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Placenta Previa and the Risk of Delivering a Small-for-Gestational-Age Newborn

Sari Räisänen, PhD,

Department of Epidemiology, Emory University Rollins School of Public Health, 1518 Clifton Rd NE, Atlanta, GA 30322, USA

Department of Obstetrics and Gynaecology, Kuopio University Hospital, P.O. Box 100, FI-70029 Kys, Kuopio, Finland, shraisan@student.uef.fi Tel: +358503378258, Fax: +35817172486

Vijaya Kancherla, PhD,

Department of Epidemiology, Emory University Rollins School of Public Health, 1518 Clifton Rd NE, Atlanta, GA 30322, USA, Tel: 404 727 8884, vkanche@emory.edu

Michael R. Kramer, PhD, MMSc [Assistant Professor],

Department of Epidemiology, Emory University Rollins School of Public Health, 1518 Clifton Rd NE, Atlanta, GA 30322, USA, mkram02@emory.edu

Mika Gissler, Dr.Phil, M.Soc.Sc [Professor], and

National Institute for Health and Welfare (THL), P.O. Box 30, Paciuksenkatu 21, FI-00271 Helsinki, Finland, Nordic School of Public Health, Gothenburg, Sweden, mika.gissler@thl.fi

Seppo Heinonen, MD, PhD [Professor]

Department of Obstetrics and Gynaecology, Kuopio University Hospital, P.O. Box 100, FI-70029 KYS, Kuopio, Finland

School of Medicine, University of Eastern Finland, P.O. Box 1627, FI-70211 Kuopio, Finland, seppo.heinonen@kuh.fi

Abstract

Objective—To evaluate whether there is an association between placenta previa and delivery of a small-for-gestational-age (SGA) newborn and to quantify the contribution of individual risk factors for SGA that are associated with placenta previa, stratified by maternal parity.

Methods—A cross sectional study utilizing the Finnish Medical Birth Register during 2000–2010. All singleton births (N=596,562) were included; major congenital anomalies were excluded. An association between SGA (< 2 standard deviations below the mean) and placenta previa was modeled by parity-specific unadjusted and adjusted statistical models.

Results—Placenta previa complicated 625 of 249,476 singleton births among nulliparous women (2.50/1,000) and (915 of 347,086 singleton births among multiparous women (2.64/1,000). Among nulliparous women, the most common risk factor for placenta previa was *in vitro* fertilization (IVF); placenta previa was not associated with an increased prevalence of SGA,

controlling for maternal age, smoking, IVF, socioeconomic status, and preeclampsia (aOR=0.81; 95% CI=0.57–1.17). Among multiparous women, placenta previa was associated with a two-fold increased risk of SGA, controlling for maternal age, parity, prior preterm birth, prior caesarean delivery, prior SGA newborn, prior preeclampsia, smoking, IVF, socioeconomic status, and preeclampsia (aOR=2.08; 95% CI=1.50–2.89). Further, only one fourth of the association between SGA and placenta previa could be explained by controlling for risk factors clustering with placenta previa among multiparous women.

Conclusions—Placenta previa is associated with impaired fetal growth in multiparous but not nulliparous women.

Introduction

Placenta previa occurs in about 5 in 1,000 pregnancies. (1). Advanced maternal age (2,3,4), smoking during pregnancy (2,4,5,6), in vitro fertilization (IVF) (2), prior caesarean delivery (2,4,7,8), and multiparity (2,5,6) are found to increase the risk of placenta previa. A large population-based study reported that multiparity increased the risk of placenta previa, and that cumulative effects of previous pregnancies may further contribute to the risk (9).

Neonates born to mothers with placenta previa are more likely to be delivered preterm (<37 weeks) (2,4,10,11,12), stillborn (2,6), or die early in the neonatal period (2,5,6,13). The association between placenta previa and small-for-gestational age (SGA) newborn has been inconsistent, ranging from moderate (4,10) to no risk (2,14). The relation between placenta previa and SGA may be explained by suboptimal placental implantation and decreased perfusion to the fetus. Previous studies on this association had varied findings due to differences in their study designs and sample sizes, selection and clinical criteria that define SGA, and availability and adjustment of varied confounding factors (2,4,10,11,14,15).

The aim of the present study was to evaluate the association between placenta previa and delivery of a SGA newborn, and to quantify the contribution of individual risk factors for SGA that are associated with placenta previa, stratified by maternal parity.

Materials and Methods

The data included the entire population of singleton births (N=596,562) during 2000–2010 in Finland; major congenital anomalies (n=23,934, 4.0%) and multiple births (n=18,217, 3.1%) were excluded. Births with missing information on gestational age (n=2,141, 0.4%), birth weight (n=630, 0.1%), newborns with unknown sex (n=21, 0.0%), and parity (n=667, 0.1%) were excluded from the analysis. In total, 2,135 (0.4%) singleton births were excluded from the bi-variable analyses, and 2,803 births (0.5%) from the multivariable.

Data for our analyses were acquired from two sources. The first was the Finnish Medical Birth Register (MBR), established in 1987 and currently maintained by the National Institute for Health and Welfare. The MBR contains socio-demographic characteristics, maternal reproductive history, pregnancy and delivery characteristics of the index pregnancy, and maternal and infant diagnoses on all live births and stillbirths (delivered after the 22nd gestational week or weighing 500 g or more) through the first postnatal week. Further, MBR

data were supplemented by information on selected maternal conditions from a second data source, the Hospital Discharge Register (HDR). The HDR, established in 1967, contains information on diagnoses, medical interventions and surgical procedures of outpatient and inpatient care in specialized health care in Finland. Thus, records from MBR and HDR were deterministically linked using the parturients' encrypted personal identification numbers. HDR data were used to assess maternal preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal diabetes mellitus (O24.0 and O24.1), all defined and gathered based on the *International Classification of Diseases*, 10th edition (ICD-10) codes in the HDR.

The National Institute for Health and Welfare authorized use of the data as required by the national data protection legislation of Finland (Reference number 1749/5.05.00/2011). Placenta previa was defined based on ICD-10 codes from the MBR (O44). The validity of placenta previa diagnosis was quite high in the MBR as almost 100% of the pregnant women underwent ultrasound examination during their first and second trimester (<http://www.finlex.fi/fi/laki/alkup/2011/20110339>, in Finnish), and specifically, those with placenta previa underwent repeat ultrasound examinations during the third trimester. Information on severity of placenta previa (complete or incomplete) was not available. SGA was recorded if the newborn's sex- and parity-specific birth weight was < 2 standard deviations (SD) below the mean (based on the Finnish population-based birth curves for 1996–2008) (16). Women were grouped based on number of prior childbirths as 'nulliparous' (those having no prior childbirths) and 'multiparous' (those with at least one prior childbirth). We classified parity into three groups based on prior childbirths among multiparous women (1, 2–4, and 5 or more prior childbirths). Maternal age was classified as less than 20, 20–29, 30–39, or 40 or more (advanced age). The gestational age was estimated based on first- or second-trimester ultrasonography measurements or from the date of the last menstrual period. Birth weight (grams) was used as a continuous variable. Women were classified based on self-reported smoking habits during pregnancy (reviewed during antenatal visits) as non-smoking, smoking (quitted smoking during the first trimester or continued smoking after the first trimester) or missing information on smoking (n=15,910; 2.7%). Marital status was classified as either single or in a relationship (married or living with a partner). Women were classified also by socioeconomic status (SES) (defined based on maternal occupation at birth) based on Finland's National Social Classification, which follows international recommendations (http://www.stat.fi/meta/luokitukset/ammatti/001-2001/kuvaus_en.html, in Finnish). SES was categorized as upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cleaners; others; and missing information, as categorized and published elsewhere (17). 'Others' comprised % (n=152,894; 25.6%) of all cases and included all births with unclassifiable occupations, such as entrepreneurs, students, retired, unemployed and housewives. The group with missing information on SES comprised 16.9% (n=101,182) of all births. IVF included intracytoplasmic sperm injection (ICSI) and frozen embryo transfers.

Differences between women with and without placenta previa, and with and without SGA newborns, were evaluated by chi square test for dichotomous and categorical variables, and Mann Whitney test for continuous variables. Non-SGA newborns were defined as

appropriate or large for gestational age. Unadjusted and several partially adjusted odds ratios (aOR) and 95% confidence intervals (CI) were estimated to measure all associations, using unconditional logistic regression analysis. Possible confounders were selected based on the literature, and the results of bivariable analyses ($p < 0.1$), and explored separately for nulliparous women (maternal age, smoking during pregnancy, IVF, SES, and preeclampsia) and multiparous women (maternal age, prior childbirths, prior preterm births, prior cesarean births, prior SGA newborn, prior preeclampsia, smoking during pregnancy, IVF, SES, and preeclampsia). A preliminary model (Model 1) was used to estimate the unadjusted association between placenta previa and SGA newborn. Selected confounders were added one by one to partially adjusted models 2–9 (see Table 1). Model 10 was the final model, and included all the confounders. The contribution of each confounder in models 4–10 was measured by the percentage reduction in the odds ratio (OR) of placenta previa associated with SGA newborn compared to Model 2 or 3 by using formula: $(\text{OR Model 2 or 3} - \text{OR Model } x) / (\text{OR Model 2 or 3} - 1)$. Sensitivity analyses were performed to study whether severity of placenta previa affected the results; analysis was restricted to pregnancies with placenta previa and cesarean birth, which were more likely to be severe cases. Associations were deemed to be significant if the p -value was less than 0.05. All analyses were performed using SPSS for Windows 19.0, Chicago, IL.

Permission to use the confidential register data in this study was approved on 16th February, 2012 by the National Institute for Health and Welfare in Finland (Reference number 1749/5.05.00/2011).

Results

The prevalence of placenta previa, among all singleton births not complicated by major congenital anomalies between the years 2000 and 2010, was estimated as 2.50 (95% CI=2.32–2.71) per 1,000 births among nulliparous women; and 2.64 (95% CI=2.47–2.81) per 1,000 births among multiparous women ($p=0.33$). As shown in Table 2, an increased prevalence of placenta previa in nulliparous women was associated with advanced maternal age (40 years or more), non-smoking status, SES, IVF achieved pregnancy, gestational diabetes, and maternal diabetes mellitus ($p < 0.05$). Similarly, placenta previa in multiparous women was positively associated with advanced maternal age (40 or more), higher number of prior births, prior cesarean birth, prior preterm birth, prior SGA newborn, IVF achieved pregnancy, preeclampsia, gestational diabetes and maternal diabetes mellitus ($p < 0.05$). Infants affected by placenta previa during pregnancy were more likely to be delivered by cesarean at a lower gestational age, and with a lower mean birth weight compared to newborns not affected by placenta previa (Table 2).

Table 3 shows socio-demographics and delivery characteristics among women with and without SGA newborns, stratified by parity. An increased prevalence of SGA newborns was associated with advanced maternal age (40 years or more), smoking, single marital status, low SES, and preeclampsia among both parity groups. An increased prevalence of SGA was associated with male fetal sex in nulliparous women, but not in multiparous women. SGA was positively associated with higher number of prior births, prior cesarean birth, prior

preterm birth, prior SGA infant, prior preeclampsia, and placenta previa, in multiparous women.

Table 1 shows unadjusted and partially adjusted models examining the association between placenta previa and SGA, stratified by parity. In nulliparous women, placenta previa was not a risk factor for SGA after adjusting for maternal age, smoking, IVF, SES, and preeclampsia (Model 10; aOR=0.81; 95% CI=0.57–1.17). Among multiparous women, the prevalence of SGA was two-fold greater for those affected with placenta previa compared to those without (Model 10; aOR=2.08; 95% CI=1.50–2.89). Furthermore, in multiparous women, 24.5% of the association between placenta previa and SGA could be explained by adjustment for prior preterm birth, prior cesarean birth, prior SGA infant, prior preeclampsia, smoking, SES, IVF and preeclampsia during index pregnancy (Model 10). Contribution of individual factors, including prior preterm birth, prior cesarean birth, and prior SGA infant to the prevalence of SGA associated with placenta previa, was 8.4%, 7.0%, and 14.7%, respectively (models 4–6).

Sensitivity analyses were performed to study whether severity of placenta previa might affect and association between placenta previa and SGA (analyses were restricted to women with placenta previa who gave birth by cesarean), but our results were almost the same as noted in the previous analysis (data not shown).

Discussion

For births between 2000 and 2010 in Finland, the prevalence of placenta previa among singleton pregnancies not affected by major congenital anomalies was 2.5 – 2.6 per 1,000 births. These prevalence estimates were comparable with a previous review by Cresswell et al. (1). The novelty of the present study was that the association between placenta previa and prevalence of SGA newborn was substantially modified by maternal parity. Additionally, predisposing factors that led to placenta previa varied by parity; in nulliparous women placenta previa was more frequently associated with IVF, and in multiparous women with a prior cesarean birth. Placenta previa was not a risk factor for SGA in nulliparous women, but was associated with a two-fold increased prevalence of SGA in multiparous women. Of the increased prevalence of SGA associated with placenta previa in multiparous women, only 24.5% of the placenta previa-SGA association is attributable to prior preterm birth, prior cesarean birth, prior SGA infant, prior preeclampsia, smoking during pregnancy, IVF, SES, and preeclampsia, which typically cluster both with a history of previous cesarean delivery, as well as with the occurrence of placenta previa. Consequently, placenta previa is associated with a doubling of SGA prevalence among multiparous women even after accounting for known risk factors.

Our findings concerning predisposing factors of placenta previa were in accordance with previous reports and confirmed an association between IVF, prior cesarean birth and placenta previa (2,7). However, current findings did not confirm maternal smoking as a predisposing factor for placenta previa as reported by previous studies (2,4,5,6). This could be because nulliparous women with placenta previa were less likely to be smokers in our

study, and no significant association was noted in multiparous women. Many nulliparous women conceived by IVF and were of high SES, older and less likely to smoke (18).

The most important strengths of our research are size of the study population and subsequently, its generalizability. Our study included all singleton births in Finland using data from two national population registers, spanning most recent years, thus minimizing selection bias. Data quality and coverage of the national health registers has shown to be good or excellent (19,20). Further, we had information on several important confounders. As ultrasound examinations during the first and second trimester is conducted in all pregnant women in Finland as stated by the law, and cases with placenta previa underwent repeat ultrasound examinations, thus the validity of placenta previa diagnosis in our study is quite high. One limitation in our analysis is that we did not have information on the type of placenta previa (complete or incomplete).

In conclusion, the current cross-sectional study with a total population of singleton births from Finland showed that both predisposing factors for placenta previa, and the association between placental previa and SGA infant, were substantially modified by parity. Pregnancies of multiparous women with placenta previa are more likely to result in as the delivery of an SGA infant. Future studies should examine the association between placenta previa and SGA in other population-based samples, and consider parity and other factors that may potentially contribute to this association.

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Table 1

Small-for-Gestational-Age (<2 Standard Deviations) Newborns Associated With Placenta Previa After Adjustment for Socio-demographics and Pregnancy Characteristics in Nulliparous and Multiparous Women Among Singleton Births^a During 2000–2010 in Finland

SGA	NULLIPARA	*Differences with Model x	MULTIPARA	*Differences with Model x
	OR (95 % CI)		OR (95 % CI)	
Model 1 unadjusted	0.85 (0.59–1.23)	-	2.47 (1.80–3.39)	-
Model 2 adjusted by maternal age	0.81 (0.56–1.16)	1: -	2.35 (1.71–3.23)	1: 8.2%
Model 3 adjusted by age and parity	NA	2: -	2.43 (1.76–3.34)	2: -
Model 4 adjusted by Model 3 + prior preterm birth	NA	2: -	2.31 (1.68–3.18)	3: 8.4%
Model 5 adjusted by Model 3 + prior caesarean section birth	NA	2: -	2.33 (1.69–3.21)	3: 7.0%
Model 6 adjusted by Model 3+ prior SGA newborn	NA	2: -	2.22 (1.60–3.07)	3: 14.7%
Model 7 adjusted by Model 3+ <i>In vitro</i> fertilization	0.82 (0.57–1.18)	2: -	2.43 (1.77–3.34)	3: 0%
Model 8 adjusted by Model 2 or 3 + smoking	0.81 (0.56–1.16)	2: 0%	2.36 (1.71–3.25)	3: 4.9%
Model 9 adjusted by Model 2 or 3 + preeclampsia	0.81 (0.57–1.17)	2: 0%	2.36 (1.71–3.25)	3: 4.9%
Model 10 adjusted by Model 2 or 3 + all confounders ^b	0.81 (0.57–1.17)	2: 0%	2.08 (1.50–2.89)	3: 24.5%

^a Cases with major congenital anomalies were excluded.

^b In nulliparous women OR of SGA adjusted for maternal age, smoking, IVF, socioeconomic status and preeclampsia.

In multiparous women OR of SGA adjusted for maternal age, parity, prior preterm birth, prior caesarean birth, prior SGA newborn, prior preeclampsia, smoking, IVF, socioeconomic status and preeclampsia.

* (The contribution of each factor was measured by the percentage reduction in the odds ratio of placenta previa compared to Model 2 by using formula (OR Model 2 or 3 – OR Model x) / (OR Model 2 or 3 – 1).

Table 2

Delivery characteristics among women with singleton births with and without placenta previa during 2000–2010 in Finland

Characteristics	NULLIPAROUS WOMEN, n=249,476			MULTIPAROUS WOMEN, n=347,086		
	PP, n=625 (0.3%)	No PP, n=248,851 (99.7%)	p value*	PP, n=915 (0.3%)	No PP, n=346,171 (99.7%)	p value*
Mean maternal age years (SD)	30.6 (5.4)	27.3 (5.3)	0.001	32.6 (5.1)	31.0 (5.1)	0.001
Maternal age years %			0.001			0.001
Less than 20	1.9	6.0		0.1	0.4	
20–29	38.6	61.2		27.8	39.1	
30–39	54.4	31.1		63.2	55.6	
40 or more	5.1	1.6		9.0	4.9	
Mean gestational age weeks (SD)	37.7 (2.9)	39.8 (1.9)	0.001	37.1 (3.0)	39.8 (1.7)	0.001
Smoking status %			0.002			0.22
Non-smoking	85.8	80.5		83.6	84.1	
Smoking	12.0	17.5		14.2	13.0	
Missing information	2.2	2.1		2.2	3.0	
Married or in relationship %	94.2	90.7	0.003	95.4	95.1	0.72
Socioeconomic status %			0.001			0.08
Upper white-collar worker	8.0	8.0		8.5	8.6	
Lower white-collar worker	39.0	31.8		34.4	36.6	
Blue-collar worker	11.4	13.7		15.4	15.0	
Others ^b	20.8	27.1		23.3	24.5	
Missing	20.8	19.3		18.5	15.2	
Number of prior deliveries %	NA	NA				0.007
1				56.4	57.3	
2–4				36.9	38.2	
5 or more				6.7	4.5	

Characteristics	NULLIPAROUS WOMEN, n=249,476			MULTIPAROUS WOMEN, n=347,086		
	PP, n=625 (0.3%)	No PP, n=248,851 (99.7%)	p value*	PP, n=915 (0.3%)	No PP, n=346,171 (99.7%)	p value*
Prior caesarean section %	NA	NA		28.9	17.9	0.001
Prior preterm birth %	NA	NA		13.1	7.3	0.001
Prior SGA infant %	NA	NA		7.8	5.1	0.001
Prior preeclampsia %	NA	NA		0.5	0.4	0.43
<i>In vitro</i> fertilisation (IVF) %	12.8	2.2	0.001	4.3	0.8	0.001
Preeclampsia	0.8	0.9	0.83	2.7	1.5	0.001
Gestational diabetes %	9.9	7.6	0.03	14.3	13.0	0.24
Pre-existing diabetes mellitus %	7.2	5.5	0.07	11.7	9.7	0.04
Male sex %	54.1	51.1	0.14	53.6	51.1	0.14
Mean birth weight grams (SD)	3063.4 (661)	3438.2 (539)	0.001	3038.8 (759)	3615.5 (532)	0.001
Mode of delivery %			0.001			0.001
Vaginal spontaneous	16.0	66.2		20.4	84.0	
Breech	0.2	0.7		0.3	0.5	
Vacuum assistance	3.2	13.7		1.0	2.9	
Forceps	2.7	0.1		0.7	0.0	
Caesarean section	77.9	19.4		77.6	12.7	

^b Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases

* Chi square or Mann Whitney U –test, p value significant at <0.05

NA=not applicable; PP=Placenta Previa; SD=Standard Deviation

Table 3

Delivery characteristics factors among women with singleton small-for-gestational-age (SGA, <2 SD) and Non-SGA newborn during 2000–2010 in Finland

Characteristics	NULLIPAROUS WOMEN, n=248,725		MULTIPAROUS WOMEN, n=345,702	
	SGA, n=14,378 (5.8%)	Non SGA, n=234,347 (94.2%)	SGA, n=6,370 (1.8%)	Non SGA, n=339,332 (98.2%)
			p value*	p value*
Mean maternal age in years (SD)				
Maternal age years %				
Less than 20	30.6 (5.4)	27.3 (5.3)	32.6 (5.1)	31.0 (5.1)
20–29	6.5	6.0	0.6	0.4
30–39	56.6	61.4	34.4	39.1
40 or more	34.7	31.0	56.9	55.6
	2.6	1.6	8.0	4.8
Mean gestational age weeks (SD)	37.7 (2.9)	39.8 (1.9)	37.1 (3.0)	39.8 (1.7)
Smoking status %				
Non-smoking	72.8	81.0	69.1	84.5
Smoking	24.9	17.0	28.1	12.7
Missing information	2.3	2.0	2.8	2.9
Married or in relationship %	88.9	90.8	92.7	95.2
Socioeconomic status %				
Upper white-collar worker	7.3	8.1	5.9	8.6
Lower white-collar worker	31.7	31.9	34.7	36.7
Blue-collar worker	15.0	13.7	18.3	15.0
Others ^b	26.4	27.1	25.1	24.5
Missing	19.6	19.3	16.0	15.2
Number of prior deliveries %				
1	NA	NA	38.7	57.6
2–4			55.7	37.9
5 or more			5.6	4.5

Characteristics	NULLIPAROUS WOMEN, n=248,725			MULTIPAROUS WOMEN, n=345,702		
	SGA, n=14,378 (5.8%)	Non SGA, n=234,347 (94.2%)	p value*	SGA, n=6,370 (1.8%)	Non SGA, n=339,332 (98.2%)	p value*
Prior cesarean delivery %	NA	NA		24.5	17.8	0.001
Prior preterm birth %	NA	NA		15.1	7.2	0.001
Prior SGA infant %	NA	NA		26.3	4.7	0.001
Prior preeclampsia %	NA	NA		0.9	0.4	0.001
<i>In vitro</i> fertilization %	2.0	2.2	0.08	0.7	0.8	0.17
Preeclampsia %	3.9	0.7	0.001	6.3	1.4	0.001
Gestational diabetes %	5.6	7.7	0.001	9.7	13.1	0.001
Pre-existing diabetes mellitus %	4.0	5.6	0.001	7.2	9.8	0.001
Placenta previa %	0.2	0.3	0.39	0.6	0.3	0.001
Male sex %	51.9	51.1	0.05	50.3	51.2	0.20
Mean birth weight grams (SD)	3063.4 (661)	3438.2 (539)	0.001	3038.8 (759)	3615.5 (532)	0.001

^b Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases

* Chi square or Mann Whitney U –test, p value significant at <0.05

NA=not applicable; SD=standard deviation