# Placental implantation abnormalities and risk of preterm delivery: a systematic review and metaanalysis

Sevan A. Vahanian, MD; Jessica A. Lavery, MS; Cande V. Ananth, PhD, MPH; Anthony Vintzileos, MD

We sought to evaluate the extent of the association between placental implantation abnormalities (PIA) and preterm delivery in singleton gestations. We conducted a systematic review of English-language articles published from 1980 onward using PubMed, MEDLINE, EMBASE, CINAHL, LILACS, and Google Scholar, and by identifying studies cited in the references of published articles. Search terms were PIA defined as ≥1 of the following: placenta previa, placenta accreta, vasa previa, and velamentous cord insertion. Observational and experimental studies were included for review if data were available regarding any of the aforementioned PIA and regarding gestational age at delivery or preterm delivery. Case reports and case series were excluded. Studies were reviewed and data extracted. The primary outcome was gestational age at delivery or preterm delivery <37 weeks' gestation. Secondary outcomes included birthweight, 1- and 5-minute Apgar scores, neonatal intensive care unit (NICU) admission, neonatal and perinatal death, and small for gestational age. Of the 1421 studies identified, 79 met the defined criteria; 56 studies were descriptive and 23 were comparative. Based on the descriptive studies, the preterm delivery rates for low-lying/marginal placenta, placenta previa, placenta accreta, vasa previa, and velamentous cord insertion were 26.9%, 43.5%, 57.7%, 81.9%, and 37.5%, respectively. Based on the comparative studies using controls, there was decreased pregnancy duration for every PIA; more specifically, there was an increased risk for preterm delivery in patients with placenta previa (risk ratio [RR], 5.32; 95% confidence interval [CI], 4.39–6.45), vasa previa (RR, 3.36; 95% CI, 2.76–4.09), and velamentous cord insertion (RR, 1.95; 95% CI, 1.67–2.28). Risks of NICU admissions (RR, 4.09; 95% CI, 2.80–5.97), neonatal death (RR, 5.44; 95% CI, 3.03–9.78), and perinatal death (RR, 3.01; 95% CI, 1.41–6.43) were higher with placenta previa. Perinatal risks were also higher in patients with vasa previa (perinatal death rate RR, 4.52; 95% CI, 2.77–7.39) and velamentous cord insertion (NICU admissions [RR, 1.76; 95% CI, 1.68–1.84], small for gestational age [RR, 1.69; 95% CI, 1.56–1.82], and perinatal death [RR, 2.15; 95% CI, 1.84–2.52]). In singleton gestations, there is a strong association between PIA and preterm delivery resulting in significant perinatal morbidity and mortality.

**Key words:** cesarean delivery, metaanalysis, neonatal death, neonatal morbidity, placenta accreta, placenta previa, prematurity, preterm birth, preterm delivery, vasa previa, velamentous cord insertion

One of the consequences of increasing cesarean delivery rates over the last 2 decades is an increase in placental implantation abnormalities (PIAs) including placenta previa, placenta accreta, vasa previa, and velamentous cord insertion.[1-9] Since PIAs can have catastrophic complications for both the mother and fetus, efforts have been focused on reducing maternal and fetal risk by not allowing the pregnancy to advance to term, thus resulting in preterm delivery. As a matter of fact, following ischemic placental disease, PIAs are the second most common cause for indicated preterm delivery, accounting for 5.6-8.7% of indicated preterm deliveries at <35 weeks' gestation.[10]

Given the increasing cesarean delivery rate, we undertook a systematic review and metaanalysis of PIAs in relation to preterm delivery and other adverse perinatal outcomes. The goal was to alert the clinician regarding the significance and extent of the association between PIAs and preterm delivery with its consequences.

## Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement guidelines for undertaking the systematic review and metaanalysis.[11]

### Literature review

This was a metaanalysis of studies published on singleton gestations with PIA including placenta previa, placenta accreta, vasa previa, and velamentous cord insertion. Studies chosen for review were selected on the basis of a comprehensive literature search with the use of PubMed, MEDLINE, EMBASE, LILACS, CINAHL, and Google Scholar, and by identifying studies cited in the references of published articles. Key words that were used in the search included the following exposures: "placenta pr(a)evia," "placenta accreta," "placenta increta," "placenta percreta," "morbidity adherent placenta," "c(a)esarean scar pregnancy," "low-lying placenta," "marginal placenta," "vasa pr(a)evia," "velamentous cord insertion," "accessory

From the Department of Obstetrics and Gynecology, Winthrop-University Hospital, Mineola, NY (Drs Vahanian and Vintzileos), and Department of Obstetrics and Gynecology, College of Physicians and Surgeons (Ms Lavery and Dr Ananth), and Department of Epidemiology, Mailman School of Public Health (Dr Ananth), Columbia University, New York, NY.

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Corresponding author: Sevan A. Vahanian, MD. svahanian@winthrop.org

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lobe," "succenturiate lobe," "bilobed placenta," and the following outcomes: "gestational age at birth," "preterm birth," "preterm delivery," "prematurity," and "premature birth." English-language restrictions were imposed on the search to minimize heterogeneity due to differences in practice patterns, resource utilization, and scrutiny of peer review process among non-English-language studies. Articles were included from January 1980 through April 2015.

### Eligibility criteria

Observational and experimental studies were included for review if data were available regarding any of the aforementioned PIA and regarding gestational age at delivery or preterm delivery. Case reports and case series were excluded from review. Abstracts and poster presentations were included for review if they fulfilled the above criteria. Multiple articles resulting from the same data source were included only once. However, if 2 studies came from the same data source but spanned nonoverlapping time periods of data accrual, or studied different PIA, they were both included in the metaanalysis. Searches were updated on a regular basis from November 2014 through April 2015.

In addition to placenta previa, our analysis also included instances of low-lying/marginal placenta previa by defining them as cases with internal os to placental edge distance <1 cm. The placenta accreta group included placenta increta, placenta percreta, and cesarean scar implantations as the latter have been known to be a precursor to placenta accreta.[9] In addition to searching for vasa previa, we searched for other placental abnormalities (succenturiate lobe, bilobed placenta) to capture as many cases of vasa previa as possible. We also included velamentous cord insertions because of their association with vasa previa and suspected contribution to our primary and secondary outcomes.

### Study selection

Two authors (S.A.V. and J.A.L.) were involved in retrieving studies for eligibility. We identified a total of 1421 English-language studies fulfilling our search terms that were published since 1980. Titles and abstracts were screened to determine potential inclusion of the articles. Many of these studies were excluded on the basis of lacking clinical outcome data (ie, ultrasound studies, basic science research, or animal models) or clearly stating that they were case reports or case series. This left us with 90 remaining studies that fit our inclusion criteria. These were individually reviewed and from these, information regarding PIA and their association with preterm delivery was available in only 79 studies.[2,8,12-89] These studies were critically reviewed and data were extracted by 1 author. In case of discrepancies or when the data presented in a study were unclear, a second reviewer (C.V.A. or A.V.) was consulted.

### Data collection process

Information regarding the type of PIA, type of study (descriptive vs comparative, ie, cohort or case-control), country of origin, total number of pregnancies and pregnancies complicated by PIA, and years' duration of the study were ascertained.

### Primary and secondary outcomes

The primary outcome in this metaanalysis was preterm delivery <37 weeks' gestation, which we chose because of its consistency throughout the reviewed studies. Secondary outcomes, if available, included birthweight, 1- and 5-minute Apgar scores, neonatal intensive care unit (NICU) admission, neonatal death, perinatal death, and small for gestational age. Studies that did not provide data for a comparison group (ie, outcomes of patients without the PIA) were included as descriptive studies.

### Summary measures

Statistical analysis for the metaanalysis was implemented at the biostatistics coordinating center in the Department of Obstetrics and Gynecology at Columbia University, New York, NY, through software (Review Manager, version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark). In an initial analysis, we observed substantial heterogeneity in the risk of the primary outcome (preterm delivery) and most of the secondary outcomes. Heterogeneity was assessed based on both the Cochran $Q$ statistic[90] and the Higgins $I^2$ statistic.[91] To account for the between-study heterogeneity, we performed the metaanalysis through random effects models,[92] with the study constituting the unit of analyses. The summary measure of effect was the random effects pooled risk ratio (RR) with 95% confidence interval (CI) for binary outcomes and the random effects pooled risk difference with 95% CI for continuous outcomes. Finally, we plotted the effect measure against the logarithm of the SE of the effect measure (RR or risk difference) to assess the potential for publication bias.

## Results

### Study selection and characteristics

In all, 79 studies were reviewed that met the above-mentioned inclusion criteria and for which information on the incidence of PIA and its association with gestational age at birth or preterm delivery were available (Figure 1). In all, 56 studies[8,12-66] were descriptive and did not have a comparison group. These studies instead compared different variables within the same PIA, for example: previa with hemorrhage compared to previa without hemorrhage. A total of 23 studies[2,67-89] had comparison or control groups. The characteristics of the comparative studies are outlined in Table 1.

### Risk of bias within studies

We evaluated each included study for bias based on several characteristics. These included representativeness of the population, ascertainment of the exposure (PIA), assessment of the outcomes, blinding of the investigators to the exposure (PIA), incomplete outcome data (loss to follow-up), and control for confounders. Each of these categories were assessed on 3 levels: green (indicating that the criteria was met), red (indicating that the criteria was not met), and orange (indicating an uncertain status).

### Results of individual studies

Incidence of PIA among the studies ranged from 0.14–29.8 per 1000 live births for placenta previa, 3.0–9.0 per 1000 live births for placenta accreta,