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ORIGINAL ARTICLE

Maternal serum anti-Müllerian hormone at 11–13 weeks' gestation in the prediction of preeclampsia

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Abstract

Objective: To investigate the potential value of maternal serum anti-Müllerian hormone (AMH) at 11–13 weeks' gestation in the prediction of preeclampsia (PE).
Methods: The serum concentration of AMH was measured at 11–13 weeks' gestation in cases of PE ($n = 50$) and normotensive controls ($n = 150$). Backward stepwise multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of the serum AMH in the control group and from the regression model the value in each case and control was expressed as a multiple of the expected median (MoM).
Results: In normotensive pregnancies, the maternal serum concentration of AMH is higher in Afro-Caribbean than in Caucasian women and in smokers than in non-smokers. In the PE group, the median serum concentration of AMH was significantly higher than in the controls (2.140 ng/L, IQR 1.968–2.273 versus 2.062 ng/L, IQR 1.938–2.181; $p = 0.025$), but the median MoM value of AMH was not significantly different between the PE group and the controls (1.040, IQR 0.941–1.081 versus 0.995, IQR 0.939–1.065, $p = 0.147$).
Conclusions: Maternal serum AMH is not an effective early predictor for PE.

Keywords

AMH, fetal, preeclampsia

History

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Introduction

Anti-Müllerian hormone (AMH) is a heavily glycosylated homodimeric glycoprotein with two disulfide bonds, which is produced in the somatic cells of the gonads [1]. It is a member of the transforming growth factor beta (TGF-β) super-family of growth factors playing a variety of roles in reproduction, hormonogenesis, and processes of development and differentiation [2]. Serum concentrations of AMH gradually decline throughout reproductive life, becoming undetectable by the menopause [3,4] and it is considered as a reliable predictor of ovarian reserve and aging [5,6].

There are good correlations between the AMH levels and chronological age, antral follicle count and *in vitro* fertilization (IVF) outcomes [7]. Furthermore, in pregnancies conceived by assisted reproductive technology, compared to spontaneous conception, there is an increased risk of stillbirth, preeclampsia (PE), gestational hypertension, gestational diabetes mellitus, delivery of small for gestational age (SGA) neonates and cesarean section [8]. A recent study in non-pregnant women reported that in 336 with a prior history of PE there was a significantly lower serum level of AMH compared to 329 who had normotensive pregnancies [9]. Similarly, advanced maternal age, after adjustment for potential maternal and pregnancy confounding variables, is associated with an increased risk of a wide range of adverse pregnancy outcomes, including PE and birth of SGA neonates [10].

The aim of this study is to investigate whether the maternal serum concentration of AMH at 11–13 weeks' gestation is altered in pregnancies that subsequently develop PE. The AMH is a marker of ovarian reserve, hence maternal aging, which is a risk factor for the development of PE. We therefore hypothesized to expect lower AMH serum levels in PE cases than in controls.

Methods

Study population

This was a case-control study drawn from a prospective observational study for adverse pregnancy outcomes in women attending for their routine first trimester ultrasound scan in pregnancy at King's College Hospital, London. This visit, at 11–13 weeks' gestation, included recording of maternal characteristics and an ultrasound scan to firstly, confirm gestational age from the measurement of the fetal crown-rump length [11], secondly, diagnose any major fetal abnormalities and thirdly, measure fetal nuchal translucency thickness as part of combined screening for aneuploidies [12].

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Samples of serum were stored at −80 °C for subsequent biochemical analysis. Written informed consent was obtained from the women agreeing to participate in the study, which was approved by the National Research Ethics Committee.

The study population comprised of 50 pregnancies that subsequently developed PE and the controls comprised of 150 cases matched with the cases for storage time; they did not develop any pregnancy complication and resulted in the live birth of phenotypically normal neonates.

Maternal history

Patients were asked to complete a questionnaire on maternal age, racial origin (Caucasian, Afro-Caribbean, South Asian, East Asian and Mixed), cigarette smoking during pregnancy (yes or no), method of conception (spontaneous, use of ovulation drugs and IVF), parity (parous or nulliparous if no delivery beyond 23 weeks), prior and family history of PE in the mother (yes or no). The maternal weight and height were measured and the body mass index (BMI) was calculated.

Outcome measures

Maternal demographic characteristics and biochemical results were recorded in a computer database. Data on pregnancy outcomes were collected from the hospital maternity records of the women. The obstetric records of all women with pre-existing or pregnancy-associated hypertension were examined to determine if the condition was chronic hypertension, PE or non-proteinuric gestational hypertension. The definition of PE was that of the International Society for the Study of Hypertension in Pregnancy [13].

Sample analysis

All serum samples were brought to room temperature, diluted 10-fold according to manufacturer's instructions and 50 µL was used to measure the AMH concentration by competitive inhibition enzyme-immunoassay (Human ELISA Kit for Anti-Mullerian Hormone; Uscn Life Science Inc., Wuhan, Hubei, China). The detection range was 37–3000 pg/mL with a lower limit of 13.2 pg/mL. The standard curve concentrations used for the ELISA were 3000 pg/mL, 1000 pg/mL, 333.3 pg/mL, 111.1 pg/mL, 37 pg/mL. The measurements were performed in duplicates.

Statistical analysis

Comparisons of pregnancy characteristics between outcome groups were by the Mann–Whitney *U*-test for continuous variables or χ^2-test or Fisher's exact test for categorical variables. The distribution of maternal serum concentration of AMH was Gaussian (Kolmogorov–Smirnov test: $p = 0.661$). Backward stepwise multiple regression analysis was used to determine which of the factors amongst the maternal characteristics and gestation were significant predictors of the serum AMH in the control group and from the regression model the value in each case and control was expressed as a multiple of the expected median (MoM) in the control group. The Mann–Whitney test was used to determine the significance of differences in the median serum concentrations and MoM values of AMH in the PE group to that in the controls. The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp, Armonk, NY) was used for all data analyses.

Results

The characteristics of the study population are presented in Table 1. In the PE group, compared to the control group, there was a higher median maternal weight and BMI, a higher prevalence of Afro-Caribbean racial origin and prior history of PE and there was a lower prevalence of Caucasian racial origin and parous women with no prior PE. The median gestational age at delivery and neonatal birth weight were significantly lower in the PE group than in the control group.

In the control group, backward stepwise multiple regression analysis demonstrated that for the prediction of the maternal serum AMH significant independent contributions were provided by cigarette smoking and Afro-Caribbean racial origin ($R^2 = 0.068$; Table 2) but not gestational age at screening ($p = 0.146$), maternal weight ($p = 0.215$), height ($p = 0.771$), age ($p = 0.671$), method of conception ($p = 0.872$) and parity ($p = 0.839$).

In the PE group, the median serum concentration of AMH was significantly higher than the controls (2.140 ng/L, IQR 1.968–2.273 versus 2.062 ng/L, IQR 1.938–2.181, $p = 0.025$; Table 3) but the median MoM value of AMH was not significantly different (1.040, IQR 0.941–1.081 versus 0.995, IQR 0.939–1.065, $p = 0.147$; Table 3).

Discussion

The findings of this study demonstrate that at 11–13 weeks' gestation, the maternal serum MoM values of AMH are not significantly different in pregnancies developing PE compared to those that remain normotensive. Nevertheless, the uncorrected median serum concentrations of AMH are significantly higher in the PE group than in the controls. In normotensive pregnancies, the maternal serum concentration of AMH is higher in Afro-Caribbean than in Caucasian women and in smokers than in non-smokers.

The finding that maternal serum concentration of AMH is increased in Afro-Caribbean women is in keeping with a study by Gleicher et al. [14], where it was reported that African women showed a relatively high ovarian reserve at young age, characterized by the lowest FSH, the highest AMH and the highest oocyte yield compared to other races; yet, as the African women age they demonstrate the largest decline in AMH and oocyte yield and the poorest ovarian reserve compared to Caucasian and Asian women. The finding that smokers have increased maternal serum concentration of AMH is surprising because multiple epidemiologic studies have reported that cigarette smoking leads to reduced ovarian function and fertility and earlier menopause, suggesting that smoking impairs ovarian reserve [15]. The mechanism of tobacco's toxic effect on the ovary is unclear but may be due to effects on oocyte quantity [16], oocyte quality or disruption of endocrine function [17,18]. Specifically, cotinine, a major metabolite of nicotine, has been shown to accumulate in the nucleus and cytoplasm of granulosa cells [19], and nicotine has been shown to induce granulosa cell apoptosis [20], providing a possible explanation for reduced

Table 1. Characteristics in the case-control study population.

Characteristics	Normal ($n = 150$)	Preeclampsia ($n = 50$)	p value
Maternal age in years, median (IQR)	31.9 (26.9–35.9)	32.6 (29.4–37.1)	0.195
Maternal weight in kg, median (IQR)	65.0 (57.8–73.8)	76.0 (65.7–92.9)	<0.0001
Maternal height in cm, median (IQR)	163 (160–169)	163 (159–167)	0.841
Maternal BMI in kg/m^2, median (IQR)	24.2 (21.8–27.6)	28.8 (24.0–33.5)	<0.0001
Gestation at screening in weeks, median (IQR)	12.8 (12.3–13.1)	12.6 (12.3–12.9)	0.099
Racial origin			
Caucasian, *n* (%)	94 (62.7)	17 (34.0)	0.001
Afro-Caribbean, *n* (%)	41 (27.3)	30 (60.0)	<0.0001
South Asian, *n* (%)	7 (4.7)	1 (2.0)	0.682
East Asian, *n* (%)	6 (4.0)	0	0.400
Mixed, *n* (%)	2 (1.3)	2 (4.0)	0.261
Obstetric history			
Nulliparous, *n* (%)	67 (44.7)	25 (50.0)	0.518
Parous – no prior PE, *n* (%)	80 (53.3)	16 (32.0)	0.009
Parous – prior PE, *n* (%)	3 (2.0)	9 (18.0)	0.0002
Cigarette smoker, *n* (%)	12 (8.0)	1 (2.0)	0.192
Conception			
Spontaneous, *n* (%)	147 (98.0)	48 (96.0)	0.601
Ovulation drugs, *n* (%)	1 (0.7)	0	>0.999
In vitro fertilization, *n* (%)	2 (1.3)	2 (4.0)	0.261
Gestation at birth, median (IQR)	40.5 (39.6–41.2)	35.2 (32.7–37.5)	<0.0001
Birth weight in grams, median (IQR)	3478 (3253–3691)	2015 (1533–2727)	<0.0001
Birth weight centile, median (IQR)	47.9 (29.7–61.9)	9.9 (1.7–39.5)	<0.0001

IQR = interquartile range, BMI = body mass index, PE = preeclampsia.
Comparison between outcome groups by the Mann–Whitney *U*-test for continuous variables and χ^2-test or Fisher's exact test for categorical variables.

Table 2. Fitted regression model for maternal serum anti-Müllerian hormone (ng/L) at 11–13 weeks.

Coefficient	Estimate	Standard error	LCL	UCL	p value
Intercept	2.01832	0.021598	1.97564	2.06100	<0.0001
Afro-Caribbean racial origin	0.11171	0.039664	0.033322	0.19009	0.006
Cigarette smoking	0.13226	0.065158	0.0034950	0.26103	0.044

GA = gestational age; SGA = small for gestational age; PE = preeclampsia; LCL = lower confidence limit; UCL = upper confidence limit.

Table 3. Comparison of median (interquartile range) of maternal serum concentration and MoM value of AMH of preeclampsia group with the controls.

Outcome group	Median serum concentration of AMH (ng/L)	p value	Median MoM of AMH	p value
Control ($n = 150$)	2.062 (1.938–2.181)	–	0.995 (0.939–1.065)	–
Preeclampsia ($n = 50$)	2.140 (1.968–2.273)	0.025	1.040 (0.941–1.081)	0.147

Comparison between outcome groups by the Mann–Whitney *U*-test.

AMH levels observed in smokers [21]. These studies were all conducted in non-pregnant women. Nonetheless, it is unclear as to by which mechanism smoking increases the level of AMH in pregnancy.

Yarde et al. [9] demonstrated the association between early menopause and hypertension and cardiovascular disease in a recently published paper. Since PE is associated with future cardiovascular risk factors and premature vascular aging potentially modifies the ovarian aging process, a linear regression analysis showed a relative reduction in AMH level by 20% at any age and they demonstrated that non-pregnant women with a history of PE have significantly lower AMH levels compared to women with normotensive pregnancies [9]. This study was conducted in non-pregnant women who had a history of PE. To our knowledge, there has been no publication evaluating the role of low AMH in the development of PE.

Aging is a risk factor for PE. The advanced maternal age, after adjustment for other maternal characteristics and obstetric history, is associated with increased risk for a wide range of adverse pregnancy outcomes, including PE and birth of SGA neonates [10]. AMH has been studied as a potential predictor of fetal aneuploidy, but an association between maternal AMH levels and fetal aneuploidies has not been demonstrated [22,23]. There is a statistically significant correlation between AMH and pregnancy-associated plasma protein-A (PAPP-A) in euploid pregnancies. We have therefore speculated that AMH, which is not synthesized by the placenta [22], may be related to placental function and thus could be a potential biomarker for PE.

Interestingly, in our study, the uncorrected median serum concentration of AMH was significantly higher in the PE group than in the controls. This significant increase in the AMH level is not observed in the PE group after correcting the serum concentration to MoM values by the confounders' racial origin and smoking habit. It is known that the level of serum AMH during the pregnancy is dynamic and decreases as the pregnancy advances [24], it can be hypothesized that the impaired placentation could have attributed to the increased serum levels of AMH in PE in the first trimester, although reduced levels were expected.

The new approach for early screening for PE by a combination of maternal characteristics and history with

biophysical and biochemical markers uses the algorithm incorporating the biochemical markers of serum PAPP-A and placental growth factor [25]. We hypothesized to use serum AMH as a potential marker for PE, however, our study has demonstrated that PE is not associated with a reduction in serum levels of AMH at 11–13 weeks and therefore this marker is unlikely to be useful in early screening for PE.

Declaration of interest

The authors report no declarations of interest.

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