

### **Reduced ovarian reserve is associated with an increased risk of trisomic pregnancy**

Women who have a diminished number of eggs in their ovaries, either because they are older or for some other reason such as ovarian surgery, may be more at risk of a trisomic pregnancy than women with an ovarian reserve within the normal, fertile range.

Trisomic pregnancies occur when the embryo has three copies of a chromosome rather than the normal two. The most common trisomy is Down's syndrome or trisomy 21. Most foetuses with other trisomies miscarry, but if they are born alive then they have multiple abnormalities and usually die in childhood.

Dr Maaike Haadsma, a researcher in the departments of obstetrics & gynaecology and genetics at the University Medical Center Groningen (The Netherlands) presented her findings at the 25<sup>th</sup> annual meeting of the European Society of Human Reproduction and Embryology in Amsterdam today (30 June 2009).

She said: "The results of my study support a relation between trisomic pregnancy and a decreased quantity of eggs available in the ovaries of women attending fertility clinics for IVF treatment. This finding is independent of the women's age. This suggests that the effect of a mother's age on the risk of trisomy may be explained by the age-related decrease in the numbers of eggs. Younger women may also be at increased risk of trisomic pregnancy if their ovarian reserve is reduced, either because of treatment affecting the ovaries such as surgery, or because of their genetic inheritance."

Dr Haadsma and her colleagues analysed data from a nationwide group of 19,840 women undergoing fertility treatment in The Netherlands from 1983-1995. They identified 28 women who had a trisomic pregnancy after IVF and matched them with a control group of women who had healthy children. They looked at three indications of ovarian reserve: 1) a history of ovarian surgery at the time of IVF treatment (such as the removal of benign ovarian cysts); 2) the number of eggs (oocytes) retrieved during the fertility treatment; 3) menopausal status at the end of the study period.

They found that a history of ovarian surgery increased the risks of trisomic pregnancy more than three-fold; if only four or fewer eggs were retrieved during treatment, this quadrupled the risk of trisomy (conventional IVF aims to retrieve between 8-10 eggs at one time); if there were signs of the menopause at the end of the study period, this increased the risk of a trisomic pregnancy more than five-fold.

"The biological mechanism behind our findings is, as yet, unclear," said Dr Haadsma. "It may be that women use their 'best' eggs first in their fertile life and leave their abnormal ones to the last. Women with fewer eggs would then be at increased risk of trisomic pregnancy. However,

more convincing in my opinion, is the hypothesis that the chance that a fertilised, abnormal egg is selected for embryo transfer in IVF is increased in women with reduced ovarian reserve, simply because there are fewer eggs and thus embryos to choose from. The proportion of normal and abnormal embryos may be the same in women with normal and diminished ovarian reserve, but if you only have one or two embryos available (instead of, say, six or eight) the chance that no normal embryo is available is relatively high.”

As women get older their supply of eggs decreases. In younger women, the reasons for a diminished ovarian reserve are more complex. “Next to ovarian surgery, other medical interventions, such as chemotherapy or radiotherapy, may cause a decrease in ovarian reserve. However, a woman's ovarian reserve is most likely to be mainly determined by her genes: the number of oocytes a woman is born with and the rate of depletion of her oocyte pool is believed to be heritable. This is reflected in the similar ages at menopause of mothers and daughters. However, exactly which genes are involved remains to be determined,” said Dr Haadsma.

She concluded: “Since we studied a relatively small number of women, our results should be interpreted as an indication and not as proof of a relation between ovarian reserve and trisomy risk. We have to confirm our findings in a different IVF cohort first and then determine the exact extent of the increase in trisomy risk. Then the next step would be to study our hypothesis in a fertile group of women, since results from women having IVF cannot be extrapolated to the general population right away. If our findings are indeed confirmed, women with reduced ovarian reserve should be informed about their 'new' trisomy risk. It's perceivable this may influence their choices in prenatal testing.”