with osteosarcoma, 75% experienced amenorrhea during chemotherapy. The median time to resumption of menstruation after chemotherapy was 4 months (range, 1-12 months). Only 6 of the females experienced permanent amenorrhea, and 4 of these were aged >35 years at the time of diagnosis. In all, fertility was impaired in 6 of the 207 tested females (2.8%). A total of 28 females delivered 41 healthy children. The median age at first pregnancy was 28 years (range, 17-36 yrs). Also, 5 females had a total of 4 voluntary and 2 spontaneous abortions, and there was 1 stillbirth. Among the 99 patients with Ewing sarcoma, 25 had permanent amenorrhea (15 as a result of high-dose chemotherapy (HDCT) and 6 as a consequence of radiotherapy. Four women had permanent amenorrhea, although they had not undergone any radiotherapy or HDCT; the ages of these 4 patients were 28 years, 30 years, 35 years, and 40 years. In all, early iatrogenic menopause occurred in 29 of the 99 tested patients (29.2%). Older age at the time of diagnosis of Ewing sarcoma was a predisposing factor for sterility in these patients, just as it was for the females with osteosarcoma. In all, 19 of these females became pregnant and delivered a total of 31 healthy children; only 1 premature delivery was reported. The median age at the time of the first pregnancy was 26 years (range, 20-34 years). There were 3 voluntary abortions.	The awareness of late side effects in long-term survivors of primary bone cancers should encourage longer follow-up	
(Overbeek, et al., 2017)	Systematic review	Female cancer patients: 45 studies included, describing a total of 5607 female survivors.	Different chemotherapy regimens for different cancers	Effects of chemotherapy only on the incidence of ovarian dysfunction	Median age at menopause was earlier in cancer survivors than in the general population. The prevalence of amenorrhoea varied from 0% to 83%. Those exposed to MVPP protocols were at highest risk for amenorrhoea (39–79%), as were breast cancer survivors receiving cyclophosphamide-containing regimens, in whom the prevalence of amenorrhoea was 40–80%. The most important risk factors for ovarian dysfunction were: (1) alkylating agents, specifically procarbazine and busulfan, (2) older age at treatment.	Breast cancer survivors, those treated with procarbazine or other alkylating agents and those with a higher age at diagnosis are at highest risk of diminished ovarian function. However, all studies included in this review showed methodological limitations. It is imperative that nation-wide registries guarantee long term follow-up during the adult life of cancer survivors.	
(Savage, et al., 2015)	retrospective CS	1,903 patients of whom 1203 evaluated for menopausal status	Single-agent methotrexate and folinic acid (MTX-FA) vs etoposide, methotrexate, and dactinomycin followed by cyclophosphamide and vincristine (EMA-CO)	Incidence of (second malignancy and) early menopause	The cumulative risk of early menopause was low after MTX-FA but was substantial after EMA-CO, reaching 13% by age 40 years and 36% by age 45 years.	All major treatments except MTX-FA increased the risk of early menopause.	

(Spanos, et al., 2008)	review	Female patients with colorectal cancers	Gonadotoxicity of different treatments including surgery, radiotherapy and chemotherapy	Ovarian function and fertility after different treatments	Resection below the peritoneal reflection may adversely affect fertility, based on lower fertility and fecundity rates associated with pelvic surgery for ulcerative colitis and familial adenomatous polyposis. Standard 5-FU-based chemotherapy may not have significant effects. The advent of oxaliplatin in adjuvant chemotherapy may be more harmful. Adjuvant and neoadjuvant radiation therapy may cause premature ovarian failure using current dosing schedules.	Young female patients with colorectal cancer need to be informed about the effects of treatment on fertility and options for fertility preservation. A multidisciplinary approach for appropriate consultation of these patients is mandatory.
(Wallace, et al., 2003)	Experimental study	Ovarian failure was diagnosed in six patients with a median age of 13.2 years (range 12.5-16.0) who were treated with total body irradiation (14.4 Gy) at 11.5 years of age (4.9-15.1).			Solving the differential equation, we have estimated the number of follicles left after irradiation given as sol(51 - s + r), where r equals age at treatment, s equals age at diagnosis of ovarian failure, and 51 years is the average age of menopause. The surviving fraction of oocytes as a percentage is 100 times this value divided by sol(r). The mean surviving fraction for the six cases is 0.66%. We obtain a function, g(z), which decreases in value from 100% at zero dosage to mean value at dosage z = 14.4 Gy. We have g(z) = 10(mx+c), where c = log(10)100 = 2, and m = [log(10)(0.66) - c]/14.4. Solving g(z) = 50 gives an LD(50) of 1.99.	
(Wan, et al., 2015)	retrospective CS	162 female with colorectal cancers	Treatment for colon cancer vs rectal cancer (FOLFOX / XELOX / capecitabine) vs. chemoradiation	Long-term amenorrhea (> 12 months) in women with colorectal cancer aged 40 years and younger after adjuvant treatment	All patients had regular menses before treatment; 3 patients with colon cancer (4.2%) experienced long-term amenorrhea, and 48 patients with rectal cancer (94.1%) experienced long-term amenorrhea. The incidence of amenorrhea was significantly lower in patients with colon cancer (4.2%; 3 of 72) than in patients with rectal cancer (94.1%; 48 of 51) (P < 0.01).	In this retrospective series, the incidence of amenorrhea in patients with colon and rectal cancers was 4.2% and 94.1%, respectively. These data support the fact that young female patients with CRC, especially those with rectal cancer who are scheduled to undergo pelvic irradiation, should be counseled regarding fertility preservation options, including ovarian transposition and cryopreservation of ovarian tissue, embryo, or oocyte.
(Yaish, et al., 2018)	Prospective CS	24 patients with differentiated thyroid cancer (DTC)	RAI exposure	AMH levels before and after RAI treatment	RAI treatment resulted in a significant decrease in AMH concentrations at three months, from 3.25 ± 2.75 to 1.9 ± 1.74 ng/mL (p < 0.0001). Only partial recovery was subsequently documented. Eighty-two percent of subjects had final values below baseline levels, such that at one year, serum AMH was still 32% lower than prior to treatment (2.36 ± 1.88 ng/mL; p < 0.005). The only two continuous variables that correlated with the extent of AMH reduction at three months were the woman's age (r = 0.51; p = 0.02) and the age at menarche (r = 0.48; p = 0.03). Importantly, the RAI dose was not associated with the extent of AMH reduction and neither were smoking or the use of birth control	RAI in DTC has a rapid and profound effect on ovarian reserve, with only a partial recovery potential. In an era of declining human fertility, it is of relevance to recognize the potentially adverse effect of RAI in women of reproductive age. AMH measurement may be useful as a tool in this decision-making process.

				pills. Older subjects (>35 years) were significantly more likely to experience a marked AMH reduction at three months (63.7 ± 18.5% vs. 33.1 ± 29.2%; p = 0.01). The only predictor of recovery after one year was the extent of AMH decrease at three months: the lower the decline, the higher the chances for recovery.		
Benign						
(Bermas and Sammaritano, 2015)	Observational data	Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)			Both women with RA and SLE have smaller sized families than do controls. In the case of RA factors other than fertility contribute, while in women with SLE there may be diminished ovarian reserve due to cyclophosphamide therapy and advanced maternal age. RA pregnancies can be complicated by preterm birth and small-for-gestational aged infants. SLE pregnancies have higher rates of fetal loss, in particular in those patients with co-existing antiphospholipid syndrome. SLE pregnancies are also more likely to be complicated by pre-eclampsia and hypertension and to result in preterm birth and small-for-gestational aged infants.	Appropriate fertility evaluation and careful pregnancy planning with coordinated obstetrical care help ensure better outcomes in these patient populations.	
(Brouwer, et al., 2015)	prospective cohort study	245 RA patients (PARA study), were included preconceptionally or during the first trimester.		time to pregnancy (TTP) of >12 months.	TTP exceeded 12 months in 42% of 245 patients. Longer TTP was related to age, nulliparity, disease activity (DAS28), and preconception use of NSAIDs and prednisone. These variables were independently associated with TTP, with HRs for occurrence of pregnancy of 0.96 (95% CI 0.92 to 1.00) per year of age, 0.52 (0.38 to 0.70) for nulliparity, 0.81 (0.71 to 0.93) per point increase in DAS28, 0.66 (0.46 to 0.94) for NSAIDs and 0.61 (0.45 to 0.83) for prednisone use. The impact of prednisone use was dose dependent, with significantly longer TTP when daily dose was >7.5 mg. Smoking, disease duration, rheumatoid factor, anti-citrullinated protein antibodies, past methotrexate use, and preconception sulfasalazine use did not prolong TTP.	TTP in RA is longer if patients are older or nulliparous, have higher disease activity, use NSAIDs or use prednisone >7.5 mg daily. Preconception treatment strategies should aim at maximum suppression of disease activity, taking account of possible negative effects of NSAIDs use and higher prednisone doses.	
(Clowse, et al., 2011)		42 severe granulomatosis with polyangiitis (Wegener's) (GPA) women who received (mean age 35 years)	oral cyclophosphamide (CYC) versus methotrexate (MTX) 24 had CYC exposure prior to enrollment and 28 received the drug during the study.	rate of diminished ovarian reserve AMH and FSH, endocrine markers of remaining egg supply. Diminished ovarian reserve was defined as an AMH level of <1.0 ng/ml.	women with prior CYC exposure had significantly lower AMH, higher FSH, and a higher rate of early menstruation cessation. For women with normal baseline ovarian function, 6 of 8 who received CYC during the trial developed diminished ovarian reserve, compared to 0 of 4 who did not receive CYC (P < 0.05). Changes in AMH correlated inversely with cumulative CYC dose (P < 0.01), with a 0.74 ng/ml decline in AMH level for each 10 gm of CYC.	Daily oral CYC, even when administered for less than 6 months, causes diminished ovarian reserve, as indicated by low AMH levels. These data highlight the need for alternative treatments for GPA in women of childbearing age.	
(Cocco, et al., 2008)		189 women with multiple sclerosis (MS) undergoing immunosuppre	questionnaire, paying particular attention to onset of CIA either during or post-MITO treatment, was	Occurrence of chemotherapy-induced amenorrhea (CIA)	48 (26%) patients presented CIA following MITO. The probability of CIA was increased by 2%/mg/m(2) of cumulative dose and by 18% for each year of age, whereas it was reduced by administration of EP during treatment.	MITO treatment may affect reproductive capacity in women with MS. Patients of childbearing age should be properly counseled before	

		ssive treatment with mitoxantrone (MITO) before the age of 45	administered to each patient.			MITO treatment and EP therapy should be administered to reduce the risk of CIA.	
(Condorelli and Demeestere, 2019)	review		specific issues related to providing adequate fertility counseling and management for women who have been diagnosed with the major non-oncological indications, based on the literature and on our clinical experience.		benign disease (eg benign hematological diseases, autoimmune diseases, and gynecological or genetic disorders) account for 8%-13% of the demand for fertility preservation. The risk of premature ovarian failure due to treatment, or to the disease itself, can be considered fairly high for many young women.	Counseling and adequate management of these women require particular attention due to the severe health conditions that are associated with some of these diseases. In this, we address	
(Elchuri, et al., 2015)	Cohort study	female sickle cell anemia (SCA) treated with supportive care (SCA-SC), HU (SCA-HU) and bone marrow transplant (BMT) (SCA-BMT).		Gonadal hypofunction; AMH and follicle-stimulating hormone (FSH) levels Diminished ovarian reserve (DOR) was defined as AMH level <5th percentile for age-matched controls. Subjects also with FSH >40 IU/L were classified as having POI.	14 SCA-SC (14.5 +/- 2.7 years), 33 SCA-HU (14.4 +/- 2.4 years) and 9 SCA-BMT (14.3 +/- 2.7 years) females were included. AMH was undetectable in all SCA-BMT subjects and <5th percentile in 24% of SCA-HU subjects. FSH was menopausal (>40 IU/L) in 88.9% of SCA-BMT subjects. All SCA-BMT subjects and 24% of subjects on HU had DOR; 89% of SCA-BMT subjects had POI. AMH and FSH may be useful tools in assessing ovarian reserve and function.		
(Le Page, et al., 2011)	Cohort study	802 MS patients (308 relapsing-remitting, 352 secondary progressive and 142 primary progressive) received MITOX monthly for 6 months (87%) or every 3 months (13%).		long-term safety profile of mitoxantrone (MITOX) in multiple sclerosis (MS).	The cohort was followed for 5354 patient-years (mean). One out of 802 patients (0.1%) presented with acute congestive heart failure and 39 out of 794 patients (4.9%) presented with asymptomatic left ventricular ejection fraction reduction under 50% (persistent in 11 patients (28%), transient in 27 patients (69%), on the last scan at year 5 in 1 patient). Two cases of therapy-related leukaemia (0.25%) were detected 20 months after MITOX start (one death and one with 8 years confirmed remission). Of the 317 women treated before the age of 45, 17.3% developed a persistent age-dependant amenorrhea.	This large cohort with at least 5 years of follow-up provided good insights into the long-term safety profile of MITOX in MS.	
(Manger, et al., 2006)	Cohort study	63 premenopausal women with SLE without ovarian protection and initiated the PREGO-Study	concentrations of FSH and LH, before, during and after cyclophosphamide treatment		In lupus patients treated with cyclophosphamide, 60% suffered from POF and hypergonadotropic amenorrhea. Whereas the POF rate was <50% in women below 30 years, it was 60% between 30 and 40 years. The cumulative dosage of cyclophosphamide also strongly influenced POF rate.	: Our present results, with a high POF rate in Cyclophosphamide treated SLE patients demonstrate the urgent need for ovarian protection in this patient group. Besides POF these women are at high risk for premature atherosclerosis which is the major cause of death in lupus.	
(Morel, et al., 2013a)	a matched cohort study	56 SLE women exposed to cyclophospham ide younger		AMH levels and the probability of pregnancy	The mean AMH level was low (1.21 ± 1.01 ng/mL) and was significantly lower in patients exposed to cyclophosphamide (P = .03) and in patients older than 30 years (P = .02). During a median follow-up	We confirmed that AMH levels are low in SLE patients and decrease significantly with age and cyclophosphamide	

		than 40 years of age and 56 age-matched control SLE women The mean age ± SD of the 112 patients was 31.6 ± 5.8 years.			(interval between sampling and the interview) period of 4.2 (range, 2.5-4.8) years, 38 patients sought to become pregnant, and 32 (84.2%) succeeded. In the univariate analysis, the risk of failure was associated with cumulative cyclophosphamide dose (P = .007) and older age (P = .02), but not with AMH.	exposure. Nonetheless, the risk of failure to conceive was low and was predicted by cyclophosphamide exposure and age, but not by AMH levels.	
(Tuin, *et al.*, 2016)	Retrospective study	94 premenopausal women with ANCA-associated vasculitis (AAV) – 67 patients received cyclophosphamide, and 27 received other, mostly immunosuppressive, medication.)		onset of menopause and the influence of cyclophosphamide	46 cyclophosphamide-treated women developed menopause, 22 of whom were considered to have primary ovarian insufficiency. None of the patients who were not treated with cyclophosphamide developed primary ovarian insufficiency. There was a significant association between a cumulative cyclophosphamide dose of >16.6 gm, versus a cumulative dose of <16.6 gm, and menopause (chi(2) = 8.72, P = 0.003; odds ratio [OR] 2.60 [95% confidence interval 1.38-4.90]). In addition, there was a significant association between a cumulative cyclophosphamide dose of <16.6 gm, versus no cyclophosphamide exposure, and menopause (chi(2) = 16.37, P < 0.001; OR 7.32 [95% confidence interval 2.79-19.20]). Both women who received cyclophosphamide and those who did not experienced involuntary childlessness.	Earlier menopause and primary ovarian insufficiency frequently develop after oral cyclophosphamide therapy in premenopausal women with AAV. Involuntary childlessness is common after the development of primary ovarian insufficiency, but it also occurs in women not treated with cyclophosphamide. These findings emphasize the importance of the use of drugs that are not toxic to gonadal function in women of childbearing age.	

INCLUDED AS BACKGROUND INFORMATION
(Adriaens, *et al.*, 2009, Barton, *et al.*, 2013, Bedoschi, *et al.*, 2016, Codacci-Pisanelli, *et al.*, 2017, Gracia, *et al.*, 2012, Horton, *et al.*, 2019, Jacobson, *et al.*, 2016) (Lambertini, *et al.*, 2017b, Letourneau, *et al.*, 2012, Meirow, *et al.*, 2007, Morgan, *et al.*, 2012, Peccatori, *et al.*, 2018, Wallace, *et al.*, 2005a, Webber, *et al.*, 2016, Wo and Viswanathan, 2009)

Q8. Is it relevant to do ovarian reserve testing, and for whom?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
Cancer							
(Anderson, *et al.*, 2013)	Cohort study	early breast cancer (eBC) (n=59, mean age 42.6 years [(range 23.3-52.5)]) before any treatment.	Pretreatment ovarian reserve markers (AMH, FSH, inhibin B)	ovarian status at 2 years	Pretreatment AMH was significantly lower in women with amenorrhoea at 2 years (4.0 +/- 0.9 pmol/L versus 17.2 +/- 2.5, P<0.0001), but FSH and inhibin B did not differ between groups. By logistic regression, pretreatment AMH, but not age, FSH or inhibin B, was an independent predictor of ovarian status at 2 years (P=0.005; odds ratio 0.013). We combined these data with a similar cohort (combined n=75); receiver-operator characteristic analysis for AMH gave AUC of 0.90 (95% CI 0.82-0.97)). A cross-validated classification tree analysis resulted in a binary classification schema with sensitivity 98.2% and specificity 80.0% for correct classification of amenorrhoea.	Pretreatment AMH is a useful predictor of long term post chemotherapy loss of ovarian function in women with eBC	
(Benaglia, *et al.*, 2013)	Multicenter retrospective cohort study	39 women with unoperated bilateral endometriomas matched with 78 unexposed control subjects.	IVF-ICSI	IVF outcome Ovarian responsiveness and oocyte quality.	Responsiveness to ovarian hyperstimulation was significantly reduced in women with bilateral endometriomas. The total numbers of developing follicles in case and control subjects were 9.6 +/- 3.3 and 14.1 +/- 6.8, respectively. The numbers of oocytes retrieved were 7.1 +/- 3.2 and 9.8 +/- 5.5, respectively. Conversely, oocyte retrieval was not hampered by the presence of the ovarian endometriomas. The rates (IQR) of oocytes retrieved per total number of developing follicles in case and control subjects were 77% (57%-88%) and 71% (63%-79%), respectively. Moreover, the quality of the retrieved oocytes did not differ. The fertilization rates (IQR) were 67% (56%-100%) and 70% (57%-100%), resp. The rates (IQR) of top quality embryos per oocyte used were 33% (25%-50%) and 33% (20%-43%), resp. The implantation rates were 22% and 23%, resp. The clinical pregnancy rate and the delivery rate also did not differ.	Although the presence of bilateral endometriomas at the time of IVF affects responsiveness to hyperstimulation, the quality of the oocytes retrieved and the chances of pregnancy are not affected.	
(Blumenfeld, *et al.*, 2002)	Prospective study	60 women aged 15-40 years with lymphoma, 10 with leukemia and 10 undergoing chemotherapeutic treatments for non-malignant diseases such	A monthly injection of depot D-TRP(6)-GnRH-a was administered from before starting the chemotherapy until its conclusion, up to	Hormonal profile [FSH, LH, E2, T, P4, insulin-like growth factor (IGF)-1, IGF-BP3 and prolactin) was taken before starting the GnRH-	Whereas all but three (40, 36 and 34 year old) of the surviving patients within the GnRH-a/ chemotherapy co-treatment group resumed spontaneous ovulation and menses within 12 months, less than half of the patients in the 'control' group (chemotherapy without GnRH-a co-treatment) resumed ovarian function and	GnRH-a co-treatment should be considered in every woman of reproductive age receiving chemotherapy	

		as systemic lupus erythematosus or other autoimmune diseases control group of 60 women who have been treated with similar chemotherapy.	a maximum of 6 months.	a/chemotherapy co-treatment, and monthly thereafter until resumption of spontaneous ovulation.	regular cyclic activity (P <0.05). The remaining 55% experienced POF. Temporarily increased FSH concentrations were experienced by about one-third of the patients resuming cyclic ovarian function, suggesting reversible ovarian damage in a larger proportion of women than those experiencing POF. Inhibin-A and -B decreased during the GnRH-a/ chemotherapy co-treatment but increased to normal levels in patients who resumed regular ovarian cyclicity, and/or spontaneously conceived, as compared with low levels in those who developed POF.		
(Ceppi, *et al.*, 2019)	Retrospective and prospective CS	198 patients with epithelial ovarian cancer (EOC) and 350 patients with nonepithelial ovarian cancer (no-EOC)	Gonadotoxicity of chemotherapy in patients undergoing fertility-sparing treatment	Menstrual and reproductive outcomes, and menopausal age	A total of 44% of the patients received chemotherapy, with a median follow-up of 15.9 years. In no-EOC patients, chemotherapy exposure conferred a higher risk for Outcomes 1 (adjusted OR [aOR] 27; 95% CI 12 to 61; P < .0001) and 2 (aOR 5.42; 95% CI 1 to 24; P = .0256) and was associated with a younger menopausal age (adjusted β−5.52; 95% CI−10.53 to −0.52; P = .0313). Overall, 57% of patients attempted pregnancy, with a conception rate of 89%. In EOC patients, no association between chemotherapy exposure and a decreased fertility was demonstrated (aOR, 3.05; 95% CI 0.72 to 12.88; P = .1298).	Chemotherapy exposure in no-EOC was associated with an increased risk of during treatment amenorrhea, posttreatment amenorrhea, and earlier spontaneous menopausal age; chemotherapy exposure in EOC was not associated with any item at study. Patients undergoing fertility-sparing treatment had reassuringly high conception rates and low premature ovarian failure rates; however, in pretreatment counseling, the risks of this approach in such young population should be discussed.	
(Dezellus, *et al.*, 2017b)	Prospective cohort study	250 Breast cancer patients	AMH levels	AMH levels in relation to chemotherapy, AMH levels in realtion to amenorrhoea		Low AMH after chemotherapy; lower basal AMH levels in women with amenorrhoea	
(Dillon, *et al.*, 2013)	Prospective cohort study.	46 adolescent and young adult women with a new diagnosis of cancer requiring chemotherapy	None	Measurements of ovarian reserve via levels of serum FSH, LH, estradiol, inhibin B, and AMH, as well as AFC and mean ovarian volume at 3-month intervals.	All measures of ovarian reserve demonstrated statistically significant changes during chemotherapy. Alkylating agent exposure and baseline ovarian reserve were acutely associated with the magnitude of impairment, and pretreatment AMH levels were associated with the rate of recovery of AMH after treatment. In adjusted models, participants with a pretreatment AMH level > 2 ng/mL recovered at a rate of 11.9% per month after chemotherapy, whereas participants with pretreatment AMH levels </= 2 ng/mL	Baseline ovarian reserve and alkylating agent exposure effect the magnitude of acute changes in ovarian reserve from chemotherapy. The rate of recovery of AMH is impacted by pretreatment levels	

					recovered at a rate of 2.6% per month after therapy.	
(Domingo, et al., 2012)	Case control study	223 women diagnosed with cancer undergoing FP Historical control group ; 98 patients diagnosed with male factor infertility	Controlled ovarian stimulation and oocyte retrieval.	Days of stimulation, total dose of gonadotropins, estrogen levels, and number of oocytes retrieved and vitrified.	No differences were found in days of stimulation, but significant differences in E(2) levels and the number of retrieved oocytes were measured, especially in the hormone-dependent cancer group.	Patients with hormone-dependent cancer had a weaker response to controlled ovarian stimulation compared with patients with non-hormone-dependent cancer. Whether the oncological disease already affects the ovaries before chemo-/radiotherapy remains to be elucidated.	
(Dunlop and Anderson, 2015)	Review		Pubmed search		The recently created field of oncofertility is focussed on refining and developing new FP strategies in order to restore ovarian function following cancer therapy-related damage. Not every patient will require such strategies and therefore an individualised approach would be extremely helpful, to allow both improved patient counselling regarding the selection of adjuvant treatments and consideration of fertility preservation strategies before cancer therapy is commenced. The measurement of serum AMH taken pre- and post-treatment is showing great promise in providing information regarding reproductive potential post-cancer. Further investigation is essential to ascertain the value of more widespread use of AMH measurements in girls and women with cancer, including further prospective long-term follow-up studies in different types of cancers with outcomes other than menstrual function. It is clear however that AMH has significant potential in improving patient information and decision-making in women with cancer.	Non-systematic review
(Grynberg, et al., 2019)	Retrospective cohort study	329 breast cancer candidates for fertility preservation using IVM between January 2014 and December 2017. (age 18-40 years; two ovaries present; no history of chemotherapy; test for BRCA 1/2 mutations performed)	Before immature oocyte retrieval, all follicles measuring 2-9 mm in diameter were precisely counted on both ovaries and serum AMH was measured irrespective of the phase of the cycle.	Number of cumulus oocyte complexes (COC) retrieved, maturation rate and number of MII oocytes cryopreserved were compared according to BRCA mutation status.	Overall, BRCA-mutated women (n = 52) and BRCA-negative women (n = 277) were comparable in terms of ovarian reserve tests (AFC: 20.5 +/- 11.4 versus 21.7 +/- 12.1 follicles, P = 0.5; serum AMH levels: 3.6 +/- 2.9 versus 4.1 +/- 3.6 ng/ml, P = 0.3, resp). The number of COCs retrieved did not differ significantly between both groups (8.9 +/- 6.9 vs 9.9 +/- 8.1 oocytes, P = 0.5). After similar IVM rates (67 +/- 24 vs 62 +/- 23%, P = 0.2), the number of MII oocytes cryopreserved was similar in patients presenting BRCA mutation or not (5.1 +/- 3.8 versus 6.1 +/- 5.1, P = 0.1, respectively).	BRCA 1/2 gene mutations do not affect the capacity of oocytes from breast cancer candidates for fertility preservation to mature in vitro.	Are the maturation rates of oocytes recovered from small antral follicles different between breast cancer patients presenting with or without a BRCA 1/2 gene mutation?
(Hamy, et al., 2016)	Retrospective observational	134 breast cancer patients, n=28 spontaneous pregnancies	AMH levels	spontaneous pregnancy		Pre and post-AMH levels do not correlate to spontaneous pregnancy	
(Iwase, et al., 2015)							
(Lawrenz, et al., 2012)	Comparative study	64 female lymphoma patients aged <40 years (84 breast cancer)	Measurement of antimullerian-hormone (AMH)	ovarian reserve before the start of chemotherapy	Female lymphoma patients have significantly lower AMH levels than healthy age-matched controls: mean value of AMH was 2.06 ng/mL in	Ovarian reserve is reduced in female patients affected by	

		age-matched healthy volunteers (control group)	levels. Ovarian hormonal stimulation to retrieve oocytes		the study group versus 3.20 ng/mL in the control group. Analysis of the stimulation results showed that in significantly younger patients with lymphoma, significantly fewer oocytes could be retrieved in comparison to those with breast cancer.	lymphoma even before the start of chemotherapy
(Lekovich, *et al.*, 2016)	Retrospective study	64 newly diagnosed lymphoma patients undergoing COH for FP 365 healthy controls (elective oocyte cryo) 128 patients with other types of malignancy prompting fertility preservation		Primary outcomes included serum anti-Mullerian hormone (AMH) levels (ng/mL) and antral follicle count (AFC).	Patients in the lymphoma group demonstrated significantly lower AMH levels and AFC and had less oocytes harvested and cryopreserved when compared to healthy controls as well as patients with other malignancies.	Patients with lymphoma demonstrate diminished ovarian reserve when compared with healthy controls and patients with other malignancies. This should be taken into consideration when deciding on the dose for COH.
<mark>(Lutchman Singh, *et al.*, 2005)</mark>						
(Moraes, *et al.*, 2019)	observational retrospective study	Participants n=187, n=164 non cancer, n=23 cancer patients	No test performed	Number of harvested and frozen oocytes.	Number of retrieved oocytes is the same between cancer patients and non cancer patients	
(Peigne and Decanter, 2014)	SR	15 articles (434 patients with different cancers including hematological malignancies)	Expsoure to different chemotherapy regimens	AMH levels before and after chemotherapy (all cancers)	Cancer patients have significantly lower AMH after chemotherapy than age-matched controls. Longitudinal studies of AMH variations before, during and after chemotherapy provide information about the degree of follicle loss for each patient according to different chemotherapy regimens. Different patterns of AMH levels during the ovarian recovery phase make it possible to discriminate between high and low gonadotoxic chemotherapy protocols. In addition, pretreatment AMH levels are shown to predict the long-term ovarian function after the end of treatment.	These results may help to better understand the ovarian toxicity mechanisms of chemotherapy and to predict the degree of the ovarian follicle loss. Therefore, it can be useful for fertility preservation strategies, fertility counseling and future family planning.
(Quintero, *et al.*, 2010)	retrospective cohort study	50 women undergoing oocyte retrieval before cancer treatment and 50 age-matched controls.	**None.**	Number of oocytes and matured oocytes retrieved, number of fertilized oocytes, days of stimulation, dose of gonadotropins.	There were no significant differences in the number of oocytes retrieved (13 vs. 11.5), the number of matured oocytes retrieved (9.7 vs. 9.6), and the number of oocytes fertilized (7.4 vs. 6.8). However, the patients with cancer had a longer duration of stimulation (10.5 vs. 9.0 days) and higher total dose of gonadotropins (4,174 IU vs. 3,416 IU).	reasonable ovarian response was achieved by women with cancer with increased doses of gonadotropins and a longer duration of stimulation
(Sermondade, *et al.*, 2019)	OBS MODERATE	. Case series BC patients undergoing IVM for FP . 18-35 yo (n=54), before starting chemotherapy . Measurement serum AMH (mean AMH levels	Multivariable analysis correlation between ovarian reserve parameters with oocytes retrieved IVM: no	number of oocytes retrieved maturation rates	. Positive correlation of AMH and AFC with COC recovered (0.43 and 0.41, p<0.001) . Positive correlation of AMH and AFC with MII oocytes after IVM (0.35 and 0.52, p<0.01) . Positive correlation with AMH and AFC with primordial fol pool, mainly for AMH (0.39 and 0.30, p<0.01)	AMH is a good predictor of primordial follicle reserve

		1.9 ng/ml , AFC (mean AFC numbers 12.5), assessement of primordial follicle density	stimulation + hCG Duration : 2013 - 2015		. Positive correlation between primordial follicle pool correlated to number of COC and MII oocytes after IVM (0.34 and 0.39, p<0.01)		
(Silva, et al., 2016)	SR	15 articles included	Different chemotherapy regimens (with or without concurrent GnRH analogs)	Treatment-induced amenorrhea (POI defined only based on menstrual function at different timepoints following the end of treatment) and AMH levels before and after different anticancer treatments	Younger age and baseline AMH levels (patient-related factors), co-administration of GnRHa, addition of taxanes to anthracycline-based chemotherapy and addition of endocrine therapy to chemotherapy (treatment-related factors) were assessed. Menses recovery was the most used marker. Younger age (≤40 years) and exposure to GnRHa were positively associated with menses recovery (OR 6.07 and 2.03, respectively) but exposure to taxanes adversely affected recovery (OR 0.49).	Younger age and GnRH agonist (GnRHa) administration during chemotherapy were significantly associated with menses recovery, but this recovery was less likely in patients exposed to taxanes	
(Son, et al., 2019)	retrospective clinical study	Breast Cancer patients, n=264 BRCA positive, n=52 BRCA negative;	AMH levels	AMH levels in relation to BRCA positivity in breast cancer patients	young breast cancer patients with BRCA1/2 mutations present lower pretreatment AMH levels than patients with no mutations		
(Su, et al., 2014)	prospective cohort study	109 participants (median age, 39 years; age range, 23-45 years) before chemotherapy		association between prechemotherapy AMH, FSH, and inhB levels and the time to return of ovarian function?	After a median follow-up of 163 days (range, 4-1009 days) after chemotherapy, 62 participants (57%) experienced return of ovarian function. In adjusted analyses, AMH levels >0.7 ng/mL (HR, 2.9; 95% CI 1.5-5.6) and FSH levels </=10 IU/L (HR, 4.7; 95% CI, 1.3-16.8) were associated with a shorter time to ovarian recovery, whereas inhB levels were not related. A prognostic score based on age <40 years, AMH >0.7 ng/mL, and BMI >/=25 kg/m(2) was used to estimate the timing of recovery.	prechemotherapy AMH and FSH levels were associated with the return of ovarian function, independent of age. A novel prognostic score incorporating AMH, age, and body size was capable of estimating the time to ovarian recovery.	
(Su, et al., 2013)	cross-sectional study	108 women (ages 28–44) with newly diagnosed breast cancer and 99 healthy women (ages 30–44) without breast cancer or infertility		ovarian reserve, as measured by AMH, FSH, and inhibin B (inhB),	The unadjusted geometric mean AMH levels (SD) for BC and controls were 0.66(3.6) ng/mL and 1.1(2.9) ng/mL, resp. Adjusting for age, BMI, gravidity, race, menstrual pattern and smoking, mean AMH levels were not significantly different between BC and controls (0.85 vs. 0.76 ng/mL, p=0.60). FSH and inhB levels did not differ by breast cancer status. In exploratory analysis, the association between AMH and BC status differed by age (p-interaction=0.02). AMH may be lower with breast cancer status in women older than 37. In younger women, AMH levels did not differ significantly by BC status.		
(Titus, et al., 2013)	Experimental study				ovarian reserve was impaired in young women with germline BRCA1 mutations compared to controls as determined by serum concentrations of AMH.	underlying mechanism behind age-induced wastage of the human ovarian follicle reserve	
(Van Tilborg, et al., 2016)	multicenter, cross-sectional study	255 healthy women; n=124BRCA carriers; n=131 BRCA non carriers	AMH levels	AMH levels in relation to BRCA positivity in healthy controls	No difference between AMH levels in carriers versus noncarriers		

Benign							
(Ashrafi, *et al.*, 2019)	case control	n=145 patients with endometrioma; n-=131 patients with male infertility factor	AMH levels	clinical pregnancy rate and live births	Patients with endometriosis haev lower AMH veles than controls. Existence of endometriomas alone has no effect on the clinical pregnancy and live birth rates after in vitro fertilization; however, the presence of deep infiltrating endometriosis alone is associated with reduced clinical pregnancy and the live birth rates in comparison to that of control group		
(Barnabei, *et al.*, 2015)	Meta-analysis	breast cancer patients data from 4 studies included		AMH/age to predict post chemo ovarian activity	both age and serum AMH are reliable predictors of post-treatment ovarian activity in breast cancer patients. Importantly, ROC/AUC analysis indicated AMH was a more reliable predictor of post-treatment ovarian activity in patients aged younger than 40 years (0.753; 95% CI: 0.602–0.904) compared with those older than 40years (0.678;95%CI:0.491–0.866).	Nomogram describing the correlations among age, pretreatment AMH serum levels, and ovarian activity at 1 year from the end of chemotherapy.	
(Candiani, *et al.*, 2018)	prospective RCT	total 60 women with endometriomas	AMH and AFC levels	AMH and AFC levels in relation to type of surgery	Co2 laser vaporisation of endometriomas has a less detrimental effect on AMH levels		
(Coccia, *et al.*, 2011)	longitudinal prospective cohort study.	302 patients undergoing laparoscopy for endometriosis mean age (+SD) of patients was 32.6+5.6 years;		menstrual pattern, symptoms and reproductive outcomes median duration of follow-up was 8.5 years (range 2–17 years)	Menopause was documented in 43 women (14.3%) at a mean age of 45.3+4.3 years (range 32–52 years). Women previously submitted to bilateral cystectomy were younger at menopause than those with monolateral endometrioma (42.1+5.1 years versus 47.1+3.5 years, P = 0.003). POF was observed in 7 of 43 (16.3%) menopausal patients; the majority (4, 57.1%) after bilateral cystectomy. The relationship between the preoperative ovarian endometriomas total diameter and menopausal age was significant in case of surgery for bilateral endometriomas (R2 = 0.754, P = 0.002).		
(de Araujo, *et al.*, 2014)	cross-sectional study	57 adult childhood-onset SLE female patients and 21 healthy controls The median current age was similar in adult c-SLE patients and controls (27.7 vs. 27.7 years, p = 0.414).		anti-corpus luteum antibodies (anti-CoL) Ovarian reserve was assessed by: FSH,LH, oestradiol, AMH and AFC menstrual abnormalities, disease activity, damage, and treatment	The medians of AMH(1.1 vs. 1.5 ng/mL, p=0.037) and AFC (6 vs. 16, p<0.001) were significantly reduced in SLE patients compared to controls without significant menstrual abnormalities. Anti-CoL were solely observed in c-SLE patients (16% vs. 0%, p = 0.103) and were not associated with demographic data, ovarian reserve para-meters, disease activity/damage, and treatment. c-SLE patients treated with cyclophosphamide revealed a higher median of FSH levels compared to c-SLE patients not treated with CP and controls (8.8 vs. 5.7 vs. 5.6 IU/L, p =0.032) and lower median AMH (0.4 vs. 1.5 vs. 1.5 ng/mL, p = 0.004) and AFC (4.0 vs. 6.5 vs. 16 IU/L, p = 0.001) levels. 19 patients treated exclusively with methotrexate demonstrated a negative correlation between the cumulative dose and AMH levels (p = 0.027, r = –0.507).		

(Henderson, et al., 2013)	Meta-analysis of RCTs	Patients with biopsy-proven proliferative lupus nephritis (classes III, IV, V+III, and V+IV) 45 trials (2,559 participants) of induction therapy and 6 (514 participants) of maintenance therapy	Immunosuppressive treatment regimens used for induction and maintenance therapy	Mortality, renal remission and relapse, doubling of creatinine level, proteinuria, incidence of end-stage kidney disease, ovarian failure, alopecia, leukopenia, infections, diarrhea, vomiting, malignancy, and bladder toxicity.	In induction regimens comparing mycophenolate mofetil (MMF) with intravenous cyclophos-phamide, there was no significant difference in mortality (7 studies, 710 patients; risk ratio [RR], 1.02; 95% CI, 0.52-1.98), incidence of end-stage kidney disease (3 studies, 231 patients; RR, 0.71; 95% CI, 0.27-1.84), complete renal remission (6 studies, 686 patients; RR, 1.39; 95% CI, 0.99-1.95), and renal relapse (1 study, 140 patients; RR, 0.97; 95% CI, 0.39-2.44). MMF-treated patients had significantly lower risks of ovarian failure (2 studies, 498 patients; RR, 0.15; 95% CI, 0.03-0.80) and alopecia (2 studies, 522 patients; RR, 0.22; 95% CI, 0.06-0.86). In maintenance therapy comparing azathioprine with MMF, the risk of renal relapse was significantly higher (3 studies, 371 patients; RR, 1.83; 95% CI, 1.24-2.71).	
(Inal, et al., 2019)		n=60 women with endometrioma; n=60 women without endometrioma	AMH levels and AFC	number of oocytes retrieved	Lower number of oocytes retrieved in patients versus controls. AFC and not AMH levels correlate to oocytes retrieved in patients with endometrioma	
(Karadag, et al., 2019)	prospective observational	total n=140 with ovarian cysts, n=80 endometrioma; n=60 benign cysts	AMH levels	AMH Levels correlation to endometrioma size and bilaterality	AMH levels decreases with endometrioma size.	
(Kasapoglu, et al., 2018)	prospective observational study	n=40 women with endometrioma; n=40 healthy controls	AMH levels	Change in AMH levels	Women with endometrioma have a progressive decline in serum AMH levels, which is faster than in healthy women	
(Lawrenz, et al., 2011)	prospective study	33 premenopausal females with SLE, who had not undergone previous treatment with cyclophosphamide and 33 healthy, premenopausal, age-matched controls		Age of onset, duration of illness, current medication and previous treatment were recorded The SLE Activity Index (SLEDAI) and European Consensus Lupus Activity Measurement (ECLAM) AMH	We found that the AMH values in the SLE group were significantly lower than in the healthy control group. No significant differences between the groups regarding number of children and miscarriages were noted and no correlation between the AMH value and the duration of illness or the SLEDAI as an indicator of disease activity was found. Despite mild disease activity SLE patients had a significantly lower ovarian reserve than age-matched healthy women. This could be a sign that SLE itself has a negative influence on the ovarian reserve. L	
(Liu, et al., 2012)	Meta-Analysis of Randomized Controlled Trials	6 RCTs	Progesterone LPS stop after pregnancy test Progesterone LPS continued until week 6/7	Live birth rate Ongoing pregnancy rate	Stopping vs continuing Live birth rate 77.3% (143/185) vs 81.5% (150/184); RR 0.95, 95% CI 0.86-1.05) Ongoing pregnancy rate 503/585 vs 514/581; RR 0.97, 95% CI 0.901.05), I²=73%	we find no convincing evidence to support the routine use of P supplementation during early pregnancy in women undergoing IVF/ICSI

(Mak, et al., 2009)	meta-analysis	847 proliferative lupus nephritis patients in 10 RCTs	Mycophenolate mofetil versus cyclophosphamide		MMF offers similar efficacy in inducing renal remission as CYC (RR 1.052; 95% CI 0.950, 1.166) and the risks of death (RR 0.709; 95% CI 0.373, 1.347) and ESRF (RR 0.453; 95% CI 0.183, 1.121) were comparable. Significantly fewer patients receiving MMF developed amenorrhoea (RR 0.212; 95% CI 0.094, 0.479) and leucopenia (RR 0.473; 95% CI 0.269, 0.832) while the risks of herpes infection and pneumonia tended to be lower and that of diarrhoea appeared higher in the MMF groups.		
(Marcellin, et al., 2019)	Observational cross-sectional study	total n=267 with ovarian cysts; n=148 with endometrioma; n=119 benign cysts	AMH levels	AMH Levels correlation to endometrioma size	Serum AMH levels increases with cyst size.		
(Morel, et al., 2013b)	RCT	Total n=112 SLE patients. n=56 SLE exposed to CP, and n=56 unexposed	AMH levels	Spontaneous pregnancy	Amh levels decrease after CP treatment. Low risk to conceive was predicted by age and CP levels, not by AMH levels		
(Muzii, et al., 2018)	Meta-analysis	17 studies, n=968 patients endometrioma, n=1874 no endometriomas (ovarian cysts and healthy controls)	AMH levels	AMH levels in correlation to disease	Pretreatment AMH levels are lower in endometrioma patients in comparison to controls (ovarian cysts and healthy controls)		
(Oktem, et al., 2016)	Background review	SLE			In summary the discussion of fertility preservation options with the patients is particularly important if they have; - the presence of active disease and/or its complications such as nephritis and vasculitis necessitating the use of cyclophosphamide - advanced age (age > 33-35) - diminished ovarian reserve - higher risk of disease flare - not completed childbearing even if the disease is in remission since flare-up of the disease and/or development of its complications in the future may necessitate the use of cyclophosphamide urgently.		
(Raffi, et al., 2012)	A Systematic Review and Meta-Analysis	Endometriosis 8 prospective cohort studies	Surgery	Ovarian reserve (AMH)	Pooled analysis of 237 patients showed a statistically significant decrease in serum AMH concentration after ovarian cystectomy (weighted mean difference -1.13 ng/ml; 95% CI -0.37 to -1.88), although heterogeneity was high. Sensitivity analysis for studies with a preoperative serum AMH level of 3.1 ng/ml or greater improved heterogeneity but also still showed a significant postoperative fall in serum AMH (weighted mean difference -1.52 ng/ml, 95% CI -1.04 to -2).		
(Reinblatt, et al., 2011)	Retrospective Cohort	13 women with bilateral endometriomas 39 women without endometriomas	IVF	proportions of good, fair, and poor embryos	The proportions of good, fair, and poor embryos were found to be similar (endometrioma vs control) (47.2% vs. 41.1%, 28.3% vs. 32.8%, and 24.3% vs. 26.0%, resp).	the presence of bilateral endometriomas during IVF treatment is not associated with reduced embryo quality.	

(Shabanova, _et al._, 2008)		94 female systemic lupus erythematosus (mean age of 29.2±7.0 years). The mean SLEDAI score was 11.4±8.1. 79 had a current use of gluco-corticoids (GC) with a median dose of 10 mg/day (8-15). 40 healthy age matched controls	40% of the patients were treated and high doses of GC (>30 mg/day); 68% from this group of patients were treated GC in combination with cyclophosphamide (CYC).	gynecological history and a gynecological examination FSH, LH; prolactin, estradiol, progesterone	Menstrual cycle disorders with oligomenorrhea as dominant aspect were observed in 54% of SLE patients. The hormonal studies showed decreased progesterone level in 52% of patients, reduced E2 concentration in 25% of patients; increased levels of LH, FSH and prolactin were observed with the lower frequency (13%, 9%, 10% respectively). Menstrual cycle disorders and the hormonal unbalance such as decreased progesterone level and hyperprolactinemia were found related significantly to high SLEDAI score ($p<0.05$, $p=0.001$, $p<0.05$). In the group of non-treated SLE patients the menstrual and hormonal disorders were observed in the same spectrum and with the same frequency as in all the examined SLE patients. SLEDAI score was found correlated significantly with the frequency of menstrual cycle disorders in non-treated SLE patients ($p<0.05$).	The reported study shows the disease activity as a major factor associated with menstrual cycle disorders in SLE patients before treatment with alkylating agents and high doses of GC.	
(Somigliana, _et al._, 2011)	opinion	endometriosis			need to improve surgical techniques 1) preventing the injury to the follicular reserve that follows surgical excision of ovarian endometriomas and 2) preventing post-surgical formation and re-formation of adhesions. The comparison between the excision/stripping and the vaporization/coagulation techniques represents the main point of debate on what is the best procedure to remove ovarian endometrioma. Randomized controlled trials showed that the excision technique is associated with a higher pregnancy rate and a lower rate of recurrence although it may determine severe injury to the ovarian reserve. Improvements to this latter aspect may be represented by a combined excisional-vaporization technique or by replacing diathermy coagulation with surgical ovarian suture. Barrier agents reduce but not eliminate the post-surgical adhesion formation in women with endometriosis. Encouraging evidence has been reported with Interceed, Oxiplex/AP gel and Adept solution.		
(Somigliana, _et al._, 2015)	opinion	endometriosis			Fertility preservation may be of interest for women with endometriosis, in particular for those with bilateral unoperated endometriomas and for those who previously had excision of unilateral endometriomas and require surgery for a contralateral recurrence. Young age at diagnosis may be an independent but pivotal additional factor to be taken into consideration in the balance of the pros and cons of fertility preservation. On the other hand, we argue against the introduction of fertility preservation for endometriosis in routine clinical practice. To date, only few cases have been reported and there are insufficient data for robust cost-utility analyses. It is noteworthy that endometriosis is a relatively common disease and systematically including affected women in a fertility preservation program would have profound clinical, logistic and financial effects.		
(Sweed, _et al._, 2018)	prospective RCT	total 122 women with endometriomas	AMH and AFC levels	AMH and AFC levels in relation to type of surgery	Laparoscopic cyst deroofing of endometriomas has a less detrimental effect on AMH levels		
(Turkcuoglu and	Prospective observational	total 63 women; n=23 endometrioma with surgery, n=23= endometrioma no	AMH and AFC levels	Relation AMH and AFC levels and surgery	AMH levels are lower in women that had surgery for endometrioma (albeit no significant)		

Melekoglu, 2018)		surgery; n=23 healthy controls					
(Wang, et al., 2019b)	open-label prospective study	139 patients with endometrioma	AMH levels before and afetr treatment	AMH levels relation to surgery	Lower post-operative decline of AMH levels in patients with large and bilateral endometriomas		
(Younis, et al., 2019)	Meta-analysis	12 studies. N=489 patients with unilateral endometrioa. N=294 patients with bilateral endometrioma.	AMH and AFC levels	AMH and AFC levels before surgery	AMH levels are lower in women with bilateral endometriomas in comparison to women with unilateral		
(Zaitoun, et al., 2013)	RCT	121 patients with benign ovarian endometroitic cysts	laparoscopic ovarian cystectomy using bipolar electrocoagulation (61 patients) or laparotomic ovarian cystectomy using sutures (60 patients).	FSH, AMH, AFC, mean ovarian diameter, and ovarian stromal blood flow velocity were measured at 6, 12 and 18 months after surgery	A statistically significant increase of serum FSH was found in the laparoscopy group at 6-, 12 and 18-month postoperatively compared to laparotomy group. Also, a statistically significant decrease of the mean AMH value occurred in laparoscopy group at 6-, 12 and 18-month follow- up compared to laparotomy group. Basal antral follicle number, mean ovarian diameter and peak systolic velocity were significantly decreased during the 6-, 12,18 -month follow- up in laparoscopy group compared to laparotomy group.		
(Zhou, et al., 2019)	prospective cohort study	n=124 endometrioma patients. N=52 being pregnant	AMH levels	Natural pregnancy (AMH in relation to natural pregnancy)	Preoperative AMH levle might be a useful marker to predict the ocurrence of natural pregnancy in patients with endometriomas.		
AGE							
(Dewailly and Laven, 2019)	Systematic review - debate				Ability of AMH to predict pregnancy, quality of embryos is low.		
(Nelson, et al., 2013)	Systematic review	ageing ovary and uterus: new biological insights Systematic review, narrative description			Mapping of the ovarian reserve, follicular dynamics and associated biomarkers, across the reproductive lifespan has recently been performed. This now allows an assessment of the effects of environmental, lifestyle and prenatal exposures on follicular dynamics and the identification of their impact during periods of germ cell vulnerability and may also facilitate early identification of individuals with shorter reproductive lifespans. If women choose to time their family based on their ovarian reserve this would redefine the meaning of family planning. Despite recent reports of the potential existence of stem cells which may be used to restore the primordial follicle and thereby the oocyte pool, therapeutic interventions in female reproductive ageing at present remain limited. Maternal ageing has detrimental effects on decidual and placental development, which may be related to repeated exposure to sex steroids and underlie the association of ageing with adverse perinatal outcomes.		
(Saumet, et al., 2018)	SOGC CLINICAL PRACTICE GUIDELINE				In social egg freezing cycles we evaluated thawed oocyte survival rates, fertilization rates, embryo quality, pregnancy rates, and live birth rates. We also review how these outcomes are impacted by age, ovarian reserve, and the number of eggs cryopreserved. Finally, we discuss the risks of social egg freezing, the alternatives, the critical elements for counselling and informed consent, and future reporting of egg freezing outcome data.	SOGC CLINICAL PRACTICE GUIDELINE	

(Sonigo, et al., 2019)	Narrative review				Relation AMH and in vitro response to stimulation is clear. Its ability to predict pregnancy and live births not so clear.	Clinical Implications of Serum AMH Levels for FP	

INCLUDED in TABLE 9- other diseases

(Brouwer*, et al.*, 2013, Caanen*, et al.*, 2015, Cil*, et al.*, 2009, Clowse*, et al.*, 2011, Ferreira*, et al.*, 2019, Frederick*, et al.*, 2018, Freour*, et al.*, 2012, Hagen*, et al.*, 2010, Hamza*, et al.*, 2018, Henes*, et al.*, 2015, Karakus*, et al.*, 2017, Kim*, et al.*, 2016, Kopeika*, et al.*, 2019, Magri*, et al.*, 2015, Mont'Alverne*, et al.*, 2015, Peng*, et al.*, 2017, Rohr*, et al.*, 2008, Saglam*, et al.*, 2015, sahIn*, et al.*, 2017, Sanders*, et al.*, 2009, Senates*, et al.*, 2013, Sepulveda*, et al.*, 2016, Sklavos*, et al.*, 2014, Sklavos*, et al.*, 2015, Talaulikar*, et al.*, 2019, Tsafrir*, et al.*, 2010, Vega*, et al.*, 2016, Wellons*, et al.*, 2017, Welt*, et al.*, 2004, Yamakami*, et al.*, 2014)

INCLUDED AS BACKGROUND INFORMATION

(Dewailly*, et al.*, 2014, Ferraretti*, et al.*, 2011, Hancke*, et al.*, 2011, Iwase*, et al.*, 2014)

Q10 Is oocyte cryopreservation effective and safe for fertility preservation?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Alvarez and Ramanathan, 2018)	retrospective study	Women who had fertility preservation and returned to attempt a pregnancy. A total of 306 patients underwent ovarian stimulation for oocyte or embryo cryopreservation before cancer therapy.	Frozen embryo transfer		32 embryo transfer cycles have been done in 22 cancer patients who have returned to attempt pregnancy after overcoming their disease. Mean time interval between the ovarian stimulation to the first embryo transfer cycle was 31 months. 12 women were planned initially for surrogacy; the most common reason was hysterectomy for gynaecological malignancy or advice against pregnancy by oncologist for medical reasons. Two of them have returned and underwent embryo transfer in a gestational carrier. Pregnancy rate per transfer cycle was 43.75%, and cumulative pregnancy rate per patient was 54.5%. The miscarriage rate was 57.1% per pregnancy; therefore, the cumulative live birth rate per transfer was 18.75%, and the live birth rate per patient was 22.72%. A total of 8-term healthy babies have been born. 4 pregnancies by natural conception	Only few patients have come back to attempt pregnancy after being cured from their disease. Slow freezing, high miscarriage rate and low live birth rate per transfer are other limitations of this study. The main strength of our study is the large sample size and that this is the largest series analysing different types of cancer separately. Further studies when more of these patients return to attempt pregnancy are needed to determine long-term outcomes, clinical implications and potential success rates. To provide precise information in this field is invaluable, as young patients with cancer will not only be concerned with cure and survival, preservation of fertility will be an important issue for their quality of life.	
(Armuand, et al., 2017)	prospective study	15 adult transgender men referred for FP- (age 19–35); none had given birth and 8 had a partner.		Individual in-depth qualitative interviews were conducted shortly after FP treatment	three main categories: the journey to FP, reactions to the FP proceedings and strategies for coping. The referral for FP was an important part of the assessment and diagnosis and sometimes lined with frustrating waits and doubts. The reaction to the FP proceedings revealed that the genital examinations and the physical changes associated with discontinuation of testosterone or hormonal stimulation treatment triggered gender incongruence and dysphoria. However, for some, the negative expectations were not met. The participants used several coping strategies in order to manage the procedure, such as focusing on their reasons for undergoing FP, reaching out to friends and family for support and the cognitive approaches of not	procedures required prior to oocyte cryopreservation, such as hormonal ovarian stimulation and TVS, have a negative impact on gender dysphoria as they are closely linked to the men's female assigned sex at birth, which is incompatible with their current status.	

					hating their body or using non-gendered names for their body parts. The results demonstrate the importance of contextual sensitivity during FP procedures.		
(Azim, et al., 2008)	Case control	215 women with breast cancer:

79 elected to undergo COS with letrozole and gonadotropins for embryo or oocyte cryopreservation. The remaining 136 underwent no FP and served as controls. | effect of controlled ovarian stimulation (COS) using a combination of letrozole with standard fertility medications | disease-free survival | Time between surgery and chemotherapy was longer for IVF patients (45.08 v 33.46 days; P < .01). Peak estradiol levels ranged from 58.4 to 1,166 pg/mL (mean, 405.94 +/- 256.64 pg/mL or 1,486.76 +/- 942.13 pmol/L) in COS patients. The median follow-up after chemotherapy was 23.4 months (range, 7.5 to 63.6 months) in the COS group and 33.05 months (range, 4.5 to 63.6) in the control group. The hazard ratio for recurrence after IVF was 0.56 (95% CI, 0.17 to 1.9), and the survival was not compromised compared with controls (P = .36). | Ovarian stimulation with gonadotropins and letrozole for the purpose of fertility preservation is unlikely to cause substantially increased recurrence risk. | |
| **(Cobo, et al., 2018)** | Retrospective, observational multicenter study | 6362 women elective-FP for age-related fertility decline or FP before cancer treatment (EFP = 5289 patients; 7044 cycles + Onco-FP = 1073 patients; 1172 cycles) had their oocytes vitrified for FP. | COS and vitrification

Warming and attempt pregnancy | oocyte survival and live birth.

The cumulative live birth rate (CLBR) per utilized oocyte according to age at vitrification | Age at vitrification was significantly older in EFP patients (37.2 +/- 4.9 vs. 32.3 +/- 3.5 year; P < 0.0001). Fewer oocytes were retrieved and vitrified per cycle in EFP (9.6 +/- 8.4 vs. 11.4 +/- 3.5 and 7.3 +/- 11.3 vs. 8.7 +/- 2.1, respectively; P < 0.05), but numbers became comparable when analyzed per patient (12.8 +/- 7.4 vs. 12.5 +/- 3.2 and 9.8 +/- 6.4 vs. 9.5 +/- 2.6). Storage time was shorter in EFP (2.1 +/- 1.6 vs. 4.1 +/- 0.9 years; P < 0.0001). In all, 641 (12.1%) EFP and 80 (7.4%) Onco-FP patients returned to attempt pregnancy (P < 0.05). Overall oocyte survival was comparable (83.9% vs. 81.8%; NS), but lower for onco-FP patients among younger (</=35 year) subjects (81.2% vs. 91.4%; P > 0.05). Fewer EFP cycles finished in embryo transfer (50.2% vs. 72.5%) (P < 0.05). The implantation rate was 42.6% and 32.5% in EFP versus Onco-FP (P < 0.05). Ongoing pregnancy (57.7% vs. 35.7%) and live birth rates (68.8% vs. 41.1%) were higher in EFP patients aged </=35 than the Onco-FP matching age patients (P < 0.05). The reason for FP per se had no effect on oocyte survival (OR = 1.484 [95%CI = 0.876-2.252]; P = 0.202) or the CLBR (OR = 1.275 [95%CI = 0.711-2.284]; P = | Although success rates were lower in cancer patients, there was no statistically significant association between malignant disease and reproductive outcome after correction for age and controlled-ovarian stimulation (COS) regime. | Is the indication for FP related to success in IVF cycles after elective-FP (EFP) for age-related fertility decline and FP before cancer treatment (Onco-FP)? |

				0.414). Conversely, age (<36 vs. >/=36 y) impacted oocyte survival (adj.OR = 1.922 [95%CI = 1.274-2.900]; P = 0.025) and the CLBR (adj.OR= 3.106 [95%CI = 2.039-4.733]; P < 0.0001). The Kaplan-Meier analysis showed a significantly higher cumulative probability of live birth in patients <36 versus >36 in EFP (P < 0.0001), with improved outcomes when more oocytes were available for IVF.		
(Druckenmill er, et al., 2016)	Retrospective cohort study	176 K (75 BC / 51 Gyneco / 35 Hemato / 18 others) 182 cycles No comparative group	GnRHa and GnRH antago protocols hCG or GnRHa trigger COSTLES in estrogen sensitive diseases Random start	No of oocytes cryopreserved

PR after thawing | No of oocytes recovered: 15 No of mature oocytes frozen: 10

11 frozen thaw cycles in 10 patients: 5 live births | 10 oocytes frozen/cycle. LBR 44% per ET.
Oocytes cryopresevation is feasible for female FP | |
| **(Goldrat, et al., 2015)** | prospective observational study | 21 breast cancer patients undergoing letrozole-associated COS with 21 infertile patients undergoing standard COS for IVF and/or ICSI. | COS with a GnRH antagonist protocol. In the fertility preservation group, ovulation induction was started in the follicular or luteal phase depending on the chemotherapy schedule and in 10 cases a GnRH antagonist was administered during luteal phase to induce luteolysis. Final oocyte maturation was induced by hCG in all patients. | Estradiol and progesterone levels were measured on the day of hCG, at oocyte retrieval, and on days 3 and 8 after oocyte retrieval. | While estradiol levels were significantly lower in the FP group (P < 0.001), progesterone levels were similar at all times, including patients receiving a GnRH antagonist during the luteal phase. | During the luteal phase of letrozole-associated COS cycles (triggered with human chorionic gonadotrophin (hCG)) progesterone levels are similarly elevated to those obtained after standard COS without letrozole. | |
| **(Gunnala, et al., 2019)** | Retrospective cohort study | 795 oocyte cryopreservation patients, comprising BRCA carriers with and without malignancy (n = 57) and BRCA noncarriers (n = 738).

Cancer cohort : BRCA-positive (n = 38) ; BRCA-negative breast cancer (n = 53); non-BC malignancies (n = 85). Cancer-free cohort: BRCA carriers (n = 19); elective egg freezing (n = 600). | | AFC, AMH, day-3 follicle-stimulating hormone (FSH) level, number of harvested oocytes, and number of mature/cryopreserved oocytes. | BRCA status was associated with a higher day-3 FSH level in the cancer cohort, but we found no changes in the other outcomes compared with the BRCA-negative cancer groups. BRCA carriers without cancer exhibited a higher AFC and number of mature oocytes compared with the patients undergoing planned egg freezing. Overall (cancer and cancer-free cohorts), the BRCA carriers had an increased AFC (15.5 +/- 4.6 vs. 12.6 +/- 5.7) and number of mature/cryopreserved oocytes (14.0 +/- 7.9 vs. 10.4 +/- 6.9) compared with | BRCA carriers with and without malignancy exhibit comparable ovarian reserve and responses to ovarian stimulation compared with women with BRCA-negative cancers and cancer-free controls. | |

					the BRCA noncarriers but had no differences in other outcomes.		
(Hipp, *et al.*, 2019)	Retrospective cohort study	women younger than 20 years of age older women.	Ovarian stimulation + oocyte cryopreservation	Response Cycle cancellation complications	OC cycles in adolescent women were most likely performed for FP for impending gonadotoxic treatment. The women were most likely to be non-Hispanic white and reside in the Northeast. Ten percent of the cycles were cancelled, most commonly for low response, compared with 6.6% of cycles in other age groups. There was no difference in mean oocytes retrieved in women younger than 20 years (n = 18.0) compared with women 20-29 years (n = 18.4). Complications, including OHSS, were very rare.	OC cycles in adolescent women are similar with regard to stimulation characteristics and oocyte yield to those in women of other age groups. There is, however, a higher likelihood of cancellation because of poor response.	
(Lefebvre, *et al.*, 2018)	Retrospective cohort study	105 women recently diagnosed with cancer, with gonadotoxic treatment scheduled - aged between 18 and 40 years and referred for FP The women were divided into three groups: breast cancer, lymphoma or other cancer	oocyte vitrification after ovarian stimulation with antagonist protocol.		Baseline antral follicle count and anti-Mullerian hormone were no different between women with breast cancer, lymphoma or other cancer. The number of cancelled cycles for poor ovarian response was similar between the groups. The number of FSH units per mature oocyte, the number of mature oocytes (metaphase II) retrieved, and the oocyte maturity rate were not significantly different between the three groups.	the type of cancer does not seem to significantly affect ovarian reserve and ovarian response to ovarian stimulation	
(Lekovich, *et al.*, 2016)	Retrospective study	64 newly diagnosed lymphoma patients undergoing COH for FP 365 healthy controls (elective oocyte cryo) 128 patients with other types of malignancy prompting fertility preservation		Primary outcomes included serum anti-Mullerian hormone (AMH) levels (ng/mL) and antral follicle count (AFC).	Patients in the lymphoma group demonstrated significantly lower AMH levels and AFC and had less oocytes harvested and cryopreserved when compared to healthy controls as well as patients with other malignancies.	Patients with lymphoma demonstrate diminished ovarian reserve when compared with healthy controls and patients with other malignancies. This should be taken into consideration when deciding on the dose for COH.	
(Loren, *et al.*, 2013)	systematic review	222 new publication			RECOMMENDATIONS: As part of education and informed consent before cancer therapy, health care providers (including medical oncologists, radiation oncologists, gynecologic oncologists, urologists, hematologists, pediatric oncologists, and surgeons) should address the possibility of infertility with patients treated during their reproductive years (or with parents or guardians of children) and be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, the Update Panel encourages providers to advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation. The discussion should be documented. Sperm and embryo cryopreservation as well as oocyte cryopreservation are considered standard practice and are widely available.	No need for an update of the 2006 ASCO guideline, but suggestion for classifications

					Other fertility preservation methods should be considered investigational and should be performed by providers with the necessary expertise.	
(Mangili, *et al.*, 2017)	Cohort study	125 and 73 patients treated at different periods (and hence receiving different COH)	RANDOMSTART VS FIRST CYCLE DAYS	mean time required to complete COS mean number of frozen oocytes	Between the 2 periods, a reduction in the mean number of days required from first counselling to the initiation (6.45 +/- 1.058 vs 1.61 +/- 0.228) and the end of the COS (17.83 +/- 1.227 vs 13.70 +/- 0.393) was observed (p<0.0001). No differences exist in the groups between the mean time required to complete COS (11.38 +/- 0.360 vs 12.17 +/- 0.309; p = 0.11) and mean number of frozen oocytes (8.458 +/- 1.060 vs 10.30 +/- 0.919; p = 0.22). Furthermore, in the second period, the number of patients who accepted FP increased (46.15% vs 64.38%; p<0.05).	8-10 oocytes collected, no complic reported
(Manuel, *et al.*, 2020)	Multi-site retrospective cohort	41 adolescent and young adult (AYA) patients (ages 13-21)	oocyte cryopreservation for FP	feasibility	41 patients began COH of which 38 patients successfully underwent oocyte retrieval, with mature oocytes obtained and cryopreserved without any adverse outcomes. To treat this group of patients, we use a multidisciplinary approach with a patient navigator. When dividing patients by ages 13-17 vs. 18-21, the median doses of FSH used were 2325 and 2038 IU, the median number of mature oocytes retrieved were 10 and 10, and median number frozen oocytes were 11 and 13, respectively. Median days of stimulation were 10 for both groups. There was no statistical difference in BMI, AMH, peak E2, FSH dosage, days stimulated, total oocytes retrieved, mature oocytes retrieved, and oocytes frozen between the two groups. 3 patients were canceled for poor response.	
(Oktay, *et al.*, 2018)	systematic review			None of these publications prompted a significant change in the 2013 recommendations	Recommendations Health care providers should initiate the discussion on the possibility of infertility with patients with cancer treated during their reproductive years or with parents/guardians of children as early as possible. Providers should be prepared to discuss fertility preservation options and/or to refer all potential patients to appropriate reproductive specialists. Although patients may be focused initially on their cancer diagnosis, providers should advise patients regarding potential threats to fertility as early as possible in the treatment process so as to allow for the widest array of options for fertility preservation. The discussion should be documented. Sperm, oocyte, and embryo cryopreservation are considered standard practice and are widely available. There is conflicting evidence to recommend gonadotrophin-releasing hormone agonists (GnRHa) and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility	

				preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. GnRHa should not be used in place of proven fertility preservation methods. The panel notes that the field of ovarian tissue cryopreservation is advancing quickly and may evolve to become standard therapy in the future.		
(Oktay, *et al.*, 2010)	retrospective-prospective study	74 breast cancer patients who desired FP, with normal ovarian reserve and < 45 years of age received letrozole 5mg/day plus recombinant FSH 150-300 IU/day for ovarian stimulation.	HCG 5000-10,000 IU (n=47) or leuprolide acetate 1mg (GnRHa, n=27) as trigger.	oestrogen exposure cycle outcomes OHSS	In the GnRHa group, oestradiol concentrations dropped significantly after the trigger than the HCG group (P=0.013) and there was a lower incidence of OHSS. GnRHa trigger resulted in a higher number and percentage of mature oocytes and a higher number of cryopreserved embryos or oocytes compared with HCG. GnRHa trigger improves outcomes by increasing the yield of mature oocytes and embryos in aromatase inhibitor cycles and also decreases the post-trigger oestradiol exposure as well as OHSS risks in women with breast cancer.		
(Quinn, *et al.*, 2017)	retrospective cohort analysis	589 patients: recent breast cancer diagnosis (n = 191) and elective FP (n = 398)	ovarian stimulation for FP:	antral follicle count (AFC) nr of mature oocytes retrieved maturity rate (MII/total oocytes retrieved)	Baseline AFC was not different between the breast cancer patients and controls (15.4 ± 10.4 [mean ± SD] vs 15.4 ± 10.0, P = NS), even after categorization by age. Total (19.4 ± 0.9 [mean ± SEM] vs 17.0 ± 0.5, P = NS) and MII oocytes retrieved (13.7 ± 0.7 vs 13.2 ± 0.4, P = NS), adjusted for age, BMI and total gonadotropin dose, were also similar between the two groups. Letrozole use was associated with a decreased maturity rate vs elective FP (0.71 ± 0.01 vs 0.77 ± 0.01, P < 0.001), although the mature oocyte yield [MII/AFC] was comparable (1.01 ± 0.06 vs 0.93 ± 0.03, P = NS).		
(Rienzi, *et al.*, 2012)	observational longitudinal cohort multicentric study	486 cycles performed in 450 couples	oocyte cryopreservation outcomes in IVF/ICSI cycles	efficacy and reproducibility	2721 oocytes were warmed and 2304 of them survived cryopreservation (84.7%). Of the 2182 oocytes subjected to ICSI, the rates of fertilization and development to top-quality embryos were 75.2 and 48.1%, respectively. A total of 128 deliveries were obtained (26.3% per cycle and 29.4% per transfer) for 450 patients (28.4%) and 147 babies were live born from 929 embryos transferred (15.8%). The forward logistic regression analysis on a per patient basis showed that female age [OR: 0.93, 95% CI: 0.88–0.98], number of		Not fertility preservation – indirect evidence

					vitrified oocytes (OR: 1.08, 95% CI: 1.01–1.17) and the day of transfer (OR: 1.97, 95% CI: 1.14–3.42) influenced DR. By recursive partitioning analysis, it can be estimated that more than eight oocytes vitrified are required to improve the outcome (22.6 versus 46.4% DR, respectively). When fewer oocytes are available in women aged >38 years, results are dramatically reduced (12.6 versus 27.5% DR, respectively). Conversely, when >8 oocytes are available, blastocyst culture represents the most efficient policy (62.1% DR; data from one center only).		
(Rodriguez-Wallberg, et al., 2018)	matched cohort study	breast cancer [exposed women (n = 188), age-matched unexposed controls (n = 378)]	fertility preservation (FP), with or without hormonal stimulation,	risk of breast cancer recurrence (Breast cancer relapse rates)	Most women attempted FP by hormonal stimulation treatment (n = 148, 79%) with the objective of freezing their eggs or embryos. A smaller group elected FP methods without hormone stimulation (n = 40, 21%). Women who received hormone stimulation did not present with a higher relapse rate than unexposed control women in a model adjusted for age and calendar period of diagnosis (IRR 0.59, 95% CI 0.34-1.04). The results remained virtually unchanged after adjustment for tumor size, estrogen receptor status, affected lymph nodes, and chemotherapy treatment (IRR 0.66, 95% CI 0.37-1.17).	No evidence that FP with or without hormonal stimulation was associated with an increased risk of breast cancer recurrence.	
(Rodriguez-Wallberg, et al., 2019a)	prospective study	1254 females including 1076 adults and 178 girls who received fertility preservation counseling for either oncologic (n = 852) or benign indications (n = 402)	fertility preservation counseling and/or treatment	trends in female patients' choices after counseling and fertility preservation outcomes during follow up in relation to benign vs malignant indications.	Adult women generally elected to undergo oocyte retrieval after COS for cryopreservation of embryos or oocytes (n = 538, 73%), whereas a minor proportion opted for cryopreservation of ovarian tissue (n = 221, 27%). More than half of the women with a partner chose either not to fertilize their oocytes aiming at cryopreservation of oocytes or to share obtained oocytes attempting both cryopreservation of oocytes and embryos. All pre-pubertal (n = 48) and 73% of post-pubertal girls (n = 66) elected OTC. In recent years, an increasing number of teenagers have opted for COS aiming at cryopreservation of oocytes, either before (n = 24, 17%) or after	Women with previous malignancy had lower live birth rates than women with benign fertility preservation indications.	

					completion of cancer treatment (n = 15, 10%). During follow up, 27% of the women returned for a new reproductive counseling, additional FP or to attempt pregnancy. Utilization rates among individuals who were alive and of childbearing age indicated 29%, 8% and 5% for embryos, oocytes and ovarian tissue with LBR of 54%, 46% and 7%, resp. Women with benign indications were significantly younger than women with previous malignant indications at the time of attempting pregnancy. Although the pregnancy rates were similar among both groups, the LBR was significantly higher in benign vs previous malignant indications (47% vs 21%, P = .002).	
(Rodriguez-Wallberg*, et al.*, 2019b)	Narrative review				General discussion of oocyte cryopreservation in ART and fertility preservation	
(Rudick*, et al.*, 2010)	Survey	Survey of centers in USA, elective 66%. Cancer 18%.		LBR PR	Efficacy: 337 live births of 857 thawed cycles, Pregnancy rate 39,3%	
(Steward*, et al.*, 2014)	Cohort study	256,381 cycles SART registry all fresh nondonor IVF cycles performed in the U.S. from 2008 to 2010 five groups based on retrieved oocyte number no info on LH suppression regime	0–5, 6–10, 11–15, 16–20, 21–25, and >25. LBR, OHSS (moderate and severe) The LB rate increased up to 15 oocytes, then plateaued (0–5: 17%, 6–10: 31.7%; 11–15: 39.3%; 16–20: 42.7%; 21–25: 43.8%; and >25 oocytes: 41.8%). However, the rate of OHSS became much more clinically significant after 15 oocytes (0–5: 0.09%; 6–10: 0.37%; 11–15: 0.93%; 16–20: 1.67%; 21–25: 3.03%; and >25 oocytes: 6.34%).		ROC curve for retrieved oocyte number asa predictor of OHSS. Oocyte number thresholds: A: 5; B: 10; C: 15; D: 20; E: 25	Retrieval of >15 oocytes significantly increases OHSS risk without improving LB rate in fresh autologous IVF cycles.

| (Zolton, et al., 2018) | Case series | 9 patiens planned for HSCT for GATA2 deficiency | Ovarian stimulation | YES 1/9 patients developed DVT and Pulmonary embolism during OCH | 1/9 patients developed DVT and Pulmonary embolism during OCHMean: 6.7 oocytes MII obtained | In GATA2 patients, risk to DVT is 25%. Stimulation with a protocol with letrozole should be considered | |

INCLUDED AS BACKGROUND INFORMATION
(Cobo, et al., 2013, Goisis, et al., 2019, Goldman, et al., 2015, Massarotti, et al., 2017, Noyes, et al., 2009, Practice Committee of American Society for Reproductive Medicine, 2013, The ESHRE Guideline Group on Ovarian Stimulation, et al., 2020)

Q11 Is Embryo cryopreservation effective and safe for fertility preservation?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Alvarez and Ramanathan, 2018)	retrospective study	Women who had fertility preservation and returned to attempt a pregnancy. A total of 306 patients underwent ovarian stimulation for oocyte or embryo cryopreservation before cancer therapy.	Frozen embryo transfer		32 embryo transfer cycles have been done in 22 cancer patients who have returned to attempt pregnancy after overcoming their disease. Mean time interval between the ovarian stimulation to the first embryo transfer cycle was 31 months. 12 women were planned initially for surrogacy; the most common reason was hysterectomy for gynaecological malignancy or advice against pregnancy by oncologist for medical reasons. Two of them have returned and underwent embryo transfer in a gestational carrier. Pregnancy rate per transfer cycle was 43.75%, and cumulative pregnancy rate per patient was 54.5%. The miscarriage rate was 57.1% per pregnancy; therefore, the cumulative live birth rate per transfer was 18.75%, and the live birth rate per patient was 22.72%. A total of 8-term healthy babies have been born. 4 pregnancies by natural conception	Only few patients have come back to attempt pregnancy after being cured from their disease. Slow freezing, high miscarriage rate and low live birth rate per transfer are other limitations of this study. The main strength of our study is the large sample size and that this is the largest series analysing different types of cancer separately. Further studies when more of these patients return to attempt pregnancy are needed to determine long-term outcomes, clinical implications and potential success rates. To provide precise information in this field is invaluable, as young patients with cancer will not only be concerned with cure and survival, preservation of fertility will be an important issue for their quality of life.	
(Barcroft, et al., 2013)	Cohort study	42 oncology patients (mean 31.9 +/- 3.9 years)	embryo cryopreservation treatment (n = 33 IVF, n = 6 ICSI).	The outcomes of IVF/ICSI cycle	COS with GnRH antagonist protocol (n = 34; 81 %) yielded fewer oocytes than GnRH agonist protocol (n = 8; 19 %) (9.4 +/- 6.3 vs. 15.3 +/- 8.9; p = 0.04) resp. There was no significant difference in mean (+/-SD) duration of ovarian stimulation (11.6 +/- 2.6 vs.10.6 +/- 2.7), median gonadotrophin dose (1950 vs. 1670 IU), median day 5-6 oestradiol level (1124 vs.1129 pmol/l) or embryo yield (6.2 +/- 4.1 vs. 8.8 +/- 4.3; p = 0.07) between GnRH antagonist and agonist treatment cycles respectively. 39 patients cryopreserved embryos and three had their cycle cancelled. During this study period, of those who cryopreserved embryos, 5 patients underwent 9 frozen-thaw cycles (13 %), resulting in 2 live births (1 twin, 1 singleton, live birth rate 22 %). 6 patients died (15 %), 3 conceived naturally (8 %) and 2 couples separated (5 %). 14 patients discarded their embryos (36 %). 22 patients' (56 %) have embryos remaining in storage.	embryo cryopreservation in female oncology patients gives a satisfactory live birth rate. However, there are concerns regarding cost-effectiveness, resulting from high disposal/non-usage of embryos, and further studies are required.	

| (Cobo, et al., 2018) | Retrospective, observational multicenter study | 6362 women elective-FP for age-related fertility decline or FP before cancer treatment (EFP = 5289 patients; 7044 cycles + Onco-FP = 1073 patients; 1172 cycles) had their oocytes vitrified for FP. | COS and vitrification

Warming and attempt pregnancy | oocyte survival and live birth.

The cumulative live birth rate (CLBR) per utilized oocyte according to age at vitrification | Age at vitrification was significantly older in EFP patients (37.2 +/- 4.9 vs. 32.3 +/- 3.5 year; P < 0.0001). Fewer oocytes were retrieved and vitrified per cycle in EFP (9.6 +/- 8.4 vs. 11.4 +/- 3.5 and 7.3 +/- 11.3 vs. 8.7 +/- 2.1, respectively; P < 0.05), but numbers became comparable when analyzed per patient (12.8 +/- 7.4 vs. 12.5 +/- 3.2 and 9.8 +/- 6.4 vs. 9.5 +/- 2.6). Storage time was shorter in EFP (2.1 +/- 1.6 vs. 4.1 +/- 0.9 years; P < 0.0001). In all, 641 (12.1%) EFP and 80 (7.4%) Onco-FP patients returned to attempt pregnancy (P < 0.05). Overall oocyte survival was comparable (83.9% vs. 81.8%; NS), but lower for onco-FP patients among younger (</=35 year) subjects (81.2% vs. 91.4%; P > 0.05). Fewer EFP cycles finished in embryo transfer (50.2% vs. 72.5%) (P < 0.05). The implantation rate was 42.6% and 32.5% in EFP versus Onco-FP (P < 0.05). Ongoing pregnancy (57.7% vs. 35.7%) and live birth rates (68.8% vs. 41.1%) were higher in EFP patients aged </=35 than the Onco-FP matching age patients (P < 0.05). The reason for FP per se had no effect on oocyte survival (OR = 1.484 [95%CI = 0.876-2.252]; P = 0.202) or the CLBR (OR = 1.275 [95%CI = 0.711-2.284]; P = 0.414). Conversely, age (<36 vs. >/=36 y) impacted oocyte survival (adj.OR = 1.922 [95%CI = 1.274-2.900]; P = 0.025) and the CLBR (adj.OR= 3.106 [95%CI = 2.039-4.733]; P < 0.0001). The Kaplan-Meier analysis showed a significantly higher cumulative probability of live birth in patients <36 versus >36 in EFP (P < 0.0001), with improved outcomes when more oocytes were available for IVF. | Although success rates were lower in cancer patients, there was no statistically significant association between malignant disease and reproductive outcome after correction for age and controlled-ovarian stimulation (COS) regime. | Is the indication for FP related to success in IVF cycles after elective-FP (EFP) for age-related fertility decline and FP before cancer treatment (Onco-FP)? |
| (Courbiere, et al., 2013) | Survey | 14 centres reported emergency IVF (56 cycles in total) before gonadotoxic treatment in 52 patients. The patients had a mean age of 28.9 +/- 4.3 years, and a median length of relationship of 3 years (1 month-15 years). Emergency IVF was indicated for haematological cancer (42%), brain tumour (23%), sarcoma (3.8%), mesothelioma (n = 1) and bowel cancer (n = 1). Gynaecological problems accounted for 17% of | emergency IVF | | Among the 52 patients concerned, 28% (n = 14) had undergone previous courses of chemotherapy before beginning controlled ovarian stimulation (COS). The initiation of gonadotoxic treatment had to be delayed in 34% of the patients (n = 19). In total, 56 cycles were initiated. The mean duration of stimulation was 11.2 +/- 2.5 days, with a mean peak estradiol concentration on the day on which ovulation was triggered of 1640 +/- 1028 pg/ml. Three cycles were cancelled due to ovarian hyperstimulation syndrome (n = 1), poor response (n = 1) and treatment error (n = 1). A mean of 8.2 +/- 4.8 oocytes were retrieved, with 6.1 +/- 4.2 mature oocytes and 4.4 +/- 3.3 pronuclear-stage embryos per cycle. The mean number of embryos frozen per cycle was 4.2 +/- 3.1. During follow-up, 3 patients died from the consequences of their disease. For the 49 | : Pregnancy rates after emergency IVF, cryopreservation of embryos, storage, thawing and embryo transfer (embryo transfer), in the specific context of the preservation of female fertility, seem to be similar to those reported for infertile couples undergoing ART. | |

		indications. In 7.7% of cases, emergency IVF was performed for autoimmune diseases.			surviving patients, 22.5% of the couples concerned (n = 11) requested embryo replacement. A total of 33 embryos were thawed with a post-thawing survival rate of 76%. Embryo replacement was performed for 10 couples with a total of 25 embryos transferred, leading to one biochemical pregnancy, one miscarriage and three live births. CPR and LBR per couple who wanted a pregnancy after cancer were, resp, 36% (95% CI = 10.9-69.2%) and 27% (95% CI = 6.0-61%).	
(Debrock, *et al.*, 2015)	RCT	Patients <40 years old undergoing their first oocyte retrieval (OR), with embryo transfer and with supernumerary embryos on Day 3, were randomized.	vitrification vs slow freezing of Day 3 embryos with >/=6 cells, <25% fragmentation and morphologically equal blastomeres	LBR per embryo thawed/warmed	200 embryos were thawed after slow freezing in 95 cycles for 79 patients and 217 embryos were warmed after vitrification in 121 cycles in 90 patients. The LBR per embryo thawed/warmed was significantly higher after vitrification (16.1% (35/217)) than after slow freezing (5.0% (10/200); P < 0.0022; relative risk (RR) 3.23; 95% confidence interval (CI) 1.64-6.35). Similarly, the implantation rate per embryo thawed/warmed was higher after vitrification (20.7% (45/217) than after slow freezing (7.5% (15/200); P = 0.0012; RR 2.76; CI 1.59-4.81). The survival rate was significantly higher after vitrification (84.3% (183/217) than after slow freezing (52.5% (105/200); P < 0.0001). Significantly more embryos were fully intact after vitrification (75.4% (138/183) than after slow freezing (28.6% (30/105); P < 0.0001). The number of transfers was significantly higher after vitrification (90.1% (109/121)) than after slow freezing (73.7% (70/95); P = 0.0024).	LBR per embryo thawed/warmed was higher after vitrification than after slow freezing on Day 3, based on better embryo survival, quality and availability of embryos in the vitrification group.
(Dolmans, *et al.*, 2005)	Retrospective study	11 young patients diagnosed with cancer wanting FP	Stimulation and IVF before or soon after chemotherapy treatment.	number and quality of embryos obtained after stimulation in cancer patients undergoing IVF before or soon after chemotherapeutic treatment	4 patients underwent IVF in the interval between two regimens of chemotherapy. Two of them had no follicular development; one underwent follicular puncture but no oocytes were retrieved; and, in one, six oocytes were harvested but only one good quality embryo was obtained. In the seven patients who underwent IVF before starting chemotherapy, between 4 and 11 embryos were obtained per patient, the majority being good quality embryos.	Because the efficacy of IVF is dramatically reduced after even one round of chemotherapy, IVF should be performed before chemotherapy.
(Dolmans, *et al.*, 2015b)	retrospective study	54 cancer patients	ovarian stimulation and IVF for FP. Embryos were slow-frozen and stored	long-term embryo cryopreservation, utilization, and success rate	54 women underwent 66 oocyte pick-up procedures in total, and embryos were obtained from 52 of the 54 patients. 4 patients died before their frozen embryos could be thawed. Of the remaining 48, 9 women returned to use their embryos, resulting in 6 pregnancies (66% cumulative pregnancy rate), 2 of which ended in miscarriage. The LBR per patient was thus 44% (4/9). The true come-back rate, calculated after applicable exclusions, was found to be 23%.	the cumulative live birth rate was similar to that achieved with fresh embryos in non-cancer patients. The utilization rate of this fertility preservation method can be considered high.

(Luke, et al., 2016)	cohort study	Women using embryo banking in their first ART cycle: two groups with cancer (222 women without an infertility diagnosis and 48 women with an infertility diagnosis) and a control group without cancer (68 women with the infertility diagnosis of male factor only).		Return rate LBR	RESULTS: Women with cancer without an infertility diagnosis returned for a subsequent ART cycle at a lower rate (10.8 %) than those with an infertility diagnosis (31.3 %, p = 0.0010) or the control group (85.3 %, p < 0.0001). Among those who returned for a subsequent cycle, women with cancer waited a longer time to return (14.3 months without an infertility diagnosis and 8.3 months with an infertility diagnosis, p = 0.13) compared to the control group (2.8 months, p = 0.0007). The live birth rate among women who did not utilize embryo banking in their second cycle did not differ significantly across the three study groups, ranging from 25.0 and 42.9 % for women with cancer with and without an infertility diagnosis, respectively, to 36.2 % for women in the control group	Women with cancer without an infertility diagnosis are either less likely to return for subsequent treatment or will wait a longer time to return than women with an infertility diagnosis or those that do not have cancer
(Rienzi, et al., 2017)	Systematic review and meta-analysis		slow-freezing versus vitrification	cryosurvival rate, clinical pregnancy rate (CPR), live-birth rate (LBR) or delivery rate for slow-frozen or vitrified human oocytes or embryos	One RCT study comparing slow-freezing versus vitrification of oocytes was included. Vitrification was associated with increased ongoing CPR per cycle (RR = 2.81, 95% CI: 1.05-7.51; P = 0.039; 48 and 30 cycles, respectively, per transfer (RR = 1.81, 95% CI 0.71-4.67; P = 0.214; 47 and 19 transfers) and per warmed/thawed oocyte (RR = 1.14, 95% CI: 1.02-1.28; P = 0.018; 260 and 238 oocytes). One RCT comparing vitrification versus fresh oocytes was analysed. In vitrification and fresh cycles, respectively, no evidence for a difference in ongoing CPR per randomized woman (RR = 1.03, 95% CI: 0.87-1.21; P = 0.744, 300 women in each group), per cycle (RR = 1.01, 95% CI: 0.86-1.18; P = 0.934; 267 versus 259 cycles) and per oocyte utilized (RR = 1.02, 95% CI: 0.82-1.26; P = 0.873; 3286 versus 3185 oocytes) was reported. Findings were consistent with relevant cohort studies. Of the 7 RCTs on embryo cryopreservation identified, three met the inclusion criteria (638 warming/thawing cycles at cleavage and blastocyst stage), none of which involved pronuclear-stage embryos. A higher CPR per cycle was noted with embryo vitrification compared with slow-freezing, though this was of borderline statistical significance (RR = 1.89, 95% CI: 1.00-3.59; P = 0.051; 3 RCTs; I2 = 71.9%). LBR per cycle was reported by 1 RCT performed with cleavage-stage embryos and was higher for vitrification (RR = 2.28; 95% CI: 1.17-4.44; P = 0.016; 216 cycles; 1 RCT). A secondary analysis was performed focusing on embryo cryosurvival rate. Pooled data from 7 RCTs (3615 embryos) revealed a significant improvement in embryo cryosurvival following vitrification as compared with slow-freezing (RR = 1.59, 95% CI: 1.30-1.93; P < 0.001; I2 = 93%).	
(Rodriguez-Wallberg, et al., 2019a)	prospective study	1254 females including 1076 adults and 178 girls who received fertility preservation counseling for either oncologic (n = 852) or benign indications (n = 402)	fertility preservation counseling and/or treatment	trends in female patients' choices after counseling and fertility preservation outcomes during follow up in relation to benign vs malignant indications.	Adult women generally elected to undergo oocyte retrieval after COS for cryopreservation of embryos or oocytes (n = 538, 73%), whereas a minor proportion opted for cryopreservation of ovarian tissue (n = 221, 27%). More than half of the women with a partner chose either not to fertilize their oocytes aiming at cryopreservation of oocytes or to share obtained oocytes attempting both cryopreservation of oocytes and embryos. All pre-pubertal (n = 48) and 73% of post-pubertal girls (n = 66) elected OTC. In recent years, an increasing number of teenagers have opted for COS aiming at cryopreservation of oocytes, either before (n = 24, 17%) or after completion of cancer treatment (n = 15, 10%).	Women with previous malignancy had lower live birth rates than women with benign fertility preservation indications.

| | | | | During follow up, 27% of the women returned for a new reproductive counseling, additional FP or to attempt pregnancy. Utilization rates among individuals who were alive and of childbearing age indicated 29%, 8% and 5% for embryos, oocytes and ovarian tissue with LBR of 54%, 46% and 7%, resp. Women with benign indications were significantly younger than women with previous malignant indications at the time of attempting pregnancy. Although the pregnancy rates were similar among both groups, the LBR was significantly higher in benign vs previous malignant indications (47% vs 21%, P = .002). | |

INCLUDED AS BACKGROUND INFORMATION

(De Geyter, *et al.*, 2018, Goisis, *et al.*, 2019, Hargreave, *et al.*, 2019, Lee, *et al.*, 2006b, Loren, *et al.*, 2013, Maheshwari, *et al.*, 2018, Nakajima, *et al.*, 2015, Practice Committee of American Society for Reproductive Medicine, 2013, Rodriguez-Wallberg, *et al.*, 2020, Rossi, *et al.*, 2011, Yasmin, *et al.*, 2018)

Q12 How should ovarian stimulation be performed in cancer patients undergoing FP treatment?

Evidence section was largely based on the ESHRE Guideline on ovarian stimulation, published in 2019(The ESHRE Guideline Group on Ovarian Stimulation, *et al.*, 2020).

References included in the guideline on ovarian stimulation (and included in the evidence tables of that guideline)
(Alvarez and Ramanathan, 2018, Boots*, et al.*, 2016, Cardozo*, et al.*, 2015, Chan*, et al.*, 2015, Checa Vizcaino*, et al.*, 2012, Das*, et al.*, 2011, Devesa*, et al.*, 2014, Domingo*, et al.*, 2012, Druckenmiller*, et al.*, 2016, Garcia-Velasco*, et al.*, 2013, Goldrat*, et al.*, 2015, Johnson*, et al.*, 2013, Kuang*, et al.*, 2014, Lawrenz*, et al.*, 2010, Lee*, et al.*, 2010, Meirow*, et al.*, 2014, Muteshi*, et al.*, 2018, Oktay*, et al.*, 2003, Oktay*, et al.*, 2005, Oktay*, et al.*, 2006, Pereira*, et al.*, 2016, Reddy*, et al.*, 2014, Revelli*, et al.*, 2013, Rodgers*, et al.*, 2017, Shapira*, et al.*, 2015, Vaiarelli*, et al.*, 2018)

Literature searches were updated to include most recent data. The searches were limited to papers published between 1 november 2018 (deadline for inclusion of papers in the ESHRE Guideline on ovarian stimulation) and 1 november 2019.

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Adeleye, *et al.*, 2019)	Retrospective chart review	13 transgender men (7 using HRT)and cisgender women seeking ovarian stimulation (OS) matched by BMI and age		AFC Nr of oocytes retrieved estradiol level per oocyte meiosis II oocyte yield maturity rate (MII/oocytes) LBR	When comparing transgender men with and without a history of HRT, there were no differences in the baseline follicle count, cycle length, or FSH and hmG used (p = 0.193, 0.306, 0.200, and 0.197, respectively). Transgender men who used HRT had lower peak estradiol and oocytes retrieved compared to transgender men with no HRT use; peak estradiol levels of 1175 pg/mL IQR [559.5-2684]) vs 2713.5 pg/mL IQR [2335-3105]; oocytes retrieved 12 IQR [4-26]) vs. 25.5 [18-28] (p = 0.046. and 0.038, respectively). There were no differences in the estradiol level per oocyte, meiosis II oocyte yield, or maturity rate between the two groups (p = 1.000, 0.148, and 0.147, respectively). Peak estradiol levels were lower among transgender men compared to cisgender women (p = 0.016), but the remaining cycle characteristics were similar between the two groups. Three successful pregnancies were conceived using the oocytes of transgender men who used HRT.		
(Armuand, *et al.*, 2017)	prospective study	15 adult transgender men referred for FP- (age 19–35); none		Individual in-depth qualitative interviews were	three main categories: the journey to FP, reactions to the FP proceedings and strategies for coping. The referral for FP	procedures required prior to oocyte cryopreservation, such as hormonal ovarian	

		had given birth and 8 had a partner.		conducted shortly after FP treatment	was an important part of the assessment and diagnosis and sometimes lined with frustrating waits and doubts. The reaction to the FP proceedings revealed that the genital examinations and the physical changes associated with discontinuation of testosterone or hormonal stimulation treatment triggered gender incongruence and dysphoria. However, for some, the negative expectations were not met. The participants used several coping strategies in order to manage the procedure, such as focusing on their reasons for undergoing FP, reaching out to friends and family for support and the cognitive approaches of not hating their body or using non-gendered names for their body parts. The results demonstrate the importance of contextual sensitivity during FP procedures.	stimulation and TVS, have a negative impact on gender dysphoria as they are closely linked to the men's female assigned sex at birth, which is incompatible with their current status.	
(Campos, *et al.*, 2018)	Prospective observational study	26 women with cancer, with an indication to start cancer treatment within the next 20 days and wishing to preserve their fertility. A total of 13 women had breast cancer, 4 ovarian cancer, 3 Central Nervous System cancer, 3 endometrial cancer, 2 cervical cancer and one bowel cancer.	Ovarian stimulation started immediately with FSH followed by GnRH antagonist for pituitary suppression and GnRH agonist for oocyte maturation. Treatment started from day 1 to day 14 of the menstrual cycle was considered to be in the follicular phase, and that started from day 15 to day 28 was considered to be in the luteal phase. Oocyte retrieval was performed 34 h after GnRH agonist administration. After identification and maturity classification, metaphase II oocytes were cryopreserved using vitrification	duration of treatment total dose of FSH, number of ampoules of GnRH antagonist, mean number of follicles identified at ultrasound on the day of trigger and retrieval, number of aspirated oocytes Nr of Metaphase II oocytes.	Thirteen patients started treatment during follicular phase and 13 during luteal phase. We found similar results for the duration of treatment, total dose of follicle stimulating hormone, number of ampoules of gonadotropin releasing hormone antagonist, mean number of follicles identified at ultrasound on the day of trigger and retrieval, number of aspirated oocytes and Metaphase II oocytes.	Random-start controlled ovarian stimulation for emergency fertility preservation for minimizing delay in oncologic treatment for cancer patients does not interfere with the number of metaphase II oocytes	
(Cavagna, *et al.*, 2018)	Cohort study	109 breast cancer patients Mean age 31.27 +/- 4.23 years.	assigned to a specific random-start ovarian stimulation protocol for oocyte cryopreservation	numbers of oocytes retrieved and of mature oocytes cryopreserved, the total number of days of ovarian stimulation, the total dose of gonadotropin	The average duration of cos was 10.0 +/- 1.39 days. The mean number of oocytes collected was 11.62 +/- 7.96 and the mean number of vitrified oocytes was 9.60 +/- 6.87. The mean estradiol concentration on triggering day was 706.30 +/- 450.48 pg/mL, and the mean dose of gonadotropins administered was 2610.00 +/- 716.51 IU. When comparing outcomes		

				administered, and the estradiol level on the day of the trigger.	by phase of the cycle in which cos was commenced, we observed no significant differences in the numbers of oocytes collected and vitrified, the length of ovarian stimulation, and the estradiol level on trigger day. The total dose of FSH and hMG administered was statistically greater in the group starting cos in the luteal phase than in the late follicular phase group.		
(Leung, et al., 2019)	Matched retrospective cohort study.	26 female-to-male transgender 130 matched cisgender cohort.(matched during the same time period by age, BMI and AMH.)	Not applicable	Cycle outcomes, including oocyte yield, number of mature oocytes, total gonadotropin dose, and peak E2 levels.	The mean number of oocytes retrieved in the transgender group was 19.9 +/- 8.7 compared with 15.9 +/- 9.6 in the cisgender group. Peak E2 levels were the same between the two groups. The total dose of gonadotropins used was higher in the transgender group compared with the cisgender group (3,892 IU vs. 2,599 IU). Of the 26 patients, 16 performed oocyte banking only. Seven couples had fresh or frozen transfers, with all achieving live births.		
(Marklund, 2020)	A prospective multicenter study	401 women with BC	Treatments differed in the use or not of concomitant letrozole, a conventional or random-cycle day COS initiation and the use of hCG versus GnRHa trigger for oocyte maturation.	efficacy and safety: Numbers of cryopreserved oocytes and embryos. Pregnancy attempts, reproductive outcomes and long-term survival	Using letrozole or not resulted in similar numbers of oocytes and embryos cryopreserved (mean oocytes=9.7 versus 10 and mean embryos 4.0 versus 5.3, respectively), similar to COS with random versus conventional start (mean oocytes 9.0 versus 10.6 and mean embryos 4.8 versus 4.8). In COS with letrozole, a GnRHa trigger was associated with a higher number of oocytes retrieved (P<0.05) and embryos cryopreserved (P<0.005), compared with conventional hCG trigger. Of 99 women who returned to fertility clinics after cancer treatment, 32 proceeded to thawing of oocytes or embryos and 10 of them had live births. The all-cause survival between the women that underwent COS and those who did not was similar and did not differ between the two groups.	In women with BC undergoing COS aiming at egg/embryo cryopreservation, letrozole-based protocols and those randomly started were equally effective compared with conventional COS, and the overall survival was similar between the women that proceeded to FP and those who did not.	
(Vaiarelli, et al., 2020)	Observational study	100 women satisfying ≥2 of the following characteristics: maternal age≥40 years and/or ≤3 oocytes retrieved after previous conventional stimulation and/or reduced ovarian reserve (i.e., AFC <7	luteal-phase stimulation (LPS) versus follicular-phase stimulation (FPS) in a single ovarian cycle (DuoStim) for poor responder patients fulfilling the Bologna criteria.	cumulative live birth rate (CLBR)	Patients (100) underwent FPS (maternal age, 42.1 +/- 1.4 y; previous IVF cycles with </=3 collected oocytes, 0.7 +/- 0.9; AFC, 3.8 +/- 1.2 follicles; and AMH, 0.56 +/- 0.3 ng/mL). 91 patients completed DuoStim. All patients were included in the analysis. More oocytes were obtained after LPS with similar developmental and chromosomal competence as paired FPS-derived ones. The CLBR per ITT increased from 7% after FPS to 15% after DuoStim. Conversely, the CLBR per ITT among the 197 patients that chose a conventional controlled ovarian		

		follicles or AMH <1.1 ng/mL).			stimulation strategy was 8%, as only 17 patients who were not pregnant returned for a second stimulation after the first attempt (drop-out rate, 81%).		

INCLUDED AS BACKGROUND INFORMATION

(Oktay, *et al.*, 2010)

Q13 Should ovarian tissue cryopreservation vs. no intervention be used for fertility preservation?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Andersen, *et al.*, 2018)	quality control	Recommendation regarding quality control during implementation of OCT program	NA		NA	Step 1: Approval iof the clinical service: equipment, documentation , training- identification- transport- STEP 2 OCT setting: policy- agrement- collaboration-financial issue	
(Yding Andersen, *et al.*, 2019)	Review	Description of the OTC techniques and indications	NA	Techniques and indications	NA	OTC may be used beyond for fertility, and the coming years will hopefully show benecial effects of OTC in many other aspects. The technical aspects of OTC, including follicle survival from freezing/thawing and fragment size, is now slowly becoming more standardised	
(Anderson and Wallace, 2011)	Review	NA	general review discussing the FP technics and criteria and legislation	NA	NA	Relevant legislation varies from one country to another (HFEA licence requirement, allotransplantation forbitten in UK and not in USA or Belgium)- Criteria for OTC: age max 35 y, no existing children, good chance of survival, no POI	General review but intersting for some legislation and difference in practices issues
(Asadi, *et al.*, 2017)	retrospective analysis	cryopreserved samples from 34 female cancer patients at median age of 15 years (range 1-35): 14 collected at the time of diagnosis and 20 after initiation of chemotherapy (alkylating agents). Data compared with 4 healthy control who donate the tissue for research during CS	Tissue culture for 7 days after thawing. Samples were exposure to phosphatase and tensin inhibitor (1 µM; Calbiochem, Merck Chemicals Ltd.) for the first 24 hours of the culture period to activate the growth of ovarian follicles.	Viability and development of ovarian follicles		density of primordial follicles was similar in ovarian samples collected before and after the initiation of chemotherapy . more atretic follicles and fewer follicles in primary or sec- ondary stages were seen in samples exposed to chemotherapy. The decrease in the proportion of intact follicles was more notable in samples exposed to chemotherapy (before 46%, after culture 6%, P<0.001) than in samples that were not exposed (before 82%, after 28%, P = 0.001).After culture for seven days, both age and exposure to alkylating agents independently predicted viability of ovarian follicles.	Exposure to alkylating agents prior to ovarian cryopreservatio n may decreases survival of cultured human ovarian follicles. Negative Impact on success after graft not demonstrated
(Aubard, *et al.*, 2001)	Review	NA	Discuss the rational to offer ovarian tissue cryopreservation in Gynaecological cancer	NA	NA	OTC could be offer as an alternative to gametes cryopreservation even if uterus is compromise and surrogate mother is not allowed. Can be associated with ovarian transposition.	Detailed the different gynecological pathologies

(Backhus, et al., 2007)	Book Chapter	NA	Eligibility criteria for OCT	NA	NA	Patient <42years old; cannot or did not want to do IVF cycle; no POI; no surgical contraindication, consent, having children is not an exclusion criteria	
(Baram, et al., 2019)	Systematic review	Peer-review including 39 papers from 2001 onwards	Psychological and medical-based papers were analysed	desire to have children; fertility preservation (FP) discussions, counselling and referrals provided by healthcare providers; FP utilization; the attitudes, knowledge and beliefs; and barriers to accessing FP , hormone treatment and FP options and outcomes	NA	Desire to have children is more important before hormonal treatment than during tretament. FP counselling frequency is highly variable according to the center. There is a lack of high-quality medical data specific to FP counselling practice for this population	
(Beckmann, et al., 2016)	Review	16 publications with a total of 1898 woman for whom the surgical procedure of OTC was described and 15 publication with a total of 455 woman for whom surgical technique of OTT was described	Publications between January 2004 and December 2015	Surgical approaches	N/A	**OCT:** Laparoscopy is commonly described for OCT - mini laparotomy was reported in children- 1⁄3 (254 women) or ⁄3 of the ovary (446 women) removed in the majority of the cases. Avoid electric current is recommended (coagulation should be performed after tissue collection) **OTT:**Laparoscopy was done in 329 women (52%)	
(Bjelland, et al., 2014)	Retrospective cohort study	1055 Norwegian women who underwent unilateral oophorectomy and were included in the population-based HUNT2 Survey during the years 1995 – 1997 were compered to 22525 women who have both intact ovaries	Questionnaire about reproductive life and age at menopause	Age at menopause		The women who had undergone unilateral oophorectomy entered menopause 1 year earlier than women with two ovaries intact.	No data on the influence of the age at surgery
(Bystrova, et al., 2019)	Cohort study	16 patients who underwent heterotopic ovarian tissue transplantation	Heterotopic transplantation of cryopreserved ovarian tissue at different sites: forearm (FA) (2 cases), abdominal wall (AW) (11 cases), the peritoneal lining (P) (3 cases). Follow-up of 36 months	Menstrual cycle and hormone level. Reproductive outcomes		The heterotopic sites is efficient to restore ovarian function but probably less efficient than orthotopic site for fertility restoration	
(Condorelli and Demeestere, 2019)	Review	NA	NA	NA		Counseling for non-oncological indication can be complex and need to be address with caution regarding the potential adverse events of the procedure according to the diseases	

(Corkum, et al., 2017)	Review	22 articles selected	report descriptive details in regards to the operative technique for OTC	Technique used and post-operative outcomes	NA	Laparoscopy is the standrad procedure-Biopsy, single block of ovarian cortex have been performed- For biopsy/single block (1/4 to 2/3 of ovarian tissue, often right ovary) , an area away from the hilum that is free of visible predominant follicles and/or luteal tissue is preferred as the site of biopsy. Hemostasis was achieved with bipolar electrocautery after biopsy. No complication except one blood lodss requiring transfusion. Oophorectomy: no difference in surgery complication compared to biopsy (single center comparaison)- one superficial infection. consensus was lacking in terms of how much ovarian tissue	
(Diaz-Garcia, et al., 2018)	Cohort study	Patients who underwent fertility preservation procedure between 2005 and 2015	Oocyte vitrification-OV (n=1024) and OTC (n=800)	LBR and Pregnancies after using the stored oocytes (n=49) or ovarian tissue (n=44)	Large cohort	OV: Twenty-eight positive pregnancy tests were obtained after 51 fresh ET cycles and 17 frozen ETs, eight of which were biochemical pregnancies and four were clinical miscarriages (8.2%) .Overall LBR was 32.6% OCT:41 out of 44 patients (93.2%) resumed menstruation or improved their menopausal symptoms. Overall CPR and LBR per patient of 27.3% and 18.2%, respectively. No patients aged beyond 36 years at OCT achieved LB. OV is more effctive in older patients. OCT should no longer be considered as experimental when OV is not a feasible alternative.	First comparison of the outcomes of the two procedures in the same center
(Dittrich, et al., 2013)	Retrospective study	14 patients between 24 and 35 years of age (median 29)	Ovarian stimulation and OCT just after eggs retrieval	Histological section of pre-frozen tissue- surgical complication		Normal follicular count- no bleeding during laparoscopy	No outcomes of the ovarian tissue after graft neither on the spontaneous ovarian function restoration
(Dolmans, et al., 2014)	retrospective study	16 patients aged 27.1 ± 4.2 years (range: 21-34 y) compared to 100 matched control (non cancer patients)	combined bilateral ovarian cortex cryopreservation (Biopsy) following by ovarian stimulation for IVF. COS was started one or two days before laparoscopy or on the same day.	Number of oocytes collected - maturation rate		The number of collected oocytes was not statistically different between the 2 groups, with 10.7 ± 9.9 oocytes per study patient and 10.8 ± 6.2 oocytes per control patient (p = 0.3716) as well as the number of good quality embryo	Combined procedure can be proposed when time available before treatment

						obtained (respectively 4.2 ± 5 and 4.4 ± 4.1)	
(Donnez and Dolmans, 2017)	Narrative review			SELECTION CRITERIA for OTC		Gonadotoxicity is age-dependent. First-line cancer treatment does not compromise the ovarian reserve by more than 10% in girls under 10 years of age,7,32-35 whereas girls who are 11 or 12 years of age have an estimated 30% decline in their ovarian reserve. There is a marked association between the intensity of the treatment received and the likelihood of premature ovarian insufficiency, even in young girls,13,34,35 but it is impossible to predict exactly who will have premature ovarian insufficiency after aggressive chemotherapy. Selection criteria clearly need to be applied, the most important being an age of less than 35 years (when the ovarian reserve is still relatively high), a realistic chance of surviving for 5 years, and at least a 50% risk of premature ovarian insufficiency.	
(El Issaoui, et al., 2016)	other	63 patients younger than 18y reffered for fertility preservation between 2002-2014. A total of 32 and 31patients received low-risk gonadotoxic chemotherapy before OTC or not, respectively.	Oophorectomy for OTC	Follicular density according to previous treatment		No significant difference in follicular density between both group but ovaries was smaller when prior chemotherapy was administered	Study performed in a chort of patients younger than 18y that is not the population discussed in this guideline
(Fabbri, et al., 2016a)	Retrospective study	3 patients aged 31 to 36 years	Thawing after 18y storage (SF)	Immunohistology- morphology- apoptosis- proliferation- ultrastucture and LIVE/DEATH assay		Long-term storage (18y) did not affect follicular morphology and survival	No outcomes after graft
(Gellert, et al., 2018)	Review + new data from the Danish cohort (48 women)	360 OTT procedures in 318 women from 21 countries. Included all studies with information about OCT and OTT. Excluded studies using fresh tissue or diagnosed with PIO at the time of OTC.	Systematic review. No time/ follow-up limitation	Safety (Recurrence of the diseases), indications, transplantation sites and amount of tissue transplanted, endocrine and fertility outcomes	NA	87% of the indications were malignant diseases (230/264); 9 out of 230 experienced a recurence, none of them were related to the transplantation procedure. Orthotopic transplantation (ovary and peritoneal pocket) was performed in the majority of the cases (67% of the first graft)- Restoration of endocrine function ovccurs in 95% of the cases. 87 live births were reported in 69 women, and a total of 93 children born age of patients who succeeded in having a live birth (LB) or ongoing pregnancy (OGP) (26.4 years (SD 6.3), range 9–38 years) were significantly younger at OTC (P value = 0.0019) compared to patients who failed to conceive but had a pregnancy wish (29.6 years (SD 5.4), range 14–39 years). ovarian function described up to 10 years	

(Haino, et al., 2018)	Cohort study	24 woman aged 15 to 39 years	Histological analysis of fresh tissue from cancer/POI/autopsied patients	Follicular classification and localization (depth)		the depth of primordial and primary follicles did not change with age in adults. In infants, primordial follicles were located <400 lm. in POI patients, some of the primordial and primary follicles were detected at >1 mm below the surface of the ovarian cortex from the ovarian surface. Overall, 1mm ovarian thikness is enough for OCT in cancer patients and 1.5 in POI patients	
(Hoekman, et al., 2020)	cohort study	69 patients who underwent OCT between 2012 and 2015	OCT and OTT	IOP rate after OCT and reproductive outcomes after OTT		39.2% of the patients faced IOP. Transplantation was performed in 7 patients (8.7%). LBR 57%. Low return rate but high efficient technic	
(Huober-Zeeb, et al., 2011)	Retrospective study	12 patients (aged 31.1+-6.2) combined the procedure OCT (half of one ovary) following by ovarian stimulation compared to 28 patients (aged 27.6 +- 5.0) who underwent ovarian stimulation alone	Ovarian biopsy for OCT + stimulation	oocyte numbers and quality	Limited number of patients	no difference in the duration of the stimulation and number of oocytes retrived.The total number and the average number of aspirated oocytes per patient and per ovary were lower in those ovaries that had been treated by surgery. However, this difference was not statistically significant. Interestingly, both the percentage of MII oocytes and the fertilization rate tended to be higher in the ovaries that were biopsied.	No outcomes after using oocytes
(Imbert, et al., 2014)	Cohort study	225 patients who underwent ovarian tissue cryopreservation from March 1999 through June 2011, 45 (20%) were minors aged between 0.8 and 17	OCT (biopsy or ovariectomy)			Breast cancer was the most frequent diagnosis in the post-pubertal population, while haematological disease was the most frequent in children. 12.4% die during the FU. 90% of women have low concentrations of AMH (AMH; 0.5 ng/ml) and 30.7% experience premature ovarian failure (follicle- stimulating hormone 40 IU/l). 1death after OCT-no other severe AE	
(Jadoul, et al., 2017)	Retrospective analysis and survey	study population included all patients who underwent OTC for fertility preservation between April 1997 and December 2013 (n=545)- Mean age at OCT 22.3 ± 8.8 years (range: 6 months– 39 years). Questionnaire sent to 451 patients (143 patients	OCT- transplantation	descriptive analysis-Satisfaction-complications -outcomes		29% (n = 157) were under 18 years of age at the time of the procedure - main indications were haematological pathologies (35%) and BC (17%)- Fifty-four patients had died from their disease since the procedure (9.9%)- Based on questionnaire,31.5% (n = 29) were menopausal and 68.5% (n = 63) had functional ovaries. (36.4%) attempted to conceive naturally, 37 of whom succeeded (71%)-at least	

						96% of patients did not report any complications out of the 140 patients -Five minor complications (bleeding) and one major adverse event were encountered-96% were satisfied with the procedure,	
(Karavani, _et al._, 2018)	retrospective cohort study	231 Patients under 40 years of age who underwent oophorectomy for OCT . Mean age 20.1 ± 8.5 years	OCT by 2- or 3-port laparoscopic surgery (MPLS) or by Single-incision laparoscopic surgery (SILS)	Time of the procedure-time intervall to chemotherapy- Duration of OTC, hospital stay (days), and overall complications rates		Duration of OTC, hospital stay (days), and overall complications rates were similar in both groups - 2 complications (1 in each group: bowel perforation and ovarian bleeding) No difference in the time interval and nber of oocytes collected.SILS appears to be non-inferior as compared with standard laparoscopy in volume of ovarian tissue preserved. Single- port laparoscopy was well received by patients, has a reasonable learning curve, and yields favorable results.	
(Kikuchi, _et al._, 2013)	Observational	6 patients performed oophorectomy for OCT	3 patients 2 port laparoscopy and 3 SILS (single port laparoscopy)- 2 port was preferred for patients with endometriosis or myoma			mean time 39min- no complication	Reduced port laparoscopy is feasable and safe- may allow faster recovery as less invasive but required trained surgeon and should not be performed in cases of additional pelvic diseases
(Lambertini, _et al._, 2018a)	Cohort study	101 patients who performed fertility preservation and had known BRCA status (29 patients with BRCA mutation). Median age of 31 years [interquartile range (IQR) 28–33].	oocyte cryopreservation (N= 29) or OTC (n=72)	Ovarian reserve (AMH) and performance of cryopreservation procedure was compared between BRCA-mutated and non-mutated patients		A consistent trend for reduced reproductive potential and performance of cryopreservation strategies was observed in BRCA-mutated breast cancer patients	Results must be confirmed on larger cohort
(Lotz, _et al._, 2016)	survey	306 patients who underwent OCT from 1998 to 2016 aged 7 to 49years	OCT- survey (147 answer(45%))	Oucomes-The mean follow-up period was 6 years; descriptive analysios-survey		(93%) underwent the procedure for conditions involving malignancy. haematological malignancy (45%, n = 61) and breast cancer (27%, n = 37)- 34 died (11%)-FU: 48 patients (33%) were amenorrhoeic-62 women (42%) tried to conceive during the follow- up period-29 women (20%) reported that they had tried to become pregnant but had been unsuccessful up to the time of the survey.none of the 147 women who responded to the	

						questionnaire regretted having chosen to have ovarian tissue cryopreserved	
(McLaughlin, et al., 2017)	other	14 ovarian cortex from patients with lymphoma (13 HL; 1 non-Hodgkin lymphoma). 11 patients received one or two chemotherapy regimen before OCT. Mean patient age was 20.2 ± 1.5 years.	Data were compared with results obtained from contemporaneous ovarian biopsies obtained from adult women undergoing elective Caesarean section (age range 23–39 years, n = 12)	Follicular density, morphology and survival after in vitro culture according to previous treatment		ABVD treatment does not diminish the ovarian reserve but follicles have a reduced capacity for development in vitro	
(Pacheco and Oktay, 2017)	Meta-analysis	19 original studies or reviews with 309 OTT in 255 patients	Include studies from 1999 until October 2016	Endocrine function and fertility restoration	NA	OTC included malignancy in 78% (160 of 205) Amount of tissue transplantated around 1/3 per procedure- 45patients required 2 OTT to achive pregnancy- 73%were performed by laparoscopy. 37.7% (65 of 172) per woman-mean graft longevity from the time of OTT was 26.9 (25.6) months (range: 4-144 months)-endocrine function restored versus not was similar, 28.5 (6.0) versus 31.0 (10.0), P 1/4 .89.	
(Pampanini, et al., 2019)	other	43 patients (age ranging from 1 to 24 years) who underwent OCT between 203 and 2018, from who 25 received previous line chemotherapy with alkylating angents and/or anthracyclines	Analysis of ovarian tissue (oophorectomy for OTC)	Follicular density, morphology, immunohislogy and survival after culture		Ovarian cortex from treated patients have a lower follicular density and atretic rate compared to untreated patients but no difference in the marker of follicular activation was observed. During culture, lees steroids were secreted by the cortex from treated patients. Healthy follicles did not contain more DNA damage	
(Paradisi, et al., 2016)	Cohort study	191 patients (mean age 26.4 ± 6.9, range 12–38y) who underwent OCT between January 2008–December 2013		ovarian reserve at OCT		No difference in hormonal profile compared to healthy women. Define AMH and AFC as criteria to perform OCT with treshold at 0.4ng/ml and 5 follicles, respectively.	No evidence regarding reproductive outcomes using these criteria
(Peigne and Decanter, 2014)	Review	Aim to evaluate the clinical value of AMH levels before and after chemotherapy. Included 15 selected articles until December 2013	NA	NA		pretreatment AMH levels are shown to predict the long-term ovarian function after the end of treatment.	
(Poirot, et al., 2019b)	retrospective	31 consecutive patients who performed OTT including 22 who had prior chemo before OTC	OTT in patients wishing children	Ovarian function recovery and pregnancy rates		the cumulative incidence of OFR was 83% (93% in patients exposed to chemotherapy and 67% in others (P = 0.14))A low follicular density (<0.3 foll/mm2) in the transplant and a low number of grafted fragments (<16) were significantly	

						associated with a delayed OFR. Graft survival at 2 years after OTT was 77%. It was significantly lower in patients exposed to bifunctional alkylating agents before ovarian cryopreservation and in patients with a low follicular density.The cumulative incidence of pregnancy (Kaplan-Meier) at 3 years after OTT was 36% overall and 49% in case of previous chemotherapy, with no difference related to previous chemotherapy exposure.	
(Schmidt, *et al.*, 2013)	survey	143 patients who underwent OCT (oophorectomy) mean FU 58months		ovarian function after the procedure		112 of 143 (78%) women who had been treated for a malignant disease (BC and Hemato) and had one ovary cryopreserved for fertility preservation recovered with intact ovarian function and conceived naturally after cryopreservation. risk of premature ovarian failure was low (22%) Among the 57 women who had tried to become pregnant after their treatment, 41 (72%) had succeeded. 80% of women planned to use their tissue if requeried	Having only one ovary does not seem to affect their fertility.
(Stern, *et al.*, 2013) + (Stern, *et al.*, 2014)	Case report	Patient had undergone oophorectomy for a granu-losa cell tumour 9 years previously followed by prophylactic removal of the remaining ovary and subsequent ovarian tissue cryopreservation. After repeated assessments revealed no tumour recurrence, and no evidence of tumour in the stored tissue,	she had frozen-thawed ovarian tissue grafted to the anterior abdominal wall on two occasions. There was no evidence of tumour seen at either laparoscopy. The patient underwent low-dose stimulation and in vitro fertilization resulting in 2 embryos which were transferred.		Pregnancy proceeded uneventfully apart from a brief admission at 26 weeks for threatened preterm labour and a shortened cervix, which remained stable. The patient subsequently had an elective lower segment Caesarean section at 37 weeks and delivered two healthy girls weighing 3320 and 3262 g. At operation there was macroscopic evidence of tumour involving the diaphragm and a peritoneal deposit at the left pelvic brim. There was no evidence of tumour in the graft sites. All macroscopic tumour was resected and histology confirmed granulosa cell tumour. Recurrent tumour development could be directly related to grafting of ovarian tissue. It could also be due to a recurrence of peritoneal deposits precipitated by the hormonal environment provided by a pregnancy, in a tumour known to be sensitive to hormonal stimulation. Whilst the absence of tumour extraperitoneally at or near the graft sites might support hormonal reactivation, we cannot exclude the possibility that tumour recurrence resulted from the grafted tissue.		
(Wallace, *et al.*, 2014)	Retrospective study	Jan 1, 1996, and June 30, 2012: 34 (8%) of the 410 patients diagnosed with cancer met the Edinburgh selection criteria and 20 underwent OCT. Median age 16·9 years (IQR 15·5–21·8)	three to five ovarian cortical strips from one ovary were dissected with scissors, without diathermy, with the aim of removing roughly 70% of the ovarian cortex.	seven (35%) of 20 patients offered ovarian tissue cryopreservation had developed premature ovarian insufficiency, compared with one (1%) of 141 of those not offered ovarian tissue cryopreservation.	Validation of the edinburgh criteria:Age younger than 35 years, No previous chemotherapy or radiotherapy if aged 15 years or older at diagnosis, but mild, non-gonadotoxic chemotherapy acceptable if younger than 15 years, A realistic chance of surviving for 5 years, A		

						high risk of premature ovarian insufficiency (>50%), Informed consent (from parents and, where possible, patient)Negative serology results for HIV, syphilis, and hepatitis B, Not pregnant and no existing children	

Q14 Should vitrification vs slow freezing be used for ovarian tissue cryopreservation for fertility preservation?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Abir, *et al.*, 2017)	Experimental study in mice		Human ovarian tissue was preserved by needle-immersed vitrification or slow-freezing and transplanted into immune deficient mice, either untreated(groups A and C, resp) or treated with the improvement protocol (groups B and D, resp).		Follicle number in the recovered grafts was limited. The number of atretic follicles was significantly higher after vitrification with/without the improvement protocol and slow-freezing than that after slow-freezing + the improvement protocol. Stroma cell apoptosis was the lowest in the group D. PECAM staining showed a peripheral and diffuse pattern in the group D (mostly normal follicular morphology) and a diffuse pattern in all other groups (few follicles, mostly atretic), with significantly higher diffuse levels in the vitrification groups. Ki67 staining was identified in all normal follicles. Follicles did not survive transplantation in the vitrification groups.		
(Amorim, *et al.*, 2012)	Other	Ovarian cortex from 7 women from 30 to 41 years old	Slow freezing versus vitrification (2 protocols) and xenograft into mice- 33 tissue fragments recovered after 1 week	Follicular density, morphology, proliferation, fibrosis	No difference between morphological normal follicles between protocols (slow freezing 60.2%, vitrification protocol 1 57.9%, and vitrification protocol 2 62.2%). Higher percentage of follicles with DNA damage in SF group and no difference in the stroma cells		
(Dalman, *et al.*, 2017)	Other	Ovarian tissue from 7 women aged from 27 to 38 years	Control versus Slow-freezing versus vitrification	Intact primordial follicles (692 follicles analyzed)/ WNT pathways and apoptosis genes expression	97.42% and 91.42% of the follicles were intact in slow frozen and vitrified tissues . The number of normal secondary follicles significantly decreased in the vitrify compared to the slow frozen and control groups (P < 0.05). Apoptosis gene expression in favour of slow-freezing		
(Dolmans, *et al.*, 2015a)	Other	Monkeys (n=5)	Ovarian autograft after freezing using vitrification (V) versus slow freezing (SF) technique. Ovarian tissue were tranplanted in the hilum (healed bed after complete ovariectomy=HB) or in hilum after removed residual ovary (freshly decorticated bed after partial ovariectomy= FDB). The groups were compared to fresh tissue. Tissues were analysed 1 and 6 months after graft.	Follicle growth, density and quality, vascularisation, fibrosis	Follicular density reduced in all groups, no significantly different between cryopreservation methods (both lower than fresh tissue). Normal follicles are less frequently observed in transplanted tissue than in fresh. No difference between transplanted groups except lower survival rate in SF-HB. V-HB showed a decrease (34.2%) in the percentage of primary follicles, no difference in the other groups. Antral follicles were however more frequently observed in V-FDB group as well as proliferation and vascularisation. This group has also the highest rate of apoptosis. No significant difference in AMH staining and fibrosis. Both techniques allow long-term survival and grow of follicles after transplantation.		

					Preparation of the grafting site constitutes the major factor.		
(Fabbri, *et al.*, 2016b)	Other	Ovarian tissue from 6 patients aged 14–34 years	Slow freezing versus vitrification versus fresh: 892 follicles analysed for morphology/ 63 follicles analysed for ultrastructure/ 125 follicles analysed for bio energic and oxidative status	Morphological, ultrastructure and mitochondrial/ROS analysis in both conditions	Morphological characteristics were comparable between group, except for damage observed in the stroma in SF/RT samples and in some follicles for V/W samples. The SF protocol allowed better functional tissue integrity than the vitrification procedure. Mitochondrial activity is better preserved in SF than vitrification groups		
(Gellert, *et al.*, 2018)	Review + new data from the Danish cohort (48 women)	360 OTT procedures in 318 women from 21 countries. Included all studies with information about OCT and OTT. Excluded studies using fresh tissue or diagnosed with PIO at the time of OTC.	Systematic review. No time/ follow-up limitation	Safety (Recurrence of the diseases), indications, transplantation sites and amount of tissue transplanted, endocrine and fertility outcomes	87% of the indications were malignant diseases (230/264); 9 out of 230 experienced a recurrence, none of them were related to the transplantation procedure. Orthotopic transplantation (ovary and peritoneal pocket) was performed in the majority of the cases (67% of the first graft)- Restoration of endocrine function occurs in 95% of the cases. 87 live births were reported in 69 women, and a total of 93 children born age of patients who succeeded in having a live birth (LB) or ongoing pregnancy (OGP) (26.4 years (SD 6.3), range 9–38 years) were significantly younger at OTC (P value = 0.0019) compared to patients who failed to conceive but had a pregnancy wish (29.6 years (SD 5.4), range 14–39 years). ovarian function described up to 10 years		
(Herraiz, *et al.*, 2014)	Other	8 human ovarian cortex from 8 patients	Vitrification (4 different protocols- VT1 to VT4) versus slow freezing compared to fresh in vitro. One vitrification protocol selected for further in vivo studies (xenograft in mice for 6 months)	Follicular density, morphology, proliferation , vascularization, fibrosis	No difference between groups in in vitro study except an advantage of VT1 compared to the other (more healthy follicles). In vivo, VT1 showed a better follicular survival than SF. No difference in other parameters. After transplantation, higher number of quiescent follicles was observed after VT1 compared to SF, suggesting that SF induces massive follicular activation		Open system for vitrication
(Lee, *et al.*, 2019b)	Other	19 patients (15-32 years old) who performed benign ovarian surgery	Ovarian cortex biopsies distributed in slow freezing, vitrification or fresh group. Xenotransplantation in SCID mice for 4 weeks	Morphology and ultrastructure, immunohistochemistery , apoptosis, proteins expression (AMH, caspase-3)	slow freezing method is superior to vitrification in terms of primordial follicle preservation, vascularization, follicular cell proliferation, DNA damage, and AMH expression.		

(Pacheco and Oktay, 2017)	Meta-analysis	19 original studies or reviews with 309 OTT in 255 patients	Include studies from 1999 until October 2016	Endocrine function and fertility restoration	OTC included malignancy in 78% (160 of 205) Amount of tissue transplantated around 1/3 per procedure- 45patients required 2 OTT to achive pregnancy- 73%were performed by laparoscopy. 37.7% (65 of 172) per woman-mean graft longevity from the time of OTT was 26.9 (25.6) months (range: 4-144 months)-endocrine function restored versus not was similar, 28.5 (6.0) versus 31.0 (10.0), P 1⁄4 .89.		
(Rahimi, et al., 2010)	Other	Ovarian cortex from 5 patients from 30 to 39 years old- each fragment divided in 3: SF, V or fresh	Xenograft under the skin of SCID mice- fragment recovered after 3 days and weekly during one month. Mice were stimulated with FSH every second day.	Neovascularization and follicular count	Vascularisation occures afre 3 days irrespective of the freezing techniques. No difference in the decrease of the follicular density.		
(Shi, et al., 2017)	Meta-analysis	Slow-freezing versus vitrification: 14 non randomized comparative studies including 3 to 26 patients aged 14 to 43 years	Intact Primordial follicles (12 studies): 176 to 1015 follicles analysed. DNA fragmentation in follicles (6 studies): 56 to 781 follicles analysed. Stroma cells apoptosis (6 studies). Follicular density (3 studies)	Proportion of intact primordial follicles and apoptosis	No significant difference in the proportion of intact primordial follicles (OR = 0.98; 95% CI, 0.74–1.28; P = 0.86). Significantly less DNA damage in primordial follicles with vitrification compared to slow freezing (RR = 0.71; 95% CI, 0.62–0.80; P < 0.00001). Significantly more normal stromal cells after vitrification than after slow freezing (RR = 1.69; 95% CI, 1.47–1.94; P < 0.00001). No significant differences in primordial follicle density between vitrification and slow freezing (IV = 3.44; 95% CI, −5.09–11.98; P = 0.43)		No difference in the number of intact follicles after both techniques but vitrification is more effective to limit DNA damage induced by cryopreservation . There was a large heterogeneity in the protocol used for vitrification and effect of the protocol could not be evaluated.
(Ting, et al., 2011)	Other	Ovarian cortex from 4 Rhesus macaques	Slow freezing versus vitrification versus fresh	Histology, tissue culture for 48h, in vitro culture of isolated secondary follicles for 5 weeks (follicular survival and growth)	No difference in the morphology of primordial follicles but secondary follicles better preserved after vitrification		

(Wang, et al., 2016)	Original study	11 women aged21 years to 49 years	129 in vitro grown follicles after slow freezing or vitrification	Morphology/ ability to growh on vitro	No difference in morphological damage. The survival rate of follicles in the Fresh, Slow and Vit groups were 72.7, 62.5 and 60%, respectively, at Day 8 of IVC with no differences among groups (P . 0.05) No difference in follicular viability after 8 days although AMH mRNA expression was lower after vitrification		

Q 15 Which safety issues should be considered when replacing ovarian tissue?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Abir, et al., 2010)	Other	Fragments of ovarian tissue from 8 patients aged 13-20 years with Ewing sarcoma	Evaluation of the ovarian involvement using histology (adhesion receptor CD99 marker) and molecular markers (EWS-FLII)	Detection of MRD	1/8 patients had positive molecular markers without pathological evidence (pelvic disease)		Ovarian involvement is possible
(Andersen, et al., 2018)	quality control	Recommendation regarding quality control during implementation of OCT program	NA		Step 1: Approval of the clinical service: equipment, documentation , training- identification- transport- STEP 2 OCT setting: policy- agreement- collaboration- financial issue		
(Anderson, et al., 2017d)	Review	English-language literature on ovarian tissue cryo- preservation and IVM of ovarian follicles using conventional search methods.	NA	Selection of patients for OTC, effectiveness and risk of malignant cells contamination. Discuss the alternatives approaches	Girls and young women having ovarian tissue cryopreservation should be counselled and have their data collected in a research context, to improve the evidence base underpinning this approach.		
(Azim, et al., 2013)	Multicenter Retrospective Study	333 patients who became pregnant any time after BC were matched (1:3) to 874 patients with BC with similar ER, nodal status, adjuvant therapy, age, and year of diagnosis. 686 patients had an ER-positive disease		Disease free survival	No difference in DFS was observed between pregnant and nonpregnant patients in the ER-positive (HR ⬚ 0.91; 95% CI, 0.67 to 1.24, P =.55) or the ER-negative (HR=0.75; 95% CI, 0.51 to 1.08, P=.12) cohorts. However, the pregnant group had better OS (HR = 0.72; 95% CI, 0.54 to 0.97, P = .03), with no interaction according to ER status (P = .11).	Pregnancy outcome and BC– pregnancy interval did not seem to impact the risk of relapse.	
(Bastings, et al., 2013)	Systematic review	289 studies selected in English language and last updated mid-June 2012 on the risk of reintroducing malignancy	Included studies focussing on detection of residual disease in ovarian tissue. Studies were excluded if:(i) their patient population included women with a premalignancy, primary ovarian cancer, widespread intraperitoneal malignant disease or atumour directly adhering to the ovary; (ii) they only reported on ovarian metastases as the first site of recurrence; (iii) their patient population	Parameters collected: type of assessment of MRD and presence in the ovarian tissue (molecular biology/histology/ histochemistery/ immunohistochemical staining/xenograft/autop sy/clinical FU), patients' menstrual status, patients tumoral characteristics, metastasis)	Based on current literature, it is advisable to refrain from ovarian tissue autotransplantation in survivors of leukaemia. The safety of autotransplantion should be comprehensively discussed with survivors of all other malignant diseases. The most reassuring data regarding autotransplantation safety were found for lymphoma patients.		

		included women with a hereditary cancer syndrome associated with an increased risk of ovarian cancer, such as a BRCA1 or BRCA2 mutation, Lynch type II or Peutz Jeghers syndrome. Studies including patients with tumours that already showed spread or metastases to other sites than the ovary were included only when a homogeneous study group was described. Included if patients were premenopausal and if not specified, <51 years old					
(Beckmann, et al., 2017)	Retrospective study	All patients in whom ovarian tissue removal (n=399; median age 25.1 years (range 14–39 years)) or transplantation (n=38; median age 34.8 years (range 27–44 years)) was performed between January 2007 and December 2015	OCT and OTT	Desciption of the procedure, complications and ovarian function outcomes after OTT	No surgical complications occurred either intraoperatively or postoperatively during the removal and transplantation of ovarian tissue in this group of patients.		
(Beckmann, et al., 2018)	Retrospective study	1302 patients suffering from a fertility threatening conditions (oncologic and non-oncologic).	A questionnaire was sent to all the centres that had transplanted ovarian tissue and had to be returned by June 30, 2016. Centers selection criterias: at least five removals of ovarian tissue or at least three ovarian tissue transplantations. Thirteen centers in Germany and Austria participated with 1302 patients recruited.	The outcomes measured were: indication of the intervention, surgical procedure, surgical complications, follow-uo of ovarian transplantation.	Laparoscopic removal and transplantation of ovarian tissue gives a low complication rate, an increasing numbers of pregnancies and births, and an increasing expertise is available in centres. It has become a standard procedure that should be offered to patients for fertility protection in cases of cancer.		Even though the study is a retrospective collection from a database without controls, it has the advantages to include a large number of patients, with different pathologies and from a multicenter international setting.
(Bittinger, et al., 2011)	case report	19 years old patient diagnosed with extensive abdominal and pelvis HL	Histological analysis of 2 fragments of ovarian tissue	Immunohistology (CD30, CD15, CD20, CD3, CD79a, CD68 , cytokeratine)	One fragment showed normal stroma with 17 primordial follicles and no secondary follicles. The other fragment contained no normal ovarian tissue but was entirely composed of neoplasic cells		
(Bockstaele, et al., 2015)	Other	Ovarian cortex from non–breast cancer patients (n = 17) and from breast	Ovarian tissue analysis-Positive control (tumor and cell lines)	Histology, qPCR (GCDFP-15,MGB-1,MGB-2,and	MGB-1, GCDFP-15, and MGB-2 can serve as molecular markers for the detection of breast cancer micrometastaseswithin the		

		cancer patients (n = 15, 5 early and 10 advanced stage)		SBEM) and xenograft (n=4)	ovarian tissue of breast cancer patients. However, the clinical relevance of such a highly sensitive assay must be further investigated as none of the mice grafted with ovarian tissue expressing these markers developed cancerous disease.		
(Byrom, et al., 2015)	Meta-analysis	5 selected studies out of 304 citations on the oncological outcomes of women who get pregnant after melanoma treatment	Five databases (Cochrane Database, MEDLINE, EMBASE, CINAHL, and PubMed) were searched for studies assessing the effect of subsequent pregnancy on risk of melanoma death or recurrence.	OS and DFS after 11 to 20 y of FU	There was no significant effect of subsequent pregnancy on melanoma mortality after 11 to 20 years of follow-up (pooled hazard ratio, 0.81; 95% confidence interval, 0.60-1.09) and no significant differences in melanoma recurrence.		Only one study included patients with all stages of melanoma beyond Stage 1.
(Chae, et al., 2019)	retrospective study	49 patients with stage IA, grade 1-2 endometrioid endometrial cancer who underwent fertility-sparing treatment and tried to conceive	Twenty-two (44.9%) patients became pregnant resulting in 20 full term LB	Reproductive and oncological FU	The median disease-free survival duration was 26 months (range 20–38) and 12 months (range 4–48) in the pregnant and non-pregnant groups, respectively (P<0.05, log-rank test). Successful pregnancy might be a factor in preventing recurrence.		Poor power due to small size
(Demeestere, et al., 2015)	Case report				first live birth after autograft of cryopreserved ovarian tissue in a woman with primary ovarian failure after a myeloablative conditioning regimen as part of a hematopoietic stem cell transplantation performed for homozygous sickle-cell anaemia at age 14 years.		
(Demeestere, et al., 2009)	Review	Relevant articles up to January 2009 and centre data	NA	Factors affecting the outcomes and methods	Research needed to improve the survival rate after OTT. No evidence for clinical benefit of exogenous factors. Descriptive report on two step laparoscopy but no proved benefit		
(Dolmans, et al., 2013)	Review	Review of the literature addressing the risk of the presence of neoplastic cells in ovarian tissue from cancer patients. Reported data on 18 patients diagnosed with CML (n=6) or ALL (n=12)	Analysis of cryopreserved cortex + review of literature	Molecular detection of neoplastic cells+ xenograft	Leukaemia patients are at high risk of MRD in ovarian tissue. Using disease-specific PCR techniques, the authors found contamination of ovarian tissue in 33% and 70% of CML and ALL patients, respectively. High risk confirmed by xenograft experiments. Other patients with high risk included Neuroblastoma and Burkitt Lymphoma		
(Dolmans, et al., 2016)	Other	48 patients recruited having diagnosed with bone and soft tissue tumors. 26 patients selected for this study: Ewing sarcoma family of tumors (n = 14), rhabdomyosarcoma (n = 7), synovial sarcoma (n = 2), clear cell sarcoma (n = 2) and a malignant peripheral nerve sheath tumor (n = 1)	Ovarian tissue analysis	FISH, qPCR and IHC was performed on the primary tumor if available and qPCR. IHC (n=26) and qPCR (n=19) was performed in a fragment of cryopreserved ovarian tissue	No tumoral marker in the 26 ovarian tissue that could be analyzed. These results are reassuring regarding the risk of malignant sarcomatous cells in the ovary, as it involves a large series that includes different types of sarcomas.		Tissue from 26 out of 48 sarcoma patients can be analysed. The results were confirmed by xenograft model.

(Donnez, *et al.*, 2004)	Case Report	A 25 years old patients who cryopreserved the ovarian tissue after being diagnosed with Hodgkin Lymphoma. Four years later, she underwent ovarian tissue transplantation to achieve pregnancy	Ovarian tissue transplantation	Menstrual cycle and hormone level	Spontaneous pregnancy and live birth was obtained after transplantation of ovarian tissue		First case report of successful procedure
(Fabbri, *et al.*, 2012)	Other	94 BC patients who underwent OCT (73% receptor positive tumor) from January 2002 until April 2012 - Age 21–38 years (mean: 32.1 ± 4 years)	Ovarian tissue analysis	Histology	No micrometastasis observed-follicular density was dependent on patient age in fresh and thawed samples- The number of total follicles in mm2 statistically decreased after cryopreservation (2.6 ± 2.9 vs 1.6 ± 1.7; p < 0.05).		Sensitivity of the detection method is low
(Gellert, *et al.*, 2018)	Review + new data from the Danish cohort (48 women)	360 OTT procedures in 318 women from 21 countries. Included all studies with information about OCT and OTT. Excluded studies using fresh tissue or diagnosed with PIO at the time of OTC.	Systematic review. No time/ follow-up limitation	Safety (Recurrence of the diseases), indications, transplantation sites and amount of tissue transplanted, endocrine and fertility outcomes	87% of the indications were malignant diseases (230/264); 9 out of 230 experienced a recurrence, none of them were related to the transplantation procedure. Orthotopic transplantation (ovary and peritoneal pocket) was performed in the majority of the cases (67% of the first graft)- Restoration of endocrine function occurs in 95% of the cases. 87 live births were reported in 69 women, and a total of 93 children born age of patients who succeeded in having a live birth (LB) or ongoing pregnancy (OGP) (26.4 years (SD 6.3), range 9–38 years) were significantly younger at OTC (P value = 0.0019) compared to patients who failed to conceive but had a pregnancy wish (29.6 years (SD 5.4), range 14–39 years). ovarian function described up to 10 years		
(Greve, *et al.*, 2012)	other	xenograft of ovarian tissue from 25 leukaemia patients - 17 were in complete remission at the time of collection but 4 of them were positive for MRD before xenograft	Analysis by RT-PCR 20 week after xenograft	MRD detection (RT-PCR) in ovarian tissue from leukaemia patients in complete remission, before and after xenograft	No disease detection in ovarian tissue collected in patient in remission after first-line chemotherapy		
(Greve, *et al.*, 2013)	Other	Ovarian tissue fragments from 16 sarcoma patients (9 with Ewing sarcomas, 4 with osteosarcomas,2 with synovial sarcomas and 1 with chondrosarcoma)	Ovarian tissue analysis	Histology, molecular marker when available (n=9) and xenograft (20 weeks)	No sign of sarcoma using histology or molecular marker and all fragments were negative for the presence of neoplastic cells after xenograft. Ovarian tissue from patients with sarcoma appears to be without metastatic malignant cells in numbers that allow detection.		
(Jahnukainen, *et al.*, 2013)	Other	ovarian tissue collected between 1999-2012 from 16 leukaemia patients (6 ovarian tissue were cryopreserved before any	Analysis was performed using molecular methods and/or flow cytometry on the bone marrow and ovarian tissue	MRD	All the six ovarian samples collected at the diagnosis showed evidence of ovarian MRD varying between 0.2% and 57%while 2 out of the 10 patients, whose specimens were collected at remission, showed positive		

				treatment, 11 after an initial treatment) who had specific molecular markers available		ovarian MRD. Postponing the fertility preservation measures to the time of leukemia remission (negative bone marrow MRD) results in less or no leukemic contamination in the ovarian material.		
(Klotz, et al., 2000)	other	Rats	Ovariectomy and transplantation to the right part of the liver	Histological analisis of the liver up to 18 months after transplantation	The occurrence of one hepatocellular adenoma and three carcinoma 18 months after intra-hepatic ovarian tissue transplantation suggests a causal association between the local long-term hyperestrogenism in the liver acini downstream of the transplants and the development of hepatocellular neoplasms.		No clinical implication but illustrates the need of follow-up at heterotopic site
(Kristensen, et al., 2017)	Case report	A 23-year-old woman diagnosed with stage 1C ovarian mucinous cystadenocarcinoma.	Ovarian tissue transplantation at heterotopic site after ovarian cancer treatment and refreezing again after the removal.	Outcomes: pregnancies, hormonal values, histologic examination of the tissue and of xenografted mice at different steps of the procedure. 4.5 years of follow up after grafting and 2 months follow-up after the complete removal of the grafted ovarian tissue.	Possible way of handling cancer patients with a low risk of ovarian primitive cancer or malignant cell recurrence.		ovarian tissue transplantation after ovarian cancer is exceptional. It showed also that completely removal of the tissue after pregnancy is recommended but might be challenging in heterotopic site.
(Lambertini, et al., 2018b)	Case-control study	333 patients with pregnancy after breast cancer were matched (1:3) to 874 nonpregnant patients of similar characteristics, adjusting for guaranteed time bias.		Safety of pregnancy Survival estimates were calculated using the Kaplan-Meier analysis;	At a median follow-up of 7.2 years after pregnancy, no difference in disease-free survival was observed between pregnant and nonpregnant patients with ER-positive (hazard ratio [HR] = 0.94, 95% CI = 0.70 to 1.26, P = .68) or ER-negative (HR = 0.75, 95% CI = 0.53 to 1.06, P = .10) disease. No overall survival (OS) difference was observed in ER-positive patients (HR = 0.84, 95% CI = 0.60 to 1.18, P = .32); ER-negative patients in the pregnant cohort had better OS (HR = 0.57, 95% CI = 0.36 to 0.90, P = .01). Abortion, time to pregnancy, breastfeeding, and type of adjuvant therapy had no impact on patients' outcomes. This study provides reassuring evidence on the long-term safety of pregnancy in breast cancer survivors, including those with ER-positive disease.		
(Lambertini, et al., 2018a)	RCT	2862 premenopausal patients with HER2-positive breast cancer	chemotherapy plus trastuzumab vs. lapatinib vs. lapatinib-->trastuzumab vs. lapatinib + trastuzumab	Treatment-induced amenorrhea (POI defined only based on menstrual function following the end of treatment)	Rates of treatment-induced amenorrhea were 72.6%, 74.0%, 72.1%, and 74.8% in the trastuzumab, lapatinib, trastuzumab -->lapatinib, and trastuzumab + lapatinib arms, respectively (P = 0.64). As compared with trastuzumab alone, no difference in treatment-induced amenorrhea risk was	There was no association between rates of treatment-induced amenorrhea and type of anti-HER2	

					observed with lapatinib (OR 1.13, 95% CI 0.90-1.43, P = 0.29), trastuzumab-->lapatinib (OR 0.99, 95% CI 0.79-1.24, P = 0.91), and trastuzumab+lapatinib (OR 1.19, 95% CI 0.94-1.51, P = 0.14). In the multivariable analysis, the only factors that remained statistically significantly associated with higher risk of treatment-related amenorrhea were older age at diagnosis (adjusted OR 2.84, 95% CI 1.93-4.17, P < .001), addition of taxanes to anthracycline-based chemotherapy (adjusted OR 1.92, 95% CI 1.44-2.56, P < .001), administration of TCH (design 2B) regimen (adjusted OR 2.24, 95% CI 1.18-4.27, P = 0.01), and use of adjuvant endocrine therapy (adjusted OR 2.84, 95% CI 1.85-4.35, P < 0.001).	treatment in premenopausal patients with HER2-positive early breast cancer	
(Lotz, *et al.*, 2011)	Other	23 patients aged 16 to 38 years (median age, 26.5 years) with ovarian tumours who underwent OCT	Histological analysis of ovarian tissue + xenograft for 24 weeks before analysis	Immunohistology (pancytokeratine)	No carcinoma cells were seen in any of the hematoxylin and eosin– stained slides examined or in any of the slides with antibodies against cytokeratins.		Low sensitivity of detection technique
(Luyckx, *et al.*, 2013)	Other	13 advanced stage breast cancer patients (aged 17-35 years)	Xenograft of ovarian fragments (6 months)	histology and immunohistochemistry (epithelial membrane antigen, Her2/neu and gross cystic disease fluid protein 15 identification), and 2) detection of the MGB2 gene by qPCR.	No malignant cells were evidenced by histology and immunohistochemistry. None of the mice died during the 6 month grafting period, nor developed macroscopically visible masses. MGB2 was detected in some samples		
(Masciangelo, *et al.*, 2018)	Other	Ovarian tissue cryopreserved between 1997 and 2017 from 11 BOT patients (mean age 29.33 years) were used for detection of neoplastic cells. Two of them died from the disease during FU.	Tissue from BOT patients was compared with tissue from healthy patients	Ovarian tissue from BOT patients was analysed by histology, IHC, RT-PCR and xenografting. Positive and negative controls were used for IHC and RT-PCR.	Presence of specific markers of BOT + development of BOT or BOT markers in SCID mice after transplantation in 1/11 patients. Different analysis and xenografts should be used (when possible) to assess the presence of neoplastic cells in OTC before safe transplantation		COH for FP in BOT is preferable, so OCT is a secondary technique, and transplantation has not been reported.
(Mueller, *et al.*, 2005)	other	Rats	Transplantation of ovarian tissue in splenic capsule	Tissue analysis after up to 300 days		Sex cord stromal tumours, consisting mainly of granulosa cells, were found in all of the rats.	
(Oktay, *et al.*, 2016)	Prospective study of 2 cases	2 subjects with hemophagocytic lymphohistiocytosis (patient A) and non-Hodgkin lymphoma (patient B) who underwent ovarian tissue cryopreservation at the	we transplanted ovarian cortical tissues to the contralateral menopausal ovary 7 and 12 years later, using a human ECTM scaffold and robotic assistance. The ECTM scaffold tissue		Ovarian follicle development was observed approximately 10 (patient A) and 8 (patient B) weeks after ovarian tissue transplantation. Following 8 and 7 cycles of in vitro fertilization, 9 and 10 day-3 embryos were cryopreserved (patients A and B, respectively). While the baseline follicle-stimulating hormone (range 3.6-15.4 mIU/mL) levels near normalized by 7 months and remained steady postovarian transplantation in patient A, patient B showed improved but elevated follicle-stimulating hormone		

		age of 23 years, before receiving preconditioning chemotherapy for hematopoietic stem cell transplantation. Both experienced ovarian failure post chemotherapy	compatibility was shown in preclinical studies. Patients also received estrogen supplementation and baby aspirin preoperatively to aid in the revascularization process.		levels throughout (range 21-31 mIU/mL). Highest follicle yield was achieved 14 (8 follicles; patient A) and 11 (6 follicles; patient B) months postintervention. Patient A experienced a chemical pregnancy after the third frozen embryo transfer attempt. She then conceived following her first fresh in vitro fertilization embryo transfer and the pregnancy is currently ongoing. Patient B conceived after the first frozen embryo transfer attempt and delivered a healthy girl at term.	
(Oktay, et al., 2019)	Other	2 OTT by robotic laparoscopy including one using Alloderm and one case illustrating percutaneous heterotopic transplantation	technical description	Video	Feasibility of the procedure	
(Pacheco and Oktay, 2017)	Meta-analysis	19 original studies or reviews with 309 OTT in 255 patients	Include studies from 1999 until October 2016	Endocrine function and fertility restoration	OTC included malignancy in 78% (160 of 205) Amount of tissue transplantated around 1/3 per procedure- 45patients required 2 OTT to achive pregnancy-73%were performed by laparoscopy. 37.7% (65 of 172) per woman-mean graft longevity from the time of OTT was 26.9 (25.6) months (range: 4-144 months)-endocrine function restored versus not was similar, 28.5 (6.0) versus 31.0 (10.0), P 1⁄4 .89.	
(Poirot, et al., 2019a)	retrospective	31 consecutive patients who performed OTT including 22 who had prior chemo before OTC	OTT in patients wishing children	Ovarian function recovery and pregnancy rates	the cumulative incidence of OFR was 83% (93% in patients exposed to chemotherapy and 67% in others (P = 0.14))A low follicular density (<0.3 foll/mm2) in the transplant and a low number of grafted fragments (<16) were significantly associated with a delayed OFR. Graft survival at 2 years after OTT was 77%. It was significantly lower in patients exposed to bifunctional alkylating agents before ovarian cryopreservation and in patients with a low follicular density.The cumulative incidence of pregnancy (Kaplan-Meier) at 3 years after OTT was 36% overall and 49% in case of previous chemotherapy, with no difference related to previous chemotherapy exposure.	
(Rodriguez-Iglesias, et al., 2015)	Other	13 breast cancer patients with metastasis	Ovarian tissue analysis. Ovarian tissue from BC patients are compared with 10 healthy patients and 4 primary tumors	Histology (GCDFP15, MGB1, and SBEM markers), PCR (qRT-PCR) for GCDFP15, MGB1, SBEM, MUC1, NY-BR- 01, and WT-1, invasion assay and xenograft (6 months)	GCDFP15, MGB1, and SBEM were the most sensitive molecules to create a diagnostic panel for BC malignant cell contamination, which may make ovarian tissue cryopreservation and transplantation a safe technique for fertility preservation in BC patients.	
(Schmidt, et al., 2011)	Retrospective study	12 women with chemotherapy-induced premature ovarian failure:	Monitoring of hormonal parameters and results of 56 IVF cycles in 10 women.	Levels of gonadotropins and sex steroids, functional life span of the grafts, and results of IVF.	All 12 women regained ovarian function between 8 and 26 weeks (mean 19 weeks) after transplantation. 10 women underwent a total of 56 IVF cycles, 76	

					follicles developed, 49 oocytes were aspirated, 18 were fertilized, and 16 embryos were transferred resulting in six pregnancies: two biochemical, one clinical that miscarried in week 7, and two ongoing resulting in the delivery of two healthy infants born at term to two women. One of these women subsequently conceived spontaneously and delivered another healthy infant. The life span of the transplanted tissue was between 6 months and still functioning after 54 months.		
(Shapira, _et al._, 2018)	Case Report	19 years old patient treated for AML.	Ovarian tissue was frozen during complete remission before bone marrow transplantation. OTT at 32 years old	Reproductive and oncological FU after OTT (2y). Assessment of the MRD in the cryopreserved tissue using molecular and xenograft methods before OTT	Harvested tissue during complete remission allow safe OTT procedure		

Q16 Should In vitro maturation (IVM) vs. no intervention be used for fertility preservation?

Reference	Study Type Quality	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Abir, et al., 2016)	OBS HIGH (large series, single centre)	n=42 girls age 2-18, large number of oocytes, correls with age and AMH, 31% maturation rate .2-18 yo cancer patients (n=42)	2 groups of investigation of immature oocytes collected from ovaries (ex vivo IVM): before (n=22) and after (n=20) starting chemotherapy . Duration : 2007 - 2014	Retrieval rate Maturation rate	. 12 and 13 oocytes could be collected before and after chemotherapy . 78% oocytes could be harvested by ex vivo OTC .mostly oocytes matured and vitrified were from patients before chemotherapy . Positive correlation of vitrified/matured oocytes with patients age (older more oocytes matured, p=0.001) and AMH levels, p=0.03		Prepubertal patient population and post pubertal should be cited as a feasibility of the method for younger patients when ovariectomy is indicated
(Chian, et al., 2009)	OBS MODERATE (retrospective)	. Infertilie patients (n=58) .18 - 35 yo . Groups comparable at baseline	. 2 groups of comparison : oocytes vitrified from COH patients (n=38) vs IVM-infertile patients (n=20) IVM: no stimulation + hCG Duration : 2003 - 2007	Oocyte survival Outcomes of use (implantation, live birth)	Significantly more oocytes survived vitrification from COH group (81% vs 68%) and fertilized (75% vs 64%) . IR were higher in COH group (19% vs 10%, NS) . CPR and live birth were higher in COH group 50% vs 20%, NS and 40% vs 20%, NS . 4 live births from vitrified oocytes out of 20 IVM patients with no adverse effects	No adverse effects on perinatal outcomes of babys born from oocyte vitrification from COH and IVM cycles	
(Combelles and Chateau, 2012)	REVIEW MODERATE	. 8 studies : vitrification before vs after IVM : . Only 2 studies with sibling oocytes : . 4 studies with vitrification and 4 with SF . All used rescued IVM oocytes after COH (so not same population than IVM for oncofertility)	. More than 1000 oocytes frozen before or after IVM: ~ 500 GVs and ~500MII	Maturation	maturation is higher if oocytes are frozen after IVM No risks identified	Better to vitrify after IVM than vitrify immature oocytes	Freezing/vitrification effects on egg quality
(Creux, et al., 2017)	OBS MODERATE (Retrospective? low number of patients no analysis of pregnancy)	164 cancer patients for urgency IVM-FP (n=192 cycles) (69% breast cancer, 16% hematological cancer, 16% others) 23 - 37 yo, prior chemotherapy Groups comparable at baseline	IVM-FP: no stimulation + hCG 3 groups of comparison (L vs F): . Early follicular phase (n=46) . Late follicular phase (n=107) . Luteal phase (n=39) Duration : 2003 - 2015	number of oocytes retrieved	. Number of oocytes retrieved, in vivo and in vitro matured and fertilised: NS among groups . Number of oocytes/embryos cryopreserved: NS among groups (mean number of 3 / patient)	IVM can be offered as an alternative method when IVF is contraindicated or no time available independently of the phase of the menstrual cycle where oocytes are retrieved	No difference in outcomes in F vs L phase, long duration
(Creux, et al., 2018)	OBS – MODERATE (Retrospective, low number of patients)	.353 cancer patients for FP of oocytes and/or embryos (48% breast cancer, 27%	IVF-FP : Stimulation (GnRH ago or anta) +/- aromatase inhibitor + hCG IVM-FP: no	number of oocytes retrieved Fertilisation rate	Number of oocytes matured utilised and cryopreserved : IVF (n=10) > IVM (n=5) p <0.001 Number of cryopreserved oocytes:	First pregnancy resulted from frozen embryo transfer from IVM retrieval. IVF superior in	in view of relatively low success rate

		hematological cancer , 2% other cancers) : . 28 - 30 yo, prior chemotherapy (IVF younger p<0,001) . Groups comparable at baseline	stimulation + hCG . n=187 IVF-FP (stimulated) . n=207 IVM-FP (urgency and stimulation contraindicated) Duration : 2003 - 2015	Outcomes of use of stored material	IVF (n=5) > IVM (n=3) p<0.007 . fertilization rate: IVF = IVM . embryos cryopreserved: IVF (n=5) > IVM (n=3) p<0.007 → 6.5% patients returned (NS between groups): . IVF-FP oocyte thaw= 1 LB / 3 ET . IVM-FP oocyte thaw = 0 LB/4 ET . IVF-FP embryo thaw = 5 LB / 16 ET . IVM-FP embryo thaw = 1 LB/ 10 ET . mixed transfer IVM/IVF embryo thaw = 1 LB/1 ET Gestational age and birth weight normal in both groups NS for CPR, miscarriages and live births per embryo transfer similar between IVF-FP and IVM-FP	oocyte and embryo collection than IVM, higher for CPR (NS) IVF and IVM can be effective for FP	Preference given to IVF
(De Vos, et al., 2011)	Prospective cohort study	39 consecutive patients <37 years old with PCO or PCOS, who underwent 73 cycles of immature oocyte retrieval.	Immature oocyte collection after ovarian stimulation with a cumulative dose of 450 IU uFSH or highly purified hMG, but without hCG priming. IVM of oocytes followed by ET if endometrium thickness >/= 6 mm. Embryo vitrification at the cleavage stage. ET in an artificial cycle.	Implantation rate (IR) and clinical pregnancy rate (CPR).	Fresh ET after IVM resulted in an IR of 6.9% (5/72) per ET and a CPR of 9.4% (5/53). ET of vitrified-warmed IVM embryos in an artificial cycle resulted in significantly better outcomes (IR 21.9% [7/32] and CPR 31.8% [7/22] per ET)	A non-hCG-primed IVM system in PCO or PCOS performs poorly when embryos are transferred in a fresh cycle. Transfer of vitrified-warmed IVM embryos in an artificial cycle leads to significantly improved clinical outcomes.	
(Demirtas, et al., 2008)	case report	. 3 cases cancer patients undergoing IVM in luteal- and follicular - phase for FP . 21, 30 and 40 yo	IVM: no stimulation + hCG : oocytes in L- phase (n=19) vs and in F-phase of same patients (n=34) cryopreserved	number of oocytes retrieved	Vitrified MII oocytes in luteal phase IVM (n=13) vs and in follicular phase of same patients (n=25) cryopreserved	oocyte retrieval and maturation after IVM is possible in luteal phase and of the same cycle patients cycle when needed	first report on IVM luteal phase
(El Hachem, et al., 2018)	OBS LOW (retrospective)	. Cancer patients undergoing IVM for FP . 18-40 yo (n=373), before starting chemotherapy . 2 groups of comparison: hCG vs GnRH agonist trigger	Outcomes of IVM patients for FP (FSH unstimulated) . 2 groups of comparison: hCG (n=235) and GnRH agonist (n=138) : Duration : 2009 - 2015 , agonist starting on 2012	number of oocytes retrieved maturation rates	. Higher total oocytes retrieved in GnRH agonist vs hCG (9 vs 8, p=0.04) . Similar IVM rates (59 vs 64) and MII frozen (5.2 vs 4.9)	No differences between GnRH-agonist trigger and hCG, both can be used for IVM-FP	Retrospective, two time frames, no information on the numbers of retrieved in vivo matured oocytes. The statement that no PCOS patients were included is doubtful
(Grynberg, et al., 2016)	OBSERVATIONAL MODERATE	248 breast cancer patients neoadjuvant therapy with > 10 AFC. 18-40 yo	IVM-FP: no stimulation + hCG 2 groups of comparison (L vs F): Follicular phase (n=127) Luteal phase (n=121)	number of oocytes retrieved	Number of eggs retrieved: NS Number of in vivo MII oocytes : increased in F-phase data not shown, only mentioned	IVM outcomes are similar independently of the phase of the menstrual cycle where oocytes are retrieved	for good responders , no differences in IVM outcomes in urgent FP

	Prospective _ Doubt on the prospective nature of the study + not randomized	Groups comparable at baseline. Luteal phase = >3ng/ml	Duration : 2011 - 2014		Number % of IVM oocytes: NS Number cryopreserved oocytes: NS (mean number of 6.5/ patient) % fertilization: NS		between F vs L phase OR, but no data on CPR
(Grynberg, et al., 2019)	OBS HIGH	. Case series BC BRCA1/2 patients undergoing IVM for FP . 18-40 yo (n=329), before starting chemotherapy . Groups comparable at baseline	. 2 groups of comparison: BRCA-mutated women (n=52) and BRCA-negative women (n=277) IVM: no stimulation + hCG Duration : 2014 - 2017	number of oocytes retrieved maturation rates number of oocytes cryopreserved	. Number of retrieved COC similar between groups BRCA-mutated or not (8.9 vs 9.9, NS) . Similar IVM rates (67 % vs 62%, NS) . Number of MII cryopreserved oocytes similar between groups (5.1 vs 6.1, NS)	Although BRCA are known to alter DNA repair mechanisms , it seems not impair IVM capacity	Lack of data on developmental potential of oocytes
(Grynberg, et al., 2020)	case report	One 29 yo patient with breast cancer after tumorectomy before chemotherapy	. 7 immature oocytes collected after aspiration	number of oocytes retrieved	6 oocytes matured and vitrified Five years later , oocytes were warmed and fertilised oocytes resulting in transfertof one day 3 embryo	IVM can be considered and viable and option for FP	First live birth from vitrified IVM oocytes
(Hourvitz, et al., 2015)	OBS MODERATE (novel combinations)	. 255 cancer patients . 10 - 40 years old	. 142 patients underwent OTC; 56 OTC + ex vivo IVM; 9 IVM retrieval and 48 OTC + ex vivo + IVM . IVM : FSH 3 days + hCG . Duration : 2007 - 2013	Oocyte recovery Maturation Fertilisation Safety aspects	More oocytes recovered, higher maturation rate (62%) and fertilisation (p<0.01) and more cryopreserved oocytes (p<0.05) when three procedures were performed vs IVM or OTC + ex vivo alone . IVM retrieval with FSH + HCG or no stimulation no adverse affects of stimulation before ovariectomy	IVM aspiration before ovarian tissue harvesting has the privilege to recuperate more oocytes than IVM or ex vivo IVM alone IVM with FSH + hCG gave rise to more oocytes collected and more MII at retrieval	Authors show that up to three days FSH at 150 IU max did not cause hypervascularis ation at ovariectomy even after hCG
(Huang, et al., 2008)	Case report	16 yo turner mosaic	11 oocytes aspirated ex vivo for IVM for OTC		8 oocytes were matured and cryopreserved (73%)	ex vivo OTC worth to be performed	
(Isachenko, et al., 2004)	Case report	2 cases	Combination of cryopreservation of human ovarian tissue and in-vitro matured germinal vesicle (GV) oocytes retrieved during tissue dissection		Ten or eight GV-stage oocytes were recovered		First description
(Isachenko, et al., 2009)	Experimental study			optimal time and temperature for long-distance transport.	Prolonged suprazero temperature exposure of ovarian tissue for 26 hours has no negative influence on follicle quality.		
(Kasapi, et al., 2017)	LOW	. Use rescued IVM oocytes after COH (so not same population than IVM for oncofertility) (n=104 oocytes donors)	. 3 groups of comparison: group 1 , GV-vitrified/warmed then IVM (n=107); group 2, IVM then vitrified /warmed(n=105); group 3, IVM without vitrification (n=106). . Duration 2013 - 2014	SURVIVAL Maturation	Survival was similar between groups 1 and 2 . Maturation lower in group 1 compared to groups 2 and 3 (51% vs 82%, p<0.01) ; group 1 had maturation of 27% lowest normal spindle conformity = 41%	Better to vitrify after IVM than vitrify immature oocytes	type of materiel used

(Kedem, et al., 2018)	OBS MODERATE (large series from single centre)	large case series n=119, embryos thawed in 8 women, one pregnancy. No fertilisation of 6 warmed eggs (all vitrified). . 9-41 yo cancer patients	in vivo oocyte asp before OTC, better MII rates . Cancer patients underwent IVM oocyte aspiration and ex vivo IVM from OTC . IVM aspiration performed after 3d FSH + hCG and ex vivo IVM soon after half ovaries were removed . Duration : 2007 - 2015	Fertilization rate Outcomes of use	. Overall 74% fertilization rate from IVM (retrieval + ex vivo) . No embryos were transferred after thawing of 2 IVM oocytes . 35 embryos frozen from IVM were thawed and 29 transferred (82% survival) resulting in 1 pregnancy from IVM retrieval	Combining IVM retrieval + ex vivo IVM from OTC increases the yield of immature oocytes	First pregnancy of retrieved IVM oocytes
(Maman, et al., 2011)	OBS LOW (retrospective)	. Cancer patients undergoing IVM for FP . ≤ 35 yo, before starting chemotherapy . Groups comparable in ovarian reserve: age, reserve, AMH (3,7 vs 6,4 ;NS)	. IVM: no stimulation + hCG 2 groups of comparison: L vs F . Follicular phase (n=5) . Luteal phase (n=13) Duration 2007 - 2009	number of oocytes retrieved	Higher but not significant (NS) number of oocytes retrieved (13 vs 17), matured (48% vs 58%) and frozen (6.4 vs 7.8) in Follicular-P compared to Luteal-P, but similar fertilization	IVM during luteal phase is feasible when no time available before chemotherapy	first report of to compare IVM in luteal vs fol. -phase
(Moria, et al., 2011)	TRIAL LOW (retrospective)	. Cancer patients for FP (68% breast cancer, 13% hemato) vs IVM infertile patients . 25 - 32 yo, before starting chemotherapy . Groups comparable at baseline	Outcomes of BC IVM patients (n=87) vs IVM-infertile patients (n=79) IVM: no stimulation + hCG Duration : 2003 - 2009	number of oocytes retrieved	. Significantly fewer oocytes were retrieved in BC patients compared to IVM infertile patients . Same rates of IVM between groups	reduced number of oocytes in IVM cycles in BC patients compared to infertile patients	good number of patients but retrospective
(Nogueira, et al., 2012)	REVIEW LOW – narrative _ infertile population	Literature review avec data				Different methodologies are existent for IVM procedures , need for consistency	
(Prasath, et al., 2014)	Case report	. 1 case ovarian cancer 21 yo	Ex vivo immature oocyte harvest after ovariectomie for IVM Duration: 14 months from harvest to transfer		4 immature oocytes IVM . 3 embryos slow freezing-thawed and transferred . 1 delivery healthy cjild	this case of successful ex vivo validates the procedure	
(Segers, et al., 2015)	HIGH (large series, single centre)	. 34 cancer patients . 1 - 34 yo	501 immature oocytes collected from ovaries (ex vivo IVM) - 3 h transportation in ice . Duration : 2007 - 2014	Maturation Outcomes of use	. Maturation started to be obtained after 3 year-old towards . 36% maturation , 65% fertilization in 8 patients, in 79% of patients FP was possible . 1 live birth from a 26 yo patient of 1 embryo thawed derived from IVM	ex vivo IVM procedure is feasible with possibility of success	Prepubertal patient population and post pubertal should be cited as a feasibility method for younger patients when ovariectomy is indicated
(Sermondade, et al., 2019)	OBS MODERATE	. Case series BC patients undergoing IVM for FP . 18-35 yo (n=54), before starting chemotherapy . Measurement serum AMH (mean AMH levels 1.9 ng/ml , AFC (mean AFC numbers 12.5),	Multivariable analysis correlation between ovarian reserve parameters with oocytes retrieved IVM: no stimulation + hCG Duration : 2013 - 2015	number of oocytes retrieved maturation rates	. Positive correlation of AMH and AFC with COC recovered (0.43 and 0.41, p<0.001) . Positive correlation of AMH and AFC with MII oocytes after IVM (0.35 and 0.52, p<0.01) . Positive correlation with AMH and AFC with primordial fol pool, mainly for AMH (0.39 and 0.30, p<0.01) . Positive correlation between	AMH is a good predictor of primordial follicle reserve	Authors claim strong correlation. To makes such conclusion, more samples would needed to be analysed

		assessment of primordial follicle density			primordial follicle pool correlated to number of COC and MII oocytes after IVM (0.34 and 0.39, p<0.01)		
(Shirasawa, et al., 2019)		14 patients with endometrial adenocarcinoma average ages in the transportation and non-transportation groups were 40.1 +/- 2.0 and 39.6 +/- 1.8 years, respectively	Oocytes obtained from the resected ovaries of seven patients were transported with HFF by railway (transportation group). Samples of HFF from the other seven patients were not transported, and IVM was performed promptly (non-transportation group).	results of oocyte retrieval in vitro maturation (IVM) outcomes	The average numbers of collected oocytes were 8.1 +/- 8.4 and 5.1 +/- 5.1 in transportation and non-transportation groups. There was a significant negative correlation between the number of collected oocytes and age. The proportions of oocytes that reached meiosis II (maturation rate) after IVM were 38.6% and 69.2% in the transportation and non-transportation groups, respectively (P = 0.013).	the usefulness of the transportation of HFF was limited.	
(Sonigo, et al., 2016)	OBS MODERATE	Breast cancer patients undergoing IVM for FP . 18-41 yo (n=340), before starting chemotherapy. Measurement serum AMH (mean AMH levels 4.4 ng/ml . AFC (mean AFC numbers 21.4)	Multivariable analysis correlation between ovarian reserve parameters with number of oocytes retrieved IVM: no stimulation + hCG Duration : 2009-2015	number of oocytes retrieved	AFC above 28 follicles, AMH above 3,9 ng/ml are required for obtaining 15 frozen oocytes (after IVM) AFC above 20 follicles, AMH above 3,7 ng/ml are required for obtaining 10 frozen oocytes . AFC above 19 follicles, AMH above 3,5 ng/ml are required for obtaining 8 frozen oocytes . with sensitivity between 0.82 and 0.90	AMH and AFC above 3,7 ng and 20 are needed to obtain >10 oocytes. Advices a combination of OTC and IVM retrieval to optimise chances	Although not specified by authors, the patient population seems to include a significant proportion of PCOS patients
(Takae, et al., 2015)	OBS MODERATE (detailed description of all cases)	OTC+IVM n=27 . 25 - 41 yo breast cancer patients	. 15 patients underwent OTC+ ex vivo IVM at F-phase of cycle; 10 at L-phase and 2 not known . Duration : 2010 - 2014	Maturation Fertilisation	. No differences in oocyte recovery rate or maturation in F-phase (31%) vs L-phase (23%), NS . Positive correlation between AMH and number of recovered oocytes (r=0.6) and negative correlation with age =0.4)	OTC + ex vivo IVM can be performed at any phase of menstrual cycle for obtaintion of immature oocytes and is correlated with AMH and age	low maturation rate , transport at 37°C in saline solution . Animal studies: outcomes seem better when kept in cold during transport
(Uzelac, et al., 2015)	Case report	first live birth after combined IVM. Embryo not egg freezing . 23 y o cancer patient with borderline tumor	. 10 immature oocytes collected from ovary post ovariectomy for ex vivo IVM	Maturation Fertilisation Outcomes of use	4 oocytes matured and 3 embryos frozen, 2 survived and subsequently transferred 2 years later . Delivery healthy child	ex vivo IVM procedure is feaseable with possibility of succes	1 live birth embryo derived from ex vivo IVM
(Wilken-Jensen, et al., 2014)	OBS MODERATE (good details, but IVM experimental only)	n=69, good details of maturation rates . 0 - 38 yo	. 69 patients underwent OTC+ ex vivo IVM, 2-5 hours transportation in ice . Duration : 2011 - 2012	Maturation rates	Poor maturation rates of 3%	ex vivo IVM might be considered but show very poor maturation rates	May not be considered for evaluation of efficacy of ex vivo IVM but rather for technical challenges

| (Yin, et al., 2016) | OBS

MODERATE (experimental only) | oocytes from medulla, proof of concept . . 8-41 yo cancer patients (n=36) | . 393 immature oocytes collected from ovaries (ex vivo IVM) | Maturation rate

Oocytes survival rate after thawing | . More maturation from younger patients <20 yo (52% vs 29%) . Oocytes survival rate after thawing 64% | 5 hours transport in ice seems not to affect viability of oocytes after transport | |

INCLUDED AS BACKGROUND INFORMATION
(Foix-L'Helias, et al., 2014, Mostinckx, et al., 2019, Provoost, et al., 2014, Roesner, et al., 2017, Sauerbrun-Cutler, et al., 2015)

Q17 Should GnRH agonists vs. no treatment be used for ovarian protection in patients undergoing gonadotoxic treatment?

Reference	Study Type Quality	Patients	Interventions (+comparison)	Outcome measures	Effect size	Authors conclusion	Comments
(Ben-Aharon, *et al.*, 2010)	SR (no IPD) MODERATE/LOW	43 GnRHa group/40 control group; all premenopausal patients with lupus; age between 18 and 43 years; all treated with cyclophosphamide (different doses)	Chemotherapy (cyclophosphamide) with or without GnRHa; follow-up between 1 to 15 years	Efficacy endpoints: premature ovarian insufficiency (POI, defined as per primary endpoint of each trial) --> the only endpoint reporting separate results for lupus patients only	GnRHa vs. control: POI: 2% vs. 45% (RR 0.12; 95% CI 0.03-0.41; p<0.001)	GnRHa appears to improve menstruation resumption. Nevertheless, randomized prospective trials are less conclusive for their real value in conserving ovarian reserve and pregnancy.	To be considered only for benign diseases; for the RCTs in breast cancer and lymphoma patients, the metanalyses by Lambertini et al, Ann Oncol 2015 and Senra et al, Ultrasound Obstet Gynecol 2018 are larger/more updated and are the ones being considered for the recommendation
(Brunner, *et al.*, 2015)	RCT MODERATE/LOW	25 GnRHa group/6 placebo group; all premenopausal patients with lupus; median age 15.4-17.8 years (all <21 years)	Chemotherapy (cyclophosphamide) with or without GnRHa (given 4-6 days after the first dose of chemotherapy); patient-months of follow-up between 47.1 to 439.9years	Efficacy endpoint: dose of GnRHa needed to obtain complete ovarian suppression	Complete ovarian suppression in 90% of patients with the dose of 120 ug/kg	High doses of GnRHa are needed to achieve and maintain conplete ovarian suppression	To be considered as evidence for benign diseases (lupus)
(Demeestere, *et al.*, 2013)	RCT MODERATE/LOW	AMH available in a total of 37 patients out of 45 included in the GnRHa group and 39 included in the control group; all premenopausal lymphoma patients (both HL and NHL); mean age between 25.5 and 27.3 years	Chemotherapy (all types) with or without GnRHa started at least 10 days before chemotherapy; median follow-up was 5.33-5.58 years	AMH levels at 1 year, 2-4 years, and 5-7 years (plus POI rates, values of FSH/E2, post-treatment pregnancies, OS events)	AMH in GnRHa vs. control: 1) 1-year: 1.40 vs. 0.56 (p=0.40); 2) AMH at 2-4 and 5-7 years: no difference between the two groups	GnRHa is not efficient in preventing chemotherapy-induced POI in young patients with lymphoma	To be considered as evidence for impact on AMH levels (for the efficacy in terms of POI, it is being considered in the IPD metanalysis by Senra et al,

(Gilani, _et al._, 2007)	RCT LOW - Selection bias (randomization procedure not clear); performance bias (no placebo-controlled trials)	15 GnRHa group/15 control group; all premenopausal ovarian cancer patients; median age between 21 and 22 years; different histology	Chemotherapy (all types) with or without GnRHa started prior to chemotherapy; median follow-up not reported	Efficacy endpoint: premature ovarian insufficiency (POI, defined as amenorrhea at 6 months and FSH>20)	GnRHa vs. control: POI: 0% vs 33% (p=0.02)	The GnRH analog co-treatment should be considered in every woman of reproductive age receiving chemotherapy	To be considered as evidence in tumor other than breast cancer or lymphoma
(Lambertini, _et al._, 2015)	SR (no IPD) MODERATE	616 GnRHa group/615 control group; all premenopausal breast cancer patients; median age between 29 and 46 years; both ER+ and ER-patients	Chemotherapy (all types) with or without GnRHa started at least one week before chemotherapy; median follow-up variable between few months up to 7.3 years	Efficacy endpoints: premature ovarian insufficiency (POI, defined as per primary endpoint of each trial); amenorrhea rates at 1 year after chemotherapy; post-treatment pregnancies. Safety endpoints: disease-free survival (DFS)	GnRHa vs. control: 1) POI: 18.5% vs 33.5% (OR 0.36; 95% CI 0.23-0.57; p<0.001); 2) 1-year amenorrha: 31.0% vs. 42.9% (OR 0.55; 95% CI 0.41-0.73; p=0<0.001); 3) post-treatment pregnancies: 33 vs. 19 (OR 1.83; 95% CI 1.02-3.28; p=0.041); 4) DFS: HR 1.00; 95% CI 0.49-2.04; p=0.939	Temporary ovarian suppression with LHRHa in young breast cancer patients is associated with a reduced risk of chemotherapy-induced POF and seems to increase the pregnancy rate, without an apparent negative consequence on prognosis	Includes 12 of the 13 available RCTs (all except the OPTION trial)
(Lambertini, _et al._, 2018c)	SR (IPD) HIGH/MODERATE	436 GnRHa group/437 control group; all premenopausal breast cancer patients; median age 38-39 years; 40% ER+; no difference between the two groups	Chemotherapy (all types) with or without GnRHa started at least one week before chemotherapy; median follow-up 5.0 years	Efficacy endpoints: premature ovarian insufficiency (POI, defined as per primary endpoint of each trial); amenorrhea rates at 1 year and 2 years after chemotherapy; post-treatment pregnancies. Safety endpoints: adverse events, disease-free survival (DFS) and overall survival (OS)	GnRHa vs. control: 1) POI: 14.1% vs 30.9% (OR 0.38; 95% CI 0.26-0.57; p<0.001); 2) 1-year amenorrha: 36.8% vs. 40.4% (OR 0.92; 95% CI 0.66-1.28; p=0.623); 3) 2-year amenorrha: 18.2% vs. 30.0% (OR 0.51; 95% CI 0.31-0.85; p=0.009); 4) post-treatment pregnancies: 37 vs. 20 (IRR 1.83; 95% CI 1.06-3.15; p=0.030); 5) adverse events (see supplementary tables manuscript); 6) 5-year DFS: 79.5% vs. 80.0% (HR 1.01; 95% CI 0.72-1.42; p=0.999); 7) 5-year OS: 90.2% vs. 86.3% (HR 0.67; 95% 0.42-1.06; p=0.083)	Our findings provide evidence for the efficacy and safety of temporary ovarian suppression with GnRHa during chemotherapy as an available option to reduce the likelihood of chemotherapy-induced POI and potentially improve future fertility in premenopausal patients with early breast cancer	Only 5 of the 13 available RCTs provided individual patient-level data fro this study (55.2% of the potentially eligible population
(Lambertini, _et al._, 2019b)	R (not S) LOW - non-systematic review	Not applicable/28 preclinical studies included	Experiments in mice, rats, primates and human models; exposure to different chemotherapy agents with or without GnRHs	Ovarian reserve, hormonal levels, fertilization rates, embryo development, toxicity	Protective effects on different efficacy parameters observed in some experiments but not confirmed in others	The potential mechanisms of action for the protective effects of GnRHa during chemotherapy are still not clearly identified. Well-designed and adequately conducted in vitro and in vivo experiments including in species other than rodents should be further encouraged in the coming years.	To be considered only for discussing preclinical evidence/mechanism of action;
(Leonard, _et al._, 2017)	RCT MODERATE	AMH available in 37-56 patients in GnRHa (out of 103 included) and 36-53	Chemotherapy (all types) with or without GnRHa started at least one week	AMH levels at 3 months, end of treatment, 12 and 24 months (plus POI	AMH fall to 5% pretreatment levels in control group and 7% in GnRHa group (not significant)	The amount of 'saved' ovarian function is modest, but may be of	To be considered as evidence for

		(out of 118 included) in control; all premenopausal breast cancer patients; median age between 38 and 39 years; both ER+ and ER- patients (43% ER+)	(preferably 2 weeks) before chemotherapy; median follow-up not reported	rates, values of FSH/LH/E2, post-treatment pregnancies, OS events)		clinical consequence particularly in younger women where it might allow an increased opportunity for fertility.	impact on AMH levels (for the efficacy in terms of POI, it is being considered in the IPD metanalysis by Lambertini et al, JCO 2018)
(Marder, *et al.*, 2012)	CS LOW	10 GnRHa group/11 control group/27 no treatment; all premenopausal patients with lupus; median age 33.1 years	Chemotherapy (cyclophosphamide) with or without GnRHa (given at least 10 days before the first dose of chemotherapy) or no treatment; median follow-up not reported	Efficacy endpoint: AMH levels after treatment	GnRHa vs. control: 0.86 vs. 0.18 (p=0.018)	Post-treatment AMH levels were significantly higher among patients receiving GnRHa with cyclophosphamide suggesting that GnRHa co-administration mitigates cyclophosphamide-induced ovarian injury	To be considered as evidence for benign diseases (lupus) only for AMH
(Moore, *et al.*, 2019)	RCT MODERATE	105 GnRHa group/113 control group; all premenopausal breast cancer patients; median age 37.7 years; all ER-	Cyclophosphamide-containing chemotherapy with or without GnRHa started at least one week before chemotherapy; median follow-up 5.1 years	Efficacy endpoints: premature ovarian insufficiency (POI, defined as amenorrhea in the preceeding 6 months and post-menopasual FSH levels at 2 years); ovarian dysfunction and post-treatment pregnancies. Safety endpoints: adverse events, disease-free survival (DFS) and overall survival (OS)	GnRHa vs. control (updated analysis): 1) 5-year cumulative incidence of pregnancy 23.1% vs. 12.2% (OR 2.34; 95% CI 1.07-5.11); 2) DFS (HR 0.55; 95% CI 0.27-1.10); 3) OS (HR 0.45; 95% 0.19-1.04)	In this long-term analysis of POEMS/S0230, we found continued evidence that patients randomly assigned to receive goserelin plus chemotherapy were not only more likely to avoid premature menopause, but were also more likely to become pregnant without adverse effect on disease-related outcomes	To be considered for post-treatment pregnancies being the only RCT having pregnancy rate as a pre-specified secondary endpoint
(Regan, *et al.*, 2017)	RCT MODERATE/LOW	1242 GnRHa group/630 control group; all premenopausal breast cancer patients; median age 39-43 years; all ER+	Chemotherapy (all types) with or without GnRHa during chemotherapy; median follow-up 4.7-4.9 years	Safety endpoints: breast cancer-free interval (BCFI) and distant recurrence-free interval (DRFI)	GnRHa vs. control: 1) 4-year BCFI: 89.1% vs. 89.0% (HR 1.11; 95% CI 0.72-1.72; p=0.72); 2) 4-year DRFI: 90.8% vs. 90.5% (HR 0.96; 95% 0.60-1.53; p=0.86)	Neither detrimental nor beneficial effect of concurrent administration of GnRHa with chemotherapy on the efficacy of adjuvant therapy that includes chemotherapy was detected	Joint analysis of 2 RCTs designed to investigate the efficacy of different adjuvant endocrine therapy options; this is an exploratory analysis to be considered for the safety of GnRHa use during chemotherapy in ER+ breast cancer patients

(Senra, *et al.*, 2018)	SR (no IPD) MODERATE	53 GnRHa group/56 control group; all premenopausal lymphoma patients; median age approximately 25-26 years; HL all trials (except Demeestere et al: 40% were NHL)	Chemotherapy (all types) with or without GnRHa started at least one week before chemotherapy; median follow-up not reported	Efficacy endpoints: premature ovarian insufficiency (POI, defined as per primary endpoint of each trial); post-treatment pregnancies. Safety endpoints: none.	GnRHa vs. control: 1) POI: 18.9% vs 32.1% (OR 0.70; 95% CI 0.20-2.47; p=0.58); 2) post-treatment pregnancies: 17 vs. 18 (IRR 1.13; 95% CI 0.66-1.93; p=0.66)	Evidence, albeit of low quality, supports the use of GnRHa before and/or during chemotherapy to reduce the risk of POI and increase the probability of spontaneous pregnancy in the short term. Further high quality RCTs with more accurate assessment of ovarian reserve are needed to support definitive recommendations for clinical practice.	To be considered only for the lymphoma RCTs; for the breast cancer RCTs, the metanalysis by Lambertini et al, Ann Oncol 2015 is larger/more updated and is the one being considered for the recommendation
(Sinha, *et al.*, 2018)	CS (prospective) LOW	45 GnRHa group/43 control group; all premenopausal breast cancer patients; median age 35 years; both ER+ and ER- patients (61% ER+)	Chemotherapy (all types) with or without GnRHa during chemotherapy; median follow-up not reported	Efficacy endpoint: antral follicle count (AFC)	Maximum ovarian recovery to 56% of their baseline AFC 7-9 months after chemotherapy as compared to 27% in the control group by 3-5 years (p=0.032)	Treatment with GnRHa during chemotherapy is assoaciated with higher degree of AFC recovery; findingings useful for counselling patients when fertility preservation care is not possible or have limited oocyte yeld	To be considered only for AFC (potential impact in preserving ovarian reserve)
(Wilson, *et al.*, 2016)	RCT MODERATE/LOW Performance bias (no placebo-controlled trials); attrition bias (not all included patients were analyzed)	Bone markers available in 26-34 patients in GnRHa (out of 103 included) and 31-32 (out of 118 included) in control; all premenopausal breast cancer patients; median age between 38 and 39 years; both ER+ and ER- patients (43% ER+)	Chemotherapy (all types) with or without GnRHa started at least one week (preferably 2 weeks) before chemotherapy; median follow-up not reported	Bone markers (BALP and NTX) levels at 6, 12, 18, 24, 36 months (plus POI rates, values of FSH/LH/E2/AMH, post-treatment pregnancies, OS events)	GnRHa vs control: 1) NTX at 6 months (57.82 vs. 40.81; p=0.0074) with normalization thereafter; 2) BALP at 36 months (5.845 vs. 8.5; p=0.0006)	Addition of GnRHa to chemotherapy increases bone turnover during treatment with normalization after cessation of treatment suggesting GnRHa may offer sufficient ovarian protection against chemotherapy-induced POI to negate longstanding altered bone turnover associated with POI	To be considered as evidence for bone safety (for the efficacy in terms of POI, it is being considered in the IPD metanalysis by Lambertini et al, JCO 2018; for the efficacy in terms of AMH is being considered as Leonard et al, Ann Oncol 2017)

INCLUDED AS BACKGROUND INFORMATION
(Behringer, *et al.*, 2005, Webber, *et al.*, 2016)

Q18 Should Transposition of ovaries vs. no treatment be used for ovarian protection?

Reference	Study Type	Patients	Interventions	Outcome measures	Effect size	Authors conclusion	Comments
(Du and Qu, 2017)	obs - retrospective	86 young patients with cervical cancer who received radical hysterectomy and ovarian transposition	13 wo underwent OT unilat and 73 bilateral. 65 patients with pathological high-risk factors were administered adjuvant radiotherapy-20 of them received three-dimensional conformal radiotherapy (Observation Group A), 24 patients received IMRT with no limitation on radiation dose to ovaries (Observation Group B), and 21 patients underwent IMRT with limited radiation dose(V10 <20%) to ovaries (Observation Group C). Twenty-one patients without any predetermined high-risk factors did not received radiation therapy (Control Group D).	relationship between ovarian function and ovarian limited dose in radiotherapy the novel ovarian dose limit for a better preservation of ovarian function in intensity-modulated radiation therapy (IMRT) was determined.	The levels of sexual hormones (E2 , P, FSH, LH) before radiation, postradiation, 3 month, and 6 month after the radiation therapy in patients from all three observation groups were significantly lower than those in patients of the control group (P < 0.05). There was no statistically significant difference in the levels of sex hormones in patients of the control group at different time points (P > 0.05). Within each observation group, there was a statistically significant difference in the sex hormone levels in patients before the radiation and after the radiation (P < 0.05); however, when data from all three observation groups were compared, only the difference in the levels of FSH and LH between the patients from Group A and Group C was statistically significant (P < 0.05). The results of receiver-operating characteristic (ROC) curve analysis suggested that limiting ovarian radiation dose to V7.5 < 26% in IMRT prevents the disruption of ovarian function (area under ROC curve was 0.740, confidence interval [CI] = 0.606-0.874).	In young patients with cervical cancer who underwent radical hysterectomy and ovarian transposition without receiving adjuvant radiotherapy, ovarian endocrine function was well preserved. In patients who received any type of postoperative radiotherapy, ovarian function was affected, suggesting that the standard ovarian limited dose used in IMRT disrupted ovarian function. The results of the ROC curve analysis suggested that the new optimal dose limit of V7.5 < 26% should be used in IMRT to preserve ovarian function (P = 0.003).	
(Gomez-Hidalgo, et al., 2015)	Case report	two cases of ovarian torsion as complication					
(Grabenbauer, et al., 1991)	Observational study	female patients of child bearing age receiving total lymphoid irradiation including pelvic and inguinal nodes for Hodgkin diseases. 15/17 patients underwent prophylactic bilateral oophoropexy during staging laparotomy: 10 had lateral, 5 had midline ovarian transposition.	Medial versus lateral ovarian transposition	Reproductive and ovarian function was investigated in 13 patients	Normal cyclic ovarian activity was found in seven out of nine patients following lateral oophoropexy (including one pregnancy), but only in one out of four cases after midline fixation. Median calculated dose was 325 cGy (range 260 to 500 cGy) to the laterally fixed ovaries and 490 cGy (range 390 to 500 cGy) for midline transposition.	lateral ovarian transposition resulted in better outcomes	

(Gubbala, et al., 2014)	Review	Summary of indications presented			Ovarian transposition resulted in preservation of ovarian function in 90% of patients (different outcome measures across studies though)		
(Hoekman, et al., 2019)	review	Fertile women undergoing ovarian transposition prior to pelvic radiation therapy. 38 eligible studies with a total of 765 patients.	studies, containing >5 patients, treated with OT prior to radiation therapy.	Primary outcome was the ovarian function after radiotherapy and ovarian transposition. Secondary outcomes were complication-rate.	ovarian survival (OS) after ovarian transposition (OT) and EBRT ranged from 20% to 100%. The median follow-up ranged from 7 to 102 months. OS was higher after OT and brachytherapy (OS 63.6-100%) when compared to OT and EBRT (20-100%) and OT concomitant chemoradiotherapy (0-69.2%). Only 22 studies (with 112 patients) reported on complications: among these studies the complication-rate was 0%-28.6%.	preservation of ovarian function after OT prior to EBRT is successful in 20-100% of patients. Most favorable outcome with regard to preservation of ovarian function is seen in patients after OT and BT, followed by OT and EBRT and OT and RT combined with chemotherapy.	
(Hoekman, et al., 2018)	retrospective control study	women 27 women (aged < 45 years) after OT (prior to pelvic radiation) and 29 controls (ie women diagnosed with cervical cancer and treated with hysterectomy/trachelectomy and radiation therapy) Women were censored at recurrence.		The 5 years OS rate was calculated, with a sub-analysis for age (25-30; 31-35 and 36-40 years). Ovarian failure	The radiation dose was 44.8 Gy (25.0-63.0 Gy) and 46.3 Gy (45.0-50.0 Gy), respectively. The 5-year ovarian survival rate was 60.3% versus controls 0% (p < 0.001 95% CI 3.48-11.50). Despite the decrease in ovarian survival after OT with increasing age, in all age groups (25-30, 30-35 and 35-40) ovarian survival after OT was significantly better compared to women without OT (p = 0.001; p = 0.004 and p = 0.000, respectively). Neither intra-vaginal radiation therapy of concomitant chemotherapy in addition to pelvic radiation significantly altered ovarian survival.	ovarian transposition prior to pelvic radiation is effective in women until the age of 35 years	effectiveness of ovarian transposition (OT) prior to radiation therapy (RT) and to evaluate the effect of age on ovarian survival (OS) after OT.
(Huang, et al., 2007)	observational	14 consecutive cases of premenopausal women with a gynecologic malignancy requiring pelvic irradiation	Laparoscopic surgery was conducted to transpose bilateral ovaries. Ovaries were transposed to a high anterolateral position, 3-4 cm above umbilical line.		No conversion to laparotomy. The mean operating time was 128 min (range, 83-181 min) and average blood loss was 74 mL (range, 10-150 mL). No intraoperative or immediate postoperative complication was observed. The mean follow-up period was 72 months (range, 42-142 months) and only one of the seven (14.29%) patients under 39 years old became ovarian failure after receiving concurrent chemoradiation.	simple and safe procedure	new method of laparoscopic ovarian transposition
(Jang, et al., 2019)	Case report	A 24-year-old nulligravid patient recently diagnosed with colorectal carcinoma underwent ovarian transposition prior to radiation.	IVF		Right ovary demonstrated nonviability due to failed transposition and radiation. Left ovarian oocytes were not able to be harvested due to risk of left kidney puncture via transvaginal ultrasound [TVUS]. Interventional Radiology [IR] was involved and performed a transabdominal US guided egg retrieval which led to successful IVF.		
(Moawad, et al., 2017)	Systematic review	79 articles identified, 55 selected, available data up to 2017			Summary of indications and techniques,surgical clips should be placed. 2 reports of spontaneous intrauterine pregnancies (2 refs), 2 reports (2 refs) ART treatments and 3 reports of oocyte retrieval and surrogate pregnancy		

					(3 ref), and combination of methods with cryopreservation + cases of complications such metastasis (2 refs), benign cysts requiring oophorectomy in 2 pat and 2 ovarian metastasis of cervical cancer 3 years after treatment		
(Morice, et al., 1998)	prospective study	27 women with cervical cancer (treated with surgery, bilateral ovarian transposition and radiotherapy) and 10 women with ovarian dysgerminoma (treated with surgery, unilateral ovarian transposition and radiotherapy)		pregnancy rates	pregnancy rates: 15% (4/27) and 80% (8/10) 3 women underwent repositioning of the ovaries after persistent infertility, with pregnancy achieved in one of them. The median time interval between the end of tumour treatment and the first conception was 4.3 years (range 2-7 years). Of 18 pregnancies, 5 ended in a miscarriage (28%) and 13 successful pregnancies produced 15 liveborn children		
(Selvaraj, et al., 2019)	Case report	31-year-old woman with PCOS	modified radical hysterectomy and right ovarian transposition to the anterior abdominal wall for endometrioid adenocarcinoma Grade II.		Three cycles of IVF were performed using GnRH antagonist in the first two attempts and GnRH agonist in the third attempt, with percutaneous technique of oocyte retrieval from the transpositioned right ovary. In the third attempt, 5 oocytes were retrieved and subsequently froze 3 embryos and 1 blastocyst. The surrogate underwent sequential transfer which resulted in a positive clinical singleton pregnancy and delivery		
(Terenziani, et al., 2009)	Retrospective evaluation	ov transposition in 11 women with Hodgkin's lymphoma (ovarian transposition at a median age of 13 years.)	The ovaries were positioned behind the uterus		14 pregnancies, with 12 live births (1 twin) and 3 miscarriages. None of these women needed the ovaries to be relocated, and none of them resorted to artificial insemination. Their median age at the time of first pregnancy was 31 years, and the median time elapsing since ovarian transposition was 14 years.	oophoropexy can preserve ovarian function and enable future pregnancy.	
(Yin, et al., 2019)	retrospective analysis	118 patients with cervical cancer who received a radical hysterectomy and ovarian transposition before pelvic irradiation: 105 patients underwent IMRT with a limited radiation dose to the ovaries; 48 of these patients received unilateral ovary limitation, while 57 received bilateral ovary limitations.		sex hormone levels (estrogen [E2], follicle stimulating hormone [FSH]) and menopausal symptoms one year after their radiation therapy.	41 out of 105 patients (39.0%) who underwent IMRT with a limited radiation dose to the ovaries preserved their normal ovarian function. The cutoff dose of comparatively lower side ovarian maximum dose was 9.985Gy and the cutoff of mean dose was 5.32Gy. The optimal dose-volume constrains to ovaries was V5.5 < 29.65%. Age </= 38 (P = 0.001) was an independent predictors of ovarian function	Using IMRT, preservation of ovarian function was possible when the limited dose was as low as possible to the ovaries regardless of bilateral or unilateral limitation to the ovaries. The ovarian maximum dose of less than 9.985Gy, the mean dose less than 5.32Gy and V5.5 < 29.65% could be better at preventing ovarian dysfunction. Patients younger than 38 years old were more likely to keep normal ovarian function while limited ovarian side numbers did not appear to exert an obvious effect.	

INCLUDED AS BACKGROUND INFORMATION

(Koh*, et al.*, 2019, Lee*, et al.*, 2006a, Oktay*, et al.*, 2018, Wallace*, et al.*, 2005b)

Q22 What is the effect of previous gonadotoxic treatments/underlying condition on obstetric outcomes? (not necessarily FP or ART)

Reference	Study Type	Patients	Interventions (+comparison)	Outcome measures	Effect size	Authors conclusion	Comments
(Akhtar, *et al.*, 2015)	retrospective analysis	All female patients age 14–40 years (at HDC =high dose chemotherapy auto-SCT) who underwent HDC auto-SCT for diffuse large B-cell lymphoma and Hodgkin L from 1997 to December 2012 included Median age of patients at HDC auto-SCT was 25 years (14–40 years).	Median follow-up from HDC auto-SCT was 65 months (24– 190 months), HL in 71 (80%) and diffuse large B-cell lymphoma in 18 (20%). Primary chemotherapy was adriamycin, bleomycin, vinblastin and dacarbazine (ABVD) in 60 (68%) and cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) in 16 (18%; Table 1). Median number of chemotherapy cycles before HDC was 10 for these 89 patients; same as for those who actually became pregnant (9.5 cycles).		176 females underwent HDC auto-SCT. 87 were excluded: 62 were dead at the time of this analysis (32/62 persistent/progressive disease, 8/62 treatment-related mortality, 16/62 died due to relapsed disease within 24 months and 6/62 died of an other reason). Eighteen were 440 years, three had active disease and four with no information. Finally, 89 patients (424 months follow-up) were evaluable for both menstrual cycles and pregnancy .Twenty-six patients (65%) became pregnant 50 times (range 1–6 times). Median age at first pregnancy post-HDC auto-SCT was 27 years (range 20–37 years) ; Of these 50 pregnancies, 43 (86%) were live births and 7 (14%) miscarriages, including 1 still birth (at 28 weeks).The first pregnancy was observed from 5 to 114 months after HDC auto-SCT;Birth defects were observed in two live births as reported by the patients	Our patients have uniform treatment and no TBI.16 We have only included patients o40 years old at HDC auto-SCT. We have observed 29% pregnancy in the entire potential group of 89 patents and 65% pregnancy in those patients who actually tried (40 patients) to become pregnant. This is the highest incidence of pregnancies ever reported after HDC auto-SCT. Furthermore, 86% normal pregnancies and 14% miscarriage +stillbirths is almost the same in this group of patients as observed before auto-SCT (12%). Our data highlights a significantly higher than perceived incidence of successful pregnancies with normal deliveries after auto-SCT in patients younger than 40 years.	
(Anderson, *et al.*, 2017a)	**Details of this publication are included in Table 11**						
(Bentivegna, *et al.*, 2016b)	Systematic Review	944 pregnancies were analysed	Patient with invasive cervical cancer stage IB underwent vaginal minimally invasive trachelectomy vs laparotomic radical trachelectomy		The overall live birth rate and prematurity rate were 70% and 38 %. The pregnancy rate was higher in women who had vaginal minimally invasive trachelectomy but live birth rate was similar. The prematurity rate was lower in women who had undergone simple trachelectomy/ cone resection and neoadjuvant chemotherapy compared with conservative surgeries. Most of the premature deliveries were secondary to rupture of membranes.	Prematurity rate ranged from 39% to 57% according to the radical trachelectomy used. Therefore couple who decide to conceive should be followed in a centre with mternity service well versed in the management of high preterm and low birth weight infants. The pathogeneisis of these fetal losses is related to the shortened uterine cervical lenght.In the second	Search literature 1987-2016

						trimester these loss were due to PROM secondary to clinical and subclinical chorioamnionitis. There was a consensus in promoting a delivery via Caesarean section and massiva cervical bleeding was reported after vaginal delivery.	
(Bentivegna, et al., 2016a)	systematic review	1150 early-stage epithelial ovarian cancer (EOC) and 139 relapsing patients reported by 21 teams. Borderline ovarian tumours and non-EOCs were excluded	fertility-sparing surgery (FSS)		This conservative treatment can be safely carried out for stage IA and IC grade 1 and 2 disease and stage IC1 according to the new FIGO staging system. Nevertheless, the number of patients reported with grade 2 disease is too small to definitively confirm whether FSS is safe in this subgroup. For patients with 'less favourable' prognostic factors (grade 3 or stage IC3 disease), the safety of FSS could not be confirmed, but patients should be informed that radical treatment probably may not necessarily improve their oncological outcome, because the poorest survival observed could be related to the natural history of the disease itself and not specifically to the use of conservative therapy. FSS could probably be considered in stage I clear-cell tumours but should remain contraindicated for stage II/III disease (whatever the histologic subtype).		
(Brandt, et al., 2019)	review	transgender men who are ≥35 years old, termed the "new" advanced paternal age	review of preconception care and focus on fertility issues, the impact of stopping gender-affirming hormonal treatment, and age-appropriate health maintenance. Review of antepartum and postpartum care, including labour and delivery, monitoring for perinatal depression, contraception, and chest feeding.	obstetrical care for transgender men with advanced paternal age	The psychological impact of pregnancy on gender dysphoria is unknown. The profoundly gendered experience of pregnancy, including labour and delivery, is likely be exacerbate the dysphoria. It can be assumed that the rates of depression during pregnancy and postpartum are higher for transgender men, but the prevalence and long-term impact is unknown. A key element of the postpartum care for transgender men is follow up. The recently delivered transgender man may benefit from more frequent assessment during the puerperium. In addition, the obstetrical provider needs to ensure a seamless transition from postpartum care to the team of gender affirming providers that manage his medical and gynecologic healthcare needs. There is limited data about the obstetrical management and outcomes for transgender men who are ≥35 years old. Most aspects of the obstetrical care for transgender men with advanced paternal age are similar to the care of pregnant women with advanced maternal age.		
(Chao, et al., 2011)	SR/retrospective analysis	67 patients with early stage of endometrial cancer (grade 1 and 2)	group 1 conceived after ART and group 2 after IUI or naturally		group 1 had 23 livebirths (4 twins and 2 triplets) and group 2 had 54 livebirths (2 twins and 1 triplets)Group 1 had more multiple gestations,	There was no consensus on when to start ART as soon as the patient achieved	1990-2005 retrospective analysis and

		conceived after conservative treatment (progestagin treatments).			preterm labour, caesarean section and obstetrical complications than group 2	remission or after 2 consecutive negative endometrial samplings 3-6 months apart. F/U every 3-4 months by ultrasound. This meta-analysis shows a significant increase in hypertensive disorders, preterm labour, multiple pregnancies and caesarean section in women who conceived after ART but no difference was shown in placental abnormalities, placental abruption or fetal chromosomal abnormali-ties. Long term surveillance is required even after delivery for the risk of recurrence of endometrial cancer. Recurrences are more common within a median of 40 months in patients preserving fertility. hysterectomy for the purpose of avoiding recurrence after childbearing is proposed.	Medline search (1968-2005)
(Colombo, et al., 2016)	Consensus statement	European Society for Medical Oncology (ESMO), European SocieTy for Radiotherapy & Oncology (ESTRO) and European Society of Gynaecological Oncology (ESGO) consensus conference on endometrial cancer			Recommendation 2.10: Patients not undergoing hysterectomy should be re-evaluated clinically every 6 months Level of evidence: IV Strength of recommendation: B Consensus: 97.3%(36) yes, 2.7%(1) abstain (37 voters) Recommendation 2.11: After completion of childbearing, a hysterectomy and salpingo-oophorectomy should be recommended. The preservation of the ovaries can be considered depending on age and genetic risk factors Level of evidence: IV Strength of recommendation: B Consensus: 100% yes (37 voters)	
(Critchley and Wallace, 2005)	Narrative review	Impact of Cancer Treatment on Uterine Function				Narrative review on the topic	
(do Rosario, et al., 2006)	retrospective analysis	We retrospectively analyzed 78 pregnancies of 66 women submitted to total thyroidectomy,	In all patients, conception occurred one year after ablative therapy (mean of 30 months). Age ranged form 19 to 36 years		The patients were maintained on suppressive levothyroxine therapy (TSH< 0.3 mIUII) even during pregnancy. Four (5.1%) of the 78 pregnancies resulted in spontaneous abortions without apparent cause. Three (4%) of the 74	We conclude that pregnancies that occur 12 months after ablative therapy are safe	

		followed by radioiodine therapy (3.7–5.5 GBq 131I, mean 4.64 GBq).	(mean of 30.6 years) at the time of radioiodine treatment and from 23 to 39 years (mean of 32.8 years) at the time of conception.		deliveries were preterm, two at 32 and one at 33 weeks of gestation, and there was no case of stillbirth. The birthweight was > 2500 g in 94.6% of the children (mean ± SD: 3350 ± 450 g). Only one infant (1.3%) presented an apparent malformation at birth (intraventricular communication), while no anomaly was diagnosed during the first year of life in the other children.	
(Fossa, *et al.*, 2005)	**Details of this publication are included in Table 11**					
(Gunderson, *et al.*, 2012)	SR	hormonal treatment (progestigins) in grade 1 adenocarcinoma and endometrial hyperplasia	F/U of 39 months		38 studies provided pregnancy data; out of 315 patients 114 (36.2%) become pregnant at least once; 41% with complex hyperplasia and 34.8% with carcinoma. Out of 114 pregnancy there were 117 live births.	reproductive outcomes do not seem to differ between the cohorts.	
(Haggar, *et al.*, 2013)	retrospective controlled analysis	Selection of cancer survivors was based on the following criteria: diagnosed with histologically confirmed CRC in the study period 1 January 1982 to 31 December 2007; underwent CRC surgery; had a pregnancy following their CRC surgery; and resident in WA at time of both cancer diagnosis and pregnancy. A 1-year wait period between final cancer treatment and estimated date of conception was imposed.	The study population included 232 CRC survivors who subsequently had a pregnancy. Of these, 153 (66 %) women underwent open CRC surgery and 79 (34 %) were treated laparoscopically.		Women in the treatment groups were more likely to be aged older than 30 years at time of delivery, to be of lower parity (more likely to be having a first pregnancy).In comparison with those treated laparoscopically, women with a history of open surgery had a significantly higher risk of antepartum hemorrhage (ORs versus no cancer: 2.13 versus 1.25) and postpartum hemorrhage (ORs versus no cancer: 3.31 versus 1.61). compared with those having no cancer history. we found history of radiation therapy for CRC to be a significant independent predictor of composite maternal outcomes (OR 4.24, CI 2.19–8.23) and composite neonatal outcomes (OR 2.81, CI 1.09–7.25). Chemotherapy was marginally associated with adverse maternal outcome (OR 1.11, CI 1.00–1.23). However, we found no evidence to link chemotherapy and adverse neonatal outcomes, although the confidence intervals were wide (OR 0.98, CI 0.34–2.57).resected rectal cancer was associated with both composite adverse outcomes (maternal outcomes: OR 3.73, CI 1.36–10.26; neonatal outcomes: OR 2.73, CI 1.30–5.72). Open CRC surgery was also associated with both composite adverse outcomes (maternal outcomes: OR 1.54, CI 1.30–1.83; neonatal outcomes: OR 1.29, CI 1.10–1.53).Women with a history of CRC treated by either open or laparoscopic surgery had a significantly higher risk than women with no cancer history of antepartum hemorrhage (open: OR 2.13, CI 1.97–3.32; laparoscopic 1.25, CI 1.19–1.36), postpartum hemorrhage (open: 3.31, CI 2.78–3.93; laparoscopic: 1.61, CI 1.46–1.77), and Cesarean delivery (open: 4.24, CI 1.32–13.6; laparoscopic: 2.42, CI 1.94–3.15).	Previous CRCs, particularly rectal and radiation-treated tumors, appear to confer an increased likelihood of adverse outcomes in subsequent pregnancies. Laparoscopic technique for CRC surgery may reduce adverse gestational outcomes. The site of surgery was also associated with worse outcome, with women undergoing rectal surgery having an increased risk of adverse outcomes compared with those who underwent colonic resections.	Retrospective cohort study compared maternal and neonatal outcomes of first postcancer pregnancies among women CRC survivors against randomly selected pregnancies of women with no cancer history (study period 1983–2007)

				Open but not laparoscopic surgery imparted significantly elevated risks for gastrointestinal obstruction (1.17; CI 1.08–1.27), spontaneous abortion (1.26, CI 1.04–1.52), and prolonged postpartum hospitalization (3.11, CI 1.42–7.73).		
(Hartman and Eslick, 2016)	Meta-analysis	patients diagnosed with breast cancer during pregnancy or up to 5 years postpartum 41 studies met our inclusion criteria (cases = 4929; controls = 61,041)		overall (OS) and disease-free survival (DFS	There was an overall increased risk of death amongst patients compared to non-pregnant controls [HR 1.57; 95 % CI 1.35-1.82]. Subgroup analysis indicated poor survival outcomes for those diagnosed either during pregnancy or postpartum (PABC) [HR 1.46; 95 % CI 1.17-1.82] as well as those diagnosed during pregnancy alone [HR 1.47; 95 % CI 1.04-2.08]. Those diagnosed postpartum had the poorest overall survival [HR 1.79; 95 % CI 1.39-2.29]. Similarly, patients with PABC had decreased DFS compared to controls [HR 1.51; 95 % CI 1.22-1.88]. Those diagnosed postpartum were the most at risk of disease progression or relapse [HR 1.86; 95 % CI 1.17-2.93]. 19 studies met our inclusion criteria (cases = 1829; controls = 21,907) for pregnancy following breast cancer diagnosis. Such women had a significantly reduced risk of death compared to those who did not become pregnant [pHR 0.63; 95 % CI 0.51-0.79]. A subgroup analysis to account for the "healthy mother effect" generated similar results [pHR 0.65; 95 % CI 0.52-0.81].	Pregnancy that occurs before or concurrently with a diagnosis of breast cancer is more likely to result in death and decreased disease-free survival. On the other hand, pregnancy occurring after a breast cancer diagnosis reduces the risk of death.	
(Hartnett, *et al.*, 2018)	Retrospective study	Women who conceived their first pregnancy after diagnosis between ages 20 and 45 years with any invasive cancer or ductal carcinoma in situ		risks of adverse pregnancy outcomes.:	Women who conceived </=1 year after starting chemotherapy for any cancer had higher risks of preterm birth than comparison women (chemotherapy alone: relative risk [RR], 1.9; 95% confidence interval [CI], 1.3-2.7; chemotherapy with radiation: RR, 2.4; 95% CI, 1.6-3.6); women who conceived >/=1 year after starting chemotherapy without radiation or >/=2 years after chemotherapy with radiation did not. In analyses imputing the treatment end date for breast cancer survivors, those who conceived >/=1 year after finishing chemotherapy with or without radiation had no higher risks than women without cancer. The risk of preterm birth in cervical cancer survivors largely persisted but was somewhat lower in pregnancies conceived after the first year (for pregnancies conceived </=1 year after diagnosis: RR, 3.5; 95% CI, 2.2-5.4; for pregnancies conceived >1 year after diagnosis: RR, 2.4; 95% CI, 1.6-3.5).	: In women who received chemotherapy, the higher risk of preterm birth was limited to those survivors who had short intervals between treatment and conception	
(Hauerberg, *et al.*, 2015)	Prospective data	120 unselected consecutive Vaginal Radical Trachelectomies (VRT)		Oncologic, fertility and obstetrical outcomes	85.8% of the patients had stage IB1 disease, 68.3% squamous cell carcinomas, 30.0% adenocarcinomas and 1.7% adenosquamous carcinomas. Six recurrences (5.1%) and 2 deaths (1.7%) occurred. Four women with	This unselected national single center referral study confirms the oncological safety of Vaginal Radical Trachelectomy.	

					adenocarcinomas (10.5%) had recurrences, compared to two women with squamous cell carcinomas (2.5%). Seventy-two women (60.0%) desired to conceive and 55 women obtained a total of 77 pregnancies. Of the 72 women 40 were referred to fertility treatment. First and second trimester miscarriage rates were 21.6% and 2.7%, respectively. A total of 53 children were born of which 41 were delivered after gestational week 34.		
(Iqbal, et al., 2017)	population-based, retrospective cohort study	7553 women included ; excluded the following: women younger than 20years and 45 years or older, women with a history of hysterectomy or oophorectomy and with a history of previous cancer (except skin cancer) and women with stage 0 or unknown stage breast cancer.	From January1,2003,to December31,2014. ; 5 years F/U		The mean age at diagnosis of breast cancer was 39.1years (median,40 years; range, 20-44years); Of all women, 5832 (77.2%) had no pregnancy, 1202 (15.9%) had 1 pregnancy, 398 (5.3%) had 2 pregnancies, and 121 (1.6%) had 3 pregnancies or more from 5 years before, until 5 years after, the index date of diagnosis of breast cancer; 1302 women (17.2%) had a live birth, 14 (0.2%)had a stillbirth, and 700 (9.3%) had an abortion; Most abortions (94%) occurred before the diagnosis; The5-year actuarial survival rate was 96.7% (95%CI, 94.1%-99.3%) for women who had a live birth or stillbirth 6 months or more after diagnosis of breast cancer (vs 87.5% [95%CI, 86.5%-88.4%] for women with no pregnancy) (age-adjusted HR,0.22; 95%CI, 0.10-0.49;P<.001);The annual absolute mortality rate for women who had livebirth or stillbirth 6 months or more after diagnosis was 0.5%.	Pregnancy did not adversely affect survival in women with breast cancer. The ER status is the strongest factor that discriminates between pregnancy-associated breast cancer and breast cancer in non pregnant women. However, adjusting for the ER status did not influence the risk of death. For breast cancers survivors who wish to conceive, the risk of death is lowest if pregnancy occurs 6months or more after diagnosis.	
(Ishioka, et al., 2018)	retrospective	Patients with an ultra-short uterine cervix as a result of large conization, repeated conization or radical trachelectomy (RT), who had undergone transabdominal cerclage (TAC) of the uterine cervix . All patients had a history of second trimester fetal loss or early preterm delivery as a result of cervical incontinence after a uterine cervical operation, and a lack of space to perform transvaginal cerclage.		TAC was performed safely without any complications. The mean operative duration was 53 10 min, and the mean blood loss during the operation was 49 64 mL. Seven women conceived within 2 years after TAC. Their pregnancy courses were favourable. Five of the women underwent scheduled caesarean sections, while two pregnancies are ongoing.	A retrospective review of 11 cases in which TAC was performed between 2013 and 2016 at Sapporo Medical University Hospital was conducted	Although there are risks of various complications as a result of the use of non-absorbable thread and the need for two extra laparotomies, TAC can be a safe and useful option for patients who show cervical incompetence after large uterine cervical operations, such as RT or large conization. With the development of conservative operations for invasive uterine cervical cancer, the importance of TAC will increase. It is important that a common consensus on this treatment modality is reached to improve obstetric prognosis and prevent unexpected complications.	

(Ji, *et al.*, 2016)	Details of this publication are included in Table 11					
(Kyrgiou, *et al.*, 2017)	Systematic Review and meta analysis	All studies reporting on obstetric outcomes (more than 24 weeks of gestation) in women with or without a previous local cervical treatment for any grade of CIN or early cervical cancer (stage IA1) were included. Treatment included both excisional and ablative methods. Studies that had no untreated reference population, reported outcomes in women who had undergone treatment during pregnancy or had a high-risk treated or comparison group, or both were excluded	women who had treatment for cervical cancer vs. general population

included 69 studies (6,357,823 pregnancies: 65,098 pregnancies of treated and 6,292,725 pregnancies of untreated women). | Pregnancy / obstetric outcomes | Women who had treatment were at increased overall risk of preterm birth (PTB) (less than 37 weeks) (10.7% versus 5.4%, RR 1.75, 95% CI 1.57 to 1.96, 59 studies, 5,242,917 participants, very low quality), severe (less than 32 to 34 weeks) (3.5% versus 1.4%, RR 2.25, 95% CI 1.79 to 2.82), 24 studies, 3,793,874 participants, very low quality), and extreme prematurity (less than 28 to 30 weeks) (1.0% versus 0.3%, (RR 2.23, 95% CI 1.55 to 3.22, 8 studies, 3,910,629 participants, very low quality), as compared to women who had no treatment. The risk of overall prematurity was higher for excisional (excision versus no treatment: 11.2% versus 5.5%, RR 1.87, 95% CI 1.64 to 2.12, 53 studies, 4,599,416 participants) than ablative (ablation versus no treatment: 7.7% versus 4.6%, RR 1.35, 95% CI 1.20 to 1.52, 14 studies, 602,370 participants) treatments and the effect was higher for more radical excisional techniques (less than 37 weeks: cold knife conisation (CKC) (RR 2.70, 95% CI 2.14 to 3.40, 12 studies, 39,102 participants), laser conisation (LC) (RR 2.11, 95% CI 1.26 to3.54, 9studies, 1509 participants), large loop excision of the transformation zone (LLETZ) (RR 1.58, 95% CI 1.37 to 1.81, 25 studies, 1,445,104 participants). The risk of overall prematurity increased with increasing cone depth (less than 10 mm to 12 mm versus no treatment: 7.1% vs 3.4%, RR 1.54, 95% CI 1.09 to 2.18, 8 studies, 550,929 participants, very low quality; more than 10 mm to 12 mm versus no treatment: 9.8% versus 3.4%, RR 1.93, 95% CI 1.62 to2.31, 8 studies, 552,711 participants, low quality ;more than15mm to 17mm vs no treatment: 10.1 vs 3.4%, RR2.77, 95% CI 1.95 to 3.93, 4 studies, 544,986 participants, very low quality; 20 mm or more versus no treatment: 10.2% versus 3.4%, RR 4.91, 95% CI 2.06 to 11.68, 3 studies, 543,750 participants, very low quality).pPROM (6.1% versus 3.4%, RR 2.36, 95% CI 1.76 to 3.17, 21 studies, 477,011 participants, very low quality), low birth weight (7.9% vs 3.7%, RR 1.81, 95% CI1.58 to 2.07, 30 studies, 1,348,206 participants, very low quality), NICU admission rate(12.6% vs 8.9%, RR 1.45, 95% CI 1.16 to 1.81, 8 studies, 2557 participants, low quality) and perinatal mortality (0.9% versus 0.7%, RR 1.51, 95% CI 1.13 to 2.03, 23 studies, 1,659,433 participants, low quality) were also increased after treatment. | Women with CIN have a higher baseline risk for prematurity. Excisional and ablative treatment appears to further increases that risk. The frequency and severity of adverse sequelae increases with increasing cone depth and is higher for excision than it is for ablation. However,theresultsshouldb einterpretedwithcautionast heywerebasedonloworveryl owquality(GRADEassessmen t)observational studies, most of which were retrospective. | |

(Lambertini, et al., 2018b)	Case-control study	333 patients with pregnancy after breast cancer were matched (1:3) to 874 nonpregnant patients of similar characteristics, adjusting for guaranteed time bias.		Safety of pregnancy Survival estimates were calculated using the Kaplan-Meier analysis;	At a median follow-up of 7.2 years after pregnancy, no difference in disease-free survival was observed between pregnant and nonpregnant patients with ER-positive (hazard ratio [HR] = 0.94, 95% CI = 0.70 to 1.26, P = .68) or ER-negative (HR = 0.75, 95% CI = 0.53 to 1.06, P = .10) disease. No overall survival (OS) difference was observed in ER-positive patients (HR = 0.84, 95% CI = 0.60 to 1.18, P = .32); ER-negative patients in the pregnant cohort had better OS (HR = 0.57, 95% CI = 0.36 to 0.90, P = .01). Abortion, time to pregnancy, breastfeeding, and type of adjuvant therapy had no impact on patients' outcomes. This study provides reassuring evidence on the long-term safety of pregnancy in breast cancer survivors, including those with ER-positive disease.		
(Lambertini, et al., 2019c)		patients with HER2-positive early breast cancer : unintentionally exposed to trastuzumab and/or lapatinib during gestation (the exposed group) those who became pregnant after trastuzumab and/or lapatinib completion (the unexposed group).		Pregnancy outcomes	92 patients (12 in the exposed group and 80 in the unexposed group) had a pregnancy. Seven patients (58.3%) in the exposed group and 10 patients (12.5%) in the unexposed group opted for an induced abortion; in the unexposed group, 10 patients (12.5%) had a spontaneous abortion. No pregnancy/delivery complications were reported for the remaining cases, who successfully completed their pregnancy, with the exception of 1 fetus with trisomy 21 (Down syndrome). No significant difference in DFS (adjusted hazard ratio, 1.12; 95% CI, 0.52-2.42) was observed between young patients with a pregnancy (n = 85) and young patients without a pregnancy (n = 1307).	For patients with HER2-positive early breast cancer, having a pregnancy after treatment completion appears to be safe without compromising fetal outcome	Part of the : (NeoALTTO) trial and the (ALTTO) trial
(Lee, et al., 2019a)	retrospective	Compared to 10,164 childbirths among 91,400 women without breast cancer (incidence rate: 22.3/1000), 855 childbirths occurred among 18,280 breast cancer survivors (incidence rate: 9.4/1000); the adjusted hazard ratio (HR) for childbirth was 0.41 (95% CI 0.38–0.44).	Chemotherapy, endocrine therapy, and target therapy were associated with the decreasing childbirths among survivors, with corresponding adjusted HRs of 0.61 (0.53–0.70), 0.44 (0.38–0.51), and 0.62 (0.45–0.86), respectively. Breast cancer survivors had a lower probability of full-term delivery and a higher frequency of preterm labour than controls, with corresponding adjusted ORs of 0.78 (0.68–0.90) and 1.33 (1.06–1.65), respectively.	childbirth rates and characteristics between the breast cancer survivors and the noncancer controls.	database from the National Health Insurance Service in South Korea of women who were between 20 and 40 years old between 2007 and 2013.	Breast cancer survivors should be aware that they have a higher risk for preterm labour and are less likely to have a full-term delivery than women without a history of breast cancer.	

(Light, *et al.*, 2014)	cross sectional study	transgender men who had been pregnant and delivered after transitioning from female-to-male gender. Participants were not required to have been on hormone therapy to be eligible. Inclusion criteria were: age older than 18 years, self-identification as male before pregnancy, pregnancy within the last 10 years, and the ability to fill out the survey in English.	web based survey from March to December 2013		41 self-described transgender men completed the survey. Before pregnancy, 61% (n525) had used testosterone. Most transgender men became pregnant within 4 months of trying, only 15% had a preconception medical consultation, and 7% used fertility drugs to become pregnant. Mean age at conception was 28 years with a standard deviation of 6.8 years. 88% of oocytes (n536) came from participants' own ovaries. Half of the participants received prenatal care from a physician and 78% delivered in a hospital. A higher proportion of transgender men who had used testosterone underwent caesarean delivery compared with those who reported no testosterone use (36% compared with 19%, respectively), although this finding was not statistically significant. Some participants reported improvements in gender dysphoria, feeling new connections with their bodies. Others felt an increase in dysphoria, and for some, that dysphoria continued into the postpartum period. Combined with feelings of isolation postpartum, many participants specifically mentioned having postpartum depression. Many participants called for better treatment from the health care system through acknowledging the unique identities of pregnant transgender men and grounding health care provider– patient interactions in compassion and respect.	Our results demonstrate that transgender men desire children and are willing and able to conceive, carry a pregnancy, and give birth. Participants repeatedly expressed a desire for more information regarding fertility options and access to reproductive health care providers who respect, support, and understand their gender identity. Our findings suggest that transgender men may represent a high-risk population for postpartum depression and, although further research is warranted, future recommendations should emphasize assessment of peripartum depression in this population. We also suggest all health care providers discuss fertility preservation options with patients before initiating testosterone use in accordance with inter-national standards of care.	
(Longhi, *et al.*, 2000)	interview	female patients who received adjuvant and/or neoadjuvant treatment for localized osteosarcoma of the extremities.	92 patients entered the study and were interviewed.		20 patients became pregnant after chemotherapy: only 3 patients had abortions (3 voluntary and 1 spontaneous); 1 of these 3 patients had 2 abortions, 1 voluntary and 1 spontaneous; 3 were pregnant at the time of the interview; 14 patients had 19 full term pregnancies (5patients had 2 children, none had more then 2, no twins were reported)	No birth defects were seen among the 19 offspring of our patient group, similar to most of the studies done on this topic	
(Madanat-Harjuoja, *et al.*, 2013)	**Details of this publication are included in Table 11**					
(Marklund, *et al.*, 2018)	prospective cohort	31 women with previous history of cancer achieved 25 deliveries and 212 women without cancer history achieved 244 deliveries. All egg donor treatments were performed with a strict policy of single embryo			Women with a history of cancer presented with a significantly increased risk of pregnancy complications, including preterm birth (aOR 5.54, 95% CI 2.01-15.31) and preeclampsia (aOR 2.79, 95% CI 1.07-7.34), compared to women without cancer history.	The findings of this study suggest that the risks of preterm birth and preeclampsia in women with prior cancers who become pregnant by egg donor treatment significantly exceed those of women without cancer	

		transfer to reduce pregnancy and perinatal complications. Women without previous history of cancer were used as the reference group				history undergoing similar treatments.	
(Melin, et al., 2019)	retrospective analysis	Nationwide cancer and birth registries were merged to identify 1,753 first deliveries of cancer survivors (diagnosed below 40 years of age) and 5,123 first deliveries of matched female comparison subjects between January 1991 and December 2013.	between January 1991 and December 2013.	to assess pregnancy related conditions in female cancer survivors possibly underlying the elevated risk for preterm labour	Among survivors, 129 (7.4%) delivered preterm compared to 268 (5.2%) comparisons subjects (p = 0.004). A statistically significant increased risk for preterm delivery among cancer survivors with vaginal bleeding (OR 1.35, 95% CI1.07–1.71) and pre-eclampsia (1.35, 95% CI1.06–1.72) compared to comparison subjects with the same condition was found.		
(Nielsen, et al., 2018)	population-based cohort	population-based cohort of 14 611 offspring (14 580 live-born children and 31 fetuses) of 8945 Danish cancer survivors and 40 859 offspring (40 794 live-born children and 65 fetuses) of 19 536 siblings.	incidence of chromosomal abnormalities in cancer survivors diagnosed before age 35 years compared to their siblings	chromosomal abnormalities	no increased risk of chromosomal abnormalities among survivors' offspring was observed compared with their siblings' offspring (odds ratio=0.99, 95% CI 0.67 to 1.44, two-sided P=.94), with similar risk between male and female survivors.		
(Obedin-Maliver and Makadon, 2016)	review	transgender men considering or in the midst of a pregnancy.	Three studies highlight both psychological issues experienced by transgender men contemplating pregnancy or bearing a child as well as the unique medical implications for both parent and foetus. For transgender men with functioning natal reproductive organs, the major unifying medical issue regarding conceiving and delivering healthy children are related to whether they used testosterone and if so, the duration of use and timing in relation to pregnancy.		41 transgender men—individuals who had a male or masculine identity, but who had been assigned the female sex at birth.33 Of those studied, 25 (61%) reported testosterone use prior to pregnancy. Among testosterone users, 6 (24%) had an unplanned pregnancy and 14 (72%) conceived within six months. more of the transgender men, 9 (36%) who had used testosterone delivered by caesarean than those who had not used testosterone 3 (19%). In addition, among the group who had used testosterone, 3 (33%) of the individuals who had a caesarean delivery requested this mode of delivery compared with 0 among those who had not used testosterone; pregnancy, delivery, and birth outcomes did not differ according to prior testosterone use. Complications that were self-reported included hypertension (12%), preterm labour (10%), placental abruption (10%), and anaemia (7%).	They noted both internal and external struggles for parents. Internal challenges were typified by the conflict between one's identity as male and or gender variant and ''social norms that define a pregnant person as woman and a gestational parent as mother.'' Regarding the external world, contemplation and experience of pregnancy involved a constant tension about needing to ''manage others' perceptions and either disclosing or not disclosing what they were experiencing.'' Their recommendations, focused on providing affirming and inclusive care beginning	

					with preconception counselling and continuing through the postpartum period. This level of support is within the scope of any perinatal provider. However, additional support and guidance from mental health colleagues may be beneficial; should an individual's experiences raise concerns of exacerbated personal psychological distress or safety. Understanding all individuals' gender identity will support comprehensive health services. All staff from the front line receptionists to clinicians will need training to understand why gender affirming policies and behaviors are important. In particular, systems may need to be modified and specified to ask these questions accurately while treating the information confidentially and with discretion	
(Park, *et al.*, 2009)	retrospective analysis	women with borderline ovarian tumour (BOT) who underwent fertility sparing surgery vs radical surgery	176 radical vs 184 fertility sparing. Mean age significantly lower in the fertility sparing group. As well as the proportion of women with stage III advanced disease. 63-70 months follow up.	27/184 patients conceived and had 32 singleton and 1 twins all of them healthy with no congenital abnormalities. In conclusion the study suggests that fertility sparing surgery is a safe and effective modality of treatment in women with BOT who wish to preserve fertility. In addition a second round of fertility sparing surgery was feasable in women with localised recurrence.	1989-2007 medical records identified	The rate of recurrence after fertility sparing treatment has been reported 5-33%. In this series the recurrence rate was similar in the 2 groups (fertility sparing vs radical)(5.1%-4.9%)	
(Park, *et al.*, 2013)	Retrospective study	141 women with stage IA, grade 1 endometrioid adenocarcinoma of the	medical records	pregnancy outcomes	54 (38.3%) women in the study cohort had a history of infertility. Seventy (49.6%) of the 141 patients tried to conceive with 44 (62.9%) receiving fertility drugs. The median interval to	the pregnancy outcomes were very promising using assisted reproductive technology.	

					attempted pregnancy after treatment was 5 months (range 1-31 months). The median age at the time of the pregnancy trial was 32.4 years (range 23-40 years). Fifty-one (73%) of 70 women who tried to conceive were successful and 46 (66%) gave birth to 58 live neonates. The spontaneous abortion rate, ectopic pregnancy rate, and preterm delivery rates in our cohort were 24%, 2.8%, and 11.5%, respectively. The 5-year disease-free survival was similar between patients who received fertility drugs (n=44) or who did not (n=97) (73% compared with 62%, P=.335), and this rate was significantly higher in patients who achieved at least one pregnancy (n=51) than those who did not (n=90) (76% compared with 62%, P=.028).		
(Plante, _et al._, 2019)	Study protocol	Pre-menopausal women diagnosed with stage FIGO IB2, 2-4 cm cervical cancer who wish to preserve fertility	3 cycles of platinum/paclitaxel chemotherapy. Patients with complete/partial response will undergo fertility-sparing surgery. Patients will be followed for 3 years to monitor outcome. Patients with suboptimal response (residual lesion >/=2 cm) will receive definitive radical hysterectomy and/or chemoradiation.	Assess the rate of functional uterus defined as successful fertility-sparing surgery and no adjuvant therapy.	None	None	
(Sanders, _et al._, 1996)		1,326 postpubertal and 196 prepubertal patients who had received high-dose chemotherapy alone or with total-body irradiation (TBI) and marrow transplantation for aplastic anaemia or hematologic malignancy.	questionnaire requesting pregnancy history, outcome, infant birth weight, and congenital anomalies information for all clinically recognized pregnancies.	pregnancy outcome	Among 708 postpubertal women, 110 recovered normal ovarian function and 32 became pregnant. In addition, 9 formerly prepubertal girls with normal gonadal function became pregnant. 41 female patients and partners of 35 male patients had 146 pregnancies after transplant. All 76 patients responded to a questionnaire. There were 115 live births among 146 (79%) pregnancies. Spontaneous abortion terminated four of 56 (7%) pregnancies for 28 female cyclophosphamide (CY) recipients and 6 of 16 (37%) pregnancies for 13 TBI recipients (P = .02). Partners of 28 male CY recipients had four of 62 (6.4%) pregnancies terminate with spontaneous abortion, but there were no spontaneous abortions among eight pregnancies of five TBI recipients' partners. Preterm delivery occurred for eight of 44 (18%) and 5 of 8 (63%) live births for 24 CY and 8 TBI female recipients (P = .01). This 25% incidence among all female patient pregnancies is higher than the expected incidence of 8% to 10% (P = .0001). The 13 preterm deliveries resulted in 10 low birth		

				weight ([LBW] 1.8 to 2.24 kg) and three very low birth weight ([VLBW] < or = 1.36 kg) infants, for an overall incidence of 25%, which is higher than the expected incidence of 6.5% for the general population (P = .0001). Twelve of the 13 premature infants survive. Congenital anomalies were seen among two of 52 (3.8%) live-born infants of female and six of 63 (9.5%) live-born infants of male patients, which is not different from the 13% of single congenital anomalies reported for the general population.		
(Schuurman, et al., 2019)	literature review	tamoxifen exposure during gestation	Articles were included in the review if they met the following inclusion criteria: (1) full text available in English or Dutch (2) study reporting on the research question of this review. The search retrieved 595 articles. After applying the inclusion and exclusion criteria and screening the reference lists, a total of 14 articles were considered eligible.		A total of 238 cases of tamoxifen use during pregnancy were found. Of the 167 pregnancies with known outcome, 21 were complicated by an abnormal fetal development. There seems to be an increased risk of fetal abnormalities when taking tamoxifen during pregnancy (12.6% in contrast to 3.9% in the general population), but the evidence is limited and no causal relationship could be established.	
(Signorello, et al., 2010)	retrospective cohort analysis	younger than 21 years at initial diagnosis. Children conceived through in-vitro fertilisation were not eligible for this study because the use of donor eggs or sperm could not be conclusively established. Non-singleton pregnancies were excluded.	Survived for at least 5 years after diagnosis. The total radiotherapy dose was the sum of all doses from all radiation treatments. Doses to the two ovaries were estimated separately.		The 1774 survivors who were given radiotherapy reported 60 stillbirths or neonatal deaths, and 3077 livebirths. For the dose group with the highest risk (≥10·00 Gy), the mean preconception dose to the uterus was 17·52 Gy (SD 12·03) and the mean dose to the ovaries was 18·08 Gy (9·75). After adjustment for maternal age, calendar year of birth, and radiation dose to the uterus, we did not note an effect of high-dose pituitary irradiation among female survivors (17 [3%] of 510 survivors, RR 1·1, 95% CI 0·5–2·4 for ≥20·00 Gy vs no irradiation).Treatment with any alkylating drugs did not increase the risk of stillbirths or neonatal deaths among the children of female survivors (26 [2%] of 1195 survivors, adjusted RR 0·9, 95% CI 0·5–1·5)	We did not note an association between pituitary radiation exposure before conception and the risk of stillbirth or neonatal death. Uterine or ovarian irradiation greatly increased the risk of stillbirth or neonatal death, with high doses (≥2·50 Gy) associated with a greater than 12-fold risk for women treated before menarche.High-dose pelvic irradiation can permanently impair growth and blood flow to the uterus and results in a reduced uterine volume,15 and these effects of radiation are likely to be dependent on age.Evidence to support that irradiation of human germ cells results in genetic damage to the offspring is lacking. For women, however, high-dose uterine or ovarian radiation does seem to have	

					important adverse effects, which are most likely to be attributable to uterine damage. Therefore, careful management is warranted for pregnant women treated with high-doses of pelvic irradiation before they have reached puberty.	
(Smaldone, et al., 2010)	retrospective analysis	reproductive-age women (18-45 years old) with stage IA to stage IIC ovarian neoplasms (N = 161)	Patients in our cohort were observed overall median time of 7.0 years (range, 1-16 years)		Of the 161 reproductive-age women with early-stage ovarian neoplasms meeting our inclusion criteria, 61 (37.9%) had received conservative management. Complete surgical staging was performed in 57.4%of women, and 16.4%received adjuvant chemotherapy. 13 women successfully conceived 23 pregnancies, producing a pregnancy rate of 25.0% overall .There were 18 documented live births resultinginneonateswithamedianbirthweightof3 245T 380g and median Apgar scores of 9 at 1 minute and 9 at 5 minutes.	The findings of our study indicate that reproductive-age women who receive conservative surgery for stages IA to IIC ovarian cancers can have successful obstetric outcomes. Chemotherapeutic agents, particularly alkylating agents, have a direct cytotoxic effect on the ovaries, which may result in premature ovarian failure (PMOF) and subsequent infertility. Patients are extensively counselled regarding the association of fertility drugs and ovarian cancer and are monitored closely for subsequent disease recurrence. Furthermore, women with suspected epithelial ovarian cancers are counselled regarding their risk for higher disease recurrence and poorer survival with conservative surgical management.	
(Sun, et al., 2018)	SR	7 studies included in the meta analysis ; The population sizes of the studies ranged from 146 to 3 168 911.	A systematic literature search of PubMed, Embase, and Web of Science databases up to march 2017; Observational studies of the effect of breast cancer on delivery outcomes were included; After excluding each study individually, the sensitivity analysis confirmed the significant associations between history of breast cancer and increased risk of		In the pooled analysis of data from 6 687 579 pregnant patients, maternal breast cancer was associated with an increased risk of preterm delivery (pooled RR 1.82, 95% CI 1.44–2.30); significant study heterogeneity was identified (I2 71.8%, P=0.002); There were five studies including 6 687 103 pregnant women included in the meta- analysis of associations between breast cancer and the risk of low delivery weight. Breast cancer was associated with an increased risk of low delivery weight (pooled RR 1.41, 95% CI 1.15–1.74) and the study heterogeneity was not significant (I2 37.1%, P=0.174)	The meta- analysis demonstrated that maternal breast cancer was associated with an increased risk of preterm delivery (RR 1.82, 95% CI 1.44–2.30) and low delivery weight (RR 1.41, 95% CI 1.15–1.74). There are several mechanisms through which maternal breast cancer could increase the risk of preterm delivery and low delivery weight. A potential explanation is that metabolic alterations,	

			preterm delivery and low delivery weight, suggesting high stability in the meta- analysis results; No evidence of funnel plot asymmetry was observed (Fig. S1), and no publication bias was detected by quantitative analyses for preterm delivery			hormone distribution, febrile illness, and malnutrition related to the breast cancer disease process could have a damaging impact on the foetus.(Langagergaard V. Birth outcome in women with breast cancer, cutaneous malignant melanoma, or Hodgkin's disease: A review. Clin Epidemiol. 2011;3:7.)	
(Tamauchi, _et al._, 2018)	retrospective database analysis	Reproductive outcomes of malignant ovarian germ cell tumor survivors	conservative treatment	chemotherapy regimen, surgical procedure, tumour type, IFGO grading, survival outcome and period, number of pregnancies and child birth, method of delivery, gestation age, obstetrics complications	database from 1986-2016	The reproductive outcome of malignant ovarian germ cell tumor survivors is promising with fertility sparing treatment.	
(Tarin, _et al._, 2016)	narrative review	not specified	A literature search based on publications up to March 2016 identified by PubMed and references cited in relevant articles;. Only articles (whenever possible systematic reviews and meta- analyses) published in English were included.		Obstetric complications are rare in hyperprolactinemic women treated or untreated with bromocriptine, although untreated hyperprolactinemia may be a risk factor for ectopical pregnancy (25 %, 4/78 vs. 5 %, 6/25 in bromocriptine-treated pregnancies (P=0.017). Cancer survivors with decreased pulmonary diffusion capacity are more likely to report respiratory symptoms, poor physical functioning, low energy and increased fatigue than survivors without diffusion defects [53]. These effects may be exacerbated during the third trimester of pregnancy when pulmonary diffusion capacity decreases compared to non-pregnant women especially in women living at high altitude.Radiotherapy-induced structural and functional changes to the uterus may adversely affect implantation and maintenance of pregnancy increasing the risk of placental attachment disorders (placenta acreta or placenta percreta), low birth weight (RR: 1.85, p=0.03 in patients treated with pelvic irradiation, and ORs from 3.64, 95 % CI: 1.33-9.96 in survivors after abdominopelvic radiation up to 6.8, 95 % CI: 2.122.2 in patients treated with high-dose (>5 Gy) radiotherapy to the uterus), small for gestational age (OR: 4.0, 85 % CI: 1.6-9.8 in patients treated with high-dose (>5 Gy) radiotherapy to the uterus), preterm delivery (OR: 3.5, 95 % CI: 1.5-8.0 in patients	Once female cancer survivors wishing to have a child have been properly informed about the risks of reproduction, they will be best placed to make decisions of whether or not to have a biological or donorconceived child. In addition, when medical professionals be aware of these risks, they will be also best placed to provide appropriate treatments before/during pregnancy in order to prevent or alleviate the impact of these morbid conditions on maternal and offspring health.	

					treated with high-dose (>5 Gy) radiotherapy to the uterus), perinatal death, and fetal malposition. Surgical removal of the uterine cervix in cervical cancer patients is associated with increased risk of second trimester loss (10 % of pregnancies) and premature delivery in the third trimester (19 % of pregnancies)	
(Teh, *et al.*, 2014)	narrative review	childhood and adolescnce radiation vs adulthood radiation effect on pregnancy	TBI and pelvic radiation		A dose of below 4Gy appears to be the threshold dose, depending also on the associated treatment. If the uterus is directly irradiated, pregnancy is rare. Childhood radiation doses of <4Gy have not been shown to impact negatively on subsequent fertility. The incidence of spontaneous abortion (37% versus 7%) and preterm delivery (63%versus 18%)were significantly higher in TBI recipients compared to the chemotherapy-only group (*P* = 0.01). The 13 preterm deliveries resulted in 10 low birth weight (1.8 to 2.24kg) and three very low birth weight (≤1.36kg) infants, for an overall incidence of 25%, which is higher than the expected incidence of 6.5% for the general population (*P* = 0.0001). In a large study of more than 30,000 European women who had received SCT, there were 312 pregnancies from 232 patients (30 patients had ART). This study demonstrated a significantly higher than normal rate of pregnancy complications in recipients of allogeneic SCT compared to the normal population.	Although limited, the current evidence suggests that women who wish to have children and who have been exposed to radiation (TBI) are less likely to conceive and are at increased risk of pregnancy complications including preterm birth and low birth weight offspring. The increase in pregnancy complications seem to further increase when the conception results from ART. Unfortunately, there is no information in the literature about fertility and pregnancy outcome in women who have been exposed to pelvic radiation in adulthood. Appropriate counselling in regards to the safety of the irradiated uterus with carrying a pregnancy should be provided to these women who subsequently wish to utilise their stored oocytes and embryos to achieve a pregnancy. Previous uterine irradiation is associated with a smaller uterine volume; no successful pregnancy has been reported after a direct radical dose(>45Gy) to the whole pelvis. It appears that younger age at uterine radiation leads to greater adverse effects on uterine reproductive capacity, particularly in prepubertal girls.R adiation doses of >25Gy directly to the uterus in childhood appears to induce irreversible damage.	

						Exposure of adult uterus to TBI (12Gy) is associated with increased risk of miscarriage, preterm labour, and low birth weight babies.	
(van de Loo, *et al.*, 2019)	Nested cohort study	Childhood cancer survivors previously exposed to abdominal-pelvic radiotherapy (RT-exposed CCSs) as part of their treatment for childhood cancer.	Radiotherapy-exposed CCSs (n = 55) were age- and parity-matched to nonirradiated CCSs (non-RT-exposed CCSs; n = 110) and general population controls (n = 110).	Uterine volume, pregnancy complications, and pregnancy outcomes.	Among nulligravidous participants, median (interquartile range) uterine volume was 41.4 (18.6-52.8) mL for RT-exposed CCSs, 48.1 (35.7-61.8) mL for non-RT-exposed CCSs, and 61.3 (49.1-75.5) mL for general population controls. Radiotherapy-exposed CCSs were at increased risk of a reduced uterine volume (<44.3 mL) compared with population controls (odds ratio [OR] 5.31 [95% confidence interval 1.98-14.23]). Surprisingly, the same was true for non-RT-exposed CCSs (OR 2.61 [1.16-5.91]). Among gravidous participants, RT-exposed CCSs had increased risks of pregnancy complications, preterm delivery, and a low birth weight infant compared with population controls (OR 12.70 [2.55-63.40], OR 9.74 [1.49-63.60], and OR 15.66 [1.43-171.35], respectively). Compared with non-RT-exposed CCSs, RT-exposed CCSs were at increased risk of delivering a low birth weight infant (OR 6.86 [1.08-43.75]).	Uterine exposure to radiotherapy during childhood reduces adult uterine volume and leads to an increased risk of pregnancy complications and adverse pregnancy outcomes.	
(van der Kooi, *et al.*, 2018)	Details of this publication are included in Table 11						
(van der Kooi, *et al.*, 2019)	Review	female cancer survivors 22 studies included		pregnancy, perinatal or congenital risks	offspring of cancer survivors are at increased risk of prematurity (relative risk [RR]: 1.56; 95% CI 1.37-1.77) and low birth weight (RR 1.47; 95% CI 1.24-1.73) but not of being small for gestational age (RR 0.99; 95% CI 0.81-1.22). Cancer survivors have higher rates of elective (RR: 1.38; 95% CI 1.13-1.70) and emergency caesarean section (RR: 1.22; 95% CI 1.15-1.30) as well as assisted vaginal delivery (RR: 1.10; 95% CI 1.02-1.18) and are at increased risk of postpartum haemorrhage (RR: 1.18; 95% CI 1.02-1.36). The risk of congenital abnormalities also appears increased (RR 1.10; 95% CI 1.02-1.20), but this is likely to be an artefact of analysis. Although meta-analysis of the effects of radiotherapy was not possible for all outcomes, there was an increased risk of prematurity (RR 2.27; 95% CI 1.34-3.82) and consistent findings of low birth weight (RR 1.38-2.31). Risk of being small for gestational age was increased only after high uterine radiotherapy dosage.		

(van Dorp, *et al.*, 2018)	Literature review	female cancer survivors diagnosed before the age of 25 years		reproductive function and pregnancy outcomes	High-dose alkylating agent chemotherapy and abdominal/pelvic radiotherapy adversely affect gonadal function in a dose-related fashion, with older age at exposure conferring greater risk as a result of the age-related decline in ovarian reserve. Gonadal injury clinically manifests as ovarian hormone insufficiency (delayed or arrested puberty, premature ovarian insufficiency, or premature menopause) and infertility. The effect of molecular-targeted agents on ovarian function has not been established. For female cancer survivors who maintain fertility, overall pregnancy (relative risk, 0.67 to 0.81) and live birth rates (hazard ratio, 0.79 to 0.82) are lower than those in the general public. Pregnancy in cancer survivors also may be associated with risks to both the mother and the fetus related to miscarriage; preterm birth; and, rarely, cardiomyopathy. The risk for inherited genetic disease in offspring conceived after cancer treatment exposure is not increased.		
(Winther, *et al.*, 2012)	case-cohort study	472 Danish survivors of childhood and adolescent cancer and their 1,037 pregnancies.	Preconception radiation doses to the gonads, uterus, and pituitary gland and administered chemotherapy were quantified based on medical records and related to adverse outcomes using a generalized estimating equation model.		Adverse outcomes included 159 congenital malformations, 6 chromosomal abnormalities, 7 stillbirths, and 9 neonatal deaths. No statistically significant associations were found between genetic disease in children and parental treatment with alkylating drugs or preconception radiation doses to the testes in male and ovaries in female cancer survivors. Specifically, the risk of genetic disease was similar among the children of irradiated survivors when compared with nonirradiated survivors (relative risk [RR], 1.02; 95% CI, 0.59 to 1.44; P = .94). A statistically significant association between abdomino-pelvic irradiation and malformations, stillbirths, and neonatal deaths was not seen in the children of female survivors overall (P = .07) or in the children of mothers receiving high uterine doses (mean, 13.5 Gy; max, 100 Gy; RR, 2.3; 95% CI, 0.95 to 5.56).	Mutagenic chemotherapy and radiotherapy doses to the gonads were not associated with genetic defects in children of cancer survivors.	
(Zhang, *et al.*, 2017)	Systematic Review and meta analysis	375 patients were included in the CON group: 176(46.9%) stage IA1 and 167(44.5%) stage IB1. In the Radical Trachelectomy (RT) group, 2479 cases were included: 143(6.0%) stage IA1, 299(12.1%) stage IA2, 1987(79.9%) stage IB1. The median	Patients with cervical cancer stage IA1 and IB1 who had conization and patients with IA1, IA2 and IB1 who had radical trachelectomy		60 observational studies encompassing 2,854 patients were included; 17 of which evaluated CON and 43 RT. For the CON group a pregnancy rate of 36.1%(26.4%-46.2%), a spontaneous abortion rate of 14.8%(9.3%-21.2%) and a preterm delivery rate of 6.8%(1.5%-15.5%) were found. For the RT group a pregnancy rate of 20.5%(16.8%-24.5%), a spontaneous abortion rate of 24.0%(18.8%-29.6%) and a preterm delivery rate of 26.6%(19.6%-34.2%) were found. There have been more than 300	Fertility-sparing treatment including CON or RT for eCC is feasible and carefully selected women can preserve fertility and achieve pregnancy resulting in live births. CON seems to result in better pregnancy outcomes than RT with similar rates of recurrence and mortality. In our review, we found that both CON	

		age of patients included ranged from 27 to 39 years old. The length of follow-up was 9-95 months.			pregnancies reported after RT in the literature, with a live-birth rate of 68%	and RT with or without lymphadenectomy are encouraging as a fertility-sparing treatment for eCC, especially in stage IAIB1, according to the low relapse rates of conization and RT, and an additional encouraging proportion of women managed to achieve pregnancy. For patients with stage IA, conization seems much suitable for lower abortion rate and preterm delivery rate, resulted from the limited and minor injury to the cervical and parametrium, and great oncologic outcome. For stage IB, particularly IB1, patients should be evaluated comprehensively before conservative treatment and conization with pelvic lymphadenectomy may be a suitable option.	

Table 1 Overview of data from large registries on obstetric outcomes after cancer

	(van der Kooi, *et al.*, 2018)	(Anderson, *et al.*, 2017a)	(Madanat-Harjuoja, *et al.*, 2013)	(Fossa, *et al.*, 2005)	(Ji, *et al.*, 2016)
	Scotland	North Carolina	Finland	Norway	Sweden
Study group	10,271 nulliparous women diagnosed with cancer before the age of 40 years	21 716 women with a cancer diagnosis between ages 15 and 39 years	25 784 males and females	8644 women after diagnosis in cancer patients aged 15 to 45	1,977 cancer survivors who had given birth before / after their cancer diagnosis
Control group	General population	General population	44 611 full and half siblings of these patients		General population (without cancer)
BIRTH					
Antepartum haemorrhage	No difference (RR 1.13; 95% CI 0.86–1.50)				
Postpartum haemorrhage	**Increased** (RR 1.42; 95% CI 1.29–1.55)				
Operative or assisted delivery – elective	**Increased** (RR 1.59; 95% CI 1.35–1.88)	**Increased** (PR 1.08; 1.01-1.14)		**Increased** (OR 2.3; 95% CI 1.9-2.7)	
Operative or assisted delivery – emergency	**Increased** (RR 1.20; 95% CI 1.08–1.34)				
PERINATAL OUTCOMES					
Small for gestational age	**Decreased** (RR 0.82; 95% CI 0.68–0.98)	No difference (PR 0.97; 0.85-1.11)			
Low Apgar score (<7)		No difference (PR 1.18; 0.87-1.61)			
Low birth weight	No difference (RR 1.15; 95% CI 0.94–1.39)	**Increased** (PR 1.59; 95%CI 1.38-1.83)		**Increased** (singletons) (OR 2.5; 95% CI 2.0-3.2)	
Preterm birth	**Increased** (RR 1.32; 95% CI 1.10–1.59)	**Increased** (PR 1.52; 95% CI 1.34-1.71)		**Increased** (singletons) (OR 2.8; 95% CI 2.3-3.4)	
Early preterm birth		**Increased** (PR 2.03;95%CI 1.62-2.55)			
Need for intensive care or neonatal monitoring	**Increased** (RR 1.03; 95% CI 0.90–1.19)		**Increased** (OR 1.90; 95% CI 1.65 – 2.19)		
Perinatal death (< 7 days after live birth)			No difference (OR 1.35; 95% CI 0.58 – 3.18)	No difference (OR 1.2; 95% CI 0.6-2.4)	
Neonatal death (< 28 days after live birth)			No difference (OR 1.40; 95% CI 0.46 – 4.24)		No difference (OR 1.13; 95% CI 0.80–1.60)
Early death (< 1 year after birth)			No difference (OR 1.11; 95% CI 0.64 – 1.93)		
Stillbirth			No difference (OR 1.15; 95% CI 0.61 – 2.19)		No difference (OR 1.27; 95% CI 0.95–1.68)
Congenital abnormalities	No difference (RR 1.01; 95% CI 0.85–1.20)			No difference (OR 0.6; 95% CI 0.4-1.0)	

Abbreviations: PR, prevalence ratio; RR, relative risk; OR, odds ratio.

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