

6. Ethical issues related to multiple pregnancies in medically assisted procreation

The ESHRE Task Force on Ethics and Law* ¹

In this sixth statement of the ESHRE Task Force on Ethics and Law, the focus is on the ethical issues raised by multiple pregnancies resulting iatrogenically from the use of medically assisted procreation. The incidence of multiple pregnancies and the consequences for the child are discussed, together with general and specific ethical issues. Four recommendations are made—single embryo transfer, public funding for assisted reproduction, multiple pregnancies reported as complications not successes, and a uniform method of presenting results.

Key words: ethics/medically assisted procreation/multiple pregnancies

Introduction

Medically assisted procreation (MAP) includes ovarian stimulation with or without intra-uterine insemination (IUI), gamete intra-Fallopian transfer (GIFT) and IVF with or without ICSI. MAP is associated with a significant increase in the incidence of multiple pregnancies (i.e., twin and higher order). The dangers of multiple pregnancies are well documented, although not widely recognized or appreciated. For the children these are largely due to the complications of intrauterine growth retardation [or small-for-gestational age (SGA)] and preterm delivery, and their long-term consequences.

This iatrogenic event is frequently the physician's responsibility. Competition between centres, cost-effectiveness of the treatment and the increasing commercialization of medically assisted reproduction all contribute to the pressure to maximize the pregnancy rates (PR). Nevertheless this overall pregnancy rate should be balanced against the risks of multiple pregnancies.

Whilst most published figures relate to multiple gestations from IVF/embryo transfer, ovarian stimulation, with or without IUI, contributes significantly to its occurrence. It is therefore important to consider the different contributory factors to this problem. The aim of this taskforce is to analyse the ethical dimension of this issue including the decision making process and to offer guidance towards a resolution of this major health concern.

The facts

Incidence of multiple pregnancies

IVF is a successful procedure since it gives many couples with a nil or poor chance of pregnancy (<0.4% per cycle) the opportunity to conceive. Overall, more than 1 million children in the world have been conceived through this technique since 1978. However there are far too many multiple pregnancies, with their intrinsic high risk for the resulting children.

Worldwide, in 1998, oocyte recoveries resulted in 27.3% twin deliveries and 3.4% of deliveries of triplets or more. In terms of babies, for every 100 newborns, almost 49 came from a multiple pregnancy (one quadruplet, seven triplets and 41 twins). The exact numbers arising from ovarian stimulation, with or without IUI, are not known. Although many national registers record the outcome of assisted reproductive technology (ART) (IVF and ICSI), none does so for controlled ovarian stimulation. However, multiplicity is undoubtedly related to the number of leading follicles—and possibly to the number of medium size follicles produced by the stimulation. In many developed countries, triplet deliveries have increased 3–5-fold since 1970—before ovarian stimulating drugs were available (the natural incidence rate of triplets is ~1 per 10 000). For twins (spontaneous incidence amongst Caucasian populations of 1%), the increase has been 30–50%.

Triplet and twin infants are therefore major contributors to the overall preterm, SGA and mortality rates. In France, between 1986 and 1998, triplets represented 5.6% of all the IVF babies, but they accounted for 30% of the high prematurity (<33 weeks), 11% of SGA and 15% of the perinatal or neonatal mortality. For twins, the rates were respectively 37, 52, 55 and 54%.

In IVF, it is clear that multiple pregnancies are due to multiple embryo transfers. The French data show that PR increased between one and three transferred embryos (from 10 to 30%), but not afterwards, since more than three embryos are

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transferred mostly in couples with a poor chance of pregnancy. At the same time, twin rates increase from 1 to 31% and triplet rates from 0 to 6%. Moreover, although the pregnancy rate does not increase for transfers of four, five or six embryos, multiplicity continues to increase (up to 45% for twins and 16% for triplets). In the world data, when countries were grouped according to the average number of transferred embryos, the twin rate was increased from 22% in the countries where this number was <2.7 embryos to 32% in all the others. The increase in triplets occurred continuously, from 0.5, 2.7, 4.5 and 6%, if the average number of transferred embryos was respectively <2.24, 2.25–2.49, 2.50–2.99 or ≥ 3.00 . When analysing the results in a multivariate model including most of the risk factors, it becomes clear that, if the reference category is two embryos, the odds ratio of pregnancy increase slightly compared with those of multiple pregnancy, and this is particularly true for triplets and higher order pregnancies.

When countries were grouped on a regional basis (Australia, Western Europe, Eastern Europe, North America, South America, Asia, Middle East), clear differences appeared in the number of transferred embryos. The transfers involving more than four embryos represented <10% of the embryo transfers in Australia and Western Europe, 35% in Eastern Europe and $\geq 45\%$ in other countries. Pregnancy rates per ovarian puncture were not different except in North America where they were higher. However, triplets represented 1.4% of the pregnancies in Western Europe and Australia, and between 3 and 7% in the others.

Consequences for the child

The public health consequences relate not only to the multiplicity *per se*—since it carries huge socio-economic consequences to family life—but also because such pregnancies carry a high risk for the babies. Compared with ART singletons, triplets are more likely to be preterm, to be SGA (birthweight below the 10th centile of reference curves adapted for gestation and sex) and to die in the perinatal period. The risk of delivering before 28, 33 and 37 weeks gestation is multiplied by ~10, 15 and 11 (being 2.4, 28.4 and 88.7% versus 0.2, 1.6 and 8.3% respectively). The risk of being SGA is multiplied ~3.5-fold (58 versus 17%). Finally, perinatal mortality is multiplied by 5-fold (40/1000 births versus 8/1000). Those risks do not only concern the newborn status at birth, but also carry major long term consequences for childhood and adult life, since preterm delivery and intrauterine growth retardation are the major risk factors for neurodevelopmental disorders.

Furthermore, the same risks are also increased for twins compared with singletons. According to the above categories, twins have a 6.5 and 5-fold risk of preterm delivery (respectively 1.2, 7.8 and 42.5 before 28, 33 and 37 weeks gestation), a 2.5-fold risk for SGA (42.5%) and a 3-fold risk for perinatal mortality (20.8/1000 births).

In view of these facts, the goal must be a singleton pregnancy. This can only be achieved in IVF by reducing the number of embryos transferred and by multifetal pregnancy reduction. The prevention of multiple pregnancies in ovarian stimulation is a more complex task in view of the more varied

approaches regarding indications and stimulation regimens, although careful monitoring of the follicular phase and specific interventions such as not injecting hCG, selective aspiration of supernumerary follicles and conversion to IVF cycles allows the drastic reduction of the risk of multiple pregnancies in non-IVF cycles.

Consequences for the mother and the family

The incidence of stress and depression suffered by families with multiple births, and mothers in particular, is well documented, especially in the case of triplets. The effects include more maternal depression, less possibility for mothers to work outside the home, and an increased rate of divorce. This can only be compounded by the possibility of having one (or more) disabled child(ren). The financial and practical implications of looking after a large family add to the problems.

General ethical principles

All the principles outlined are taken into the context of our joint parental and professional responsibility towards the future child(ren). A recurrent theme in all matters of assisted reproduction, it is especially important when the facts show that some techniques do put the future child, a vulnerable future party, at high proven risk (see Introduction).

Autonomy versus paternalism and responsibility for the child(ren)

In normal circumstances, the physician and the prospective parents reach an agreement on the modalities of the treatment. This negotiation should enable them to balance the reproductive autonomy of the parents and the professional autonomy of the physician. Two situations arise in which these rights may conflict: (i) the decision about the number of embryos to be transferred and (ii) the decision about the performance of a multifetal pregnancy reduction.

The limits of the parental capacity to make decisions about the number of embryos to be replaced is made clear when the results of the surveys among would-be parents are scrutinized. These surveys reveal that a considerable number of the infertility patients consider even a higher-order pregnancy as a positive outcome. Most parents clearly underestimate the difficulty of raising multiples. The emotional stress of the infertility, combined with the lack of information on the consequences of multiple pregnancies and the strong wish for a child, may reduce the ability of patients to make the most appropriate choice. In addition, the financial context and the knowledge that they will only be able to pay for a limited number of IVF cycles, may bring the couple to demand the replacement of a higher number of embryos. When extensive information is provided to the patients about the risks of a multiple pregnancy and about the effect of the transfer policy on their chances to become pregnant, the conflicts between physician and patients will be very limited. In case of disagreement, the lowest number indicated by one of the parties should be followed so that no more embryos are replaced than wanted by either the physician or the parents.

The parental authority to decide this point is based on their right to decide how many children they want in their family while the physician's authority is founded on his or her responsibility for the implications of his or her actions for the mother and the future children. On the part of the physician, this is a matter of responsibility to the vulnerable rather than a paternalistic attitude towards the patient(s).

The principle of bodily integrity and the principle of reproductive autonomy give every woman the right to decide for herself whether or not to be submitted to a termination of pregnancy. In the case of a multiple pregnancy, the woman should be fully informed about the risks for her, the pregnancy and the remaining embryos when an embryo reduction is performed. Every woman, however, should also have the right to have a reduction if she estimates the social, psychological and medical risks for herself or the offspring as too high. Physicians who have conscientious objections about abortion should mention this to the patients before the start of the treatment and should take these objections into account when deciding how many embryos to replace. They also have a duty to refer to another physician if this procedure must be considered.

Justice

Financial pressure is often the main reason for patients to ask for the transfer of more than one embryo. This implies that less fortunate couples are indirectly forced to take the risk of a multiple pregnancy. There is evidence that the incidence of multiple pregnancies is lower in countries who provide public subsidies for ART. Coverage by the public health care system should be available for a reasonable number of IVF cycles, both in order to reduce this discrimination and to protect future child(ren).

Non-maleficence

A physician has the professional responsibility not to cause unnecessary harm. This responsibility extends both to the woman and to the future children. This principle largely justifies the priority that should be given to the reduction of the number of multiple pregnancies above the increase in pregnancy rates.

Specific ethical issues

The need for regulation

ART

The main ethical objection to the need for regulation/legislation is that it curtails both parental and professional autonomy. However, autonomy might conflict with the physician's responsibility for the welfare of the future child. On the basis of this principle of responsibility to the vulnerable, strict regulation, which carries some kind of sanctions, can be justified. Therefore it may be necessary to use legislation if professional codes of practice are seen to have no practical effect on outcome.

Ovarian stimulation

Regulation in the case of ovarian stimulation presents specific problems..... It should be performed only by appropriately trained practitioners with access to adequate monitoring and associated with a network (with access to hormonal assays and ultrasound).

Multifetal pregnancy reduction (MFPR)

The ethical dilemmas of MFPR are closely connected to the problem of abortion. The main difference is that in the case of MFPR it is explicitly the intention not to terminate the pregnancy but to increase the chance of development of the remaining fetuses. Especially for higher order pregnancies, not performing a reduction will increase the risk of losing the pregnancy and all the fetuses. In that sense, the reduction is medically indicated. The first priority lies with the well-being of the children that will be born.

Prevention of multiple pregnancies should be preferred to MFPR. Regardless of the information provided before the treatment, people may still experience the decision to reduce the number of embryos as psychologically and morally demanding. Patients who become pregnant after a long period of infertility attribute a high value to the embryos/fetuses and to the pregnancy. Even when neither the physician nor the couple has moral qualms about abortion, it is better not to bring people into a position where they have to take decisions that may endanger their project. Prevention is also preferable since there are indications that the original higher order pregnancy has detrimental effects (higher incidence of prematurity) on the development of the remaining fetuses that are carried to term even after the reduction.

MFPR is morally acceptable if the physician has acted according to the rules of good clinical practice and has tried to minimize the risk of a multiple pregnancy. The benefits for the remaining embryos of reducing a higher order multiple pregnancy exceed the disadvantages of carrying the pregnancy to term or risking miscarriage. With triplets, opinions vary according to personal experience and access to neonatal care. The reduction of twins to a singleton is acceptable in cases of maternal disease, poor obstetric outcome and compelling social and psychological reasons of the woman.

Recommendations

The goal of MAP must be a singleton pregnancy

Single embryo transfer is the simplest and most obvious way of avoiding multiple pregnancies. The best way is to replace good quality embryos one at a time.

However we need more accurate and simpler methods to identify the embryo most likely to implant. In the transitional period, we accept the risk of twins as a compromise between a strongly reduced pregnancy rate and the increased risk of a multiple pregnancy of a higher order.

For the present time, in selected patients (<38 years of age, with normal ovarian response and good fertilization rate) a maximum of one or two embryos should be transferred.

Further studies should be conducted in order to evaluate the appropriate number of embryos to be transferred in other

groups of patients (older women, poor responders, bad implanters). Therefore we recommend additional research on the impact of factors such as age, diagnostic categories and oocyte quality. There is also a need to improve the efficiency of the cryopreservation protocols. In all cases, priority should be given to the reduction of the multiple pregnancy rates.

Ovarian stimulation must be performed by a specialist in a network of providers of ART; it is of paramount importance to consider the following options: cancellation of the cycle, conversion to IVF or selective follicular aspiration. Further research is needed to improve the protocols and to identify the predisposing factors with a view to minimize multiple pregnancies.

Societal implications

The high number of multiple pregnancies after ART is also a public health issue. There should be public funding for a number of cycles that gives the patients a reasonable chance of having a healthy singleton birth. Given the acute and long-term needs of preterm infants, reimbursement of infertility treatment

aiming at singleton pregnancy may be cost-effective at a national level.

Collation and presentation of results

Multiple pregnancies should not be reported as successes but as complications of medically-assisted reproduction methods. The results should be published as singleton pregnancy rate per started cycle, per oocyte retrieval, and per embryo transfer. The numbers of cycles should also be included. These results should be given separately for twin, triplet and higher order multiples. The rate of multifetal pregnancy reductions should also be available.

A uniform way of presenting results based on this model of presentation should be encouraged by specialist journals.

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