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Evaluation of the impact of maternal smoking on ultrasound and endocrinological markers of first trimester placentation

E. Jauniaux [a], Sangeeta Suri [a], S. Muttukrishna [b,*]

[a] UCL EGA Institute for Women's Health, University College London, London, United Kingdom
[b] Anu Research Centre, UCC Department of Obstetrics and Gynaecology, 5th Floor, Cork University Maternity Hospital, Wilton, Cork, Republic of Ireland

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ABSTRACT

Objectives: To study the effect of maternal smoking on 2D ultrasound measurements and maternal serum (MS) levels of endocrinologic markers of placentation.
Study design: Prospective population-based cohort study of 32 smokers and 96 non-smoking controls with a normal pregnancy outcome.
Main outcome measures: Placental thickness and 2D-volume and MS levels of pregnancy-associated plasma protein A (PAPP-A) and free-beta human chorionic gonadotrophin (fβhCG) at 11–13^{+6} weeks of gestation and mid-trimester MS α-fetoprotein (AFP), unconjugated estriol (uE3) and inhibin A levels.
Results: The MS levels of fβhCG and PAPP-A were significantly ($P < 0.01$ and $P < 0.001$, respectively) lower in the serum and the level of inhibin A significantly ($P < 0.001$) higher in the smokers than in controls. There was no significant difference for the MSAFP, MSuE3 placental thickness, basal plate surface and volume between the groups.
Conclusion: The placental morphological alterations secondary to maternal smoking are mainly at the level of the villous trophoblast and are not associated with changes in the placental size or utero-placental interface during the first trimester of pregnancy.

1. Introduction

Smoking during pregnancy has been recognized as the most important modifiable risk factor associated with adverse perinatal outcomes [1]. As a consequence, the effect of active and passive maternal smoking on the development of the fetus and its placenta has been of increasing interest to international public health. In particular, the effect of active and secondhand prenatal tobacco smoke exposure on fetal and child growth has become an important public health problem in childhood and later life [2,3].

Studies of placental pathologies associated with maternal cigarette smoking have led to many interesting observations. For example, maternal smoking impairs human placental development by changing the balance between cytotrophoblast (CTB) proliferation and differentiation [4]. Other placental anatomical changes associated with maternal smoking such as the increased thickness of the villous membrane of smokers could compromise gas transfer to the fetus and thus cause fetal growth restriction (FGR) in smokers [4].

Placental morphological damage related to heavy chronic maternal smoking can be identified as early as the first trimester of pregnancy [5]. It is well established that the mean placental weight in smokers is decreased, depending on the number of cigarettes smoked by the mother per day throughout pregnancy [6]. Placental volume in utero using 3-D ultrasound is decreased in early second trimester in pregnancies presenting with a chromosomal abnormality, in particular in case of trisomy 13 and trisomy 18, indicating a severe impairment of the placental development in these cases [7]. Longitudinal studies have shown that pregnancy-related complications of later pregnancy have their pathophysiological origin in abnormal placentation during the first trimester [8]. In cases of FGR, with or without accompanying pre-eclampsia (PE), the placenta is already smaller at 12–18 weeks of gestation on ultrasound than in healthy controls [9,10].

Morphological damage of the villous trophoblast due to maternal smoking is also associated with changes in placental enzymatic and synthetic functions. In the fetus, smoking is associated with a reduction of weight, fat mass and most anthropometric parameters and as in the placenta shows alterations in protein metabolism and enzyme activity. These alterations are the results of a direct toxic effect on the fetal cells or an indirect effect through damage to, and/or functional disturbances of the placenta [4].

Changes in placental hormonal secretions associated with maternal smoking have been reported in the context of first and second

* Corresponding author at: Academic Department of Obstetrics and Gynaecology, Institute for Women Health at University College London, 86-96 Chenies Mews, London WC1E 6HX, United Kingdom. Tel.: +44 207 6796057; fax: +44 207 3837429.
E-mail address: e.jauniaux@ucl.ac.uk (S. Muttukrishna).

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trimester screening for trisomy 21 [11–15]. The aim of this study was to study the effect of maternal smoking on 2D ultrasound measurements of placentation and the corresponding maternal serum (MS) levels of pregnancy-associated plasma protein A (PAPP-A) and free-beta human chorionic gonadotrophin (fβhCG) at 11–13^{+6} weeks of gestation and between placental ultrasound measurements at 11–13^{+6} weeks and mid-trimester MS α-fetoprotein (AFP), unconjugated estriol (uE3) and inhibin A levels.

2. Patients and methods

In a prospective cohort population study, women booked for antenatal care were recruited over 40 months from the booking clinic at University College London Hospital (UCLH). All pregnant women at UCLH are offered a screening test for trisomy 21 which combines nuchal translucency (NT) measurement and MS levels of PAPP-A and fβhCG at 11–14 weeks (combined test) and/or of AFP, uE3 and inhibin-A at 15–22 weeks (integrated test). All women were recruited at the time of the NT ultrasound examination between 11 + 0 and 13 + 6 weeks of gestation (77–97 gestational days) as determined either by the last-menstrual period confirmed by the ultrasound measurement of the fetal crown-rump length (CRL), or when there was a discrepancy of more than 5 days by the CRL only.

Demographic data including maternal ethnicity cigarette smoke exposure, age and body mass index (BMI) and fetal birth weight were collected from questionnaires completed at the time of recruitment. Pregnancy outcome information was collected from the medical case notes and hospital electronic patient records. Women diagnosed with a first trimester miscarriage, fetal abnormality, medical condition, a multiple pregnancy, a pregnancy resulting from artificial reproductive technology and abnormal pregnancy outcome including PE, unexplained FGR, diabetes and preterm birth were excluded from the study. The study groups included 32 women with a spontaneous singleton pregnancy smoking between 10 and 20 cigarettes per day before and during the first trimester of their pregnancy and 96 non-smoker controls (3 per study cases), not exposed to passive smoking and matched for CRL and maternal age.

The study was approved by the Joint UCL/UCLH Committees on the Ethics of Human Research (Reference Number: 05/Q0505/82). All women received information about the study and written consent was obtained prior to the ultrasound examination.

2.1. Ultrasound measurements

Using a 3.5–5 MHz ultrasound probe the fetal NT, CRL and basic anatomy were recorded. The placental basal plate dimensions and thickness were measured by viewing the whole placenta. The longest diameter of the placental basal plate at the level of the utero-placental interface was identified in its sagittal plane (s) and the length of the basal plate was traced using electronic calipers (Fig. 1). The probe was turned through 90° and the longest diameter of the basal plate in the transverse plane (t) was traced (Fig. 2). The placental thickness (d) was measured underneath the cord insertion keeping the probe perpendicular as previously described [16,17].

We evaluated the surface of the placenta to be elliptical in shape as previously described [2] and thus we estimated the surface area of the placenta using the following formula:

$$\text{Sagittal length} \times \text{transverse length} \times \pi/4.$$

The placental volume was therefore calculated using the equation for half the volume of an ellipsoid:

$$\tfrac{1}{2}(\text{sagittal length} \times \text{transverse length} \times \text{thickness} \times 4/3\pi).$$

All the scans were performed by SS and EJ. The median intraobserver and interobserver agreements for the basal plate diameter measurements were respectively 95.6% and 92.7% as previously described [17].

2.2. Bioassays

MS PAPP-A and fβhCG, were measured using the AutoDELFIA PAPP-A, time-resolved fluoro-immunoassay (PerkinElmer, Turku, Finland). inhibin A, AFP and uE3 MS levels were measured using commercial ELISAs. The measured proteins were converted to multiple of the median (MoM) for a pregnancy of the same gestational age and were adjusted for maternal weight and ethnicity.

2.3. Statistics

The data were analyzed using the StatGraphic data analysis and statistical software package (Station, TX). Standard kurtosis analysis indicated that some values were not normally distributed and are

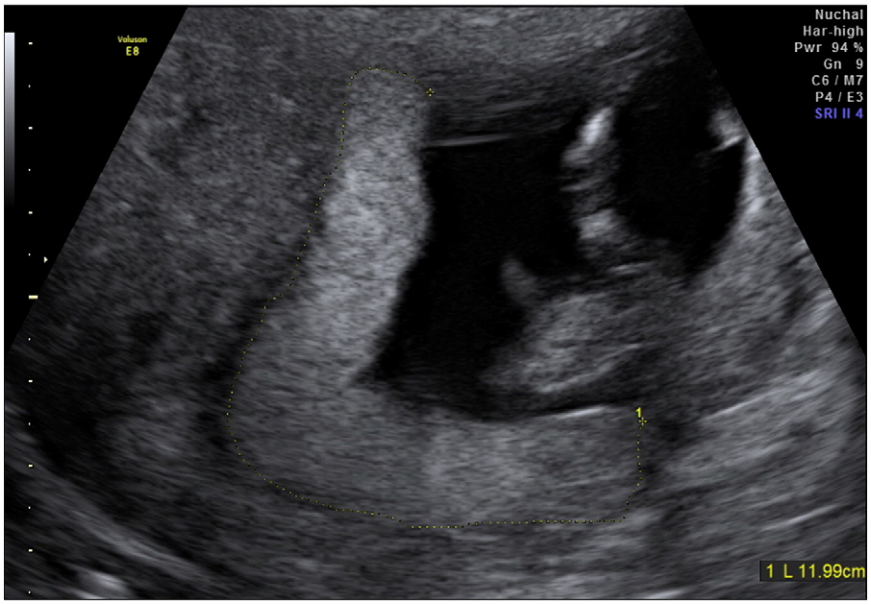

Fig. 1. Measurement of diameter of uteroplacental interface in sagittal plane at 11 weeks of gestation.