OBSTETRICS

Recurrence of small-for-gestational-age pregnancy: analysis of first and subsequent singleton pregnancies in The Netherlands

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OBJECTIVE: Small-for-gestational-age (SGA) neonates are at increased risk of adverse pregnancy outcome. Our objective was to study the recurrence rate of SGA in subsequent pregnancies.

STUDY DESIGN: A prospective national cohort study of all women with a structurally normal first and subsequent singleton pregnancy from 1999-2007. *SGA* was defined as birthweight <5th percentile for gestation. We compared the incidence and recurrence rate of SGA for women in total and with and without a hypertensive disorder (HTD) in their first pregnancy. Moreover, we assessed the association between gestational age at first delivery and SGA recurrence.

RESULTS: We studied 259,481 pregnant women, of whom 12,943 women (5.0%) had an SGA neonate in their first pregnancy. The risk of SGA in the second pregnancy was higher in women with a previous SGA neonate than for women without a previous SGA neonate (23% vs 3.4%; adjusted odds ratio, 8.1; 95% confidence interval, 7.8−8.5) and present in both women with and without an HTD in pregnancy. In women without an HTD, the increased recurrence risk was independent of the gestational age at delivery in the index pregnancy; whereas in women with an HTD, this recurrence risk was increased only when the woman with the index delivery delivered at >32 weeks' gestation.

CONCLUSION: Women with SGA in their first pregnancy have a strongly increased risk of SGA in the subsequent pregnancy and first pregnancy SGA delivers a significant contribution to the total number of second pregnancy SGA cases.

Key words: hypertensive disorder, recurrence, small-for-gestational-age

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Small-for-gestational-age (SGA) refers to a fetus or neonate who has failed to achieve a specific biometric or estimated weight threshold by a specific gestational age. *SGA neonates* are defined as those who are born with a weight below a certain percentile (2.5, 5, or 10 percentile) for gestational age. SGA neonates are a heterogeneous group comprising fetuses who have failed to achieve their growth potential, neonates who have fetal growth restriction [FGR]), and neonates who are constitutionally small. Thus, not all SGA neonates are growth restricted. The lower the percentile for defining SGA, the higher the likelihood of FGR.[1] On the other hand, a neonate with growth restriction may not be SGA.

SGA neonates are at increased risk of perinatal death and adverse perinatal and health outcome later in life.[2-6] Some studies on SGA neonates have shown that poor perinatal outcome is likely to be a reflection of the high incidence of true FGR.[7,8]

Patterns of recurrence of restricted fetal growth are important for patient counseling and adequate care in subsequent pregnancies. Previous studies found a strong tendency of SGA recurrence in subsequent pregnancies (20.1-28.7%).[9-11] However, knowledge gaps persist, particularly in the area of defining cause-specific risks.[12] Clinical maternal vascular disease that results from chronic hypertension, renal disease, diabetes mellitus, and collagen vascular disease, especially when complicated by preeclampsia, is the most common cause of impaired fetal growth and accounts for nearly one-third of FGR cases.[13] Hypertensive disorders (HTDs) during pregnancy thus play an important role in the cause of SGA. The aim of this study was to assess and describe in detail the SGA incidence and recurrence rate in general and the influence of an HTD in the first pregnancy on the recurrence rate and incidence of SGA in the second pregnancy. Moreover, we investigated whether the SGA recurrence rate depends on the gestational age at delivery in the first pregnancy.

Materials and Methods

Dataset

This study was performed in a prospective nationwide cohort with the use of The Netherlands Perinatal Registry (PRN). The PRN consists of population-based data that contain informa-

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tion on pregnancies, deliveries, and readmissions until 28 days after birth. The PRN database is obtained by a validated linkage of 3 different registries: the midwifery registry, the obstetrics registry, and the neonatology registry of hospital admissions of newborn neonates.[14,15] Records are entered in the PRN registry at the child's level. There is no unique maternal identifier available in the registry to follow up on outcomes of subsequent pregnancies in the same mother. A longitudinal probabilistic linkage procedure was performed to create a cohort with complete data on first and second deliveries of the same mother. Details on entry, linkage, aggregation, validation, and verification of the data are published elsewhere.[16]

The coverage of the PRN registry is approximately 96% of all deliveries in The Netherlands. It contains pregnancies of ≥22 weeks' gestation and a birthweight of ≥500 g and is used primarily for an annual assessment of the quality indicators of obstetric care.

Ethical approval

The data in the perinatal registry are anonymous; therefore, ethical approval was not needed. The Dutch Perinatal Registry gave their approval for the use of their data for this study (approval no. 12.39).

Inclusion and exclusion criteria

From our linked cohort,[16] we included all women who delivered 2 subsequent singleton pregnancies (first and second delivery) in The Netherlands between Jan. 1, 1999 and Dec. 31, 2007. We excluded all cases with major congenital anomalies[17] and multiple gestations.

Outcome measures

Our primary outcome measure was *SGA*, which was defined as a birthweight below the percentile for gestational age. The Dutch reference curves for birthweight by gestational age separate for parity, sex, and ethnic background were used.[18] Pregnancy dating was performed by last menstrual period or ultrasound measurements at <20 weeks' gestation (crown-rump-length or head-circumference measurement). If estimation by ultrasound measurement differed >6 days from the last menstrual period, then the ultrasound measurement was considered the dominant one.

Population characteristic and clinical characteristics

We registered demographic and obstetric characteristics that included maternal age, parity, ethnicity, and socioeconomic status. Maternal age was categorized into <25 years, 25-34 years and ≥35 years. Parity was categorized into 0 (first birth), 1 (second birth), and 2+ (third or higher birth). Ethnicity was ascribed by the woman's care provider. For this study, we differentiated between Western (native Dutch women and women from other Western nations) and non-Western (including different ethnic groups such as African/Surinamese Creole, Surinamese Hindustani, Moroccan, and Turkish). The socioeconomic status score was based on mean income level, the percentage of households with a low income, the percentage of inhabitants without a paid job, and the percentage of households with, on average, low education level in a postal code area.[18] The continuous socioeconomic status score was categorized into a high, middle, and low group based on percentile ranges (25th percentile, middle percentile, 75th percentile).

Cases were analyzed in total and stratified into 2 groups: women with an HTD in their first pregnancy and women without an HTD in their first pregnancy. HTDs included pregnancy-induced hypertension, preeclampsia, and chronic hypertension. Hypertension was a clinical diagnosis that was made when there was a systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg and/or preeclampsia and/or proteinuria.

We also stratified the analysis by gestational age at delivery in the first pregnancy into 3 groups: very preterm (24^{+0}-31^{+6} weeks' gestation), late preterm (32^{+0}-36^{+6} weeks' gestation), and term (37^{+0}-42^{+6} weeks' gestation).

Statistics

We compared the recurrence rate and incidence of SGA in the second pregnancy in women with and without SGA in their first pregnancy. For these 2 groups, we studied demographic and obstetric baseline characteristics.

Univariate analyses were performed with the Student *t* test and χ^2 test, as appropriate, to compare baseline characteristics. All statistical tests were 2-sided; a probability value of .05 was chosen as the threshold for statistical significance. Logistic regression modeling, which was used to determine the effect of the risk factors on SGA in the second pregnancy, was expressed as odds ratios with 95% confidence interval (CI). In a multivariable analysis, we adjusted for maternal age, ethnicity, socioeconomic status, and year of birth.

In addition, for each factor, we calculated the population-attributive risk (PAR) percentage, which was based on the prevalence and relative risk (RR): PAR % = (prevalence × [RR − 1])/(prevalence × [RR − 1] + 1) × 100.[19]

We tested for interaction between SGA and HTD in the first pregnancy and SGA and gestational age at delivery (in the first pregnancy). If statistically significant ($P < .001$), analyses were also performed separately for HTD and non-HTD cases and for 3 strata of gestational age at delivery in the first pregnancy.

The probabilistic linkage procedure was performed with the R statistical software environment (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria), and the data were analyzed with the SAS statistical software package (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

From Jan. 1, 1999 until Dec. 31, 2007, a total of 1,503,996 singleton pregnancies were identified in the PRN database. After the application of our inclusion and exclusion criteria, 259,481 women (518,962 deliveries) made up our study population.

Baseline characteristics of this cohort are presented in Table 1. In the first pregnancy, 12,943 fetuses (4.99%) had a birthweight below the 5th percentile for gestational age. HTDs, low socioeconomic status, younger age, nonwhite ethnicity, and preterm birth were more