Familial Risk of Placental Abruption

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Abstract

Objective: This study aims to estimate the familial risk of placental abruption using a large population database. Design: Retrospective familial aggregation study of placental abruption utilizing a case-control design. Population: The Utah Population Database is a genealogic database of over 11 million individuals, which contains medical and demographic information linked to official records dating back to the 1900s. Methods: Cases of placental abruption and controls were ascertained from birth certificates, death certificates, and inpatient medical records. Controls were matched 3:1 to cases based on age, parity, and number of relatives in the database. Familial risk of placental abruption was estimated using generalized linear mixed-effect regression and conditional logistic regression. Main outcome measures: Unadjusted and adjusted odds of placental abruption between first-, second-, and third-degree relatives. Results: Of 1,168,378 pregnancies analyzed in the Utah Population Database, 32,823 cases (2.8%) of placental abruption were identified. First-degree relatives inherit an adjusted odds of placental abruption estimated at 1.18 (95% CI: 1.12 – 1.23) when a family member has had at least one placental abruption, and 1.38 (95% CI: 1.17 – 1.63) with two or more placental abruptions. The estimated effect is lower for second- and third-degree relatives. After controlling for clinical risk factors, individuals inherit an adjusted odds of placental abruption estimated at 1.16 (95% CI: 1.03 – 1.31, p=0.014) with a first-degree family history of placental abruption. The estimates for second- and third-degree relatives using this method are not statistically significant. Conclusion: These findings represent an argument for the inheritance of genetic factors which predispose the occurrence of placental abruption.

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Conclusion: These findings represent an argument for the inheritance of genetic factors which predispose the occurrence of placental abruption.

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Main text:

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Introduction:

Placental abruption (PA) – the partial or complete separation of the placenta before delivery – occurs in approximately 1-2% of all pregnancies and is associated with considerable maternal and perinatal morbidity and mortality.\(^1\) While the pathophysiology is uncertain, the leading theory involves acute vasospasm or thrombosis in small blood vessels at the placental-uterine interface which leads to hemorrhage.\(^4\) Significant abruptions can cause maternal hemodynamic instability, coagulopathies, and often require surgical management to facilitate delivery. For the fetus or neonate, abruptions carry a 9-fold increase risk of stillbirth and are highly associated with perinatal morbidity and mortality, particularly in the setting of preterm delivery.\(^3\) PA is also associated with fetal growth restriction and hypoxic brain injury, which can lead to long-term pediatric health consequences.\(^5,6\) PA is a clinical diagnosis that is difficult to predict, and in the majority of cases, impossible to prevent. Although epidemiologic studies have identified risk factors for PA, such as pre-labor rupture of membranes (PROM), smoking, prior PA, hypertension, and a history of cesarean delivery, the majority of cases occur in the absence of risk factors.\(^1,7\)

Investigation for a genetic contribution underlying PA began after practitioners noticed a significant recurrence risk for individuals in subsequent pregnancies as well as a perceived familial heritability in pedigrees.
Initial population-based studies determined the recurrence risk of PA to be 6-10 times higher for the same individual and the odds of PA among first degree relatives to be 2-4 times higher than the baseline risk. Candidate genetic loci related to trophoblast-like cellular invasion, mitochondrial biosynthesis, angiogenesis, oxidative stress, and circadian rhythm have been identified through genome-wide association studies and candidate gene association studies. An important step towards the discovery of preventative strategies or therapeutic targets is the accurate estimation of a person’s inherited PA risk as opposed to the environmental contribution to this disease process. This study aims to estimate the familial risk of placental abruption using a large, well-characterized population database.

Methods:
The familial risk of PA was estimated through this retrospective cohort study using the Utah Population Database (UPDB), which is a genealogic database of over 11 million individuals spanning up to 17 generations. The UPDB contains individual-level medical and demographic information, linked to official statewide birth and death records dating back to the 1900s. This study was approved by the Institutional Review Board at the University of Utah and the Utah Resource for Genetic and Epidemiologic Research, which oversees studies performed using UPDB data.

Cases of PA and controls were ascertained from birth certificates (1939 – 2020), maternal death certificates (1904 – 2020), and fetal death certificates (1978 – 2020), inpatient medical records, and International Classification of Diseases (ICD) codes (1996 – 2020) from the University of Utah Health Sciences Center. While PA can occur at any time point in pregnancy, this diagnosis is often confirmed at the time of delivery and more mild cases of placental abruption are often missed on official medical records. Diagnosing PA antepartum is challenging because of the poor sensitivity of ultrasound imaging and uncertainty on the clinicians’ part to confirm the diagnosis prior to delivery. Frequently, a suspected diagnosis of PA will be based on recurrent antepartum bleeding in the absence of a more obvious explanation. Therefore, many cases are not captured within our data sources. For this reason, we included “antepartum bleeding” in the case definition. Pregancies affected by placenta previa, multifetal gestations, cases with inadequate demographic information allowing pedigree linkage, or cases that were listed as gestational carriers were excluded. Controls were 3:1 matched to cases based on age, parity, number of eligible female relatives in the UPDB, and availability of eligible first-degree relatives (FDRs), second-degree relatives (SDRs), or third-degree relatives (TDRs) for analyses.

Statistical analysis included relatives of all PA cases and controls. Demographic and clinical variables were compared using Pearson’s Chi-squared test for categorical variables and Wilcoxon rank sum test for continuous variables. Clinical variables described were restricted to the index pregnancy, i.e., the pregnancy affected by PA, for cases. Familial risk of PA was estimated using generalized linear mixed-effect regression for FDRs, SDRs, and TDRs, clustering around cases and controls to account for non-independence of observations within families. The analysis included all cases and controls with at least one eligible relative in the UPDB. Family members of controls were used as the reference group in all analyses. Variables adjusted for in the primary analysis included age, year of pregnancy, race, ethnicity, education level, and parity. A stratified analysis was performed estimating familial risk of PA stratified by the number of pregnancies affected by placental abruption (at least 1 vs. 2 or more vs. 0). A sensitivity analysis was performed excluding cases coded as “antepartum bleeding,” which excluded 50.4% of cases.

A secondary analysis was performed, which included cases and controls with available data in the medical record to adjust for clinical risk factors. This analysis was performed using an alternative familial risk statistical method, referred to as an “ego-driven” familial analysis as opposed to “relative-driven”. Ego-driven familial risk analyses estimate the risk of PA for a case and control depending on whether a family member was affected. The method allows for adjusting for important clinical risk factors and medical comorbidities because they are only required to be available for the case or control, as opposed to all the relatives in the analysis. Familial risk of PA using this method was estimated using conditional logistic regression, adjusting for all demographic characteristics and potentially confounding clinical risk factors complicating the pregnancy affected by PA. These risk factors included smoking, drug use, diabetes, uterine
anomaly, hypertension, or pre-labor rupture of membranes (PROM) complicating the pregnancy affected by PA, and a history of cesarean delivery in prior pregnancies. Maternal drug use was noted to be co-linear with smoking and was not adjusted for in multivariable analysis. Clinical risk factors were selected based on prior published work evaluating risk factors for PA1,5,7,8 and our univariate analyses. Statistical analyses were carried out using R version 4.2.2 [R Core Team, Vienna, Austria].

Results:

We analyzed 1,168,378 pregnancies in the UPDB and identified 32,823 cases (2.8%) of PA over the years 1939 – 2020 after excluding for missing data or ineligible pedigrees. Relatives included in the primary analysis were 313,823 FDRs, 559,116 SDRs, and 1,242,936 TDRs (Fig. 1). 16,542 (50.4%) of these cases were identified by the term “antepartum bleeding” without a known diagnosis of placenta previa. The majority of cases were identified based on birth certificate data (83.7%), with the remaining cases identified from medical records (13.4%), fetal death certificates (2.3%) and maternal death certificates (0.5%). Individuals affected by PA were more likely to smoke (8.6% vs. 6.4%, \( p \)-value < 0.001), use drugs (1.2% vs. 0.5%, \( p \)-value < 0.001), have pre-gestational diabetes (0.4% vs. 0.3%, \( p \)-value < 0.001), hypertension (7.5% vs. 5.6%, \( p \)-value < 0.001), or a uterine anomaly (0.2% vs. 0.1%, \( p \)-value < 0.001), experience PROM (4.3% vs. 1.3%, \( p \)-value < 0.001), have less than a high school education (8.7% vs. 6.1%, \( p \)-value < 0.001) and were more likely to be Hispanic (9.5% vs. 8.2%, \( p \)-value < 0.001) and less likely to be White (95.1% vs. 96.0%, \( p \)-value < 0.001). See Table 1 for full details.

Table 2 represents results from the primary PA familial risk analysis. PA appears to be heritable, with a statistically significant risk transmitted to FDRs and SDRs. FDRs inherit an increased odds of PA with an aOR 1.18 (95% CI: 1.12 – 1.23, \( p < 0.001 \)). SDRs also inherit an increased odds of PA with an aOR 1.09 (95% CI: 1.06 – 1.13, \( p < 0.001 \)). TDRs do not appear to inherit a significant PA risk with an aOR 1.01 (95% CI: 0.99 – 1.03, \( p =0.428 \)). When stratified by number of pregnancies affected by PA, FDRs of cases with two or more PAs inherit a more significant odds of PA with aOR 1.38 (95% CI: 1.17 – 1.63, \( p < 0.001 \)). The measures of association are also higher for SDRs and TDRs when their family member was affected by two or more PAs, with the estimation for SDRs nearing statistical significance (Fig. 2). Through a sensitivity analysis in which cases of PA obtained by the code “antepartum bleeding” were removed, the risk inherited by FDRs increased to an aOR 1.20 (95% CI: 1.12 – 1.27, \( p < 0.001 \)), while the risk for SDRs was similar at an aOR 1.09 (95% CI: 1.05 – 1.14, \( p<0.001 \)). The association for TDRs did not reach statistical significance (Table 3). All relative-driven familial risk analyses were adjusted for by available demographic variables for relatives: age, year of pregnancy, race, ethnicity, education level, and parity.

For the ego-driven subgroup analysis, we analyzed 1,168,378 pregnancies in the UPDB and identified 53,072 cases (4.5%) of PA matched to 159,124 controls over the years 1939 – 2020 after excluding for missing data (Fig. S1). The majority of cases were identified based on birth certificate data (82.2%), with the remaining cases identified from medical records (14.9%), fetal death certificates (2.5%) and maternal death certificates (0.4%). Demographic differences between cases and controls were similar to the relative-driven method. See Table S1 for full details. Table 4 depicts clinical risk factors with estimated adjusted odds ratios associated with PA. Of these, PROM was most highly associated with PA with an OR 2.18 (95% CI: 1.80 – 2.64, \( p<0.001 \)). The presence of a uterine anomaly was also highly associated with PA with an OR 2.17 (95% CI: 1.18 – 3.97, \( p =0.004 \)).

Table 5 represents the results of the ego-driven familial risk analysis adjusting for demographic and potentially confounding clinical variables. If an individual has a first-degree family history of PA, their odds of developing PA is estimated at an aOR 1.16 (95% CI: 1.03 – 1.31, \( p =0.014 \)). Using this alternative method of analysis, the odds estimated for an individual with second- and third-degree relatives affected by PA is not statistically significant.

Discussion:

Main findings:
Placental abruption (PA) occurs in 1-2% of pregnancies and incurs considerable maternal and perinatal morbidity and mortality. While the majority of research underlying the causes of PA has been directed at evaluating environmental risk factors (e.g. PROM, smoking, prior PA, hypertension, history of cesarean delivery), recent studies have assessed genetic causes. A pivotal step in the distinction between environmental and genetic causes for PA is the estimation of familial risk in a population. We estimated 18-20% as the inherited odds for PA in FDRs, and 9% and 0-1% respectively, for SDRs and TDRs. We noted an elevated odds of PA for all degrees of relation for the highest risk individuals, or individuals who experienced two or more PAs.

With use of the ego-driven familial analysis, known clinical risk factors such as PROM, smoking, and hypertension were adjusted for, which diminished the estimated increased odds of PA for an individual towards the null (16% vs. 20% with the relative-driven analysis). We see that these environmental risk factors outweigh genetic heritability at the second- and third-degree relation level as those estimations were not statistically significant.

Strengths and limitations:
Our study is unique in its size and breadth, including over one million individuals, stretching as far back as 1939. The size of the study allowed us to calculate a precise estimate for the familial risk of PA. While the UPDB allows for population-level results, we were able to collect data at the individual level using birth and death certificates as well as electronic medical records. This allowed for careful inclusion of cases, stratification of separate pregnancies for each individual, and the ability to address confounding environmental and clinical risk factors. We used a novel alternative method for evaluating heritability, the “ego-driven” risk analysis, which allowed for adjustment of clinical confounders as well as evaluating familial risk using the relatives as the study population rather than the individual. One limitation to generalizability is that our cohort arises from a population of individuals living in a single state in the US. While the state’s current population resulted from a smaller founder population in the 1800s, recent genetic investigations have revealed a similar proportion of genetic heterogeneity to the rest of the US population. The inclusion of all cases of PA in research is often limited by under-reporting and reliance on the subjective judgement of health care professionals. We attempted to mitigate this limitation by including cases of “antepartum bleeding” while excluding placenta previa in our case definition. While there might be causes of antepartum bleeding independent of PA, like cervical or vaginal bleeding, PA is the most common leading cause of vaginal bleeding throughout pregnancy. Our results revealed a trend towards the null with the inclusion of “antepartum bleeding”: from 20% estimated heritability to 18%. While we attempted to adjust for all known risk factors for PA in our heritability analyses, one possible confounding factor includes shared environments in family pedigrees, which could have led to an overestimation in our risk.

Interpretation:
The genetics of PA is difficult to study given the clinical ambiguity of the diagnosis and research towards this realm has been limited. Acknowledging the inherent limitations of population-based studies, the ability to evaluate a large cohort of people with multiple pregnancies is valuable in estimating an individuals’ inherited risk of PA. We estimated 18-20% as the inherited increase in odds for PA in FDRs, which is similar to the results of a smaller study performed in Norway. Rasmussen et. al (2009) performed a population-based study including greater than 160,000 families and estimated the heritability among FDRs to be 16%. Our estimates for SDRs and TDRs, 9% and 0-1% respectively, reveal a strong argument for the presence of genetic changes shared among relatives with declining heritability for more distantly related individuals in a pedigree. At the third-degree level, the estimated heritability is equivalent to the suspected baseline risk of PA in the US population of 1-2%. An elevated odds of PA was estimated for the highest risk individuals, or individuals who experienced two or more PAs, which further supports the hypothesis that shared genetic changes may predispose to PA occurrence. After adjusting for possibly confounding clinical risk factors with the ego-driven familial analyses, the effect estimates were noted to be lower than those without considering these risk factors, which raises the suspicion of shared environments among family members.
Conclusion:
This study offers a precise estimate of the familial risk for placental abruption, an obstetric complication previously associated with predominantly environmental risk factors. This research advances our understanding of genetic predisposition to adverse outcomes associated with placental dysfunction and will further advance our goal of discovering preventative and therapeutic targets in the future.

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Statements and Declarations:

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Author contributions: All authors contributed to the study conception and design. Material preparation, data collection and analyses were performed by Huong Meeks, Alison Fraser, and Devin Etcitty. The first draft of the manuscript was written by Susan Dalton and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval & Informed consent: Approval was obtained by the Institutional Review Board at the University of Utah (IRB# 00012636) and the Utah Resource for Genetic and Epidemiologic Research (UPDB# 00000441) before data collection or analyses were begun. This is a retrospective observational study of de-identified data and written informed consent of research participants was waived.

References:


Table and Figure headings:

Table 1. Demographic and clinical characteristics compared between placental abruption cases and controls. Clinical characteristics are specific to the pregnancy affected by placental abruption.

Table 2. Results from primary analysis of familial risk of placental abruption.
*Variables adjusted for include age, year of pregnancy, race, ethnicity, education level, and parity.

Table 3. Results from sensitivity analysis of familial risk of placental abruption excluding cases with “antepartum bleeding”.
*Variables adjusted for include age, year of pregnancy, race, ethnicity, education level, and parity.

Table 4. Clinical risk factors with estimated odds ratios associated with placental abruption.

Table 5. Results from subgroup analysis of familial risk of placental abruption adjusting for demographic and clinical risk factors.
Demographic variables adjusted for include age, year of pregnancy, race, ethnicity, education level, and parity. Clinical variables included smoking, diabetes, uterine anomaly, hypertension, and pre-labor rupture of membranes (PROM) in the pregnancy affected by placental abruption, and cesarean delivery in a prior pregnancy.

**Figures:**

**Figure 1** Flow chart of included cases and controls and number of first-, second-, and third-degree relatives available for familial risk analyses.

**Figure 2** Results from stratified analysis of familial risk of placental abruption when estimating odds between cases and controls stratified by number of pregnancies affected by placental abruption.

**Supplementary material:**

**Table S1.** Demographic and clinical characteristics compared between placental abruption cases and controls for subgroup analysis. Clinical characteristics are specific to the pregnancy affected by placental abruption.

**Figure S1** Flow chart of included cases and controls for subgroup analysis including clinical risk factors.
First Degree Relatives = 313,823
Second Degree Relatives = 559,116
Third Degree Relatives = 1,242,936

Cases = 53,508
Controls = 159,124

Missing birth dates
N = 96

Cases = 53,417
Controls = 159,124

No eligible UPDB relatives
N = 20,286

Cases = 33,133
Controls = 98,387

Cannot match to controls
N = 309

Cases = 32,823
Controls = 98,387

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Cases = 53,508
Controls = 159,124

Missing birth dates
N = 96

Cases = 53,417
Controls = 159,124

Cannot match to controls
N = 345

Cases = 53,072
Controls = 159,124

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Table 5.docx available at https://authorea.com/users/460175/articles/649810-familial-risk-of-placental-abruption