OBSTETRICS

Risk of placental dysfunction disorders after prior miscarriages: a population-based study

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OBJECTIVE: The objective of the investigation was to study the association between prior miscarriages and the risks of placental dysfunction disorders, including preeclampsia, stillbirth, birth of a small for gestational age (SGA) infant, placental abruption, and spontaneous preterm birth.

STUDY DESIGN: In a population-based cohort study including 619,587 primiparous women, we estimated risks of placental dysfunction disorders for women with 1 (n = 68,185), 2 (n = 11,410) and 3 or more (n = 3823) self-reported prior miscarriages. Risks were calculated as odds ratios by unconditional logistic regression analysis and adjustments were made for maternal age, early pregnancy body mass index, height, smoking habits, country of birth, years of formal education, in vitro fertilization, chronic hypertension, pregestational diabetes, hypothyroidism, systemic lupus erythematosis, fetal sex, and year of childbirth.

RESULTS: Compared with women with no prior miscarriage, women with 1 prior miscarriage had almost no increased risks. Women with 2 prior miscarriages had increased risks of spontaneous preterm birth, preterm (<37 weeks) SGA infant, and placental abruption. The rates of all disorders were higher for women with 3 or more prior miscarriages compared with women without prior miscarriages: preeclampsia, 5.83% vs 4.27%; stillbirth, 0.69% vs 0.33%, SGA infant, 5.09% vs 3.22%, placental abruption, 0.81% vs 0.41%; and spontaneous preterm birth, 6.45% vs 4.40%. The adjusted odds ratios for preterm (<37 weeks) disorders in women with 3 prior miscarriages were approximately 2.

CONCLUSION: History of 2 or more miscarriages is associated with an increased risk of placental dysfunction disorders and should be regarded as a risk factor in antenatal care.

Key words: intrauterine growth restriction, miscarriage, placental abruption, preeclampsia, spontaneous preterm birth, stillbirth

Cite this article as: Gunnarsdottir J, Stephansson O, Cnattingius S, et al. Risk of placental dysfunction disorders after prior miscarriages: a population-based study. Am J Obstet Gynecol 2014;210:xx-xx.

Failure of implantation has been suggested to be involved not only in the pathogenesis of miscarriage but also in pregnancy complications associated with placental dysfunction (ie, preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth).[1-3] Implantation and placentation can be presented as a continuous process regulated by complex signaling between decidua, immune cells, and fetal tissue.[3]

Vascular adaptation of the uterus, including angiogenesis and spiral artery remodeling, is a key feature in early placental development.[4] Former studies have shown that both miscarriage and placental dysfunction disorders are associated with an imbalance in angiogenic activity, disturbances in uterine blood supply, and placental oxidative stress.[4-7] It has been hypothesized that a complete implantation/placentation failure may result in a miscarriage, whereas a partial failure may result in late pregnancy complications associated with placental dysfunction.[5,8]

Based on the similarities in pathogenesis of miscarriage and placental dysfunction disorders, a history of prior miscarriages might be associated with increased risk of placental dysfunction disorders. This hypothesis is supported by a few previous studies, in which the exposure was either miscarriage or in vitro fertilization (IVF).[9-14] In some of these studies, parity was not controlled for,[10-12] or primiparous women exposed for prior miscarriages were compared with parous women.[13,14] Comparing primiparous women with prior miscarriages with a reference group of parous women might overestimate risks because placental dysfunction disorders are more prevalent in primiparous compared with parous women.[15]

In this study we had the opportunity to obtain data on the number of prior miscarriages and pregnancy complications from more than 600,000

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Received Sept. 24, 2013; revised Dec. 13, 2013; accepted Jan. 28, 2014.

This study was supported by grants from Swedish Government funds for clinical research (ALF; Uppsala for J.G., H.Å., and A.-K.W.; Stockholm for O.S. and S.C.).

The authors report no conflict of interest.

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0002-9378/$36.00 • http://dx.doi.org/10.1016/j.ajog.2014.01.041

primiparous women. We hypothesized the following: (1) there is an association between prior miscarriage and the placental dysfunction disorders preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth in primiparous women; (2) the strength of the association increases by the number of previous miscarriages; and (3) risks are higher in preterm (<37 weeks) than in term placental dysfunction disorders (≥37 weeks) because preterm disorders are stronger related to placentation failure than term disorders.[16,17]

Materials and Methods

The Swedish Medical Birth Register contains data on more than 98% of all births in Sweden since 1973,[18] including demographic data, information on reproductive history and complications during pregnancy, delivery, and the neonatal period. In Sweden antenatal care is standardized and free of charge. During the first antenatal visit, usually taking place at the end of the first trimester,[19] the mother is interviewed about her medical and obstetric history. Information about maternal characteristics such as weight, height, and smoking habits are also recorded.

After delivery, the responsible doctor records women's diseases and complications during pregnancy and delivery, according to the *International Classification of Diseases* (ICD). Information about pregnancy and delivery is forwarded to the Birth Register through copies of standardized antenatal, obstetric, and pediatric records. Individual record linkage between the Birth Register and other registries is possible through each individual's unique personal registration number, assigned to each Swedish resident.[20]

Study population and exposure variable

Women giving birth to their first singleton infant at 22 weeks of gestation or later during the period 1995-2009 (n = 619,587) were included. Exposure variable was number of self-reported prior miscarriages, recorded by the midwife at the first antenatal visit. Number of miscarriages was categorized into no prior miscarriage (n = 536,169), 1 miscarriage (n = 68,185), 2 miscarriages (n = 11,410), and 3 or more miscarriages (n = 3,823).

Outcomes

Placental dysfunction disorders included preeclampsia, stillbirth, intrauterine growth restriction, placental abruption, and spontaneous preterm birth.

Preeclampsia was defined through the ICD-9 and ICD-10 codes 642E-G and O14-O15. The clinical definition of preeclampsia during the study period was a rise in blood pressure (≥140/90 mm Hg) combined with proteinuria (≥0.3 g/24 hours or +1 or more on dipstick on at least 2 occasions). The quality of the diagnosis of preeclampsia has been validated previously: of 148 pregnancies coded as preeclampsia in the Birth Register, 137 (93%) had the disease according to the individual records.[21] During most of the study period (before July 1, 2008), stillbirth was defined as fetal death at 28 weeks of gestation or later. Analysis of stillbirth was therefore restricted to births at 28 weeks or later. The total population when calculating risk of stillbirth included 617,708 births.

Being born small for gestational age (SGA) was used as a proxy for intrauterine growth restriction. SGA was defined as a birthweight below 2 SD from the mean birthweight for gestational age, according to the sex-specific Swedish fetal growth curve.[22] Only live births were included in this analysis, and pregnancies with missing information on infant's birthweight were excluded (n = 2252). The total population when calculating risk of SGA included 615,130 births. Placental abruption was defined through ICD-9 and ICD-10 codes 641C and O45.

Preeclampsia, stillbirth, birth of an SGA infant, and placental abruption were categorized into preterm (birth before 37 weeks of gestation) and term (birth at 37th week of gestation or later). In Sweden, gestational age is assessed by ultrasound scans in 97% of women, usually around the 17th week of gestation.[23] If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery.

Spontaneous preterm birth was defined as a birth before 37 gestational weeks with a spontaneous onset. At delivery, the responsible midwife records start of labor using the check boxes; spontaneous labor, induced or caesarean section. A total of 6720 births had no information on labor onset and were excluded from this analysis. All births with a diagnosis of preterm premature rupture of the membranes (ICD-9 and ICD-10 codes 658B and O42) were defined as a spontaneous onset in the study. Spontaneous preterm births were categorized into very preterm births (birth before 32 weeks of gestation) and moderately preterm births (birth from 32 to 36 full weeks of gestation). The birth of an SGA infant was excluded from the analysis. The total population when calculating the risk of spontaneous preterm births included 596,659 births.

Covariates

Information about maternal age and fetal sex was collected at delivery, whereas information about body mass index (BMI), height, smoking habits, cohabitation with infant's father, and IVF was collected from the first antenatal visit. The variables were categorized according to Table 1. To achieve information on the mothers' country of birth and highest level of formal education, individual linkages with the Register of Total Population and the Education Register (Dec. 31, 2010) were performed. The mother's country of birth was categorized to Nordic (Denmark, Finland, Iceland, Norway, and Sweden) and non-Nordic countries, and years of formal education were categorized into 3 levels according to Table 1.

Women with chronic hypertension, pregestational diabetes, hypothyroidism, or systemic lupus erythematosis (SLE) were identified with check boxes from the first antenatal visit and/or diagnostic codes from hospital discharge: chronic hypertension (check box; ICD-9 codes 642A-C; ICD-10 codes O10-11 and I10-15), pregestational diabetes (check box; ICD-9 codes 648A and 250; ICD-10 codes E10-E14 and O240-O243),