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Determinants of Maternal Sex Steroids During the First Half of Pregnancy

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Abstract

Objective—To examine the associations of maternal and child characteristics with early pregnancy maternal concentrations of testosterone, androstenedione, progesterone, 17-hydroxyprogesterone and estradiol.

Methods—We analyzed these hormones among 1,343 women with singleton pregnancies who donated serum samples to the Finnish Maternity Cohort from 1986 to 2006 during the first half of pregnancy (median, 11 weeks). The associations of maternal and child characteristics with hormone concentrations were investigated by correlation and multivariable regression.

Results—Women above age 30 had lower androgen and estradiol but higher progesterone concentrations than women below that age. Multiparous women had 14% lower testosterone, 11% lower androstenedione and 17-hydroxyprogesterone, 9% lower progesterone, and 16% lower estradiol concentrations compared to nulliparous women (all $P<.05$). Smoking mothers had 11%, 18%, and 8% higher testosterone, androstenedione, and 17-hydroxyprogesterone levels, respectively, but 10% lower progesterone compared to non-smoking women (all $P<.05$). Estradiol concentrations were 9% higher ($P<0.05$) among women with a female fetus compared to those with a male fetus.

Conclusions—Parity, smoking, and to a lesser extent maternal age and child gender are associated with sex steroid levels during the first half of a singleton pregnancy. The effects of

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smoking on the maternal hormonal environment and the possible long-term deleterious consequences on the fetus deserve further evaluation.

Introduction

The surge in sex steroids during pregnancy has been increasingly implicated in the development of disease in later life in both the mother and the child. In the mother, sex steroids are believed to underlie the association of pregnancy with risk of breast (1) and ovarian (2) cancers. In the child, an increasing body of evidence suggests that maternal sex steroids may influence the in-utero environment which may result in increased risk of atopy (3), autism spectrum and attention deficit hyperactivity disorders (4), polycystic ovary syndrome (PCOS) (5), testicular cancer (6), and probably breast cancer (7). High maternal testosterone concentrations have also been associated with low birth weight in the off-spring (8), with its attendant negative cardiovascular and metabolic sequelae (9).

Since the hormonal environment during pregnancy is likely to be a predictor of health outcomes for both mother and child, it is important to have an understanding of the factors which can affect it. Furthermore, the identification of characteristics that could serve as surrogate measures of hormonal exposure will be useful in future epidemiological research to circumvent some of the huge logistic difficulties in the conduct of studies directly relating hormone concentrations during pregnancy to risk of chronic disease years after.

Because most studies have investigated the correlates of maternal hormones during mid- or late pregnancy, comparatively little is known about their determinants during the first half of pregnancy (10). Early pregnancy is especially important to the fetus because this is the period when organogenesis takes place.

Our objective was to investigate the associations of maternal sex-steroids with maternal and fetal characteristics. Using data from control subjects in a case-control study nested within the Finnish Maternity Cohort, we examined the associations of maternal age, parity, smoking and child gender, birth weight, height and Ponderal index with maternal sex steroids, including testosterone, androstenedione, progesterone, 17-hydroxyprogesterone, and estradiol measured during the early parts (mostly first trimester) of a singleton pregnancy.

Materials and Methods

The Finnish Maternity Cohort, the world’s largest bio-repository of serum specimens from pregnant women, was established in 1983. Following an informed consent, first trimester and early second trimester blood samples are taken from pregnant women in order to screen for intrauterine infections (11). After testing, the leftover sera are stored at −25°C in a central repository and can be used for scientific research with the aim of maintaining population health and preventing diseases. Currently the Finnish Maternity Cohort has >1.5 million samples from over 850,000 women.

Study subjects were selected among the controls included in an ongoing nested case-control study on pregnancy hormones and ovarian cancer within the Finnish Maternity Cohort. Eligibility criteria for the original study included blood donation between the 6th and 20th gestational weeks of a singleton pregnancy with duration ≤301 days and no history of invasive cancer (except non-melanoma skin cancer). Data on gestational age at blood donation in the Finnish Maternity Cohort have been collected since 1986 and only controls who donated a blood sample after 1986 were considered eligible for the current analyses.

Sixty-nine women with incomplete information on maternal/child characteristics were also excluded leaving 1,343 women for the study.

Data on index pregnancy was obtained by performing a linkage with the high quality Finnish Medical Birth Registry, which has information on more than 98% of all births in the country since 1987 (12). Data collection is through a standardized form that must be sent to the Finnish Medical Birth Registry within 7 days of each childbirth by the hospital where the delivery took place (12). Information was available on maternal characteristics during the index pregnancy such as age, parity, pregnancy length, smoking and child characteristics (gender, birth weight and length). Information on breast cancers diagnosed among parents and siblings of the study subjects was obtained through separate linkages with the Population and Cancer Registries.

The study was approved by the ethical committees of the National Institute for Health and Welfare, Finland and the German Cancer Research Center, Germany.

The assays of sex steroids were performed in the Laboratory of Clinical Chemistry at the Umeå University Hospital, Umeå, Sweden. In addition to the routine laboratory quality controls, a pool of serum from the cohort was created at the beginning of the study and 2 aliquots, undistinguishable from the test samples were inserted in each laboratory run. Sex steroids were quantified by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS), on an Applied Biosystems API4000 triple stage quadrupole mass spectrometer. Laboratory quality controls at: 0.10/5.0 ng/mL for testosterone, 0.25/5.0 ng/mL for androstenedione, 0.25/5.0 ng/mL for 17-hydroxyprogesterone, 2.0/75.0 ng/mL for progesterone, and 0.1/5.0 ng/mL for estradiol, showed inter-run coefficients of variation (CV) of 10.3/5.2%, 7.0/5.0%, 8.8/6.1%, 9.0/5.2%, and 12.2/5.4%, respectively. The mean steroid concentrations of the blinded pool controls were 0.9 ng/mL for testosterone, 1.8 ng/mL for androstenedione, 2.4 ng/mL for 17-hydroxyprogesterone, 25.2 ng/mL for progesterone and 2.6 ng/mL for estradiol. Inter- and intra-run CV based on the blinded pool of quality controls were 3.6% and 7.6% for testosterone, 3.8% and 8.1% for androstenedione, 5.2% and 8.0% for 17-hydroxyprogesterone, 3.5% and 6.8% for progesterone, and 5.2% and 6.3% for estradiol.

Prior to analysis, hormone levels were $\log_2$-transformed to limit heteroscedasticity. The concentrations of all hormones with the exception of testosterone varied linearly with gestational age (Figure 1), and to account for these variations, all statistical analyses were adjusted for gestational age (a linear term). No outliers, defined as concentrations exceeding 3 times the interquartile range, for any of the hormones were identified. Ponderal index of the newborns was calculated by dividing birth weight by birth length^3.

Association between continuous variables was evaluated by Spearman partial correlations (adjusted for gestational day). Multivariable regression models (adjusted for gestational age, maternal age, parity, smoking, term birth and child sex and Ponderal index (with the exception of models for birth weight and height) were used to assess the independent effect of maternal and child characteristics on hormone concentrations. For these analyses maternal age was categorized to age <30 and ≥30 years. As there was no indication that any of the associations with birth weight, length or Ponderal index followed a non-linear association (by visual inspection of plots and introducing quadratic terms in the regression models) the results are presented for an increase of 100 grams, 5 centimeters and 5 units of Ponderal index, respectively. Laboratory batch had no effect on regression estimates and was omitted from the fully adjusted model. Additionally, stratified analyses by gestational age period (6–8, 8–12 and 12–20 week, corresponding to corpus luteum, transitional and placental phases) were conducted and interaction terms with gestational age period included

in the main regression models. All analyses were performed by using Statistical Analysis System (SAS) software, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Maternal and newborn characteristics and hormone concentrations during early pregnancy are presented in Table 1. Median maternal age was 32 years (range 17 to 46 years) and twenty-five percent (n= 331) of the women were primiparous. The median gestational age at blood donation was 11 weeks (range 6 to 20 weeks). Fourteen percent (14%) of the women smoked during the index pregnancy.

Hormone concentrations were in the range expected for the period of pregnancy the samples were collected. Gestational age correlated strongly with estradiol (rs=0.71), moderately with progesterone (rs=0.52), inversely (weakly) with androstenedione (rs=−0.12) and 17-hydroxyprogesterone (rs=−0.31), but not with testosterone (Figure 1). The two androgens were strongly correlated (rs=0.87). The correlations of testosterone and androstenedione with the other hormones were 0.50, 0.56 with 17-hydroxyprogesterone, 0.45, 0.37 with estradiol and 0.13, 0.16 with progesterone. Estradiol was more strongly correlated with progesterone (rs=0.41) than with 17-hydroxyprogesterone (rs=0.23). The correlation between progesterone and 17-hydroxyprogesterone was 0.46 (Table not shown).

Table 2 shows the percentage changes in serum sex steroid concentrations across maternal and newborn characteristics. Women who were older than age 30 at index pregnancy had significantly lower testosterone (6%), androstenedione (11%) and estradiol (6%, p=0.053), but higher progesterone (6%) concentrations than women below that age. The interaction term between maternal age and gestational age period was significant for estradiol - the decrease in maternal estrogen was confined to women who donated a blood sample after 12 gestational weeks. All studied hormones were significantly lower in multiparous than in primiparous women, ranging from 9% for progesterone to 16% for estradiol (p-values < 0.05). Serum testosterone and androstenedione concentrations were higher (11% and 18% respectively) but progesterone concentrations were lower (10%) in smokers compared to non-smokers (all p-values ≤0.05). Women who delivered before the 37th week of gestation had lower progesterone concentrations than women who delivered at term, but possibly due to the small number of women with preterm birth, the difference was of marginal significance (p=0.09).

Estradiol concentrations were 9% higher among women with a female fetus than women with a male fetus. The interaction term between child sex and gestational age period was significant for progesterone, with significantly lower progesterone concentrations (6%) in mothers of girls compared to mothers of boys after gestational week 12. Birth weight, length and Ponderal index were not significantly associated with any of the investigated maternal hormone concentrations, although there was a non-significant tendency for decreased androgens with birth length.

There was no significant difference in hormone concentrations by family history of breast cancer, although women with such history tended to have lower androgen, but higher estradiol concentrations.

Discussion

We observed that maternal age, parity, smoking, and child gender are associated with circulating sex steroids concentrations during the first half of a singleton pregnancy.

During the very first weeks of pregnancy, estrogens, progesterone and 17-hydroxyprogesterone are produced exclusively by the corpus luteum. Gradually, for estrogens and progesterone, the major site of synthesis shifts to the placental trophoblast (13–15) and their concentrations continue to increase. However, the placenta lacks 17 α-hydroxylase activity necessary for the synthesis of 17-hydroxyprogesterone and its concentrations decrease after the 5th gestational week (15). Maternal testosterone increases gradually throughout pregnancy, while androstenedione concentrations remain relatively stable (16,17).

The observed decrease in androgen concentrations with maternal age is in line with previous findings during the three trimesters of pregnancy (10, 18, 19). It is unlikely that the reduction is pregnancy-specific as androgen concentrations decrease with age also in non-pregnant women (20). The reported association of maternal age with estradiol throughout pregnancy has been less consistent (19, 21–23), although two studies reported a decrease in first trimester estradiol concentrations with maternal age (10, 22). In our data, the decrease in estradiol was evident after gestational week 12, suggesting diminished placental production. One possibility is that the concomitant decrease in androgen concentrations with age presents the growing placenta and its increasing capacity for aromatization of androgens with less substrate, which later on in pregnancy may not be evident due to increased androgen availability from fetal origin. Interestingly, despite the decrease in estrogen concentrations, there appears to be a concomitant increase in the other major placental sex-steroid, progesterone, with age (10). However the mechanisms underlying such increase remain to be determined.

Primiparous pregnancies were characterized by higher concentrations of estradiol in comparison with multiparous pregnancies, findings in line with previous reports throughout pregnancy (10, 23–25). The lower estradiol levels in parous women could be due to increased metabolism of the hormone as a result of a pregnancy-induced persistent increase in liver CYP3A7 activity (26). For progesterone, most previous studies have found no significant differences between the first and subsequent pregnancies (10, 24, 25). However, our study was substantially larger, thus more likely to detect an existing, albeit weaker association. The decrease in progesterone and 17-hydroxyprogesterone in multiparous compared to primiparous women, could be related to the decrease in the hormones that control its synthesis by the corpus luteum (e.g. hCG (23)) in pregnancies following the first child birth. We also observed lower maternal androgens in multiparous women, as reported previously by Troisi et al during the first trimester of pregnancy (10) and possibly at term (19).

Smoking may increase circulating androgens by having an inhibitory effect on the adrenal cortex enzymes, 21 and 11?-hydroxylase (29) or by inducing ACTH production (30). Increased androstenedione (27) and testosterone (28) have been reported among smoking, non-pregnant women. Our data add further evidence that smoking could be associated with elevations in androgen concentrations also during pregnancy.

We observed that smoking pregnant women had lower progesterone concentrations compared to non-smoking pregnant women, similar to what has been reported previously during the first trimester (10) and in non-pregnant women (27). Since high progesterone levels are needed to keep the pregnancy viable, the deleterious effects of smoking on maternal progesterone concentrations could be one of the mechanisms through which smoking may result in early pregnancy loss.

Experimental studies suggest that smoking has an anti-estrogenic effect by preferentially increasing the synthesis of 2-hydroxyestrogens, which have low estrogenic potency and are

rapidly cleared from the circulation (33, 34). However, similarly to other studies among pregnant (10, 19, 31) and non-pregnant women (32), we found no association between smoking and estradiol levels.

In contrast to the fetal ovary, the testis has the capacity to synthesis testosterone de novo. Testosterone producing Leydig cells are first detected around the 60th day of gestation and then proliferate rapidly between the 12th and 18th gestational weeks (14). It was proposed that because of the existing fetal-maternal gradient, testosterone from the male fetus could cross the placenta into maternal circulation (38). On the other hand, the high aromatase capacity of the placenta would tend to diminish fetal contribution to maternal androgens. We did not find differences in maternal androgens by child sex, as also observed by others (35–37), although higher testosterone concentrations in mothers of boys have also been reported.

Results from previous studies on pregnancy progesterone by child sex have shown either similar concentrations (39, 40) or lower concentrations in mothers of girls (25). Our findings are equally inconclusive, because though we observed no overall association, progesterone concentrations were lower in mothers of girls after gestational week 12. Most previous studies observed no differences in maternal estrogens by child sex (19, 25, 39), but in some, mothers of girls had somewhat higher estrogens (19, 39). In our data mothers of girls had significantly higher estrogens than mothers of boys. As the fetal ovary is believed to be predominantly steroidogenically quiescent throughout most of pregnancy (14) this finding awaits confirmation in other studies.

We found no relationship between circulating sex steroids and birth weight, height and Ponderal index. Most of the child's growth occurs during the third trimester (41) and it is not surprising that an association has been observed with hormone concentrations measured after 27th gestational week, but not with concentrations during the first half of pregnancy (42, 43).

Strengths of our study are its large size, the measurements of several sex-steroids and the availability of high quality information from national registries. A limitation of the study is that serum samples were stored at a relatively high temperature, −25°C, but an earlier study within the Finnish Maternity Cohort observed no deleterious effects of long-term storage on sex steroids concentrations (44) and the observed hormonal variations with gestational age were line with expectations.

In conclusion, our study showed that parity and smoking and to a lesser extent, maternal age and gender of the child are associated with sex steroids concentrations during the first half of pregnancy. The impact of smoking on maternal hormone levels, especially testosterone and progesterone deserves further evaluation since high maternal testosterone levels may be associated with low birth weight, with its attendant negative metabolic sequelae and a state of low progesterone level may not be conducive for fetal viability.

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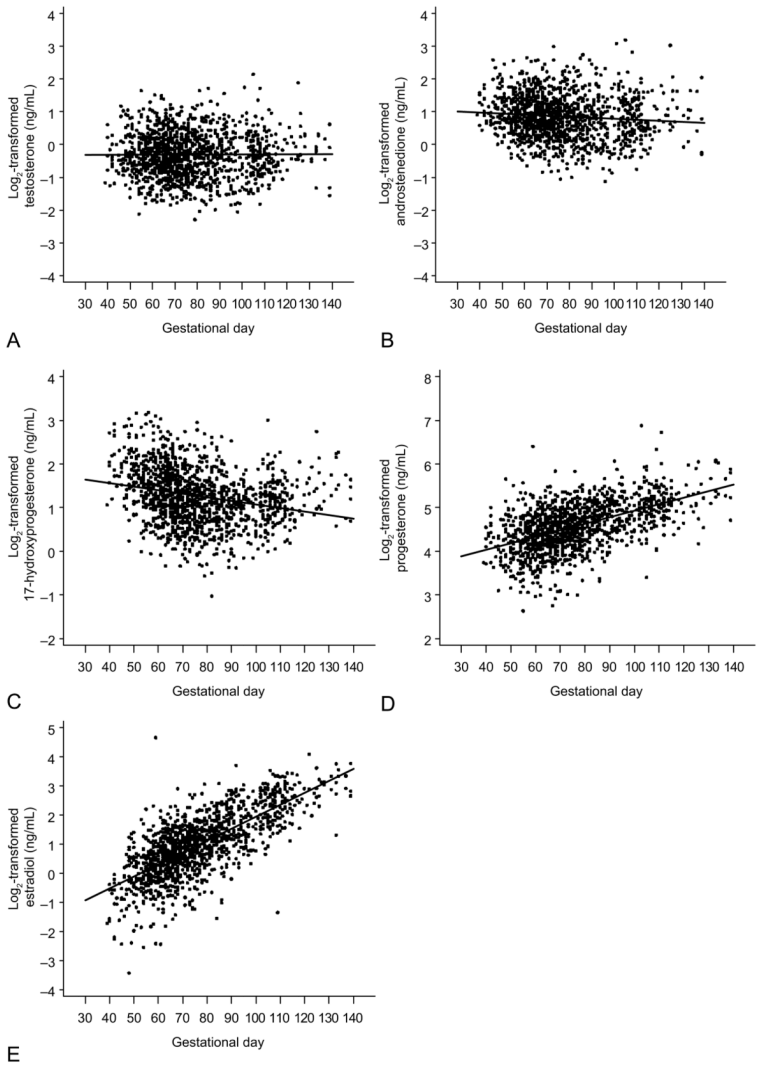

Figure 1.

Scatterplot of $\log_2$-scale testosterone (Fig 1A), androstenedione (Fig 1B), 17-hydroxyprogesterone (Fig 1C), progesterone (Fig 1D), and estradiol (Fig 1E) by gestational age in 1,343 uncomplicated pregnancies from the Finnish Maternity Cohort, 1983–2006. The solid line shows the progression of hormones during pregnancy, estimated by local linear regression.

Table 1

Maternal characteristics at enrollment and child characteristics for index birth and hormone concentrations in 1,343 uncomplicated pregnancies from the Finnish Maternity Cohort, 1983–2006

Characteristics*/hormone	n	Median(range) or percentage
Gestational week (weeks)	1,343	11 (6 – 20)
Maternal age (years)	1,343	31.6 (17.4–45.5)
Parity		
1	331	25%
2	576	43%
3	330	25%
≥4	106	8%
Pregnancy length (days)	1,343	280 (168–301)
Term delivery		
Full-term (≥ 259 days)	1,285	96%
Preterm (< 259 days)	58	4%
Maternal smoking		
Yes	191	14%
No	1,152	86%
Family history of breast cancer		
Yes	57	4%
No	1,286	96%
Child sex		
Boy	705	52%
Girl	638	48%
Birth weight (g)	1,343	3,610 (580–5,170)
Birth length (cm)	1,343	50 (25–57)
Hormone concentrations*		
testosterone (ng/mL)	1,343	0.81 (0.21–4.43)
androstenedione (ng/mL)	1,343	1.81 (0.46–9.20)
17-OH-progesterone (ng/mL)	1,343	2.40 (0.49–9.10)
progesterone (ng/mL)	1,343	23.9 (6.22–118)
estradiol (ng/mL)	1,343	1.97 (0.09–25.40)

*Geometric means of hormones concentrations

Table 2

Percentage changes (with 95% confidence intervals) in hormone concentrations associated with maternal and child characteristics from multivariate regression models in 1,343 uncomplicated pregnancies from the Finnish Maternity Cohort, 1986–2006

Independent variables	T	A	17OHP	P	E2
Maternal age (≥30 vs. <30)*	−6[b] (−12; 0)	−11[a] (−17; −6)	2 (−3; 7)	6[b] (2; 10)	−6[c] (−12; 0)
Parity (multiparous vs. primiparous)*	−14[a] (−21; −8)	−11[b] (−18; −5)	−11[b] (−17; −5)	−9[a] (−13; −4)	−16[a] (−24; −9)
Maternal smoking (yes vs. no)*	11[b] (3; 19)	18[a] (10; 26)	8[b] (1; 15)	−10[b] (−15; −5)	2 (−6; 11)
Preterm pregnancy (yes vs. no)*	−2 (−15; 11)	−3 (−16; 9)	−5 (−17; 7)	−8[c] (−17; 1)	−2 (−18; 12)
Child sex (girl vs. boy)*	3 (−2; 8)	2 (−3; 7)	1 (−3; 6)	0 (−3; 4)	9[b] (3; 15)
Birth weight (per 100 grams)**	0 (0; 1)	0 (0; 1)	0 (0; 1)	0 (0; 0)	0 (0; 1)
Birth length (per 5 cm)**	−1 (−6; 5)	−2 (−7; 4)	0 (−5; 5)	0 (−4; 4)	0 (−6; 6)
Ponderal index (per 5)**	3 (−1; 9)	3 (−2; 7)	3 (−1; 8)	−2 (−6; 1)	1 (−5; 7)
Family history of breast cancer (yes vs. no)*	−7 (−21; 6)	−7 (−21; 5)	−3 (−15; 9)	1 (−7; 10)	9 (−5; 26)

[a] p < 0.0001,

[b] p < 0.05,

[c] p<0.10;

* The models are adjusted for gestational age, maternal age, parity, smoking, preterm birth, child sex and Ponderal index;

** The models are adjusted for gestational age, maternal age, parity, smoking, preterm birth and child sex;

Abbreviations: GA (gestational day), T (testosterone), A (androstenedione), 17OHP (17-OH-progesterone), P (progesterone), E2 (estradiol);

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