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Maternal human chorionic gonadotrophin concentrations in very early pregnancy and risk of hyperemesis gravidarum: A retrospective cohort study of 4372 pregnancies after in vitro fertilization

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ABSTRACT

Objective: We investigated the association of human chorionic gonadotrophin (hCG) concentrations on a fixed day in very early pregnancy with development of hyperemesis gravidarum.
Study design: This retrospective cohort study included 3107 singleton and 1265 twin pregnancies after in vitro fertilization treated at Department of Reproductive Medicine, Rikshospitalet, Oslo University Hospital, Norway in the period 1996–2013. Maternal serum hCG concentrations was measured on day 12 after embryo transfer. Information about development of hyperemesis gravidarum was obtained by individual linkage to the Medical Birth Registry of Norway. We studied hCG concentrations in very early pregnancy according to development of hyperemesis gravidarum, in singleton and twin pregnancies separately. We estimated the odds ratios for hyperemesis gravidarum with 95% confidence intervals according to quartiles of hCG concentrations.
Results: In twin pregnancies as compared to singleton pregnancies, we found higher mean maternal hCG concentrations (219 IU/L versus 130 IU/L, $p < 0.001$ Student's *t*-test) and higher prevalence of hyperemesis gravidarum (2.7% versus 1.4%, $p = 0.002$ chi-squared test). However, both in singleton and in twin pregnancies, we found no significant difference in mean hCG concentrations between women who developed hyperemesis gravidarum and women who did not (Singletons: 122 IU/L versus 130 IU/L, $p = 0.504$. Twins: 234 IU/L versus 219 IU/L, $p = 0.417$ Student's *t*-test). We found no significant differences in odds ratios for developing hyperemesis gravidarum according to quartiles of hCG concentrations.
Conclusions: We found no association of maternal hCG concentrations on a fixed day in early pregnancy with development of hyperemesis gravidarum.

Introduction

Hyperemesis gravidarum is a condition of intractable nausea and vomiting that starts before the 22nd week of pregnancy [1,2]. Hyperemesis gravidarum can give rise to complications such as dehydration, metabolic disturbances, and electrolyte imbalance, and the condition occurs in approximately 0.3-2% of all pregnancies [3]. Hyperemesis gravidarum is distressing and debilitating for the women affected [4], and it is a major cause of hospitalization during pregnancy [5].

Several risk factors for hyperemesis gravidarum have been identified, including young age, nulliparity, psychiatric illness, female fetus, twin pregnancy, a previous pregnancy complicated by hyperemesis, and hyperthyroidism [6–8].

Elevated concentrations of maternal human chorionic gonadotrophin (hCG) have been suggested as a cause of hyperemesis gravidarum. The reason for such suggestion is that the prevalence of hyperemesis gravidarum is at its highest when the hCG concentrations is at its peak level around pregnancy week 10 [9]. Also, women with a twin pregnancy have increased risk of hyperemesis gravidarum, and in these pregnancies the concentrations of hCG is higher than in singleton pregnancies. However, no causal relationship between hyperemesis gravidarum and hCG concentrations has been established [6].

Abbreviations: hCG, human chorionic gonadotrophin; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; BMI, body mass index; OR, odds ratio; SD, standard deviation; 95% CI, 95% confidence interval.

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In early pregnancy, hCG concentrations increase by number of days since implantation of the embryo into the endometrium [10]. In spontaneous pregnancies, the time of embryo implantation is usually not known. Thus, differences in duration of pregnancy at the time of hCG quantification between women with and without hyperemesis gravidarum could cause erroneous estimates of the association of hCG concentrations with hyperemesis gravidarum. We are not aware of any previous studies of hCG concentrations at a fixed day in early pregnancy and subsequent risk of hyperemesis gravidarum. Therefore, we included 3107 singleton and 1265 twin pregnancies after in vitro fertilization (IVF) in a retrospective cohort study, and we explored the relationship between maternal hCG concentrations in very early pregnancy with the development of hyperemesis gravidarum.

Materials and methods

We used data on IVF pregnancies from Department of Reproductive Medicine, Rikshospitalet, Oslo University Hospital, Norway and the Medical Birth Registry of Norway during the years 1996–2013. The Medical Birth Registry of Norway contains information on all births in Norway after 16 weeks of gestation since 1967 [11]. We defined successful IVF pregnancies as birth after 16 weeks of gestation. By individual linkage between our two data sources, using the women's unique person identification number, we retrieved a total of 5458 successful pregnancies during the years 1996–2013 with prospective information from IVF treatment until birth.

Only women with serum hCG concentrations quantified on day 12 after embryo transfer were included in our study ($n = 4534$). Thus, out of a total of 5458 eligible women, we excluded 924 women without information about hCG concentrations at day 12 after embryo transfer (Fig. 1). We also excluded women who had outlying hCG values (> 1000 IU/L (international units per litre)) ($n = 3$), and women who were pregnant with three or more fetuses ($n = 39$). Additionally, we excluded women with outlying or missing values on other study factors ($n = 120$). Thus, our study sample included 4372 women, of whom 3107 (71%) had a singleton and 1265 (29%) had a twin pregnancy.

Of the IVF pregnancies, 54.3% were after IVF without intracytoplasmic sperm injection (ICSI), 37.3% were after IVF with ICSI, and 8.4% were after transfer of frozen-thawed embryos. Ovulation induction was performed with 6500–10000 IU/L hCG (Ovitrelle, Serono or Pregnyl, Organon) as a single dose and for luteal-phase support progesterone in oil (25 mg IM), or intravaginal capsules (600 mg Progestan, Organon) was used [12]. Ovarian stimulation, transvaginal oocyte retrieval, fertilization in vitro, culture and transfer of embryos were performed according to standard procedures [13]. Transfer of frozen-thawed embryos was performed in a natural menstrual cycle.

Information about development of hyperemesis gravidarum was obtained from the Medical Birth Registry of Norway. Doctors in antenatal care report presence of hyperemesis gravidarum on a standardized antenatal patient record, and this information is transferred to the birth notifications charts after the delivery [11,14]. Validation of the diagnosis of hyperemesis gravidarum in the Medical Birth Registry of Norway suggests high specificity (96.0%) and the sensitivity is 83.9% [14]. Hyperemesis gravidarum was coded according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision by the Medical Birth Registry of Norway, and included the following; O-21.0 (excessive vomiting starting before the end of the 22nd week of pregnancy), O-21.1 (excessive vomiting starting before the end of the 22nd week of pregnancy with metabolic disturbances) and O-21.9 (excessive vomiting of pregnancy, unspecified).

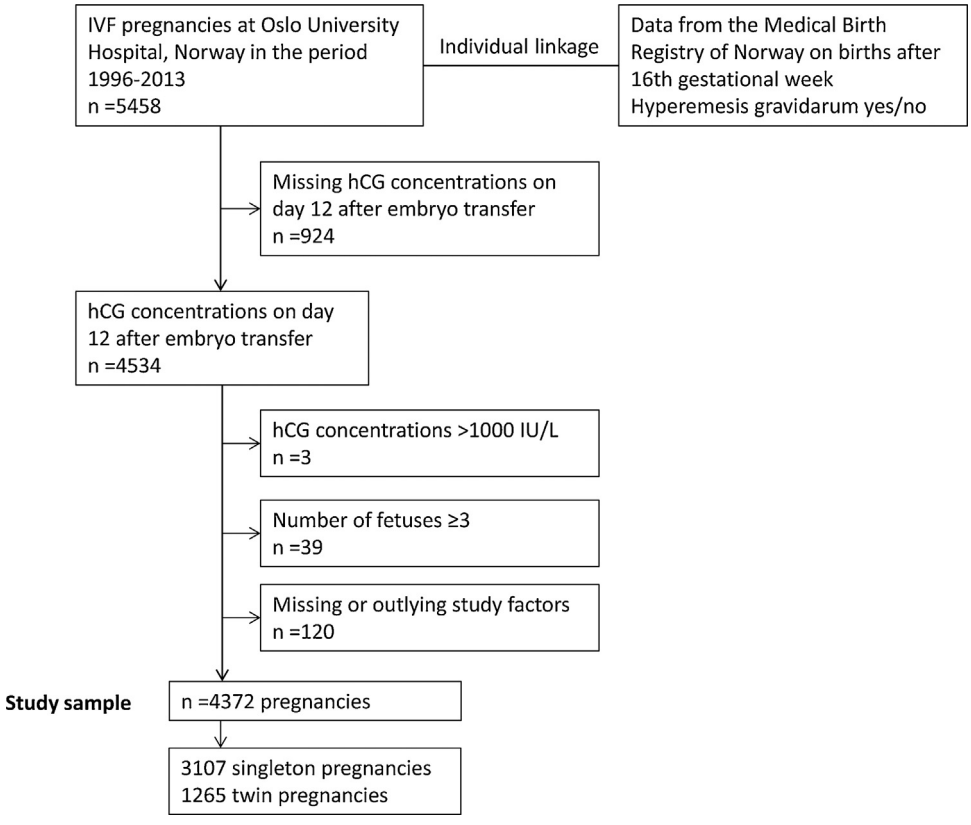

Fig. 1. Flow chart.
hCG, human chorionic gonadotrophin; IU/L, international units per litre.