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Maternal concentrations of human chorionic gonadotrophin in very early IVF pregnancies and duration of pregnancy: a follow-up study

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KEY MESSAGE

In singleton pregnancies, the concentration of HCG at a fixed time after embryo transfer varied substantially. Low HCG concentrations in very early pregnancy were associated with longer duration of pregnancy, significantly in pregnancies delivered at term only.

A B S T R A C T

Research question: Are maternal concentrations of human chorionic gonadotropin (HCG) on a fixed day after embryo transfer associated with duration of pregnancy?

Design: A follow-up study of 1917 singleton pregnancies after IVF was performed. Embryos were cultured for 2 days and maternal HCG concentration quantified on day 12 after embryo transfer. Duration of pregnancy was obtained from the Medical Birth Registry of Norway. Association of HCG concentration (log2-transformed) with duration of pregnancy was estimated as hazard ratios (HR) with 95% confidence intervals (CI) by applying Cox regression proportional hazard models, where time to delivery for pregnancies shortened because of planned Caesarean delivery or induction of labour was treated as censored.

Results: The estimated median duration of pregnancy from embryo transfer was 266 days (95% CI 266–267 days). Maternal concentration of HCG on day 12 after embryo transfer varied from 1 to 588 IU/l (median 117 IU/l). Duration of pregnancy decreased by increasing HCG concentration, significantly in pregnancies delivered at full term ([257–270 days after embryo transfer; HR 1.127, 95% CI 1.026–1.238, $P = 0.012$). For each doubling of HCG concentration on day 12 after embryo transfer, duration of pregnancy was shortened by 0.51 days. Adjustment for maternal age, prepregnancy body mass index, being a first-time mother and number of embryos transferred did not change the association.

Conclusion: High maternal HCG concentration on a fixed day after embryo transfer is likely to indicate early embryo implantation. After embryo transfer, pregnancies with early implantation are shorter than pregnancies with late implantation.

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Introduction

A normal human pregnancy lasts approximately 40 weeks from the first day of the last menstrual period. However, there is large inter-individual variation in duration of pregnancy, and durations of 37 to 42 weeks from last menstrual period are considered normal. The causes of the large variation in duration of human pregnancy remain poorly understood (Gjessing et al., 1999; Jukic et al., 2013; Lie et al., 2006).

It is conceivable that the timing of spontaneous labour in a normal pregnancy is related to the gestational age of the fetus. However, in women with the same date of last menstruation, the true gestational age of the fetus may not be the same. The interval from last menstrual period until implantation of the embryo into the endometrium may vary (Baird et al., 1995; Jukic et al., 2013; Wilcox et al., 1999). Also the interval from ovulation until embryo implantation varies, and this variation has been estimated from 6 to 12 days (Jukic et al., 2013; Wilcox et al., 1999, 2000). Thus, in pregnancies with the same number of days since the last menstrual period, the true age of the fetus may vary considerably.

In pregnancies after IVF, the time of conception and the time of embryo transfer into the uterus are known. The exact time of embryo implantation, however, is not known (Englert et al., 1984; Ertzeid et al., 2000; Richard et al., 2001). Human chorionic gonadotrophin (HCG) is synthesized in trophoblast cells, and the maternal concentrations of HCG increase rapidly during the first weeks of pregnancy with a doubling time of 1–2 days shortly after implantation (Ertzeid et al., 2000; McChesney et al., 2005). The serum concentrations of HCG in very early pregnancy are therefore likely to indicate time since embryo implantation.

If the true gestational age of the fetus since embryo implantation is related to duration of an IVF pregnancy, it is likely that pregnancies with delayed embryo implantation may last longer than pregnancies with implantation shortly after transfer. If this is true, low maternal HCG concentrations on a fixed day after embryo transfer may be associated with longer duration of pregnancy.

This study examined the associations of maternal HCG concentration on day 12 after embryo transfer with duration of pregnancy. In total, 1917 successful singleton IVF pregnancies were included in the study.

Materials and methods

The study sample was recruited from the Department of Reproductive Medicine, Oslo University Hospital, Rikshospitalet, Norway during the years 1999–2013 (**Figure 1**). During these years, there were a total of 4693 pregnancies after IVF with delivery after 16 weeks of pregnancy. In the study sample, IVF pregnancies after fertilization with and without intracytoplasmic sperm injection (ICSI) were included, and only embryos from fresh cycles were transferred. All oocytes used for treatment were autologous. Only 3277 singleton pregnancies were eligible for the study, since in twin pregnancies, the HCG concentrations are higher and duration of pregnancy is shorter than in singleton pregnancies (Bjercke et al., 1999; Bortolus et al., 1999). To avoid possible bias associated with the age of the transferred embryo, pregnancies after transfer of day 2 embryos only (n = 2120) were included. Of these, the 1919 pregnancies for which maternal HCG concentrations were measured on the morning of day 12 after embryo transfer were included. One pregnancy was excluded because of outlying maternal HCG concentration (>1000 international units per litre (IU/l)), and one pregnancy was excluded because of outlying duration of pregnancy (313 days since embryo transfer). Thus, the study sample included 1917 pregnancies with HCG concentrations measured 12 days after transfer of day 2 embryos.

The study outcome measure was duration of pregnancy (time to delivery) in days, from embryo transfer until delivery. Information on date of embryo transfer was obtained from the electronic patient record at the Department of Reproductive Medicine, Oslo University Hospital, Rikshospitalet. Information on date of delivery was obtained by individual linkage to the Medical Birth Registry of Norway (Irgens, 2000), by using the mothers' unique person identification number. The Medical Birth Registry of Norway holds information about all births after 16 weeks of gestation since 1967, and the notification of births is mandatory by law.

The main exposure measure in this study was HCG concentration (IU/l) in maternal serum sample drawn in the morning on day 12 after embryo transfer. Serum HCG concentrations were quantified at the Department of Medical Biochemistry, Oslo University Hospital, Rikshospitalet by using an electro-chemiluminescence immunoassay method (Elecesys; Roche, Basel, Switzerland), which measures intact HCG and free β-HCG chain with a detection limit of 0.5 IU/ml. Control analyses at the hospital have shown a low within-series variation (coefficient of variation <4%) and low variation over time (coefficient of variation <5%). This is in agreement with the corresponding figures given by the manufacturer (Eskild et al., 2012).

The data analyses included the following potentially confounding factors: maternal age and prepregnancy maternal body mass index (BMI; kg/m^2) as continuous variables (Bergsjø et al., 1990; Eskild et al., 2012; Haavaldsen et al., 2014). Also, parity (first time mother; yes versus no) and number of embryos transferred (1 versus 2) were included (Almog et al., 2010; Bergsjø et al., 1990; Haavaldsen et al., 2014; Pinborg et al., 2005).

Ethical approval

This study was approved by the Regional Committee for Ethics in Medical Research in Norway on 27 February 2017 (reference number 2011/2465).

Statistical analysis

The distribution of HCG concentration and duration of pregnancy are presented in figures: for all pregnancies, for pregnancies with spontaneous onset of labour (including emergency Caesarean delivery), and for pregnancies that were shortened because of planned Caesarean delivery or induction of labour.

Within the pregnancy subtypes described above, means with standard deviation (SD) are presented for continuous study factors and percentages for categorical study factors for all pregnancies: for pregnancies with delivery at early term and pregnancies with delivery at full term. Early-term deliveries were pregnancies with a duration of 243–256 days (37.0–38.9 weeks) after embryo transfer, and full-term deliveries were pregnancies with a duration of 257–270 days (39.0–40.9 weeks) after embryo transfer. The corresponding duration of spontaneous pregnancies, would be 259–272 days (37–38 weeks) for early-term delivery, and 273–286 days (39–40 weeks) for full-term delivery. For this calculation, 2 days of embryo culture and 14

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