Risk and Risk Estimation of Placental Abruption

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Short title: Risk estimation of placental abruption

CONDENSATION

Prior second trimester, third trimester, and repeated fetal loss may be used to predict increased risk of placental abruption.

ABSTRACT

Objective: Several variables related to increased risk of placental abruption are also risk factors for venous thromboembolism. Prior second trimester-, third trimester, and repeated fetal loss are reported to be associated to thrombophilias. However, it is yet not known if they are also related to placental abruption.

Study design: A retrospective case-control study of 161 women with placental abruption and 2,371 unselected gravidae without placental abruption. The medical files were scrutinized and the selected variables were investigated in relation to the development of placental abruption.

Results: As compared to controls, previous second trimester-, third trimester-, repeated fetal loss, and prior placental abruption were related to a 3-fold, 13-fold, 3-fold, and a 25-fold increased risk of placental abruption, respectively. Several other factors were associated with a roughly three-fold increased risk such as: preeclampsia, IUGR, high maternal age (> 35), **family history** of venous thromboembolism, smoking, and multiple birth. A risk score was created and as compared with those with no risk factors present, the risk of placental abruption was increasing from 2.5-fold for those with risk score = 1, to almost 100-fold for risk score 4 or above.

Conclusion: **Easily obtainable information** might be used to classify the risk of placental abruption.

Key words: placental abruption, fetal loss, risk score, prediction

INTRODUCTION

Placentae abruption is a major cause of both fetal and maternal morbidity and mortality. It occurs in 0.4% to 1.3% of all pregnancies.[1] Placenta abruption usually presents as a combination of vaginal bleeding, uterine contractions, and pain. The perinatal mortality rate varies between 2% and 67%, depending on gestational age, fetal weight, and the degree of abruption.[1] About half of perinatal deaths due to placental abruption occur in utero,[2] which also makes this disorder a major contributor to stillbirth.[2,3] The etiology of placental abruption is unknown, but it occurs more frequently among smokers, in hypertensive pregnancies, in pregnancies with intrauterine growth restriction (IUGR), in instances of trauma, with advancing maternal age, in male fetuses, and in women with a previous placental abruption.[4]

Recently, placental abruption has been reported to be more prevalent in thrombophilic pregnancies [5] and in women with a familial history of venous thromboembolism.[6]
Most risk factors for placental abruption are also related to increased risk of venous thromboembolism. It is currently not known whether prior second trimester-, third trimester-, or repeated fetal loss also are related to increased risk of placental abruption

The aim of this study was to determine if the above mentioned variables are related to placental abruption and to construct risk score in the prediction of placental abruption.

MATERIALS AND METHODS

The Ethics Committee of Lund University approved the study design. All medical records with a diagnosis of placental abruption at the Department of Obstetrics and Gynecology, University Hospital Malmö, for an eight-year period (January 1992 to December 1999) were scrutinized. Out of the 24,207 pregnancies, we identified 175 (0.7%) cases of placental abruption in 161 women, and 112 accepted to participate in the study. All medical records were scrutinized and a majority of the women underwent a detailed in-person interview regarding their medical history. The cases were compared with a prospectively-collected, unselected population of 2,371 gravidae without placental abruption.[7]

We defined placental abruption in terms of a clinical diagnosis, usually based on profuse vaginal bleeding appearing during the third trimester, painful contractions, and clinical examination of the placentae. In women with more than one episode of placental abruption only the last one was included.

First trimester fetal loss was defined as fetal loss before 13 weeks of gestation; second trimester fetal loss as between 13 and 26 weeks of gestation; and stillbirth as intrauterine death > 26 weeks of gestation. Repeated fetal loss was defined as at least three first trimester fetal losses or two second trimester fetal losses.

Smoking habits were recorded at the first visit to the antenatal clinic, which occurred at a mean of 12 weeks of gestation (standard deviation [SD] 3.3 weeks), whereby smokers were defined as those who smoked every day. High maternal age was defined as maternal age abowe 35.

Preeclampsia was defined as pregnancy-induced hypertension and proteinuria > 0.3 g/l (Albustix Boehringer Mannheim ≥ 1+). Pregnancy-induced hypertension was defined as a resting diastolic blood pressure > 90 mm Hg, measured on two occasions at an interval of at least five hours, and developing after 20 weeks of gestation in a previously normotensive pregnancy.

Gestational age was estimated by ultrasonographic measurement of biparietal diameter and femur length in 96% of the cases, and from the date of the last menstrual period in the remaining 4%.

Small-for-gestational age (SGA) was used as an approximation of IUGR. SGA was defined as a newborn with a birth weight 2 SD units or more below the mean for a Swedish reference population.[8] This corresponds to a birth weight deviation ≤ – 22%, with birth weight deviation defined as (expected birth weight according to gestational age – actual birth weight) / expected birth weight, and expressed as a percentage.[8]

Hemoglobin (Hb) values presented were as follows: First Hb-value was the initial Hb-value recorded in pregnancy, usually at 12 weeks of pregnancy, and was only included if taken before 20 weeks of gestation. Mid Hb-value was the value recorded between 20 and 30 weeks of gestation, closest to 25 + 0 weeks of gestation. Last Hb-value was the final value recorded in pregnancy and was only included if taken after the 30 weeks of gestation.

For the characterization of control and study groups, Student's *t*-test was used for the analysis of continuous variables, and the Chi-squared test or Fisher's Exact test for categorical

variables. Bivariate odds ratios (OR) for the risk of developing placental abruption were calculated by cross-tabulation with its 95% CI. All calculations were performed with SPSS software (Statistical Package for the Social Sciences, SPSS Inc., Chicago IL, USA) and *p*-values < 0.05 were considered statistically significant.

RESULTS

The characteristics of both placental abruption cases and the control population are shown in Table 1. We might note that as expected, the outcome measures such as gestational age, birth weight, umbilical pH, and stillbirth, differ between abruptio cases and controls. Placental abruption group was also characterised by a significantly higher prevalence of smokers, IUGR, preeclampsia, low APGAR scores, and Cesarean delivery. The placental abruption group was not characterised by higher Hb-values, as compared to controls, on any of the three occasions. However, in the placental abruption group 19 out of 88 (22%) had final Hb < 110 gr/L as compared to 258 out of 2,284 (11%) in the control group (OR = 2.2, 95% CI 1.3–3.7). The respective figures of high Hb values were 12 out of 88 and 370 out of 2,284 (OR = 0.8, 95% CI 0.4–1.5).

In Table 2 we present the bivariate OR of selected pregnancy variables regarding the risk of developing placental abruption. Previous second trimester and repeated fetal loss were significantly associated with increased risk of placental abruption ($p < 0.01$, and $p = 0.02$, respectively). Women with prior stillbirths or prior placental abruption were related to highly significantly increased risk for placental abruption ($p < 0.001$, and $p < 0.001$, respectively). Women with preeclampsia was associated with a three-fold increased risk of placental abruption. None of the 112 women with placental abruption, along with 0.4% (8 /2,371) of the controls ($p = 0.5$), had a previous history of venous thromboembolism. Among the abruptio cases, six (5%) reported first degree relatives with placental abruption. This question was not posed to the control group.

Based on these data a risk score was constructed with the assumption of a multiplicatory relationship between risk factors. Most risk factors were at roughly 3-fold increased risk and were assigned 1 point for each of the following risk factors; smoking, second trimester fetal loss, third trimester fetal loss, repeated fetal loss, multiple pregnancy, preeclampsia, IUGR, family history of thromboembolism, or high maternal age. Prior stillbirth was assigned 2 points and prior placental abruption 3 points. The risk points were added, forming a risk score and the distribution of risk is presented in Table 3. Using the group with risk score 0 as reference, OR for risk of placental abruption were calculated for each risk score. The risk increased from OR 2.7 for risk score 1, to OR 94.5 for risk score $\geq$ 4. The design of the study does not permit calculation of positive and negative predictive values.

DISCUSSION

In this study we have tried to estimate the risk of developing placental abruption based on known variables available before delivery. Placenta abruptio has been identified as a major cause of stillbirth. However, that a history of third trimester fetal loss poses a large risk factor for placental abruption has, to the best of our knowledge, previously not been reported. We found that women with a history of a second trimester fetal loss, and those who suffered repeated fetal loss were associated with a 3.2-fold and 3.4-fold increased risk of placental abruption.

Of interest for this study is that most variables, which were significantly associated with an increased risk of placental abruption are also related to an increased risk of venous thromboembolism. **Although not assessed in this study** women with thrombophilias have been reported to be at increased risk of pregnancy complications, including preeclampsia, placental abruption and IUGR.[5] In a prior report on almost the same material, carriers of the factor V Leiden mutation were at a non-significant 50% increased risk of placental abruption (odds ratio [OR] = 1.5, 95% confidence interval [CI] 0.9–1.6).[6] Thus, we do not consider carriership of FV Leiden as a significant risk factor for placental abruption. In addition, women with family history of venous thromboembolism were at a 3-fold increased risk of placental abruption.[6] Women with a history of third trimester fetal loss have also been reported to have increased prevalence of heritable thrombophilias.[9,10] Preeclampsia is regarded as a major risk factor for postpartum venous thrombosis.[11] Smoking has also been related to a consumption-dependent increased risk of venous thrombosis in conjunction with pregnancy for both moderate smokers (1 to 9 cigarettes per day, OR = 1.2) and heavy

smokers (≥ 10 cigarettes per day, OR = 1.4, 95% CI 1.1–1.9).[11] Second trimester fetal loss has been associated with maternal thrombohilia.[9]

Regarding factors previously known to be related to placental abruption, our findings of a 3-fold increased risk of placental abruption in pregnancies with IUGR fetuses is in a similar range as Kramer and co-workers.[4] However, they subdivided their results into women with fetuses between mild IUGR < – 15% and > – 25% (OR = 1.3) and severe IUGR ≤ – 25% (OR = 4.0).

Our estimates regarding risk of placental abruption in preeclamptic women differ somewhat from that of Kramer and co-workers.[4] They reported a doubled risk of developing placental abruption among women with preeclampsia, while in our study we found a 3.4-fold increased risk. The reason for this discrepancy is unclear, but presumably due to different diagnostic criteria. Smoking was associated with an approximately doubled risk of developing placental abruption, which is in accordance with other studies.[4,12] Our estimate of high maternal age, is in the same range as previously reported.[4] Even though not significant in our study, male fetus was associated with a 30% increased risk of placental abruption, a constant phenomenon in several studies.[4,13] The reason for this sex differences remains unexplained, but might be hormonal. The hormonal milieu differs depending on fetal sex, and female **fetuses** is related to higher maternal HCG levels in early pregnancy.[13,14] In addition, in the end of first trimester, pregnancies with high maternal urine HCG values were at a three-fold higher risk of developing preeclampsia, as compared to those with low values.[15]

We believe that these results might be of clinical value in assessment of women with third trimester hemorrhage or premature contractions. The usual risk assessment for include clinical status, anamnesis of previous placental abruption and the presence of IUGR, preeclampsia, high maternal age, duplex pregnancy, family history of venous thromboembolism**,** and maternal smoking. However, a history of second, third trimester fetal loss, repeated fetal loss, or the knowledge of thrombophilia, might improve the risk assessment and help to identify a high risk group for developing placental abruption and might benefit from more intense surveillance. Our findings need to be reproduced by other groups in order to be generalized. If validated, this approach will also give us the opportunity to identify a subgroup at increased risk and would also enable early pathophysiological research.

Although the average Hb values did not differ between placental abruption cases and controls, we found low final Hb values in 22% of the placental abruption group, as compared to 11% in the control group (OR = 2.2, 95% CI 1.3–3.7). This is in agreement with the results of Ananth and co-workers, who found a relative risk of 2.45 for placental abruption among women with maternal anemia.[16] Increased risk of pregnancy complications have been reported among women with high Hb values, although no such relationship could be seen in this study.

A potential limitation of our study is that it is hospital-based. On the other hand, Womens clinic at Malmö University Hospital is the only delivery unit in the city, and the vast majority of women (i.e., > 95% of the population of Malmö) deliver at this unit. A second and the major drawback is the retrospective case-control design with all its limitations. Furthermore,

in studies regarding placental abruption, there is a risk of bias due to both over- and underdiagnosis. However, the incidence of placental abruption in our population is in the same size as most other studies. One strength of this study is that most previously known risk factors for placental abruption were of similar size, as reported earlier.[4] The routine dating of pregnancy by ultrasound at 18 to 20 weeks of gestation, used here in the definition of IUGR and fetal loss, would represent another strength. In addition, ours is a fairly large study, including both personal interviews and an examination of medical records. Finally, the major strength is the use of a large prospectively collected unselected control group.

In conclusion, we found the history of second trimester, third trimester, and repeated fetal loss were significant risk factors for placental abruption. We constructed a risk score that may be used to access the risk of developing placental abruption. This may be used clinically to determine appropriate monitoring in cases of third trimester hemorrhage or premature contractions.

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Table 1. Clinical characteristics of women with placental abruption and control groups

	Placental abruption		Control group		Significance of
n	(n = 112)		(n = 2,371)		difference (*p*)
Mothers					
Age (years)	30.2	5.6	29.0	4.8	0.03
Nulliparae	49	43.8%	1094	46.1%	0.6
Smokers*	39	34.8%	446	18.8%	< 0.001
Pre-eclampsia	6	5.4%	39	1.6%	0.004
IUGR	16	14.3%	119	5.0%	< 0.001
Initial Hb (g/l)§	125.5	8.9	125.8	10.5	0.7
Mid Hb (g/l)§	117.3	8.6	115.6	9.9	0.6
Final Hb (g/l)§	119.8	10.2	121.6	9.6	0.07
Mode of delivery					
Caesarean delivery	91	81.3%	222	9.4%	< 0.001
Neonates					
Male fetal gender	64	51.7%	1,202	50.7%	0.2
Gestational age at birth (days)	248.9	30	278.3	12.8	< 0.001
Birthweight (g)	2605	920	3519	577	< 0.001
5-min Apgar score <7	21	18.8%	28	1.2%	< 0.001
pH umbilical vein §§	7.26	0.15	7.31	0.08	0.001
	(n = 91)		(n = 1741)		
Stillbirth	5	4.5%	3	0.1%	< 0.001

Means and standard deviations, or numbers and percentages are given. Hb = hemoglobin value
IUGR = intrauterine growth restriction

* Smokers at first visit to the antenatal health care unit, usually beetween 10th and 18th weeks.

§ Initial Hb = Hb taken at first visit in pregnancy, Mid Hb = Hb taken at 25 weeks of gestation, Final Hb = last Hb-value taken in pregnancy. Not recorded in all cases.

§§ Not investigated in all cases.

Table 2 Bivariate odds ratios (OR) for developing placental abruption

	Placental abruption (n = 112)		Control group (n = 2371)		OR	95% CI
First trimester fetal loss						
No	84		1924			
Yes	28	25.0%	447	18.9%	1.4	0.9-2.2
Second trimester fetal loss						
No	105		2322			
Yes	7	6.3%	49	2.1%	3.2	1.4-7.1
Repeated fetal loss						
No	107		2339			
Yes	5	4.5%	32	1.2%	3.4	(1.3-8.9)
Previous stillbirth						
No	105		2359			
Yes	7	6.3%	12	0.5%	13.1	5.1-34.0
Preeclampsia						
No	106		2332			
Yes	6	5.4%	39	1.6%	3.4	1.4-8.2
Intrauterine growth restriction						
No	96		2212			
Yes	16	14.3%	159	6.7%	3.2	1.8-5.5
Family history of venous thromboembolism*						
No	90		2252			
Yes	22	19.6%	119	5.0%	3.4	2.1-5.6
Prior placental abruption						
No	103		2363			
Yes	9	8.0%	8	0.3%	25.8	9.8-68.3
Smoker						
No	73		1915			
Yes	34	31.8%	446	18.9%	2.3	1.5-3.4
Unknown			10			
Male fetal sex						
No	48		1169			
Yes	64	57.1%	1202	50.7%	1.3	0.9-1,9
High maternal age (>35 year)						
No	89		2153			
Yes	23	20.5%	218	9.2%	2.6	(1.6-4.1)
Multiple pregnancy						
No	107		2334			
Yes	5	4.5%	37	1.6%	2.9	1.1-7.7

* A history of venous thromboembolism in first degree relatives (mother, father, or sibblings), which was previously presented in almost the same study population (ref 6)

Table 3. Distribution of risk score

	Placental abruption (n = 112)	Control group (n = 2371)	OR (95% CI)
Risk score 0	43	1625	Reference
Risk score 1	42	597	2.7 (1.7 - 4.1)
Risk score 2	16	130	4.7 (2.5 - 8.5)
Risk score 3	6	17	13.3 (5.0 - 35.5)
Risk score ≥4	5	2	94.5 (17.8 - 501)

Variables with roughly OR = 3 were assigned 1 point (second rimester fetal loss, repeated fetal loss, preeclampsia, IUGR, high maternal age, smoking, family history of thromboembolism, multiple pregnancy), prior stillbirth 2 points, and prior placental abruption 3 points. The points are added forming a risk score.