Study finds why some women are sub-fertile with a poor response to ovarian stimulating hormones

June 29 2010

Researchers have discovered that some women carry a genetic variation that makes them sub-fertile and less likely to respond to ovarian stimulating hormones during fertility treatment. The discovery opens the way to identifying these women and devising personalised fertility treatments that could bypass the problem caused by the genetic abnormality.

Dr Maria Lalioti told the 26th annual meeting of the European Society of Human Reproduction and Embryology in Rome today that she and her colleagues from the Yale University Medical School, New Haven (USA), had found that some women had an abnormal hormone receptor on cells surrounding oocytes (eggs). This abnormal receptor impaired the function of normal receptors that were also present and resulted in the affected women responding less well to Follicle Stimulating Hormone (FSH), which is given to women during fertility treatment to stimulate the production of more than one oocyte.

Dr Lalioti, as assistant professor in the Department of Obstetrics Gynecology and Reproductive Sciences at Yale, said: "When a woman undergoes in vitro fertilisation, she receives medication called Follicle Stimulating Hormone to produce more than one oocyte, which is the normal production each month. Cells called granulosa cells, which surround the oocyte, receive the FSH; these cells excrete other factors that 'feed' the oocyte. The granulosa cells have proteins present on their

surface called FSH receptors (or FSHR) and it is these proteins that stick to the FSH and then carry signals into the cell's interior. When we looked at a portion of these granulosa cells in the laboratory we saw that in some women, who produced very few oocytes, there were some receptors that lacked a piece of the protein, although there were still other, normal FSHR in the women's cells."

The abnormal FSHR contained a deleted sequence of protein called exon 2 that is an important part of the protein that binds the FSH; FSHR with the exon 2 deletion was only detected in women younger than 35 who had a poor response to FSH and yielded less than four oocytes in a follicle stimulating cycle.

"We produced the normal and abnormal protein in the lab in a different type of cell called HEK293 (Human Embryonic Kidney) which is a common cell type used in the labs to examine properties of proteins. We saw that when the abnormal receptor was present, the normal one could no longer work as well as it does when it is the only protein present," explained Dr Lalioti. "The receptor is normally present on the cell surface in order to meet and bind FSH, and it needs to go through a number of cellular checkpoints inside the cell that assure the quality of the protein presented on the surface. We saw that the abnormal receptor remains longer in one of these checkpoint compartments, indicating that the cell has detected a problem and is trying to correct it. In this way the abnormal FSHR can contribute to an abnormally low response to stimulation in certain women undergoing IVF."

Dr Lalioti's discovery of the mechanism behind why some young women have a poor response to FSH has important implications for future research and treatment of these women. "The importance of this finding is that it creates a link between genetic variation and sub-fertility. These women have a normal menstrual cycle and they may present to the fertility centre as patients with unexplained infertility, before their first

IVF cycle that would reveal an ovarian stimulation defect," she said.

"Our finding explains why these women have a lower response to FSH. Currently, FSH is the only medication used to stimulate ovarian response, but once other medications are available that can bypass the receptor for FSH, they can be tested on these women. Also, at present we cannot predict if the women would profit from having higher doses of medication, and, in fact, some preliminary data from other groups show the opposite: that lower FSH may be more beneficial."

Future research will examine the FSHR signalling mechanisms within the cell and investigate how newly developed drugs might bypass the problems created by the genetic abnormality. "In the future, this could lead to personalised treatments for a sub-group of patients," said Dr Lalioti.

It is not known how many women have this particular genetic variation. Dr Lalioti found it in two out of five women that she tested. "These patients are hard to recruit because most patients with a low response to FSH do not complete the IVF cycle for financial reasons," she said. "We need to recruit more patients to discover how common it is." She and her colleagues will need a year to recruit and test more women, to set up collaborations with more fertility centres and to start to test new drugs that could promote oocyte production more effectively in these women.

Provided by European Society of Human Reproduction and Embryology