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# Risk of Placental Abruption in Relation to Maternal Depressive, Anxiety and Stress Symptoms

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## Abstract

**Background—**Little is known about the influence of psychiatric factors on the etiology of placental abruption (PA), an obstetrical condition that complicates 1-2% of pregnancies. We examined the risk of AP in relation to maternal psychiatric symptoms during pregnancy.

**Methods—**This case-control study included 373 AP cases and 368 controls delivered at five medical centers in Lima, Peru. Depressive, anxiety and stress symptoms were assessed using the Patient Health Questionnaire (PHQ-9) and the Depression Anxiety Stress Scales (DASS-21). Multivariable logistic regression models were fit to calculate odds ratios (aOR) and 95% confidence intervals (CI) adjusted for confounders.

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**Author Contributions:** MAW had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit for publication. MAW conceived, designed and obtained funding for the study. NdP, CQ, SES and LH analyzed the data. NdP, SES and MAW drafted the manuscript. All authors interpreted the data, critically revised the draft for important intellectual content, and gave final approval of the manuscript to be published.

**Results—**Depressive symptoms of increasing severity (using the DASS depression subscale) was associated with AP (p for trend=0.02). Compared with women with no depressive symptoms, the aOR (95%CI) for AP associated with each level of severity of depression symptoms based on the DASS assessment were as follows: mild 1.84 (0.91-3.74); moderate 1.25 (0.67-2.33); and severe 4.68 (0.98-22.4). The corresponding ORs for mild, moderate, and moderately severe depressive symptoms based on the PHQ assessment were 1.10 (0.79-1.54), 3.31 (1.45-7.57), and 5.01 (1.06-23.6), respectively. A positive gradient was observed for the odds of AP with severity of anxiety (p for trend=0.002) and stress symptoms (p for trend=0.002).

**Limitations—**These cross-sectionally collected data may be subject to recall bias.

**Conclusions—**Maternal psychiatric disorders may be associated with an increased occurrence of AP. Larger studies that allow for more precise evaluations of maternal psychiatric health in relation to AP risk are warranted.

### Keywords

placental abruption; epidemiology; pregnancy; depression; anxiety; risk factors

## 1. Introduction

Placental abruption (PA), the premature separation of the placenta, is a life threatening obstetrical condition that complicates 1-2% of pregnancies (Macdonald et al., 1989; Younis and Samueloff, 2003; Oyelese and Ananth, 2006). The condition occurs in much higher frequencies among women with multi-fetal gestation, coagulopathies, acquired forms of thrombophilia, uterine anomalies, abdominal trauma, hypertension, premature rupture of membranes, and intrauterine infections (Ananth et al., 2004; Ananth and Wilcox, 2001; Williams et al., 1992; Williams et al., 1991; Kramer et al., 1997; Sanchez et al., 2006). Young and advanced maternal age, grand-multiparity, and maternal cigarette smoking are PA risk factors (Williams et al., 1991; Sanchez et al., 2006; Ananth et al., 1996). Pathophysiologic mechanisms involved in PA, and related perinatal disorders include uteroplacental ischemia, underperfusion, chronic hypoxia, and infarctions. Investigators have begun to conceptualize PA as an “ischemic placental disorder” characterized by acute and chronic pathophysiological features (Younis and Samueloff, 2003; Ananth et al., 2007); and data suggests that transient activation of the sympathetic nervous system might trigger PA (Jablensky et al., 2005). Little is known about the influence of psychosocial and psychiatric factors on the etiology of PA. Over 2 decades ago, panic disorders as a potential trigger of PA was reported in a case (Cohen et al., 1989). More recently, Jablensky et al (Jablensky et al., 2005) reported that PA was more strongly associated with schizophrenia (OR=3.17; 95% CI 1.55-6.49) than with depression (OR=1.36; 95% CI 0.17-2.60). Given the paucity of research in this area, we hypothesized that maternal depressive, anxiety and stress symptoms during pregnancy may be associated with increased risk of PA. We tested this hypothesis in a large case-control study of Peruvian women.

## 2. Methods

### 2.1 Study population

This case-control study was conducted at the Hospital Nacional dos de Mayo, Instituto Especializado Materno Perinatal, Hospital Edgardo Rebagliati Martins, Hospital Nacional Hipolito Unanue, and Hospital Nacional Docente Madre Niño San Bartolomè in Lima, Peru, from 2006-2008. The procedures used in this study were in agreement with the protocols approved by participating institutions. All participants provided written informed consent. PA cases were identified by daily monitoring of all new admissions to antepartum,

emergency room, and labor and delivery wards of participating hospitals. Study subjects were recruited during their hospital stay. Hospital medical records were reviewed so that clinical diagnostic signs, symptoms and physical characteristics of PA could be objectively confirmed; and so that other clinical diagnoses associated with late pregnancy vaginal bleeding could be excluded. During the study period, 424 cases were approached and 90% (n=382) elected to participate in the study. The diagnosis of PA was based on routine clinical examination performed by the attending physician. For the research diagnosis of PA, we required evidence of blood clot behind the placenta accompanied by at least two of the following signs and symptoms: 1) vaginal bleeding in late pregnancy that was not associated with placenta previa or cervical lesions; 2) uterine tenderness and/or abdominal pain; and 3) fetal distress or death. Controls were selected from eligible women who delivered at participating institutions during the study period. Eligible controls were women who did not have a diagnosis of PA and whose medical record review later confirmed this fact. Of the 429 controls approached, 86% (n=369) agreed to participate.

### 2.2. Data collection and variable specification

We used a standardized, structured questionnaire to collect information regarding maternal sociodemographic, medical, reproductive, and lifestyle characteristics during in-person interviews. Information collected during the interviews included maternal age, marital status, employment status during pregnancy, medical history, and smoking and alcohol consumption during pregnancy. We used the Patient Health Questionaire-9 (PHQ-9) to assess participants' experience of depression or depressive symptoms during pregnancy. The instrument has been demonstrated to be a reliable tool for assessing recent psychosocial stressors among obstetrics-gynecology patients (Spitzer et al., 2000) and in Spanish-speaking women (Wulsin et al., 2002). The instrument is a reliable and valid measure of depression severity and a useful clinical and research tool (Kroenke et al., 2001). The PHQ-9 scale includes nine items, and choices for responses were a) never; b) several weeks over the pregnancy; c) more than half the pregnancy; or d) nearly the whole pregnancy. The PHQ-9 total score is the sum of scores for the nine items for each woman, and ranged from 0-27. We categorized participants as exhibiting minimal (PHQ-9 score 0-4), mild (PHQ-9 score 5-9), moderate (PHQ-9 score 10-14), and moderately severe (PHQ-9 score ≥15) depressive symptoms. Maternal depressive, anxiety and stress levels were also characterized using the Depression Anxiety Stress Scales (DASS-21). The instrument has 21-items and is designed to measure the three negative affective states of depression, anxiety, and stress (Lovibond, 1998; Lovibond and Lovibond, 1995). The psychometric properties of the English and Spanish versions of DASS-21 have been extensively evaluated, and there is evidence for the convergent and discriminative validity of data obtained with the instrument (Lovibond and Lovibond, 1995; Brown et al., 1997; Daza et al., 2002). Using previously suggested cutoff scores (Lovibond, 1998; Lovibond and Lovibond, 1995), participants were categorized as exhibiting normal (DASS score <9), mild (DASS score 10-13), moderate (DASS score 14-20), and severe (DASS score ≥21) depressive symptoms. Subjects were categorized as exhibiting normal (DASS score <7), mild (DASS score 8-9), moderate (DASS score 10-14), and severe (DASS score ≥15) anxiety symptoms. The corresponding cutoff score for symptoms of stress were: normal (DASS score <14), mild (DASS score 15-18), moderate (DASS score 19-25), and severe (DASS score ≥26).

Maternal and infant records were reviewed to collect detailed information concerning antepartum, labor, and delivery characteristics, as well as conditions of the newborn. Maternal anthropometric measures were taken during participants' hospital stays. Gestational age was based on the date of the last menstrual period and was confirmed by an ultrasound examination performed before 20 weeks.

### 2.3 Analytical population and statistical analysis

The analytical population for the study is derived from the 382 PA cases and 369 controls enrolled in the study. Eight women with twin or higher-order pregnancies (8 cases and 0 controls) were excluded. Additionally 2 women (1 case and 1 control) were excluded because of incomplete information pertaining to depressive symptomatology. A total of 373 PA cases and 368 controls remained for analysis. We examined the frequency distribution of maternal sociodemographic characteristics and reproductive histories according to case-control status. Initial analyses were carried out in order to determine unadjusted odds ratio (OR) and 95% confidence interval (CI). Effect modification was evaluated by stratified analyses and by including appropriate interaction terms in logistic regression models (Rothman and Greenland, 1998). Logistic regression procedures were used to simultaneously control for confounding variables while estimating ORs and 95% CIs. Confounders were defined as those factors that altered the unadjusted OR by at least 10%. Final logistic regression models included confounders, as well as those covariates of *a priori* interest (i.e., maternal age, parity, and body mass index). Maternal educational attainment, employment status, use of prenatal care services and prenatal vitamins, as well as maternal use of tobacco, alcohol and illicit drugs were not found to be confounders and thus were not included in final models. All continuous variables are presented as mean ± standard deviation (SD). All analyses were performed using STATA 9.0 statistical software (Stata, College Station, Texas, USA).

## 3. Results

Sociodemographic and reproductive characteristics of PA cases and controls are presented in Table 1. In bivariate analyses we noted that the odds of PA increased with increasing severity of depressive symptoms as measured by the PHQ-9 questionnaire (p-value for trend=0.003). After adjusting for confounding by maternal age, parity and pre-pregnancy body mass index, moderate (aOR=3.31; 95% CI 1.45-7.57) and moderately severe (aOR=5.01; 95% CI 1.06-23.6) depressive symptoms were statistically significantly associated with increased risks of PA, compared with minimal symptoms (Table 2 top panel). The odds of PA were also positively and statistically significantly associated with depressive, anxiety and stress symptoms as measured using the DASS-21 questionnaire (Table 2 bottom panel). The OR and 95% CI were: 1.84 (95% CI 0.91-3.74), 1.25 (95% CI 0.67-2.33) and 4.68 (95% CI 0.98-22.4) for mild, moderate and severe depressive symptoms, respectively, when compared with the reference group. Compared with the reference group (anxiety symptom score ≤7) women with mild (DASS score 8-9) anxiety symptoms had a modest increased odds of PA (aOR=1.29; 95% CI 0.71-2.34). Moderate (DASS score 10-14) (aOR=1.63; 95% CI 1.00-2.64), and severe (DASS score ≥15) anxiety symptoms (aOR=2.30 95% CI: 1.1-9.6) were more strongly associated increased odds of PA, respectively. Lastly, we noted that the odds of PA increased with increasing severity of stress symptoms as measured by the DASS-21 subscale (p-value for trend=0.02). After adjusting for confounding by maternal age, parity and pre-pregnancy body mass index, mild (aOR=1.85; 95% CI 1.01-3.39), moderate (aOR=2.03; 95% CI 1.02-4.02), and severe stress (aOR=2.05; 95% CI 0.97-4.37) were statistically significantly associated with increased odds of PA.

## 4. Discussion

Women with depressive, anxiety and stress symptoms during pregnancy had higher odds of PA when compared with women without such symptoms. To the best of our knowledge, this is the first study examining associations of depressive, anxiety and stress symptoms with PA. We are aware of 2 previous studies that have evaluated PA in relation to maternal psychiatric health status. Cohen et al.(Cohen et al., 1989) in their report of a PA case, noted

that maternal sympathetic arousal and resultant hypertension, experienced during a panic attack, might adversely affect the feto-placental unit thereby precipitating PA. Additionally, in their record linkage study, Jablensky et al. (Jablensky et al., 2005) noted that maternal pre-gestational psychiatric illnesses, including schizophrenia, and to a lesser degree, depression, are risk factors of PA among Australian women. Our findings are consistent with other studies reporting associations of psychiatric disorders and psychosocial stress with adverse pregnancy outcomes including preterm birth (Gavin et al., 2009), low birth weight(Woods et al., 2009) and preeclampsia (Qiu et al., 2007; Qiu et al., 2009).

Several potential limitations should be considered when interpreting our results. First, our analyses are based on cross-sectionally collected data, which may be subject to recall bias. Second, participants did not have formal diagnostic examinations. As a result, some misclassification is possible. However, both the PHQ-9 and DASS-21 have good-to-excellent psychometric properties when compared with the structured diagnostic interviews (Brown et al., 1997; Wulsin et al., 2002). Lastly, although we adjusted for multiple confounding factors, as with all observational studies, we cannot exclude the possibility of some residual confounding.

Several biological mechanisms may plausibly account for the observed associations of maternal depressive, anxiety and stress symptoms with increased risks of PA. Increased hypothalamic-pituitary-adrenal (HPA) activity (Yehuda, 2002), a robust pathophysiological biomarker associated with affective disorders, is regarded as one important mechanism for observed associations between maternal psychiatric illness and adverse pregnancy outcomes, including preeclampsia and preterm delivery (Qiu et al., 2009). Investigators have documented altered plasma cortisol, β-endorphin corticotrophin releasing hormone, and serotonin concentrations in pregnant women with mood and/or anxiety disorders (Smith et al., 1990; Southwick et al., 1999). Chronic systemic inflammation and related endothelial dysfunction have been observed among individuals with clinical depression and depressive symptoms (Agarwal and Marshall, 1998; Lesperance et al., 2004). Endothelial dysfunction and inflammation are implicated in the pathogenesis of PA (Magriples et al., 1999; Nath et al., 2007). Alternatively, affective disorders may also confer an increased risk of PA via their influences on platelet activation. Investigators have observed augmented coagulability (Panagiotakos et al., 2004) and platelet hyperactivity (Von Kanel, 2004; Von Kanel et al., 2004) in subjects with major depression. These metabolic and genomic alterations in coagulation pathways have also been implicated in the pathogenesis of depression and PA (Ananth et al., 2008; Zdoukopoulos and Zintzaras, 2008) and in disorders like preeclampsia, which are strongly associated with PA (Sanchez et al., 2006). Additional information from clinical studies designed to assess neuroendocrine, hemodynamic and vascular effects of maternal mood and anxiety disorders (and treatment of these disorders) in pregnant women are needed before any firm conclusions can be drawn about these mechanistic hypotheses.

In summary, our results suggest that the risk of PA is increased in pregnant women with symptoms of mood or anxiety disorders. Comprehensive efforts are required to carefully characterize reproductive sequelae of psychiatric illnesses among reproductive aged and pregnant women. Longitudinal cohort studies, with prospective clinical assessment of maternal clinical and sub-clinical psychiatric illnesses are warranted. Potential public health efforts to screen and treat affected women may also modify risks of PA and possibly other associated disorders.

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**Table 1**

Socio-Demographic and Reproductive Characteristics and Infant Outcomes in the Study Population, Lima, Peru, 2006-2008

| | Placental Abruption | | | | |
|---|---|---|---|---|---|
| | Cases (N=373) | | Controls (N=368) | | |
| **Characteristics** | **n** | **%** | **n** | **%** | **p-value** |
| Maternal Age at delivery (years) | 28.4 ± 6.7* | | 28.0 ± 6.3 | | 0.37 |
| Maternal Age at delivery (years) | | | | | |
| <20 | 38 | 10.2 | 30 | 8.2 | 0.61 |
| 20-29 | 174 | 46.6 | 191 | 51.9 | |
| 30-34 | 85 | 22.8 | 78 | 21.2 | |
| ≥35 | 75 | 20.1 | 67 | 18.2 | |
| Missing | 1 | 0.3 | 2 | 0.5 | |
| Primiparity | 160 | 42.9 | 144 | 39.1 | 0.22 |
| High School Education or lower | 240 | 64.3 | 216 | 58.7 | 0.27 |
| Employed during Pregnancy | 185 | 49.6 | 176 | 47.8 | 0.63 |
| Planned Pregnancy | 131 | 35.1 | 115 | 31.3 | 0.56 |
| No Prenatal Care | 41 | 11.0 | 22 | 6.0 | 0.01 |
| No Prenatal Vitamin | 56 | 15.0 | 45 | 12.2 | 0.40 |
| Smoking during Pregnancy | 8 | 2.1 | 6 | 1.6 | 0.48 |
| Alcohol use during Pregnancy | 35 | 9.4 | 30 | 8.2 | 0.70 |
| Illicit Drug use during Pregnancy | 2 | 0.5 | 1 | 0.3 | --- |
| Pre-pregnancy Body Mass Index (kg/m$^2$) | 23.7 ± 3.7* | | 23.4 ± 3.5 | | 0.31 |
| Pre-pregnancy Body Mass Index (kg/m$^2$) | | | | | |
| < 19.8 | 39 | 10.5 | 38 | 10.3 | 0.46 |
| 19.8-26.0 | 227 | 60.9 | 245 | 66.6 | |
| 26.1-29.0 | 47 | 12.6 | 36 | 9.8 | |
| ≥ 29.0 | 27 | 7.2 | 25 | 6.8 | |
| Missing | 33 | 8.8 | 24 | 6.5 | |
| Chronic Hypertension | 20 | 5.4 | 10 | 2.7 | 0.20 |
| Infant Birth Weight (grams)** | 2471 ± 846* | | 3306 ± 502 | | <0.001 |

| | Placental Abruption | | | | |
|---|---|---|---|---|---|
| | Cases (N=373) | | Controls (N=368) | | |
| **Characteristics** | **n** | **%** | **n** | **%** | **p-value** |
| Low Birth Weight Infant (<2500grams)** | 158 | 42.4 | 17 | 4.6 | <0.001 |
| Gestational age at delivery (weeks)** | 35.3 ± 3.8* | | 38.7 ± 1.8 | | <0.001 |
| Preterm Delivery Infant (<37weeks)** | 203 | 54.4 | 20 | 5.4 | <0.001 |
| Stillbirth | 59 | 15.8 | 0 | 0 | --- |

* Mean ± SD (SD: standard deviation)

** Restricted to live birth only (314 cases and 368 controls)

## Table 2

Odds Ratio (OR) and 95% Confidence Interval (CI) for Placental Abruption in Relation to Severity of Maternal Depressive Symptoms during Pregnancy Assessed Using the Patient Health Questionnaire-9 (PHQ-9) and the Depression Anxiety Stress Scales (DASS-21) During Pregnancy, Lima, Peru, 2006-2008

| | Placental Abruption | | | |
|---|---|---|---|---|
| **Outcome Variables** | **Cases (N=373) n (%)** | **Controls (N=368) n (%)** | **Unadjusted OR (95% CI)** | ***Adjusted OR (95% CI)** |
| **Depressive Symptoms Assessed Using PHQ-9 Questionnaire** | | | | |
| Minimal (<4) | 230 (61.7) | 251 (68.2) | 1.0 (referent) | 1.00 (referent) |
| Mild (5–9) | 110 (29.5) | 107 (29.1) | 1.12 (0.81-1.55) | 1.10 (0.79-1.54) |
| Moderate (10–14) | 24 (6.4) | 8 (2.2) | 3.27 (1.44-7.43) | 3.31 (1.45-7.57) |
| Moderately Severe (≥15) | 9 (2.4) | 2 (0.5) | 4.91 (1.05-23.0) | 5.01 (1.06-23.6) |
| | *P-value for trend* | | *0.003* | *0.003* |
| **Psychiatric Symptoms Assessed Using DASS-21 Subscales** | | | | |
| Normal (0-9) | 317 (85.0) | 332 (90.2) | 1.00 (referent) | 1.00 (referent) |
| Mild (10-13) | 22 (5.9) | 13 (3.5) | 1.77 (0.88-3.58) | 1.84 (0.91-3.74) |
| Moderate (14-20) | 24 (6.4) | 21 (5.7) | 1.20 (0.65-2.19) | 1.25 (0.67-2.33) |
| Severe (≥21) | 10 (2.7) | 2 (0.5) | 4.71 (1.01-22.0) | 4.68 (0.98-22.4) |
| | *P-value for trend* | | *0.030* | *0.020* |
| **Anxiety** | | | | |
| Normal (0-7) | 262 (70.3) | 295 (81.2) | 1.00 (referent) | 1.00 (referent) |
| Mild (8-9) | 30 (8.0) | 23 (6.3) | 1.47 (0.83-2.59) | 1.29 (0.71-2.34) |
| Moderate (10-14) | 49 (13.1) | 34 (9.2) | 1.62 (1.01-2.59) | 1.63 (1.00-2.64) |
| Severe (≥15) | 32 (8.6) | 16 (4.3) | 2.25 (1.21-4.20) | 2.30 (1.23-4.31) |
| | *P-value for trend* | | *0.001* | *0.002* |
| **Stress** | | | | |
| Normal (0-14) | 294 (78.8) | 323 (87.8) | 1.00 (referent) | 1.00 (referent) |
| Mild (15-18) | 33 (8.9) | 20 (5.4) | 1.81 (1.02-3.23) | 1.85 (1.01-3.39) |
| Moderate (19-25) | 24 (6.4) | 14 (3.8) | 1.88 (0.96-3.71) | 2.03 (1.02-4.02) |
| Severe (≥26) | 22 (5.9) | 11 (3.0) | 2.20 (1.05-4.61) | 2.05 (0.97-4.37) |
| | *P-value for trend* | | *0.002* | *0.003* |

*Adjusted for maternal age (continuous), primiparity and maternal pre-pregnancy overweight status (yes vs. no)