ESHRE 2021 Virtual (26 June – 1 July 2021)

Questions for the speakers

PCC11: Reproductive medicine in the era of high throughput sequencing

High throughput sequencing for the assessment of male and female fertility - Stéphane Viville (France)

Q: In the preimplantation embryonic lethality condition how the male factor contribution is considered or excluded

A: This is an excellent question. Indeed, male factors can contribute to this phenotype, but there are less likely because most of the time it happens before the zygote genome activation. Having say that, it is known that few male genes are expressed before this ZGA. So it is not possible to exclude male factors, more research works are needed to establish how much male factors interfere with preimplantation embryonic lethality condition

Q: Could single cell sequencing of embryonic cells be useful in studying PREMBL?

A: Eventually as a research purpose, but not as a diagnostic approach. Indeed, it is always tricky to carry on conclusive experiment starting from an abnormal development. Doing so, it is hard to discern between the egg and the chicken.

Q: Would you do the diagnostics for patients from other countries if they pay for it?

A: Yes we are doing it, if you like more details you can contact me via email : stephane.viville@unistra.fr. I am working in a public hospital, which mean nonprofitable.

Q: Do you think there is a sharp divide between gene variants that cause oocyte demise and those that cause problems in the preimplantation embryo?

A: As I mentioned it during my talk, no I don't think so. Many different cases can be imagined. For some genes, variants will end up to one or the other phenotype, for others it could depend on the variant affecting the gene, some variants will give rise to strict oocyte maturation defects and others preimplantation embryonic lethality.

High throughput sequencing for prenatal testing - Brigitte H.W. Faas (The Netherlands)

Q: Is there a structural or biological reason why chromosome 7 is so often found mutated?

A: To the best of my knowledge, it is unknown why T7 is so often detected as CPM. The fact that T7 in combination with UPD7 is very rare suggests that it almost exclusively arises postzygotic. I don't think

T7 arises more often than other autosomal trisomies, but it is more logically to think that it is better tolerated in the placenta than some other autosomal trisomies. The placenta is a very rapidly dividing tissue, comparable with tumour tissue. Also in tumours and leukemia T7 can be present. Apparently, at least for some tissues, having T7 is tolerated, not a disadvantage or perhaps might even be an advantage. But again, to the best of my knowledge, this is not known and only speculating.

Q: How much more information is needed to give counselors an applicable guideline on how to manage affected pregnancies?

A: As the main topic of my presentation was the detection of RATs (Rare Autosomal Trisomies) with genome-wide NIPT, and the still insufficient amount of information we have of the clinical impact of the detection of these RATs, my answer will focus on that topic.

There already are quite some data available on the predictive value of the RATs. These are predictive values for the fetus, in other words: how often is the with NIPT detected RAT indeed present in the fetus? But even if not present in the fetus, but confined to the placenta, it might have a clinical impact, as it might impair placental functioning. This is known from Confined Placental Mosaicism (CPM) studies. By far most NIPT follow-up studies so far deal with the genetic follow-up of the with NIPT detected RATs, not with the clinical follow-up. Only a few papers on studies in high-risk populations deal with the clinical follow-up, for the general population there are no clinical follow-up data published yet.

The information that is needed for accurate counseling is “what does a certain genetic finding mean for the fetus or the pregnancy”. Therefore, studies on the clinical consequences of the finding of a RAT with NIPT are needed. As the frequency of these RATs is low, this should be large-scale studies, in order to obtain sufficient power.

Q: Does the extra information we need on outcomes for NIPT-detected RATs/CNVs just need more time to be collected, or are more (or better!) studies needed?

A: See the answer on the second question. Both are needed: we need data from well-designed large-scale studies, with sufficient genetic and clinical follow-up. This will of course take time.