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Original Article

Placenta associated pregnancy complications in pregnancies complicated with placenta previa

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ABSTRACT:

Objectives: The purpose of our study was to examine the hypothesis that pregnancies complicated with placenta previa have an increased risk of placental insufficiency associated pregnancy complications (IUGR, preeclampsia, placental abruption and perinatal mortality).
Materials and methods: Our study included all deliveries that occurred at Soroka University Medical Center (Beer Sheva, Israel) between January 1998 and December 2013. Of them 1,249 were complicated by placenta previa and represented our study group. A composite outcome was created to include conditions associated with placental insufficiency. It included hypertensive disorders (i.e. gestational hypertension, mild and severe preeclampsia, HELLP and eclampsia), small for gestational age neonates and placental abruption.
Results: Patients with pregnancy complicated by placenta previa had significantly different obstetrical characteristics including bad obstetric history (8% vs. 4%, $p < 0.001$), recurrent abortions (11% vs. 5%, $p < 0.001$). Patients with placenta previa had higher rates of vaginal bleeding in the second half of pregnancy (3% vs. 0%, $p < 0.001$), gestational diabetes (8% vs. 5.5%, $p < 0.001$), placental abruption (10% vs. 1%, $p < 0.001$), adherent placenta (4% vs. 0.5%, $p < 0.001$), preterm delivery (52% vs. 8%, $p < 0.001$), with a median gestational age of 36 vs. 39 weeks, $p < 0.001$. The composite outcome was significantly more prevalent in the placenta previa group (21% vs. 13%, $p < 0,001$).
Conclusions: Our study demonstrated an increased rate of placental insufficiency associated complications in women with placenta previa. This is of clinical relevance and suggests that a careful surveillance for women with placenta previa may help in minimizing maternal, fetal and neonatal complications.

Introduction

Successful placentation is characterized by the development of a low-impedance uteroplacental circulation after invasion of the trophoblast. This is followed by the transformation of maternal spiral arterioles in the myometrium [1–4]. When this process is impaired, a condition of defective deep placentation, characterized by faulty remodeling of the utero-placental arteries, sometimes associated to arterial lesions, may lead to insufficient placental perfusion and release of factors such as cytokines, leukotrienes and immunomodulatory hormones into the maternal circulation. These factors are suggested to cause endothelial dysfunction [5]. This in turn has been associated with the development of pregnancy complications associated with placental insufficiency such as pregnancy induced hypertension, preeclampsia and intrauterine growth restriction (IUGR) [5].

Defective deep placentation has been associated with a spectrum of major obstetrical syndromes and pregnancy complications, including preeclampsia, IUGR, preterm premature rupture of the fetal membranes (PROM), preterm birth, late sporadic miscarriage and placental abruption [4,6–8]. Sherer et al. [9] have demonstrated that preterm births are associated with both abnormal uteroplacental physiologic changes and decreased

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placental weight. This finding was evident by a tenfold increase in the incidence of placental basal plate myometrial fibers as compared with term births.

It is possible that an abnormal placental location, such as in pregnancies complicated with placenta previa, may cause faulty placentation and increase the risk of placental insufficiency associated pregnancy complications. Indeed, placenta previa has also been associated with the development of pregnancy complications related to placental insufficiency such as pregnancy induced hypertension, preeclampsia, IUGR, placental abruption and perinatal mortality [10,11]. Many epidemiological studies have discussed the risk factors, adverse maternal and perinatal outcome associated with placenta previa [10–13]. In addition, pregnancies complicated with this condition have an increased risk for bleeding. Advanced maternal age, parity, maternal smoking, infertility treatments, previous cesarean deliveries, and recurrent abortions have been implicated as risk factors for placenta previa [10–13]. With the increasing rates of pregnancy in women with advanced maternal age, fertility treatments and primary and recurrent cesarean deliveries worldwide the prevalence of placenta previa is rising [11], ranging from 0.28 to 1.5%, according to various reports [10–13].

In the present study, we aim to examine the hypothesis that pregnancies complicated with placenta previa have an increased risk of placental insufficiency associated pregnancy complications (IUGR, preeclampsia, placental abruption and perinatal mortality).

Methods

Study population

In this retrospective study we collected data on all deliveries between January 1998 and December 2013 in the Soroka University Medical Center, a 1000-bed tertiary teaching hospital. It is the only tertiary center for a population of 700,000 residing in Southern Israel. During the study period the average annual number of deliveries managed at our medical center was around 12,500.

Inclusion criteria for the study was a pregnancy complicated with placenta previa. Women with a multiple gestation and those complicated with fetal chromosomal or congenital malformations were excluded from the analysis. The Department of Obstetrics and Gynecology has a computerized database of all the deliveries. Data collected in the database included information on maternal morbidities, perinatal assessment and maternal and fetal complications. The information is captured from the patient's medical records and coded according to the ICD-9 diagnosis by trained secretaries. Our database is constantly tested and validated by the Department of Epidemiology at the Ben-Gurion University of the Negev (Beer Sheva, Israel). The study was approved by the Institutional Review Board Committee of the Soroka University Medical Center. A total of 297,141 deliveries took place between January 1998 and December 2013 at our medical center, of them 1,249 were complicated by placenta previa.

Clinical definitions

Placenta previa is diagnosed sonographically by a placenta that was located in the lower uterine segment and partially or completely obscured the internal cervical os [14]. This diagnosis was made during the hospitalization of the index delivery.

Parity groups were defined as follows: multipara (2–5 deliveries) and grand-multipara (6 or more deliveries).

Preeclampsia is diagnosed with repeated measurements of blood pressure over 140/90 combined with over 300 mg protein measured in 24 h excreted urine [15].

IUGR-intra uterine growth restriction is defined as an estimated fetal weight under the 10th percentile growth curve as defined by the regional Dollberg growth curves [16]. This diagnosis was made during the hospitalization of the index delivery, the length of time between ultrasound and delivery ranged between hours and days, with a maximum interval of seven days.

Oligohydramnion defined as fewer than 5 cm amniotic fluid measured using the amniotic fluid index (AFI) or fewer than 2 cm amniotic fluid measured in maximal vertical pocket (MVP).

Preterm delivery was defined as delivery prior to 37 weeks of gestation. *Small for gestational age* (SGA) as birth weight below 10th percentile for gestational age. *Habitual abortions* was defined as three or more first trimester spontaneous abortions.

Placental abruption-separation of the placenta from the uterine wall prior to the delivery of the fetus.

Bad obstetric history-defined as combined infant demise, habitual abortions and preterm deliveries.

Stillborn-was defied as all cases of antepartum fetal demise and all cases of intrapartum fetal demise.

Due to the rarity of some of these placental insufficiency associated complications, a composite outcome was defined. This composite outcome included hypertensive disorders (i.e. gestational hypertension, mild and severe preeclampsia, HELLP and eclampsia), small for gestational age neonates and placental abruption small for gestational age, elevated blood pressure (including mild and severe preeclampsia) and placental abruption.

A subgroup analysis for the prediction of the composite endpoint was performed on the subjects who suffered from vaginal bleeding during pregnancy, comparing those with and without placenta previa to investigate weather vaginal bleeding in patients with placenta previa has an adverse impact on pregnancy outcomes.

Data analysis

Each delivery was treated as a separate observation in the univariate analysis. The data on continuous variables with normal distribution were presented as mean ± SD, and compared between study groups using Student t-test. Continuous variables not normally distributed and ordinal variables were presented as median with inter-quartile range (IQ range) and statistical analysis was done using Mann–Whitney. Categorical data were shown in counts and percentages and the differences were assessed by Chi-Square, Fisher Exact test was used when appropriate.

Association between placenta previa and the primary composite outcome was assessed by a multivariable logistic regression model. Variable selection in multivariable modeling was based on clinical and statistical significance. The following variables were included into the models: placenta previa, previous cesarean delivery, grandmultiparity, habitual abortions, maternal age, gravidity and fertility treatment. We reported final parsimonious models. Two-sided p-value of <0.05 was considered significant.

Results

Baseline characteristics of pregnancies complicated with and without placenta previa are presented in Table 1. Patients from the study group were older (32.20 vs. 28.48±, $p < 0.001$), more likely to be of Jewish ethnicity (60% vs. 49%, $p < 0.001$), had higher gravidity and parity ($p < 0.001$ for both). A higher rate of patients with placenta previa were grand multiparous (29% vs. 22%, $p < 0.001$).

Significantly different obstetrical characteristics were noted including pregnancy following fertility treatments (8% vs. 3%, $p < 0.001$), bad obstetric history (8% vs. 4%, $p < 0.001$), recurrent abortions (11% vs. 5%, $p < 0.001$) and previous cesarean sections

Table 1
Demographic and clinical characteristics of patients with pregnancies complicated with placenta previa compared to the control group.

Variables		Placenta previa n = 1249	No placenta previa n = 294,697	p value
Background characteristics	Age	32.20 ± 5.84	28.48 ± 34.04	<0.001
	Gravidity	5.09 ± 3.21	3.93 ± 3.72	<0.001
	Parity, median	4.14 ± 2.81	3.43 ± 2.52	<0.001
	Grandmultiparity	366 (29.3)	63,526 (21.6)	<0.001
	Gestational age (week)	36 (33–38)	39 (38–40)	<0.001
Ethnicity	Bedouin	489 (39.7)	145,086 (50.6)	<0.001
	Jewish	742 (60.3)	141,484 (49.4)	
Gynecological characteristics	Previous cesarean section	378 (30.3)	36,302 (12.3)	<0.001
	Bad obstetric history	101 (8.1)	11,258 (3.8)	<0.001
	Recurrent abortions	134 (10.7)	15,164 (5.1)	<0.001
	Fertility treatments	95 (7.6)	7935 (2.7)	<0.001

Data is presented as mean ± standard deviation, median (range), percentage (number).
Bad obstetric history-defined as combined infant demise, habitual abortions and preterm deliveries.

(30% vs. 12%, p < 0.001). More gestational diabetes was found in the placenta previa group (8% vs. 5%, p < 0.001), however we believe this is due to the older maternal age in the study group. Logistic regression adjusting to maternal age showed an OR = 1.06, p = 0.56.

Pregnancy complications are presented in Table 2. Patients with placenta previa had higher rates of vaginal bleeding in the second half of pregnancy (3% vs. 0%, p < 0.001), gestational diabetes (8% vs. 5.5%, p < 0.001), placental abruption (10% vs. 1%, p < 0.001), adherent placenta (4% vs. 0.5%, p < 0.001), preterm delivery (52% vs. 8%, p < 0.001), with a median gestational age of 36 vs. 39, p < 0.001. In the univariate analysis no significant difference was found in the rate of hypertensive disorders. However, since these are more common in younger women we adjusted for maternal age and found for mild preeclampsia that the OR = 1.37 with a 95% CI of 1.11–1.70, for severe preeclampsia the OR was 2.55 with 95% CI of 2.24–2.90 and that for all hypertensive disorders the OR was with a CI 5.71–8.05.

Table 2
Pregnancy outcomes in pregnancies complicated with placenta previa compared to the control group.

Variables		Placenta previa n = 1249	No placenta previa n = 294,697	p value
Elevated blood pressure	Mild preeclampsia	22 (1.8)	9466 (3.2)	0.004
	Severe preeclampsia	20 (1.6)	3346 (1.1)	0.12
	Gestational hypertension	26 (2.1)	4292 (1.5)	0.07
Gestational diabetes		105 (8.4)	16,227 (5.5)	<0.001
Amnion fluid abnormalities	Polyhydramnion	56 (4.5)	10,001 (3.4)	0.03
	Oligohydramnion	34 (2.7)	6679 (2.3)	0.28
Intrauterine growth retardation		43 (3.4)	6099 (2.1)	0.001
Premature rupture of membranes		61 (4.9)	24,268 (8.2)	<0.001
Vaginal bleeding in the second half of pregnancy		32 (2.6)	107 (0.0)	<0.001
Placental abruption		119 (9.5)	2051 (0.7)	<0.001
Preterm delivery		645 (51.6)	23,933 (8.1)	<0.001
Cesarean section		1152 (92.2)	43,802 (14.9)	<0.001
Composite outcome		262 (21.1)	38,840 (13.3)	<0.001

Data is presented as number (percentage).
Composite outcome: hypertensive disorders (preeclampsia, gestational hypertension, eclampsia), small for gestational age and placental abruption.

Table 3 presents neonatal outcomes. Patients in the study group had a significantly higher rate of fetal distress (3% vs. 2%, p < 0.001), a higher rate of Apgar score <7 at 1st and 5th minute (p < 0.001), a higher rate of fetal demise (1.8% vs 0.8%, p < 0.001) and a lower birth weight (2497.11 ± 787.17 g vs. 3148.76 ± 579.19, p < 0.001). The rate of SGA neonates was similar. The composite outcome was significantly more prevalent in the placenta previa group (21% vs. 13%, p < 0,001).

Primary outcome

The prediction of the primary outcome comprising of a composite of small for gestational age neonates (SGA), patients with hypertensive disorders and those with placental abruption was performed using logistic regression is presented in Table 4. Placenta previa was found to be independently associated with placental insufficiency associated complications (OR 1.7, p < 0.001) adjusting for grandmultiparity, habitual abortions and a previous cesarean section.

Secondary outcome

The secondary outcome was the predication of the composite endpoint described above in the subgroup of patients with a history of vaginal bleeding during the second half of pregnancy. A total of 139 patients had a diagnosis of vaginal bleeding in the second half of pregnancy, 32 (23.0%) of which in the placenta previa group and 107 (76.9%) in the non-placenta previa group.

A multivariate analysis was performed to investigate the role of placenta previa on the composite outcome in patients complicated with vaginal bleeding in the second half of pregnancy. Bleeding in the second half of pregnancy was found to be significantly associated with a previous cesarean section (OR = 2.65, p = 0.04), however, the association between placenta previa and a diagnosis of vaginal bleeding in the second half of pregnancy lost its significance (p = 0.64).

Discussion

Main findings of the study: 1) Placenta previa is associated with a higher rate of preeclampsia, intrauterine growth retardation and fetal demise compared to uncomplicated pregnancies; 2) The rate of the composite endpoint including hypertensive disorders (i.e. gestational hypertension, mild and severe preeclampsia, HELLP and eclampsia), small for gestational age neonates and placental

Table 3
Neonatal characteristics and outcomes in pregnancies complicated with placenta previa compared to the control group.

Variables		Placenta previa n = 1249	No placenta previa n = 294,697	p value
Gender-Male		668 (53.5)	150,951 (51.2)	0.11
Fetal distress		43 (3.4)	4854 (1.6)	<0.001
Apgar ≤ 7	1st minute	375 (31.0)	18,588 (6.5)	<0.001
	5th minute	88 (7.3)	3142 (1.1)	<0.001
Birthweight (g)		2497.11 ± 787.17	3148.579 ± 19	<0.001
Small for gestational age neonate		70 (5.6)	16,534 (5.7)	
pH		7.35 ± 0.13	7.37 ± 1.01	0.89
Perinatal mortality	APD	22 (1.8)	2217 (0.8)	<0.001
	IPD	6 (0.5)	226 (0.1)	0.001
	Total neonatal death	28 (2.2)	2426 (0.8)	<0.001

Data is presented as number (percentage), mean ± standard deviation.
APD, antepartum death; IPD, intrapartum death, PPD, postpartum death.

Table 4
Risk factors that are independently associated with the placental insufficiency composite outcome.[a] Results from a multiple logistic regression model with backward elimination.

Variables	OR	95% CI	p value
Placenta previa	1.70	1.47–1.97	<0.001
Previous cesarean delivery	1.18	1.14–1.22	<0.001
Habitual abortions	1.19	1.13–1.25	<0.001
Grandmultiparity	0.89	0.87–0.92	<0.001

[a] Placental insufficiency composite outcome: small for gestational age neonates, hypertensive disorders, placental abruption.

abruption was significantly increased in patients complicated with placenta previa.

Our study was designed to investigate the association between placenta previa and adverse pregnancy outcomes, specifically placental insufficiency associated complications. It has been established that pathological placentation can be the cause for adverse pregnancy outcomes including preeclampsia, IUGR, placental abruption and fetal demise [4,6,8,17,18].

The rationale is that placental implantation at an abnormal site (such as the uterine cervix) may lead to an inadequate placental development. This may impact pregnancy outcomes in a similar way to that observed in poor placentation and subsequent ischemia that is seen in cases of placental insufficiency with a normal implantation site.

It is possible that like in pregnancies which subsequently develop preeclampsia, there is reduced placental blood flow that results from remodeling of the spiral arteries. Alternatively, it is possible that implantation in the lower uterine segment that is characterized by a high ratio of connective tissue to smooth muscle, results in a significantly lower number of spiral arteries compared with the number found in the uterine fundus that is characterized by a low ratio of connective tissue to smooth muscle. Further, pathological and morphological studies will be needed to elucidate this question.

In the literature results of studies that evaluated factors associated with placenta previa are conflicting. Sheiner et al. [10] found an association between placenta previa and preterm delivery, cesarean sections and placental abruption; however, they did not find an association with IUGR. In contrast, Rosenberg et al. [11] found an association between placenta previa and IUGR but did not find such an association with placental abruption. Yeniel et al. [19] explored only neonatal outcomes and did not find an association between either fetal growth restriction or fetal demise with placenta previa. In our study, in a multivariate analysis after adjusting for possible confounders, placenta previa was found to be significantly associated with our composite endpoint of placental insufficiency associated complications that have been associated with a faulty placentation [17,18,20–22].

Placentation requires extensive angiogenesis in order to establish a suitable network for the supply of oxygen and nutrients to the fetus. The normal placentation is composed both of the creation of a syncytial layer that transports nutrients, waste and gases between fetal and maternal blood and interstitial invasion including endovascular invasion changing the blood flow in the uterine arterioles to high flow low resistance. Faulty placentation is characterized by pathological findings including placental infarcts and sclerotic narrowing of arteries and arterioles, with characteristic diminished endovascular invasion by cytotrophoblasts and inadequate remodeling of the uterine spiral arterioles. This has been shown specifically in preeclampsia with shallow interstitial cytotrophoblast invasion and nearly absent endovascular invasion [23].

According to our hypothesis of abnormal placentation, since in placenta previa cases the placenta is located over the internal os there are greater odds for faulty placentation, including shallow cytothrophoblast invasion thus leading to more cases of preeclampsia, IUGR and other obstetrical complications originating from the pathological placentation. This is supported by our findings including an association with preeclampsia and IUGR.

In addition, we explored the effect of placenta previa on the same composite morbidity, in patients presenting with vaginal bleeding in the second half of pregnancy. It is known that vaginal bleeding in the second half of pregnancy is associated with higher perinatal mortality rates, the major etiologies being placenta previa, placental abruption or both [24,25]. We hypothesized that the vaginal bleeding in the second half of pregnancy will have a synergistic effect in pregnancies complicated with placenta previa and they would suffer a higher rate of pregnancy complication. However, no significant difference was found in the composite outcome between patients with and without placenta previa that had vaginal bleeding in the second half of pregnancy. This may be explained by other etiologies for vaginal bleeding which may include placental abruption which may arise from pathologic placentation or birth canal trauma, as well. To the best of our knowledge this is the first study to use a composite based on a pathophysiological hypothesis therefore our results have not only statistical significance but clinical significance as well.

The study strengths comprise of it being a large population based study conducted in a single center with little loss to follow up since our center is the sole tertiary medical center in the south of Israel.

Limitations of our study are inherent to the retrospective design. Deliveries occurred over more than 20 years (1988–2011), in a tertiary medical center. In this long time period, it is reasonable to assume that changes in obstetrical practice and especially higher rates of caesarean sections have influenced the outcomes. However, as the controls were taken from the same setting and time period, it is unlikely that this affected the results. Another possible weakness is the potential for missing data. To minimize this, in our hospital data is reported by the obstetrician directly after delivery and skilled medical secretaries routinely review the information prior to entering it into the database thereby minimizing recall bias. Coding was done after assessing the medical and prenatal care records together with the routine hospital documents.

There was an increased rate of placental insufficiency associated complications in women with placenta previa. We believe these findings have not only epidemiological importance but clinical relevance as well. A careful surveillance for women with placenta previa including careful monitoring during pregnancy, close fetal growth estimations, sonographic blood flow evaluation and frequent blood pressure measurements and a timely delivery may help minimize the occurrence of maternal complications associated with placenta previa.

Conflict of interest

No author has any potential conflict of interest.

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