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Could ovarian stimulation cause an increase in oocyte chromosome abnormalities?

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Ovarian stimulation undertaken by women of advanced maternal age (over 35 years) receiving fertility treatment may be disrupting the normal pattern of meiosis – a critical process of chromosome duplication followed by two specialised cell divisions in the production of oocytes and sperm – and leading to abnormalities of chromosome copy numbers (aneuploidy) that result in IVF failure, pregnancy loss or, more rarely, the birth of affected children with conditions such as Down's syndrome, which is caused by the inheritance of three copies of chromosome 21 (trisomy 21).

Researchers involved in ESHRE's polar body screening study (launched in 2009) will tell the annual conference of the European Society of Human Reproduction and Embryology today (Monday) that results from the study are leading to a new understanding about how such abnormalities are developing, and they believe that the ovarian stimulation a woman receives might be playing a part. Understanding the mechanisms involved could help older women who are trying to have a healthy baby with their own oocytes.

Professor Alan Handyside, Director of The London Bridge Fertility, Gynaecology and Genetics Centre, London, UK, and colleagues from eight countries undertook a proof of principle study of a novel method of screening polar bodies, small cells that are the by-product of oocyte development, using the new technology of microarray comparative genomic hybridisation (array CGH) in order to find whether this was a reliable method of analysing the chromosomal status of an oocyte. This

is because many more chromosome copy number abnormalities arise in the oocyte than in sperm.

"In doing so, we obtained a lot of data at the individual chromosome and chromatid level," says Professor Joep Geraedts, co-ordinator of the ESHRE Task Force on preimplantation genetic screening (PGS). (A chromatid is one of the two identical copies of DNA making up a duplicated chromosome). "So we decided to analyse these data separately to see whether they could provide us with information that could be useful in determining better treatment strategies for the future."

"In this unique study, we were able to use the new technology of array CGH to examine the copy number of all 23 pairs of chromosomes, in all three products of female meiosis in over 100 oocytes with abnormal numbers of chromosomes," says Professor Handyside. "What happens in female meiosis is that the 23 pairs of chromosomes duplicate and each pair of duplicated chromosomes comes together and the four single chromosomes, or 'chromatids', become 'glued' together along the whole length of each chromosome. This actually occurs before the woman is born and is the stage at which DNA is swapped between the grandparents' chromosomes.

"Sometimes, decades later, just before ovulation, the glue 'dissolves' first between the two duplicated chromosomes and finally after fertilisation between the two individual chromosomes. This enables pairs of chromosomes to segregate in the first meiotic division producing the first polar body. In the second meiotic division the second polar body is produced, resulting in a single set of chromosomes in the fertilised oocyte or 'zygote', which, when combined with the single set in the fertilising sperm, restores the 23 pairs," he says.

The researchers believe that ovarian stimulation may be disturbing this process in older women because the chromosomes are becoming unglued

prematurely, particularly the smaller ones like chromosome 21. Ovarian stimulation uses hormonal medication to stimulate the ovaries to release a larger number of oocytes than normal, in order to provide enough good quality oocytes for fertilisation in vitro.

Following natural conception in older mothers, Down's pregnancies are predominantly caused by errors in the first female meiotic division. "Our evidence demonstrates that, following IVF, there are multiple chromosome errors in both meiotic divisions, suggesting more extensive premature separation of single chromosomes resulting in more random segregation, which in turn results in multiple chromosome copy number changes in individual oocytes," says Professor Handyside.

"We need to look further into the incidence and pattern of meiotic errors following different stimulation regimes including mild stimulation and natural cycle IVF, where one oocyte per cycle is removed, fertilised and transferred back to the woman. The results of such research should enable us to identify better clinical strategies to reduce the incidence of chromosome errors in older women undergoing IVF."

"We also believe that our research will help identify women who want to have their own offspring but have practically no chance of doing so that we can advise them to use donor oocytes," says Professor Geraedts. "This in itself is already a big step forward that will aid couples hoping for a healthy pregnancy and birth to be able to achieve one."

Provided by European Society of Human Reproduction and Embryology