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A Danish national cohort study on neonatal outcome in singleton pregnancies with placenta previa

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Abstract

Objective. To describe the incidence of placenta previa and to assess neonatal morbidity and mortality in pregnancies with placenta previa after adjustment for previous cesarean section, smoking, multiparity, maternal age and in vitro fertilization. *Design.* National cohort study. *Setting.* Danish national IVF-, birth- and patient registers. *Population.* All pregnancies in Denmark from 1978–2006 and a subpopulation of all singleton pregnancies during the years 2001–2006 with placenta previa (n=1721) compared to pregnancies without this diagnosis. *Methods.* Incidence rates and multivariate analysis. *Main outcome measures.* Gestational age, birthweight, Apgar score after five minutes, stillbirth, neonatal mortality and admittance to neonatal intensive care unit. *Results.* The incidence of placenta previa in Denmark was 0.54% in 2006. Neonates born after pregnancies with placenta previa had a higher risk of being born at a gestational age below 37 weeks (OR 8.6; 95%CI 7.5–9.9), having an Apgar score of ≤7 at five minutes (OR 2.7; 95%CI 2.0–3.7), being transferred to a neonatal intensive care unit (OR 4.3; 95%CI 3.8–4.9) and for stillbirth and neonatal mortality combined (OR 1.8; 95%CI 1.1–3.0), compared with neonates born in pregnancies without placenta previa. No increased risk of being small-for-gestational age was found (OR 1.0; 95%CI 1.0–1.2). *Conclusion.* When adjusting for confounders, neonates born after pregnancies with placenta previa had a significantly higher risk of being born preterm, having a low Apgar score, being transferred to neonatal intensive care, and death.

Abbreviations: CI, confidence interval; CS, cesarean section; GA, gestational age; ICD, International Classifications of Diseases; IVF, in vitro fertilization; NICU, neonatal intensive care unit; OR, odds ratio; SGA, small-for-gestational age.

Introduction

Placenta previa constitutes a major complication in pregnancy, with implantation differences in relation to whether it covers or lies close to the internal os of the cervix. This potentially and frequently leads to episodes of bleeding and obstructs vaginal delivery. Major maternal morbidity is mainly associated with ante-, intra- and postpartum bleeding requiring blood transfusion, or may result in hysterectomy, septicemia, coagulopathy or even death (1–3). Neonates born after pregnancies complicated by placenta previa have a higher risk of being born preterm, being of low birthweight or asphyxiated, requiring intensive neonatal care, while stillbirth or neonatal mortality may also occur (2,4–9). Preterm delivery is related to a need for elective or emergency cesarean section before or just after the onset of spontaneous delivery and preterm delivery rates as high as around 47% have been

Key Message

Placenta previa holds an increased risk of neonatal mortality, prematurity, low Apgar scores, low birthweight and transfer to a neonatal intensive care unit. Even at term a substantially increased risk of neonatal morbidity was found.

reported (6,7). Much of the increased neonatal risk is primarily related to being preterm rather than to the placenta previa itself.

We have studied preterm and term pregnancies with placenta previa derived from a national birth cohort, adjusting for confounders such as previous cesarean section, smoking, parity, maternal age and in vitro fertilization.

Material and methods

The study was a national cohort study. Data were derived from the Danish national IVF-, birth- and patient registers, which are mandatory and cover all IVF treatments, births and admissions to hospitals in Denmark. After discharge, International Classifications of Diseases diagnostic codes (ICD-10) are assigned to all patients. There is a personal identification number in Denmark which is given at birth to every live newborn in Denmark and which is thereafter used for all national registration purposes, including health registers. This makes wide-ranging linkage between different national registers possible.

The incidence of placenta previa in Denmark during the period 1978–2007 was obtained from the National Birth Register and the National Patient Register.

Inclusion criteria for the comparative analyses were all singleton deliveries with a placenta previa diagnosis during 2001–2006 in Denmark regardless of the mode of delivery. The following ICD-10 diagnoses were included: O44 for placenta previa, O44.0 for total placenta previa without bleeding, O441 for total placenta previa with bleeding, O44.2 for marginal placenta previa without bleeding, O44.3 for marginal placenta previa with bleeding and O44.9 for placenta previa without specification. Exclusion criteria were delivery before 22 weeks. The diagnosis of placenta previa was made either by ultrasound in the third trimester or during cesarean section. According to the Danish national obstetric guidelines, the diagnosis should be restricted to women with placenta previa confirmed in the third trimester by ultrasound or when diagnosed as present in pregnancies with bleeding in the second trimester and where the placenta is definitely covering the internal os on ultrasound (10).

Every woman diagnosed with placenta previa (exposed women) was matched with five randomly selected women without the diagnosis (unexposed) using the date of delivery as matching criteria. Maternal and neonatal linkage was done through an already existing linkage in the National Birth Register.

Data collected on the neonate included gender, gestational age (GA) at delivery, birthweight, Apgar score after five minutes, stillbirth (after 22 weeks' gestation), neonatal mortality (death during the first 28 days) and admittance to neonatal intensive care unit (NICU). Delivery at term was defined as GA$\geq$37 weeks, preterm delivery as GA$<$37 weeks and extremely preterm delivery as GA$<$28 weeks. Data on neonatal outcomes were almost complete as GA, Apgar scores after five minutes, birthweight and gender were missing in less than 1%. Scandinavian gender-specific growth curves (11) were used to evaluate small-for-gestational age (SGA) as $<$10th percentile. Mode of delivery (vaginal or by elective/emergency cesarean section) was recorded. We made sub-analyses restricted to the pregnancies with placenta previa delivered by cesarean section. This was done to exclude women with a marginal placenta previa who subsequently delivered vaginally. The following variables were recorded as potential confounders: maternal age, parity, smoking, previous cesarean section, method of conception (spontaneous pregnancy, in vitro fertilization (IVF) including intracytoplasmatic sperm injection).

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health (J.nr. 7–505-29–552/1). Written informed consent from the women in the cohort was not required as only register data were used and ethical committee permission is not required by Danish law for register studies.

Statistical analysis

Data were analyzed using SPSS (Statistical Packages for Social Sciences) version 13.0 and PAWS (Predictive Analytics Software) Statistics version 18. Student's *t*-tests were used to compare mean values between continuous normally distributed data. Proportions between groups on a dichotomous response were compared with chi-squared analysis and the Mantel–Haenszel (MH) test was used when adjusting for confounders. Backward stepwise multivariate logistic regression analyses were performed to identify significant predictors of placenta previa with the following variables entered as covariates; previous cesarean section (yes/no), smoking (yes/no), parity (nulli- or multiparous), maternal age (continuous) and IVF treatment (yes/no).

Results

The incidence rate of placenta previa in Denmark in 1978–2007 is shown in Figure 1. During 2001–2006, 1721 women with placenta previa were identified and 8603 women with normal placental insertion were selected as the comparison group. Demographic data for the women are presented in Table 1. Women with placenta previa were significantly older, and more often parous and smokers compared with women with normal placental insertion. Previous cesarean section and conception by IVF was significantly more frequent with placenta previa. In the multiple logistic regression analyses the strongest independent risk factor of placenta previa was IVF, with women receiving IVF experiencing 3.1 times the

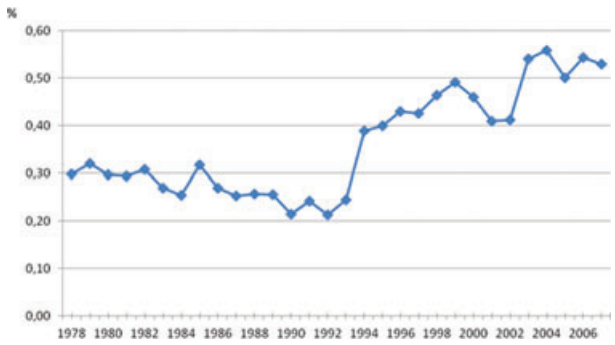

Figure 1. Incidence rates of placenta previa in Denmark 1978–2007. Data from the Danish National Birth and Patient Registers.

odds of placenta previa compared with women not receiving IVF.

In the placenta previa group 573 women (33.3%) had a vaginal delivery and 1147 (66.7%) a cesarean section. The mean gestational age for elective cesarean section was 263 (±12) days in the placenta previa group and 270 (±11) days in women without previa. Elective cesarean section was performed in 557 pregnancies (32.4%) with placenta previa. In all, 590 (34.3%) of the women with placenta previa had an emergency cesarean section compared with 955 (11.1%) without placenta previa ($p<0.001$). Table 2 shows the gestational age at which elective and emergency cesarean sections were performed in women with and without placenta previa.

Data on neonatal outcomes are presented in Table 3. Neonates born in pregnancies with placenta previa had an unadjusted risk that was more than eightfold higher of being born preterm and a fivefold higher risk of being extremely preterm. Correspondingly, birthweight was significantly lower in the previa group, whereas the risk of being SGA was equal in the two groups. Neonates born after pregnancies with placenta previa had a 2.6 times higher risk of low Apgar score after five minutes, and a four times increased risk of admissions to NICU. However, after stratification according to gestational age, these odds ratios were reduced to less than two, but they were still significantly increased. After adjustments, children born after pregnancies with placenta previa had a 50% higher risk of death at birth or within the first 28 days postpartum.

In the previa group, 1174 neonates (68.3%) were born at term vs. 8156 (94.9%) in the no previa group. Even at term, five-minute Apgar scores of ≤7 were more frequent with placenta previa (OR 1.7; 95%CI 1.0–2.6) and the proportion admitted to NICU was higher (OR 1.8; 95%CI 1.5–2.2). No difference was found in neonatal mortality (OR 1.09; 95%CI 0.4–2.8) or the risk of being born SGA (OR 0.9; 95%CI 0.7–1.1). Sub-analysis on neonates in the placenta previa pregnancies delivered by cesarean section showed even poorer neonatal outcomes than neonates in the total previa group when compared with neonates born by women without placenta previa (born vaginally or by CS) (Tables 3 and 4).

Discussion

This large national controlled cohort study showed that neonates born in pregnancies with placenta previa had a significantly higher neonatal mortality rate, risk of prematurity, low Apgar scores, low birthweight and an increased risk of being transferred to a neonatal intensive care unit. The lower birthweight was related to prematurity as there was no increased risk of SGA. Previous studies on neonatal outcome in pregnancies with placenta previa have provided very large series of women with placenta previa [9656 cases in Salihu (4) and 61.711 cases in Ananth (7)] but in those studies it has not been possible to adjust for IVF as a confounder. Our data gave us the opportunity to adjust for confounders because we could link information from the IVF register to the national birth- and patient registers using the personal identification number of the woman and child, and this study is by far the largest presented with these possibilities.

Bleeding episodes leading to emergency cesarean section as well as elective cesarean sections contribute to the

Table 1. Demographic characteristics of women with and without placenta previa in Denmark in 2001–2006.

Predictor	Previa (n=1721)	No previa (n=8603)	p value[a]	OR (95%CI)	OR adj[b] (95%CI)
Age (mean)	31.9 years	30.0 years	<0.001		1.1 (1.06–1.09)[c]
Multiparous	1078 (62.7%)	4850 (56.4%)	<0.001	1.3 (1.2–1.4)	1.0 (0.9–1.2)
Smoking	330 (20%)	1521 (18.0%)	0.06	1.1 (1.0–1.3)	1.2 (1.1–1.4)
Previous CS	270 (15.7%)	846 (9.8%)	<0.001	1.7 (1.5–2.0)	1.4 (1.2–1.7)
IVF/ICSI	129 (7.5%)	188 (2.2%)	<0.001	3.6 (2.8–4.6)	3.1 (2.4–4.0)

[a]Continuous normally distributed data were compared with Student's *t*-test and proportions between dichotomous outcomes were compared with chi-squared tests.
[b]Odds ratios adjusted for maternal age, multiparity, smoking, previous cesarean section and method of conception in multiple logistic regression analyses.
[c]Per year of maternal age.

Table 2. Frequency of different gestational ages in pregnancies delivered by elective cesarean section (CS) and emergency cesarean section according to presence of placenta previa in Denmark in 2001–2006.

Outcome:	Elective CS			Emergency CS		
Placenta: Gestational age	Previa (n=557)	No previa (n=744)	p value[a]	Previa (n=590)	No previa (n=955)	p-value[a]
<28	0.2%	0.1%	0.8	2.4%	0.6%	<0.005
≥28 and <34	3.1%	2.0%	0.2	25.1%	5.9%	<0.0001
≥34 and <37	17.4%	3.5%	<0.0001	36.6%	8.3%	<0.0001
≥37 weeks	79.3%	94.4%	<0.0001	35.9%	85.2%	<0.0001

Proportions between outcomes were compared with chi-squared tests.

increased risk of preterm delivery with placenta previa. This study showed an almost five times higher risk of emergency cesarean section before 37 gestational weeks. Furthermore, approximately 20% of elective cesarean sections in these pregnancies were performed before 37 weeks compared with 5.6% in pregnancies without placenta previa. The frequency of preterm delivery in our study of 31.7% was less than reported in earlier Canadian and American studies, where the rate of children born before 37 weeks was as high as 47% (6,7). Our data show that almost 80% of the elective cesarean sections were done after 37 gestational weeks in the pregnancies with placenta previa. The short geographic distances in Denmark make it possible to manage asymptomatic women safely at home and the recommendation in the Danish national guideline is for asymptomatic women with placenta previa to deliver after 37 gestational weeks (10).

The high risk of prematurity obviously adds to the risks of low birthweight, low Apgar scores, admission to NICU and neonatal mortality, but even in term pregnancies the risk of low Apgar scores and admission to NICU was significantly higher according to our results. The mortality was not significantly increased in term pregnancies in our study, which contradicts previous findings by Ananth (7) but may be influenced by the small number of neonatal deaths at term. Ananth reported a 4.3-fold higher neonatal mortality rate in pregnancies with placenta previa, with the association becoming stronger as gestation advanced. The study

Table 3. Neonatal outcomes in singleton pregnancies with and without placenta previa in Denmark in 2001–2006.

Outcome	Previa (n=1721)	No Previa (n=8603)	p-value	OR[a] (95%CI)	Adj OR[b] (95%CI)
GA					
Mean (days)	263±25	278±15	<0.001		
<28 weeks	1.7%	0.3%	<0.001	5.1 (3.1–8.4)	4.3 (2.4–7.6)
<34 weeks	12.1%	1.6%	<0.001	8.3 (6.7–10.4)	8.0 (6.3–10.1)
<37 weeks	31.7%	5.1%	<0.001	8.6 (7.5–9.9)	8.5 (7.4–9.9)
Birthweight					
Mean (g)	3096±780	3532±596	<0.001		
<1000g	1.6%	0.4%	<0.001	4.4 (2.7–7.4)	3.8 (2.1–6.6)
<1500g	4.1%	0.7%	<0.001	5.7 (4.0–8.0)	5.5 (3.7–8.0)
<2500g	18.4%	4.0%	<0.001	5.5 (4.6–6.4)	5.5 (4.6–6.6)
SGA	13.1%	13.6%	0.6	1.0 (0.8–1.1)	1.0 (0.8–1.2)
Apgar at 5 minutes: ≤7	3.4%	1.3%	<0.001	2.7 (2.0–3.7)	2.6 (1.8–3.6)
GA<37 weeks	6.8%	4.1%	0.08	1.7 (0.9–3.1)	
GA≥37 weeks	1.9%	1.1%	<0.05	1.7 (1.03–2.6)	
NICU	29.1%	8.4%	<0.001	4.4 (3.9–5.1)	4.3(3.8–4.9)
GA<37 weeks	70.1%	57.1%	<0.001	1.7 (1.4–2.3)	
GA≥37 weeks	10.1%	5.8%	<0.001	1.8 (1.5–2.2)	
Mortality[c]	1.2%	0.7%	<0.05	1.8 (1.1–3.0)	1.5 (0.8–2.6)
Male sex of child	54.1%	45.9%	0.06	1.1 (1.0–1.1)	1.1 (1.0–1.3)

[a]Odds ratio (OR) and 95% confidence intervals (95%CI).

[b]Adj OR: Adjusted for the possible confounders maternal age, parity, smoking, previous cesarean section and method of conception.

[c]Mortality (stillbirths after 22 weeks' gestation and neonatal mortality within 28 days). Because of small numbers these are not stratified by gestational age.

Table 4. Neonatal outcomes in placenta previa delivered by cesarean section (CS) vs. outcomes in children born after pregnancies without placenta previa with or without CS.

Outcome	Previa + CS (n=1147)	No previa (n=8603)	p-value	OR[a] (95%CI)	Adj OR[b] (95%CI)
GA					
Mean (days)	256±20	278±15	<0.001		
<28 weeks	1.3%	0.3%	<0.001	3.8 (2.0–7.1)	3.6 (1.7–6.8)
<34 weeks	15.7%	1.6%	<0.001	11.2 (8.9–14.2)	11.4 (8.9–14.7)
<37 weeks	43.0%	5.1%	<0.001	13.9 (12.0–16.2)	14.7 (12.5–17.3)
Birthweight					
Mean (g)	2926±736	3532±596	<0.001		
<1000g	1.1%	0.4%	<0.001	3.1 (1.6–5.9)	2.9 (1.4–5.8)
<1500g	4.4%	0.7%	<0.001	6.2 (4.3–9.0)	6.4 (4.2–9.8)
<2500g	23.5%	4.0%	<0.001	7.5 (6.3–8.9)	7.9 (6.5–9.6)
SGA	13.0%	13.6%	0.6	0.9 (0.8–1.1)	1.0 (0.8–1.2)
Apgar 5<7	4.1%	1.3%	<0.001	3.3 (2.3–4.7)	3.1 (2.1–4.5)
NICU	38.1%	8.4%	<0.001	6.7 (5.8–7.9)	6.6 (5.6–7.6)
Mortality[c]	0.9%	0.7%	0.4	1.3 (0.7–2.6)	1.2 (0.6–2.6)

[a]Odds ratio (OR) and 95% confidence intervals (95%CI).
[b]Adj OR (adjusted for the possible confounders maternal age, parity, smoking, previous cesarean section and method of conception).
[c]Mortality (stillbirths and neonatal mortality).

did not make adjustments for risk factors of placenta previa, such as IVF (7). In an Israeli study on 771 pregnancies with placenta previa, where these confounders were considered, placenta previa was not found to be a risk factor for perinatal mortality (2).

In the multiple logistic regression analyses we found that placenta previa was not an independent risk factor for SGA after adjusting for IVF conception. All previous studies report a significantly lower birthweight in pregnancies with placenta previa, but they have presented conflicting evidence regarding the association between SGA and placenta previa. Three small retrospective studies with 175, 179 and 305 cases, respectively, found no increased risk of low birthweight when adjusting for GA (6,8,9). However, two population-based studies on 9656 and 2744 cases of placenta previa found odds ratios of 1.12 (95%CI 1.06–1.18) and 1.44 (95%CI 1.36–1.53), respectively, for SGA in pregnancies with placenta previa (4,5). These studies did not take into account the potential effects of IVF, which have recently been shown to be a significant risk factor for placenta previa (12–14). IVF singleton pregnancies are by themselves associated with a higher risk of neonatal mortality, low birthweight, SGA and preterm labor. The pathogenesis for the higher risk of placenta previa in IVF pregnancies is not fully understood. Romundstad and colleagues suggested that lower deposition in the uterine cavity may improve implantation, which of course tends towards a preference for placing the embryo lower in the uterine cavity and thereby simultaneously increasing the risk of placenta previa (12), as 80% of embryos are implanted in the area into which they are transferred (15). Uterine contractions caused by prostaglandin release provoked by the catheter used for transferring the embryo may also contribute to low implantation.

One-third of the pregnancies with placenta previa in our study were delivered vaginally, which may be possible with a marginal previa. However, it seems likely that some of the women with placenta covering the internal os at ultrasound in the second trimester had a diagnosis of placenta previa that did not persist at delivery. The strength of register studies is the large number of individuals and the absence of selection bias. Limitations include the validity of the diagnosis, as the criteria for diagnosing placenta previa may be different. To overcome this problem we performed sub-analyses on pregnancies with placenta previa delivered by cesarean section compared with neonatal outcome in pregnancies with no previa. These sub-analyses showed even poorer neonatal outcome in the placenta previa group compared with the no previa group, which indicates that the cesarean section placenta previa pregnancies are the more severe cases of placenta previa.

Maternal age, parity, previous cesarean section and conception by IVF have previously been described as risk factors for placenta previa (2,12,13,16–18) and were confirmed to be predictors of placenta previa in this study. IVF was the strongest risk factor, with a threefold higher risk of placenta previa compared with naturally conceived pregnancies. The mean maternal age at delivery of the first child was 24.4 years in Denmark in 1978 and increased to 29.2 years in 2007 (19). Cesarean section rates in Denmark rose from 9% in 1978 to 22% in 2007 (20), and IVF treatment, which was introduced in Denmark around 1980, now accounts for 4% of newborns (21). In addition to the implementation of routine

second trimester ultrasound with placental localization in the mid 1990s, these factors have all contributed to the rising incidence of recorded placenta previa in Denmark, as shown in Figure 1.

In conclusion, this national cohort study has shown that neonates born in pregnancies with placenta previa have a high risk of neonatal morbidity, most of which is related to prematurity. This requires close obstetrical surveillance and admission to hospitals with high obstetrical and neonatal expertise and emphasizes the need for expectant management of these pregnancies. Attention must be drawn to the fact that placenta previa pregnancies, even at term, are high-risk pregnancies, with a substantial risk of neonatal morbidity. Increasing maternal age, IVF treatment and previous cesarean section are all risk factors for placenta previa and have contributed to the rising incidence of placenta previa shown in this study. Therefore intervention studies on strategies to prevent placenta previa are urgently needed.

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