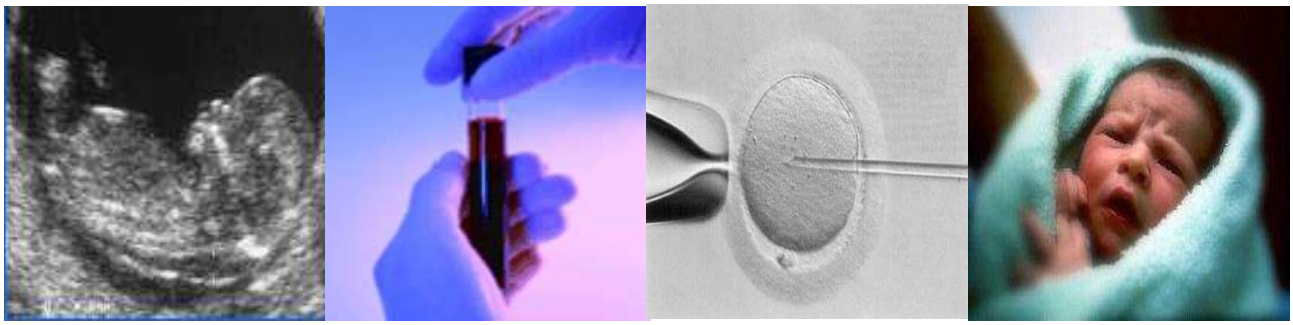

Prenatal screening and diagnosis among women pregnant after assisted reproductive technology

PhD Thesis, 2008

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This Ph.d. thesis is based on research performed at the Department of Obstetrics and Gynaecology, Hvidovre Hospital and the Department of Fetal Medicine, Rigshospitalet in the period 2004-2007. The research has been performed in close collaboration with the department of Clinical Biochemistry, Statens Serum Insititute and the Fertility Clinic, Rigshospitalet. Additionally all Danish Fertility clinics together with the major departments of Fetal Medicine have participated in acquisition of data.

The project consisted of two subprojects:

1. A retrospective register study aimed to analyse the use and results of prenatal invasive diagnostic testing in a national cohort of 8531 women pregnant after IVF/ICSI and their 10506 outcomes in the period 1995-2000. Additionally we wanted to describe to what extent second trimester serum screening was used in this cohort. The conclusion from this study was that women pregnant after ART are reluctant to have invasive testing performed. 49% had an indication for invasive testing either due to advanced maternal age (≥ 35 years) or ICSI treatment, but only 16.3% had an invasive test performed. Altogether 1586 fetuses were karyotyped. The rate of chromosome abnormalities in the overall ART group was 0.6% which is similar to what is described in background populations. The rate of chromosome aberrations was significantly increased in the ICSI group compared to the IVF group, 1.3% versus 0.5% ($p<0.0001$), respectively. Surprisingly few had second trimester serum screening performed, only 7.4%.

2. A nationwide prospective cohort study where all Danish Fertility Clinics were given the opportunity to offer first trimester combined screening with doubletest and nuchal translucency scan to women who became pregnant after IVF/IVSI, before this was introduced as a national offer. The aim was to evaluate the performance of screening, as previous studies had demonstrated that second trimester serum screening had poorer performance with a higher false-positive rate due to alterations of the screening markers when used among women pregnant after ART. Furthermore several studies, however with very limited number of cases, had suggested that this might be the case for first trimester screening as well. Additionally we wanted to assess which factors might influence the screening markers in this selected population of pregnant women.

We found that the level of PAPP-A was significantly reduced among 1,000 women pregnant after IVF and ICSI compared to a control group of 2618 spontaneously conceived pregnancies (0.78 MoM and 0.79 MoM versus 0.98 MoM ($p< 0.001$)), respectively. The concentration of free β-hCG was unchanged. Surprisingly the thickness of the nuchal translucency was decreased in the fetuses

of IVF-pregnancies. As an exception, the screening markers in women pregnant after frozen embryo transfer were equal to those in the spontaneously conceived control group.
The altered screening markers caused a significant increased false positive rate, also after adjustment for maternal age 9.0% compared to 6.0%, $p < 0.001$. We also found that the serum markers were greatly altered in a small group of women who were either diagnosed with polycystic ovarian syndrome before fertility treatment or with ovarian hyperstimulation syndrome during the pregnancy in question (median PAPP-A 0.50 MoM and median β-hCG 0.72 MoM), however the number of cases was much too small to make the difference significant.
In a sub-study we investigated whether determination of gestational age (GA) by either date of oocyte aspiration (DOA) or ultrasound assessment (CRL) for first trimester screening would influence the distribution of serum and sonographic markers and thereby potentially the performance of first trimester screening for chromosomal abnormalities. We found that CRL GA dating resulted in significantly, albeit slightly, higher mean log MoM values compared to DOA dating. The reverse was the case for mean log MoM PAPP-A. The standard deviations were similar in CRL and DOA GA dating. The effect on screening performance was assessed by Monte Carlo estimation, and it was found that at a risk cut-off of 1:250 at term the detection rate for Down's syndrome was 82% and 84% for CRL based and DOA based GA dating, respectively. In both cases the false-positive rate was 3%. We concluded that DOA and CRL are equivalent when calculating GA for first trimester serum screening.

In conclusion this thesis demonstrated that women pregnant after ART represent a highly selected group of pregnant women in regard to prenatal screening, both in regard to risk of chromosomal abnormalities, biological screening marker profile as well as psychological mechanisms. It is deemed necessary to take this into account in genetic counselling and in risk assessment.