Socioeconomic inequalities in placental vascular resistance: a prospective cohort study

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Objective: To examine the association between socioeconomic position (SEP) and umbilical and uterine placental resistance indices in the second and third trimester, and to what extent this could be explained by lifestyle-related behaviors.
Design: Prospective cohort study.
Setting: Rotterdam, the Netherlands.
Patient(s): 7,033 pregnant women of mean age ($\pm$ standard deviation) 29.9 ($\pm$5.2) years.
Intervention(s): None.
Main Outcome Measure(s): Uterine artery resistance index (UARI) and umbilical artery pulsatility index (UAPI) in second and third trimester measured with Doppler ultrasound.
Result(s): Third-trimester UARI and both second- and third-trimester UAPI were statistically significantly higher for women with lower educational levels as compared with those with higher educational levels. Educational level was strongly associated with the risk of continuously high levels of UARI and UAPI from second to third trimester of pregnancy. Notching was not associated with SEP. Smoking was a significant contributor to the association of SEP and increased placental resistance indices; body mass index, folic acid supplementation use, and alcohol use were not.
Conclusion(s): Women from low socioeconomic subgroups have higher placental resistance indices, which may cause a higher prevalence of pregnancy complications. This was mainly explained by maternal smoking during pregnancy. (Fertil Steril® 2014;101:1367–74. ©2014 by American Society for Reproductive Medicine.)
Key Words: Cohort study, maternal educational level, placental resistance indices, pregnancy complications, smoking during pregnancy

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The relationship of socioeconomic inequality to pregnancy complications and adverse birth outcomes, including preeclampsia (1, 2), fetal growth restriction (3–5), and preterm birth (6), has been well reported. Such inequalities affect a child's prospects for healthy development at the start of his or her life. Thus, reducing socioeconomic disparities during this particular period of life has been proposed as a top priority in the European strategy to tackle health inequalities (7). However, the origins of these inequalities may be rooted in prenatal life, and understanding the relevant causal prenatal mechanisms may help to develop effective interventions toward reducing these disparities.

Continued smoking and other unhealthy behaviors during pregnancy explain a substantial part of the socioeconomic inequalities in birth outcomes (8). Recently, population-based studies have emphasized the role of abnormal early placentation in the development of pregnancy complications and adverse birth outcomes, probably to some extent caused by unhealthy lifestyle-related behaviors such as smoking (9, 10). Abnormal

Received December 4, 2013; revised and accepted February 3, 2014; published online March 14, 2014.
S.H.B. has nothing to disclose. F.J.V. has nothing to disclose. R.G. has nothing to disclose. A.H. has nothing to disclose. E.A.P.S. has nothing to disclose. V.W.V.J. has nothing to disclose. H.R. has nothing to disclose.
The first phase of the Generation R Study was supported by Erasmus Medical Centre, Rotterdam, Erasmus University Rotterdam, and the Netherlands Organization for Health Research and Development (ZonMw).
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Fertility and Sterility® Vol. 101, No. 5, May 2014 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.02.001

placentation may lead to higher uterine and umbilical artery resistance patterns, which are thought to reflect impaired uteroplacental and fetoplacental blood flow (11, 12). Higher uterine and umbilical artery resistance patterns have been associated with the risk of preeclampsia, fetal growth restriction, and preterm birth (9, 10, 13). Also, consistently higher placental vascular resistance throughout pregnancy has been shown to be associated with a risk of adverse pregnancy outcomes (9).

We hypothesize that women from lower socioeconomic subgroups have higher uterine and umbilical artery resistance patterns, to some extent due to their higher levels of unhealthy behavior, including smoking in particular. We therefore investigated whether educational levels of women are associated with uterine and umbilical artery resistance indices, and whether lifestyle-related determinants could explain these associations in a population-based prospective cohort study among 7,033 pregnant women. Furthermore, we examined whether women with lower educational levels are at an increased risk of continuously high levels of placental resistance indices from the second to third trimester of pregnancy.

MATERIALS AND METHODS

Study Design

This study was embedded within the Generation R Study, a population-based prospective cohort study from early pregnancy onwards. Details have been described elsewhere (14, 15). Briefly, the cohort includes 9,778 mothers and their children living in Rotterdam, the Netherlands. Although enrollment ideally took place in early pregnancy, it was possible until the birth of the child. In total, 8,879 women were enrolled during pregnancy. All children were born between April 2002 and January 2006. Assessments during pregnancy included physical examinations, ultrasound assessments, and questionnaires and were planned in early pregnancy (gestational age <18 weeks), midpregnancy (gestational age 18–25 weeks), and late pregnancy (gestational age ≥25 weeks). The study was conducted in accordance with the guidelines proposed by the World Medical Association of Helsinki and was approved by the medical ethics committee of the Erasmus MC University Medical Centre of Rotterdam. Written consent was obtained from all participating parents (16).

Population for Analysis

The data of all participating prenatal women were available (n = 8,879). For the present study, we excluded the women who had no placental resistance indices measurements (n = 1,156). Additionally, we excluded pregnancies with the following outcomes: fetal death (n = 25), induced abortion (n = 8), loss to follow up (n = 28), and twin pregnancies (n = 3). Finally, we excluded women for whom there was no information about educational level (n = 626). Thus, the cohort for analysis comprised 7,033 pregnant women.

Socioeconomic Position

Our indicator of socioeconomic position (SEP) was the educational level of the pregnant woman. Each woman's level of education was established using a questionnaire at enrollment. The Dutch Standard Classification of Education was used to categorize four subsequent levels of education: [1] high (university degree), [2] mid-high (higher vocational training, bachelor's degree), [3] mid-low (>3 years general secondary school, intermediate vocational training), and [4] low (no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school) (17).

Placental Hemodynamic Function

Placental vascular resistance was evaluated with recorded flow velocity wave forms from the uterine and umbilical arteries in second and third trimester (18). A raised uterine artery resistance index (UARI) and umbilical artery pulsatility index (UAPI) indicate increased placental resistance (19). The indices are calculated as ratios between peak systolic velocity (A), end-diastolic peak velocity (B), and mean velocity (mean). The pulsatility index is calculated as (A − B)/mean and the resistance index as (A − B)/A (20). UARI was measured in the uterine arteries near the crossover with the external iliac artery. UAPI was measured in a free-floating loop of the umbilical cord. For each measurement, three consecutive uniform waveforms were recorded by pulsed Doppler ultrasound during fetal apnea and without fetal movement. The mean of three measurements was used for further analysis. The presence of notching was assessed in the uterine arteries and reflects an abnormal waveform resulting from increased downstream blood flow resistance. Ultrasound measurements were performed in a blinded fashion with regard to previous measurements and pregnancy outcomes. Placental resistance index measurements were performed in 87% of the 8,879 prenatally enrolled women because the placental resistance indices were measured at only one of the two research centers.

Mediators

Based on previous literature (9, 21, 22), the following factors were considered to be potential explanatory factors in the pathway between SEP and placental perfusion. Smoking and alcohol consumption were assessed by questionnaires in each trimester. From the first questionnaire, information about folic acid supplementation use was obtained. The prepregnancy weight was established at enrollment through a questionnaire. On the basis of height (cm), measured at enrollment without shoes, and prepregnancy weight, we calculated the prepregnancy body mass index (BMI; weight/height^2).

Confounders

We treated maternal age at enrollment, parity, gestational age at enrollment, ethnicity, and gestational age at time of measurement as potential confounders. Maternal age was