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Human chorionic gonadotropin, fetal sex and risk of hypertensive disorders of pregnancy: A nested case-control study

Qizhen Zheng [a,b], Yuqing Deng [a,c,*], Shilin Zhong [a], Yu Shi [a]

[a] Department of Obstetrics and Gynecology, Peking University Shenzhen Hospital, Shenzhen 518036, China
[b] Shantou University Medical College, Shantou 515041, China
[c] Shenzhen Key Laboratory of Gynaecology Diagnostic Technology Research, Shenzhen, China

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ABSTRACT

Objectives: To assess whether human chorionic gonadotropin (HCG) and fetal sex are two independent risk factors for hypertensive pregnancy in the early second-trimester of pregnancy.
Methods: This was a retrospective nested case-control study based on a cohort of 2521 singleton pregnancies, among whom we recruited 98 hypertensive pregnancies (subdivided into severe preeclampsia, $n = 34$; mild preeclampsia, $n = 29$ and gestational hypertension, $n = 35$) and 196 normotensive pregnancies. Maternal serum HCG levels were measured at 15–20 weeks of gestation and fetal sex was determined from the neonatal record. Mann–Whitney U and chi-square tests were performed to assess differences of HCG levels and fetal sex between groups. Logistic regressions were performed to evaluate the effect of HCG and fetal sex on hypertensive pregnancy.
Results: There were 35 male and 63 female fetuses in the hypertensive group, and 102 male and 94 female fetuses in the normotensive group ($p = 0.008$). HCG (MoM) levels were significantly higher in only severe preeclamptic pregnancies ($n = 34$) ($p = 0.013$). There were no significant differences of the HCG (MoM) levels between male and female fetuses in each sub-group. aOR for increased maternal HCG levels and female fetus were 2.4 (95% CI: 1.434–3.954) and 2.9 (95% CI: 1.227–6.661) respectively in severe preeclamptic pregnancies compared with normotensive pregnancies.
Conclusions: There is a female preponderance in hypertensive pregnancies. Increased HCG levels and female fetus are two independent risk factors for severe preeclampsia in the early second-trimester of pregnancy.

1. Introduction

Hypertensive disorders are major complications of pregnancy, especially preeclampsia (PE), which is commonly associated with significant maternal and fetal morbidity and mortality [1,2]. The exact pathophysiology of PE remains unclear, but it is widely acknowledged that PE is a syndromic disease with different paththophysiologic pathways, in which impaired placentation, maternal constitution, abnormal circulatory and immunological adaptation to pregnancy may play a role [3].

Human chorionic gonadotropin (HCG), a hormone comprised of an α and β subunit, is mainly produced by the placental syncytiotrophoblasts [4]. Throughout normal pregnancy, mean concentration of HCG increases rapidly and peaks at around 10 weeks of gestation and maintain a significant level to around 20 weeks [5]. Therefore, HCG levels can be used to assess placental functions in the early stage of pregnancy.

During the past decade, abnormal changes of HCG levels during pregnancy have been considered as a reliable marker of PE [5–7]. The female fetus was reported to be preponderant in hypertensive pregnancies [8,9]. Some other publications indicated that female fetus may be associated with increased HCG levels in the first or third trimester of pregnancy [10,11]. So is HCG a real promising marker for PE or is it affected by fetal sex? The aim of our study was to investigate the effect of fetal sex and HCG levels on PE/gestational hypertension (GH) compared with normotensive pregnancies (NP), and to evaluate whether there is a correlation between fetal sex and maternal serum HCG levels at 15–20 weeks of gestation.

* Corresponding author at: Shenzhen Key Laboratory of Gynaecology Diagnostic Technology Research, Shenzhen, China.
E-mail address: dengyuqing666@163.com (Y. Deng).

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2. Materials and methods

2.1. Study participants and categories

This cohort-based study was designed as a retrospective nested case-control investigation. Singleton pregnancies who underwent a 15–20 weeks aneuploidy screening and gave birth at our hospital between May 2014 and June 2015 were enrolled. The inclusion criteria was singleton pregnancy subsequently delivering a phenotypically normal live birth at term and not having developed any pregnancy complications. The exclusion criteria was pregnancy with aneuploidies or major fetal abnormalities and those ending in termination, miscarriage, or fetal death at <28 weeks' gestation. For each pregnancy with subsequent hypertensive disorder that was eligible for the study, we randomly selected two controls per case from normotensive pregnancies, and matched as closely as possible by gestational age (GA), maternal age and body mass index (BMI) at enrollment. The local ethics committee approved the study protocol and each patient was provided with written informed consent. For the outcome categories, GH was defined as the new onset of blood pressure $\geqslant$140 mm Hg systolic or $\geqslant$90 mm Hg diastolic without evidence of proteinuria. PE and subdivisions were defined according to the ACOG Practice Bulletin on Diagnosis and Managing Preeclampsia-Eclampsia [12].

2.2. Clinical data and sample collection and measurement

Demographic data consisting of maternal age, parity, race, GA and BMI was recorded by a midwife or obstetrician at enrollment. GA was calculated based on first-trimester Crown-rump Length (CRL) or last menstrual period. Pregnancy outcomes (e.g. GH/PE) and neonatal findings (e.g. gestational age at delivery, fetal gender, birth weight, neonatal death) were examined from hospital discharge records.

Five cubic millimeters of blood were drawn by venipuncture from each patient at enrollment and collected in an EDTA-containing tube. The blood samples were centrifuged at 3000 rpm for 20 min, and the serum was separated. As part of the screening, serum HCG concentrations were measured at the Department of Medical Biochemistry, Division of Diagnostics and Technology, Peking University Shenzhen Hospital with an Abbott Architect i2000sr Immunology Analyzer (Diamond Diagnostics, USA) within 24 h. Marker levels were converted to Multiple of Medium (MoM) of the normotensive pregnancies and adjusted for GA, maternal age and weight as appropriate.

2.3. Statistical analysis

Quantitative demographic data was expressed as mean ± SD. Analysis of variance (ANOVA) or t-tests were used for the comparison of continuous variables, and chi-square tests were used for categorical variables. Since HCG (MoM) distribution in the normotensive group departed from normality, descriptive statistics [median (IQR)]were generated. Comparison of HCG (MoM) levels between different groups, as well as the two fetal genders were carried out by nonparametric Kruskal–Wallis and Mann–Whitney U tests. Odds ratios (ORs) were adjusted with the use of logistic-regression analysis. p values (two-tailed) less than 0.05 were considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science; release 19.0; Chicago, IL).

3. Results

Totally 294 women were included in the final analysis. Ninety-eight women comprised the hypertensive group, as they developed either severe preeclampsia (SPE, n = 34), mild preeclampsia (MPE, n = 29) or GH (n = 35). One-hundred and ninety-six normotensive women comprised the control group. Demographic data of each group are shown in Table 1. There were no significant differences in race, maternal age, GA at enrollment and early pregnancy BMI between groups (All $p > 0.05$). There were significantly more preterm births and low birth weight infants in the severe preeclampsia group compared with the other three groups (both $p < 0.01$).

As is the shown in Table 1, female fetal gender was preponderant in hypertensive pregnancies compared with normotensive pregnancies. There were 35 male and 63 female fetuses in the hypertensive group while 102 male and 94 female fetuses in the normotensive group (p = 0.008), the female-to-male ratios were higher in each sub-group of SPE, MPE and GH, being 2.40:1.00, 1.42:1.00 and 1.67:1.00 respectively. HCG (MoM) [median (INQ)] was significantly higher in severe preeclamptic pregnancies compared with either MPE/GH or NP. [1.36 (0.81–1.97) MoM vs. 1.00 (0.80–1.32) MoM vs. 1.08 (0.55–1.34) MoM vs. 1.00 (0.74–1.28) MoM (p = 0.013). After adjusting for maternal age, parity, GA and BMI at enrollment, multiple logistic regressions found significant association between HCG levels and fetal sex with the subsequent development of severe preeclampsia. Women with increased HCG (MoM) levels or female fetuses were 2.4 and 2.9 times (adjusted OR 2.4; 95% CI 1.434–3.954 vs. 2.9; 95% CI 1.227–6.661) more likely to develop SPE than NP respectively. Fig. 1 shows there were no differences in the HCG (MoM) levels in male and female fetal sex between groups. In the severe preeclamptic group, median HCG level was moderately higher in the female-bearing pregnancies compared with male-bearing pregnancies [1.58 (0.80–1.98) MoM vs. 1.16 (0.86–2.41) MoM], but failed to yield statistical significance ($p > 0.05$).

4. Discussion

4.1. HCG and risk of preeclampsia

To date, many publications indicated changes of maternal peripheral HCG levels during pregnancy were predictive markers of preeclampsia [5,6,13,14]. Asvold and coworkers [5] suggested that high maternal serum HCG levels in the first trimester were associated with a reduced risk of preterm preeclampsia (Ptrend = 0.05), while for HCG in the second trimester, high concentrations were associated with an increased risk of preterm preeclampsia (Ptrend < 0.001). Rabie and colleague [6] detected HCG levels on day 12 of 2405 consecutive singleton pregnancies conceived by in vitro fertilization, and found that HCG levels < 50 were associated with an OR of 2.3 (95% CI: 1.2–4.7) for PE and of 4.2 (95% CI: 1.4–12.2) for SPE. Olsen and coworkers [14] conducted a retrospective study of 7767 subjects undergoing second-trimester serum aneuploidy screening and unveiled that an elevated HCG > 2MoM was associated with development of PE, OR was higher for early-onset preeclampsia (<34 weeks) than late-onset preeclampsia (>34 weeks) (3.6 vs. 2). Our study showed the early second-trimester serum HCG (MoM) levels were much higher in pregnancies which later became severe preeclamptic compared with NP (p = 0.002), whereas there were no significant differences in either MPE or GH compared with NP.

Why are the changes of HCG levels related to PE different between first-trimester and second-trimester? It is now known that the HCG decreased in the first trimester is different from that increased in the second trimester, they are hyperglycosylated HCG (hHCG) and regular HCG respectively [4,15,16]. Although both have the same α and β unit, hHCG and regular HCG are two separate molecules produced by different cells, and each has different biological functions. An summary of these two molecules is seen