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| Complete List of Authors: | Jauniaux , E; UCL, EGA Institute for Women Health<br>Grønbeck, Lene; University of Copenhagen, Department of Obstetrics, Rigshospitalet<br>Bunce, Catey; kings College london, Primary Care and Public Health Sciences<br>Langhoff-Roos, Jens; Rigshospitalet Infektionsmedicinsk Klinik,<br>Collins, Sally; University of Oxford, Nuffield Department of Women's and Reproductive Health |
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# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis

Eric Jauniaux,[1] Lene Grønbeck,[2] Catey Bunce,[3] Jens Langhoff-Roos,[2] Sally L Collins[4]

**Author affiliations**

1. EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.
2. Department of Obstetrics, Rigshospitalet, University of Copenhagen, Denmark.
3. Statistic unit, School of Population Health and Environmental Sciences, Kings College London, London UK.
4. Nuffield Department of Women's and Reproductive Health, University of Oxford, UK

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**Corresponding author:** *Professor Eric Jauniaux,*
*EGA* Institute for Women's Health, *University College London,*
*86-96 Chenies Mews, London WC1E 6HX, UK.*
Telephone numbers: +44/207/3908113
Fax: +44/207/3908115
E-mail: e.jauniaux@ucl.ac.uk

# ABSTRACT

**Objective** To estimate the prevalence and incidence of placenta previa complicated by placenta accreta spectrum (PAS) and to examine the different criteria being used for the diagnosis.

**Design** Systematic review and meta-analysis.

**Methods** PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched between August 1982 and September 2018 for studies reporting on placenta previa and placenta previa with PAS diagnosed in a defined obstetric population. Two independent reviewers performed the data extraction using a predefined protocol and assessed the risk of bias using the Newcastle-Ottawa scale for observational studies, with difference agreed by consensus. The primary outcomes were overall prevalence of placenta previa, incidence of PAS according to the type of placenta previa and the reported clinical outcomes including number of peri-partum hysterectomies and direct maternal mortality. The secondary outcomes included the criteria used for the prenatal ultrasound diagnosis of placenta previa and the criteria used to diagnose and grade PAS at birth.

**Results** A total of 258 articles were reviewed and 13 retrospective and 7 prospective studies were included in the analysis which reported on 587 women with placenta previa and PAS. The median prevalence of placenta previa was 0.56% (IQR 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35). The meta-analysis indicated a significant level of overall heterogeneity between study estimates for the prevalence of placenta previa (P<.001), the prevalence

of placenta previa with PAS and the incidence of PAS in the placenta previa cohort. The high heterogeneity between studies emphasizing the need to implement standardized protocols for the diagnoses of both placenta previa and PAS, including the type of placenta previa on ultrasound imaging and grading of villous invasiveness at delivery.

**Strengths and limitations of this study**

- ⇒ This is the first study providing a comprehensive evaluation of the prevalence of placenta previa complicated by PAS and the incidence of PAS in women presenting with a placenta previa.
- ⇒ Large amounts of heterogeneity for the prevalence and incidence of placenta previa accreta highlight the effect of the absence of standardisation in reporting on both placenta previa and placenta previa accreta in many cohort studies.
- ⇒ Thirteen out of 20 studies included in the analysis were retrospective with considerable variation between studies in both the prenatal diagnosis of placenta previa and the confirmation of the diagnosis of accreta placentation at births.
- ⇒ The lack of accurate data on the depth of accreta placentation in most studies limits the evaluation of differences in outcome between the adherent and invasive accreta previa placentation.

# INTRODUCTION

Placenta accreta is a pathological condition of placentation associated with a high risk of massive obstetric hemorrhage during delivery. Initially described in 1937 by Irving and Hertig[1] as the abnormal adherence of the placenta to the myometrium due to the partial or complete absence of decidua basalis, it was subsequently redefined by Lukes et al[2] as a spectrum of abnormally adherent and invasive placentation disorders. Placenta accreta is now graded according to the depth of the villous penetration into the uterine wall starting with the abnormally adherent placenta or creta, where the villi attach directly to the surface of the myometrium without invading it, and extending to the invasive grades of placenta increta, where the villi penetrate deeply into the myometrium up to the uterine serosa, and placenta percreta, where the invasive villous tissue penetrates through the uterine serosa often entering the surrounding pelvic tissues.[5] The different grades of the placenta accreta spectrum (PAS) can co-exist in the same specimens and can be focal (just a small area of the placental bed) or extensive (including much of the placental bed).[2]

Over the last two decades, a growing body of epidemiology research has identified the effect of the rapid increase in caesarean delivery rates on the risks of PAS.[6-10] The main additional risk factor after a previous caesarean delivery is placenta previa. A large multicentric U.S. cohort study noted that for women presenting with placenta previa and prior caesarean delivery, the risk of PAS was 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more cesarean deliveries, respectively.[7] A national case-control study using the UK Obstetric Surveillance System found that the incidence of PAS increases from 1.7 per 10,000 births overall to 577 per

10,000 births in women with both a previous caesarean delivery and placenta previa.[8]

Both abnormal adherence and invasion of villous tissue into the myometrium results in failure of the placenta to separate spontaneously from the uterine wall at delivery.[2-4] When unsuspected at the time of delivery, attempts to manually remove accreta villous tissue typically provoke rapid bleeding from the utero-placental circulation.[5,11] In invasive cases, this can lead to massive obstetric hemorrhage due to the disruption of the deep uterine vasculature of the increta or percreta area.[4,5] Not surprisingly, prenatal diagnosis of PAS has been shown to decrease maternal morbidity and mortality, and has thus become essential in improving its management.[12,13] Tabsh et al were the first in 1982 to report on the prenatal ultrasound diagnosis of a case of placenta increta.[14] A recent systematic review and meta-analysis of prenatal ultrasound diagnosis of placenta previa with PAS in women with a history of caesarean delivery has found that the overall diagnostic accuracy of ultrasound in specialist units is in 90.9%.[15] However, even in countries with well-established screening programs for fetal anomalies, over half the cases of PAS are not diagnosed before delivery.[8,10]

Accreta placentation and in particular its invasive forms are impacting maternal health outcomes globally and its prevalence is likely to increase. Women with a history of previous caesarean delivery presenting with placenta previa accreta in an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of delivery complications[16], however, their epidemiology has not been comprehensively reviewed yet. Health provision for the development of maternity centres with specialist teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with placenta previa accreta requires an accurate evaluation of its

epidemiology. The objective of this meta-analysis is to review the epidemiology of women presenting with placenta previa and to examine the different diagnostic criteria used by the authors of cohort studies to diagnose placenta previa prenatally and PAS and confirmed the diagnosis of PAS at birth.

## MATERIALS AND METHODS

A systematic review was performed for articles providing data on prevalence and incidence of PAS in women presenting with a placenta previa where the populations sampled was defined. Embase, PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched for studies published between the first prenatal ultrasound description of placenta accreta in August 1982 by Tabsh[14] et al and September 2018. The search protocol was designed a priori and registered on PROSPERO (CRD42017068589) (http://www.crd.york.ac.uk/PROSPERO). The overall search strategy was inclusive of MeSH headings for “placenta accreta, placenta increta, placenta percreta, abnormally invasive placenta, morbidly adherent placenta, low-lying placenta, minor placenta previa, major placenta previa” which were combined with terms including “prevalence, incidence, obstetric hysterectomy and caesarean hysterectomy”. Title, abstracts and full-text were independently assessed by the authors for content, data extraction and analysis. Additional relevant studies were identified from reference lists of reviews and editorials and by hand-searching key journals and websites. All search results were combined in a reference database. Duplicates were removed by hand. The search was limited to articles published in English.

Two independent authors (EJ and LG) selected studies in two stages. The abstracts of all potentially relevant papers were individually examined for suitability. Papers were only ruled out at this stage if they obviously did not meet the inclusion criteria. The remainder were obtained in full text and were independently assessed for content, data extraction and analysis. Disagreements between the two original reviewers were resolved by discussion with the third reviewer (JLR). Articles were excluded if; they were published before August 1982, contained no data on the study population such as the overall pregnancies, births and/or deliveries numbers, were case reports or were overlapping.

Study characteristics were extracted using a predesigned data extraction protocol including: author institution, year of publication, country of origin, study period, study type (retrospective, single institution, multiple institutions), total number of cases in the study population, type of placenta previa, diagnosis of PAS at birth. The need to perform a peripartum hysterectomy, direct maternal mortality and prior surgical history were also recorded. The reference standard for differential diagnosis between minor and major placenta previa was the evaluation of the placental position inside the uterine cavity on transvaginal ultrasound with relation to the internal cervical os. For the diagnosis of accreta placentation, we referred to the clinical grading based on surgical findings at delivery as previously described[17] and to histopathologic findings when a caesarean hysterectomy was performed i.e. placental villi directly attached to the myometrium without interposing decidua or invading the uterine wall.

Two independent reviewers (EJ and LG) undertook the quality assessment with difference agreed by consensus. The Newcastle-Ottawa scale for observational studies

was used to establish the risk of bias in selection, comparability, and outcome assessment.[18] Studies that scored four stars for selection, two stars for comparability, and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias. We deemed any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, to have a high risk of bias. No study was excluded based on the risk of bias assessment.

Analyses were conducted using STATA software (version 15; StataCorp, College Station, TX). Standard Kurtosis analysis indicated that some values were not normally distributed and are therefore presented as median and interquartile range (IQR). A random effects model was used to combine the studies while incorporating variations among studies unless there were three or less studies contributing to the meta-analysis in which case a fixed effect model was used. Statistical heterogeneity was assessed with the Cochran's Q-test and the $I^2$ statistic (the proportion of variation in study estimates because of heterogeneity rather than sampling error). Forest plots are presented to graphically summarize the study results and the pooled results. A test for heterogeneity between sub-groups (i.e. study types) was conducted.

## RESULTS

The initial search provided 256 records with cross-referencing providing an additional two studies, making a total of 258 potentially relevant articles. After exclusion of duplicates and the two which were not available (Figure 1), 220 remained. On screening

the titles and abstracts, a further 162 were excluded as the reported outcomes were not relevant, leaving 58 studies which were obtained for full text review. An additional 38 articles were excluded after full review including letters (n=16), narrative reviews (n= 10) commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another publication (n=1).

The quality of the studies is shown in Figure 2. Eighteen of the 20 included studies included in the final review had low or medium risk of bias for sample selection, nine had low risk of bias for outcome assessment, and six had low risk of bias for comparability of cohorts. Overall, 18 studies had low or medium risk of bias.

Table 1 presents the study characteristics and epidemiology data of the 20 studies. There were 13 retrospective[19,20,23,25-27,29-31,33-35,38] and 7 prospective[21,22,24,28,32,36,37] studies including a total of 1,197,296 births and 23,864 pregnancies. There were 15 studies from a single institution[19-24,27-30,32-34,37,38] and five from multiple institutions[25,31] or a geographical region.[26,35,36] These studies included 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

All authors except two[29,33] reported on the criteria used for the prenatal ultrasound diagnosis of placenta previa. Six studies[24,26,30,32,37,38] only included major placenta previa in their cohort as defined as the placenta completely covering or partially covering the internal os of the cervix. The others included both major and minor

placenta previa. The definition of minor placenta previa varied with two studies[31,36] using the placental edge being <2cm from the internal os, two studies using < 3cm[22,23] and one study using <3 cm or <5 cm if associated with abnormal fetal presentation.[21] The gestational age at confirmation of the prenatal diagnosis of placenta previa was reported in six studies [22,23,24,28,32,37] and ranged between 20 weeks and 34 weeks and in one study the diagnosis of placenta previa was confirmed at birth when the placenta was found to be inserted in the lower segment.[19]

The ultrasound diagnostic signs for PAS were reported in six studies[24,28,30,32,36,37] with two studies also reporting on the use of magnetic resonance imaging.[29,38] The clinical criteria used for the diagnosis of PAS at birth were reported by nine studies[19,20,23,27,28,30,33,36,37] and included a difficult delivery of the placenta without easy separation uterine wall or requiring a “piecemeal removal” associated with heavy bleeding and excessive bleeding from the placental bed after placental delivery. One author described the presence of invasive villous tissue at delivery[27] and one the need to suture the placental bed.[23] None of the other authors reported on the gross appearance of the uterus or surgical findings at the time of caesarean delivery. In 12 studies[19,23,24,27-31,33,34,36,37] the prenatal and/or clinical diagnosis was confirmed by histopathological examination with detailed description of the microscopic criterion only reported in six[19,27,28,30,31,37]. Detailed histopathological findings on the depth of villous invasiveness were reported in nine studies[24,27-29,31,33,34,36,37] out of the 20 studies. These included 283 cases of placenta previa accreta graded for 171 (60.4%) as placenta creta (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta percreta.

All authors but two[22,23] reported on prior surgical history including caesarean section[19-21,24-38], uterine curettage[28,30-32,34,37,38] and myomectomy.[28,36,37] Data on surgical management was available in 14 out of the 20 studies[19,20,23,27-31,33-38] with 314 out of 441 women presenting with a placenta previa complicated by PAS. The median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal mortality were available in 13 studies[19-21,23,25,27-30,32,35,37,38] and PAS accounted for 5 maternal deaths[19,20,25,29,30] out of 387 (1.3%) cases of placenta previa with PAS.

The meta-analysis indicated statistically significant (P<.001) level of overall heterogeneity between study estimates for the prevalence of placenta previa (Figure 3), the prevalence of placenta previa with PAS (Figure 4) and the incidence of PAS in the placenta previa cohort (Figure 5). There was strong evidence of inconsistency between study types with $I^2$ values greater 85%. The difference in heterogeneity between prospective versus retrospective studies was not statistically significantly (P=.839) different (Figure 3) whereas it was significant (P=.014) for the prevalence of placenta previa accreta (Figure 4). Adjusting for type of study (prospective versus retrospective) did not reduce inconsistency between studies. The in-between placenta previa major only versus minor and major placental previa was not significant (P=.067) for the incidence of PAS in patient with placenta previa (Figure 5).

## DISCUSSION

This study provides a comprehensive evaluation of the prevalence of placenta previa complicated by PAS and the incidence of PAS in women presenting with a placenta previa. Women with a prior history of caesarean delivery presenting with a low-

lying/placenta previa represent more than 90% of the cases of PAS.[8,10,16] The meta-analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the need to use international standardized clinical protocols for the screening and management of this complex obstetric condition. The current situation limits the capacity building of healthcare providers on improvements in training, implementation of guidelines and changes in clinical practice behaviour.

Defining the position of the placenta inside the uterus was one of the first aims of obstetric ultrasound examination.[39,40] Following the development of real-time ultrasound imaging, placental location became an integral part of the mid-pregnancy ultrasound examination.[41] Placenta previa was initially described with transabdominal scan as a placenta developing within the lower uterine segment and classified according to the relationship and/or the distance between the lower placental edge and the internal os of the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine segment down to the internal os and major placenta previa when the placenta covers the cervix. Minor placenta previa can be further subdivided into low-lying placenta when the lower edge does not reach the internal os and marginal placenta previa when it does. Major placenta previa can also be described as partial or complete depending on the amount of placental tissue covering the cervix. The use of transvaginal scanning has allowed for a more precise evaluation of the distance between the placental edge and the internal os[42,43] but as demonstrated in our meta-analysis, the reporting of the ultrasound criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we found also wide variation in the gestational age at diagnosis. The timing of the

confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.[44,45] An expert panel of the American Institute of Ultrasound in Medicine[46] has recently recommended ceasing the use of the terms 'partial' and 'marginal' and using the term 'placenta previa' only when the placenta lies directly over the internal os. The placenta should be reported as 'low lying' when the placental edge is less than 2 cm from the internal os and as normal when the placental edge is more than 2 cm from the internal os. The findings of our meta-analysis highlight the need for the use of such a classification in further studies.

Only six of the 20 studies included in the present meta-analysis provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included in the systematic review all studies published since the first ultrasound description of PAS by Tabsh et al in 1982.[14] We found no studies between 1982 and 1993 (Table 1) which corresponds to the time when high-resolution grey-scale ultrasound imaging became widely available. Colour-Doppler imaging was introduced for the diagnosis of PAS in 1992[47], however the sensitivity and specificity of grey-scale imaging alone in diagnosing for placenta previa accreta are high when performed by experience operators.[15] These findings indicate that the prenatal diagnosis of PAS can be performed using standard ultrasound equipment. Unlike placenta previa which is routinely screened for at the time of the fetal anomaly scan, PAS is currently not screened for and the data available on the prenatal diagnosis of the condition come exclusively from specialist centres.[16] In these centres, the diagnostic accuracy of ultrasound imaging is over 90%, but similarly, to placenta previa, the description of the

ultrasound signs used for the diagnosis of PAS, over the last two decades, has also been highly variable.[47,48] The European Working Group on Abnormally Invasive Placenta and the Abnormally Invasive Placenta international expert group have recently proposed a standardised description of ultrasound signs used for the prenatal diagnosis and a proforma protocol for the ultrasound assessment of PAS.[49,50] The use of these protocols in prospective studies should also facilitate the screening of patients at high risk of PAS and in particular those with multiple prior caesarean deliveries presenting with a low-lying or placenta previa.[51]

We found significant heterogeneity in the qualitative definition and diagnosis of PAS at birth among the nine studies that provided a description of the clinical findings.[19,20,23,27,28,30,33,36,37] Only one of these studies described the invasive appearance of placental tissue at delivery[27] whereas the others reported a difficult delivery of the placenta without easy separation from the uterine wall or requiring a "piecemeal removal" associated with heavy bleeding as diagnostic of PAS. These clinical criteria were first described by Irving and Hertig[4] in 1937 who did not have invasive cases in their cohort and thus their definition only applies to abnormally adherent placenta and not to placenta increta or percreta. This definition also fails to clearly differentiate between abnormal adherence and placental retention as both present with similar clinical symptoms and etiology[52] leading to possible over diagnosis of placenta previa accreta. Similarly, the finding of excessive bleeding from the placental bed after delivery of the placenta is a common complication of non-accreta placenta previa due to the implantation of the placenta in the lower uterine segment which contains less muscular fibers than the upper segment and is often thinner and

dehiscent after multiple caesarean deliveries.

Detailed histopathologic reports can only be obtained in those patients who have a hysterectomy or a partial myometrial resection and thus in many studies there is not histopathologic confirmation of the clinical diagnosis. The main histological diagnostic criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi and the superficial myometrium, is found with increasing incidence with advancing gestation in pregnancies with no clinical evidence of PAS.[5] Thus the combination of clinical criteria that do not differentiate between placenta retention and adherent accreta and the use of non-diagnostic criteria of villous invasiveness may result in the over-diagnosis of the adherent grade of PAS, in particular in those studies reporting a low rate of caesarean hysterectomy.[28,36] Overall, this can explain the wide range in the prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to 71.6%) of PAS in women presenting with placenta previa (Figures 3 and 4).

Overall, management strategies and outcomes will vary depending on the accuracy of prenatal diagnosis, local surgical expertise and more recently access to a centre of excellence with multidisciplinary team approach.[53,54] In cases of high suspicion of PAS during cesarean delivery, 60-70% of obstetricians gynecologists proceed with a peripartum hysterectomy.[55,56] By contrast with a conservative management approach, radical surgery is often considered to be safer, in particular in cases of invasive placentation.[57] The association between a placenta previa and a PAS increases the risks of both maternal morbidity and mortality. In the present study we found that a caesarean hysterectomy was the primary management option in around 70% of the patients presenting with a placenta previa and PAS. The inter-study range was wide

with four studies[19,21,29,37] reporting peripartum hysterectomy rates < 50%, five[28,31,32,34,36] had rates between 50-99% and four[22,30,35,38] had rates of 100%. This may be due to difference in study protocols, local expertise and the impact of prenatal diagnosis on management strategies but also as suggested by our analysis to difference in the rates of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed histopathologic examination confirming the diagnosis.

The main limitations of this review are the quality of the published data. Thirteen out of 20 studies included in the analysis studies were retrospective and there was wide variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed histopathology data to confirm the clinical diagnosis. This is hampering the analysis of the secondary outcome in particular the incidence of major hemorrhage at delivery and the need and amount of blood transfusion but also the choice in management protocols and in particular the use of conservative management procedures. We would not, therefore, recommend the use of the pooled estimates beyond as a driver towards the development of standardized diagnostic protocols.

The prevalence of PAS in the general population of women giving birth varies widely.[8,10,58,59] This may be due to several factors including national and local caesarean delivery rates, expertise in diagnosing the condition antenatally and access to perinatal pathologist to confirm the diagnosis at birth. There is a need for further prospective multi-centre studies with participatory methodologies involving local service providers and facility management to accurately evaluate the consequences of high caesarean sections rates on maternal health within a particular population. Within this context, accurate

epidemiologic data on PAS disorders are essential in planning screening programs and in making provision for the development of centres of excellence for the management of this increasingly common complex obstetric condition. Whilst the concept of core outcome measures within clinical trials is now well recognised and championed, greater efforts to disseminate this approach in epidemiological research to facilitate global estimation and recognition of problems emerging on a global scale. Our study supports implementation, in both clinical practice and in reporting data on placenta previa accreta in the medical literature, of standardized protocols for prenatal diagnosis of both placenta previa and PAS, for the clinical diagnosis of PAS at birth and for the histopathologic confirmation examination.

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**Table 1:** Characteristics of the 20 studies included in the review with the corresponding prevalence of placenta previa accreta and incidence placenta accreta spectrum per cohorts of placenta previa.

| | Population | Dates | Study type | Prevalence (%) | Incidence (%) |
|---|---|---|---|---|---|
| Chattopadhyay et al., 1993[19] | Saudi Arabia/ 41,206 births | 1988-1992 | Retrospective/ Institution | 26 (0.063) | 26/222 (11.7) |
| Zaki et al., 1998[20] | Saudi Arabia/ 23,070 births | 1990-1996 | Retrospective/ Institution | 12 (0.052) | 12/110 (10.9) |
| Ziadeh et al., 1999[21] | Jordan/18,651 births | 1995-1996 | Prospective/ Institution | 13 (0.070) | 13/65 (20.0) |
| Gourab et al., 2001[22] | Saudi Arabia/ 18,670 births | 1995-2000 | Prospective/ Institution | 11 (0.059) | 11/138 (8.0) |
| Bahar et al., 2009[23] | Saudi Arabia/ 42,487 births | 1996-2005 | Retrospective/ Institution | 53 (0.125) | 53/306 (17.3) |
| Hamada et al., 2011[24] | Japan/2,413 births | 2007-2009 | Prospective/ Institution¶ | 5 (0.207) | 5/70 (7.1) |
| Jang et al., 2011[25] | South Korea/ 35,030 births | 1999-2009 | Retrospective/ Institutions x 3 | 53 (0.151) | 53/560 (9.5) |
| Rosenberg et al., 2011[26] | Israel/185,476 births | 1988-2009 | Retrospective/ Region¶ | 23 (0.012) | 23/779 (3.0) |
| Kassem et al., 2013[27] | Saudi Arabia/ 29,053 births | 2009-2012 | Retrospective/ Institution | 25 (0.085) | 25/122 (20.5) |
| Maher et al., 2013[28] | Egypt/24,661 births | 2008-2011 | Prospective/ Institution | 42 (0.170) | 42/577 (7.3) |
| Alchalabi et al., 2014[29] | Jordan/16,845 births | 2003-2012 | Retrospective/ Institution* | 23 (0.137) | 23/81 (28.4) |
| Asicioglu et al., 2014[30] | Turkey/112,819 births | 2005-2010 | Retrospective/ Institution¶ | 46 (0.041) | 46/364 (12.6) |
| Sumigama et al., 2014[31] | Japan/96,670 births | 1994-2012 | Retrospective/ Institutions x 11¶ | 46 (0.048) | 46/954 (4.8) |
| Ahmed et al., 2015[32] | Egypt/3,841 births | 2014 | Prospective/ Institution¶ | 14 (0.365) | 14/52 26.9 |
| Cheng et al., 2015[33] | China/81,497 births | 1999-2013 | Retrospective/ Institution* | 39 (0.048) | 39/921 (4.2) |
| Cho et al., 2015[34] | South Korea/ 11,210 pregnancies | 1991-2013 | Retrospective/ Institution | 39 (0.348) | 39/442 (8.8) |
| Kollmann et al., 2016[35] | Austria/218,876 births | 1993-2012 | Retrospective/ Region | 13 (0.006) | 13/328 (4.0) |
| Pilloni et al., 2016[36] | Italy/108,000 births | 2011-2014 | Prospective/ Region | 37 (0.034) | 37/314 (11.8) |
| Rezk et al., 2016[37] | Egypt/12,654 pregnancies | 2012-2014 | Prospective/ Institution¶ | 53 (0.419) | 53/74 (71.6) |
| Wortman et al., 2018[38] | US/138,031 births | 2002-2011 | Retrospective/ Institution¶ | 14 (0.010) | 14/157 (8.9) |

¶= Studies including major placenta previa only; * No description of the ultrasound diagnostic signs.

# Figure legends

**Fig 1:** Flow diagram showing the selection of reports included in the review.

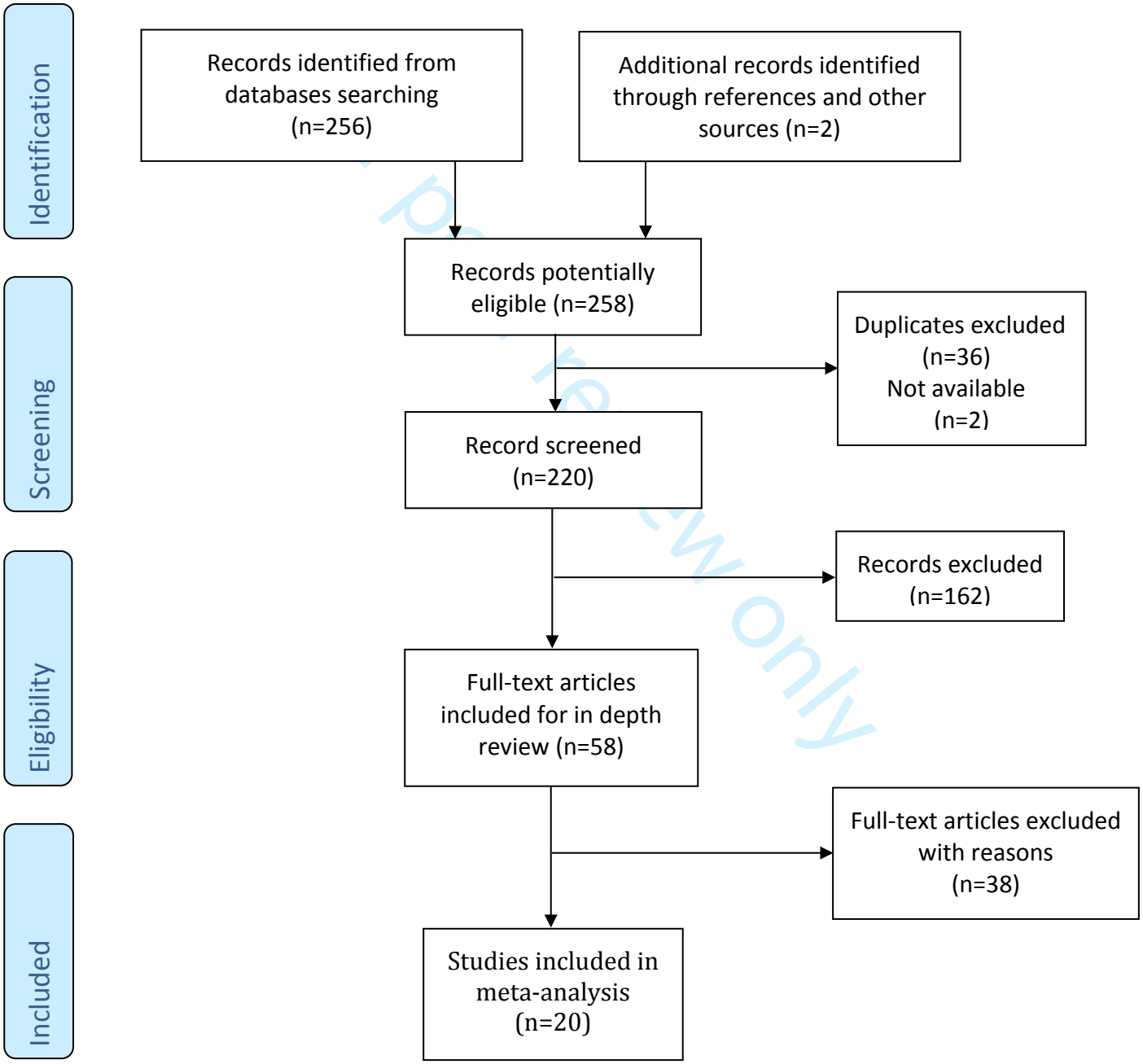


**Fig 2:** Quality assessment using the Newcastle-Ottawa Scale for cohort studies.

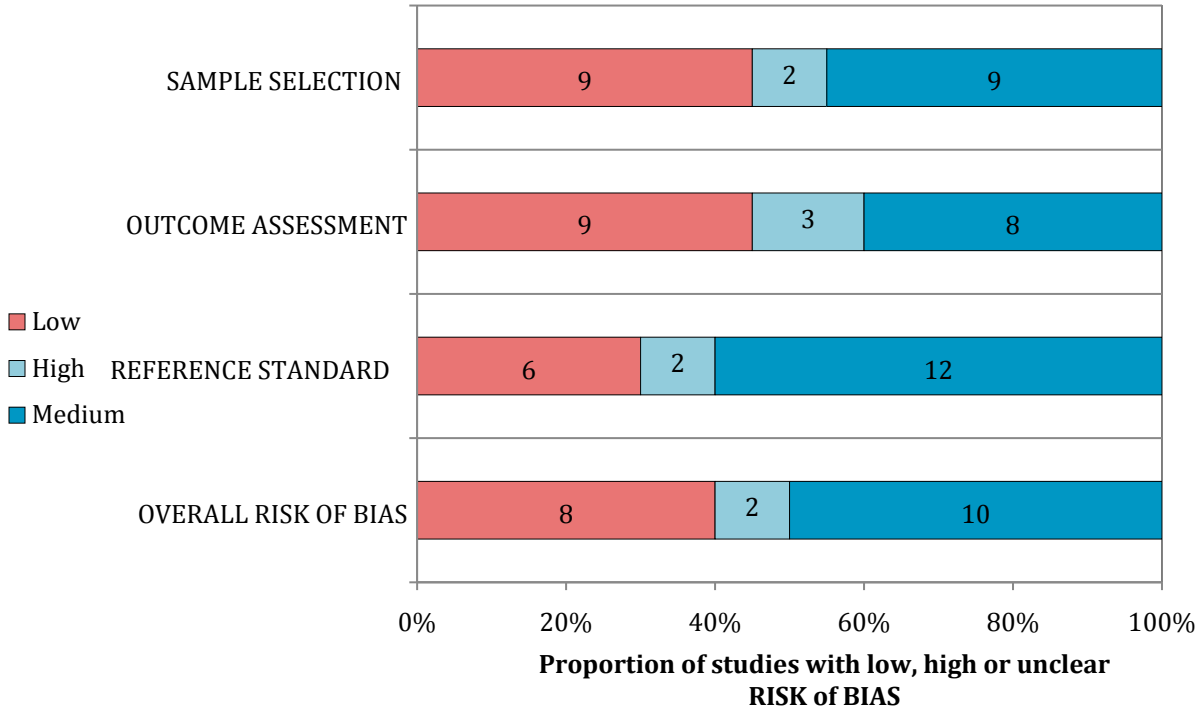
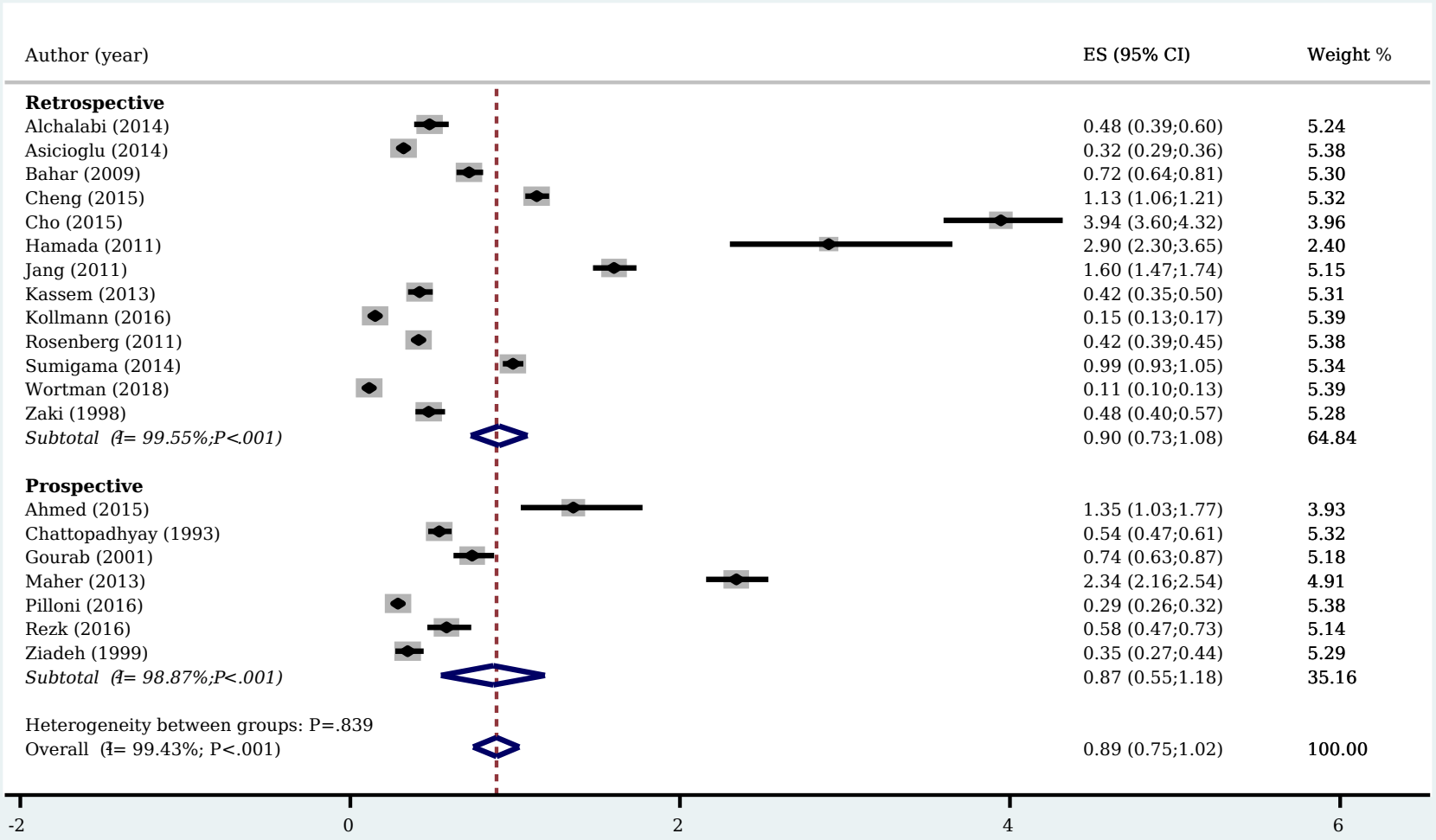


**Fig 3:** Forest plots showing the heterogeneity of prevalence data in prospective and retrospective cohort studies of women presenting with a placenta previa. Only first author's name is given for each reference.

**Fig 4:** Forest plots showing heterogeneity in the prevalence data for prospective and retrospective cohort studies of women diagnosed with placenta previa and PAS. Only first author's name is given for each reference.

**Fig 5:** Forest plots showing the heterogeneity in cohort studies reporting incidence data for women diagnosed with placenta previa major and PAS and those with either placenta previa minor or major and PAS.


Author (year)
ES (95% CI)
Weight %
Retrospective
Alchalabi (2014) 0.48 (0.39;0.60) 5.24
Asicioglu (2014) 0.32 (0.29;0.36) 5.38
Bahar (2009) 0.72 (0.64;0.81) 5.30
Cheng (2015) 1.13 (1.06;1.21) 5.32
Cho (2015) 3.94 (3.60;4.32) 3.96
Hamada (2011) 2.90 (2.30;3.65) 2.40
Jang (2011) 1.60 (1.47;1.74) 5.15
Kassem (2013) 0.42 (0.35;0.50) 5.31
Kollmann (2016) 0.15 (0.13;0.17) 5.39
Rosenberg (2011) 0.42 (0.39;0.45) 5.38
Sumigama (2014) 0.99 (0.93;1.05) 5.34
Wortman (2018) 0.11 (0.10;0.13) 5.39
Zaki (1998) 0.48 (0.40;0.57) 5.28
Subtotal (I² = 99.55%;P<.001) 0.90 (0.73;1.08) 64.84
Prospective
Ahmed (2015) 1.35 (1.03;1.77) 3.93
Chattopadhyay (1993) 0.54 (0.47;0.61) 5.32
Gourab (2001) 0.74 (0.63;0.87) 5.18
Maher (2013) 2.34 (2.16;2.54) 4.91
Pilloni (2016) 0.29 (0.26;0.32) 5.38
Rezk (2016) 0.58 (0.47;0.73) 5.14
Ziadeh (1999) 0.35 (0.27;0.44) 5.29
Subtotal (I² = 98.87%;P<.001) 0.87 (0.55;1.18) 35.16
Heterogeneity between groups: P=.839
Overall (I² = 99.43%; P<.001) 0.89 (0.75;1.02) 100.00
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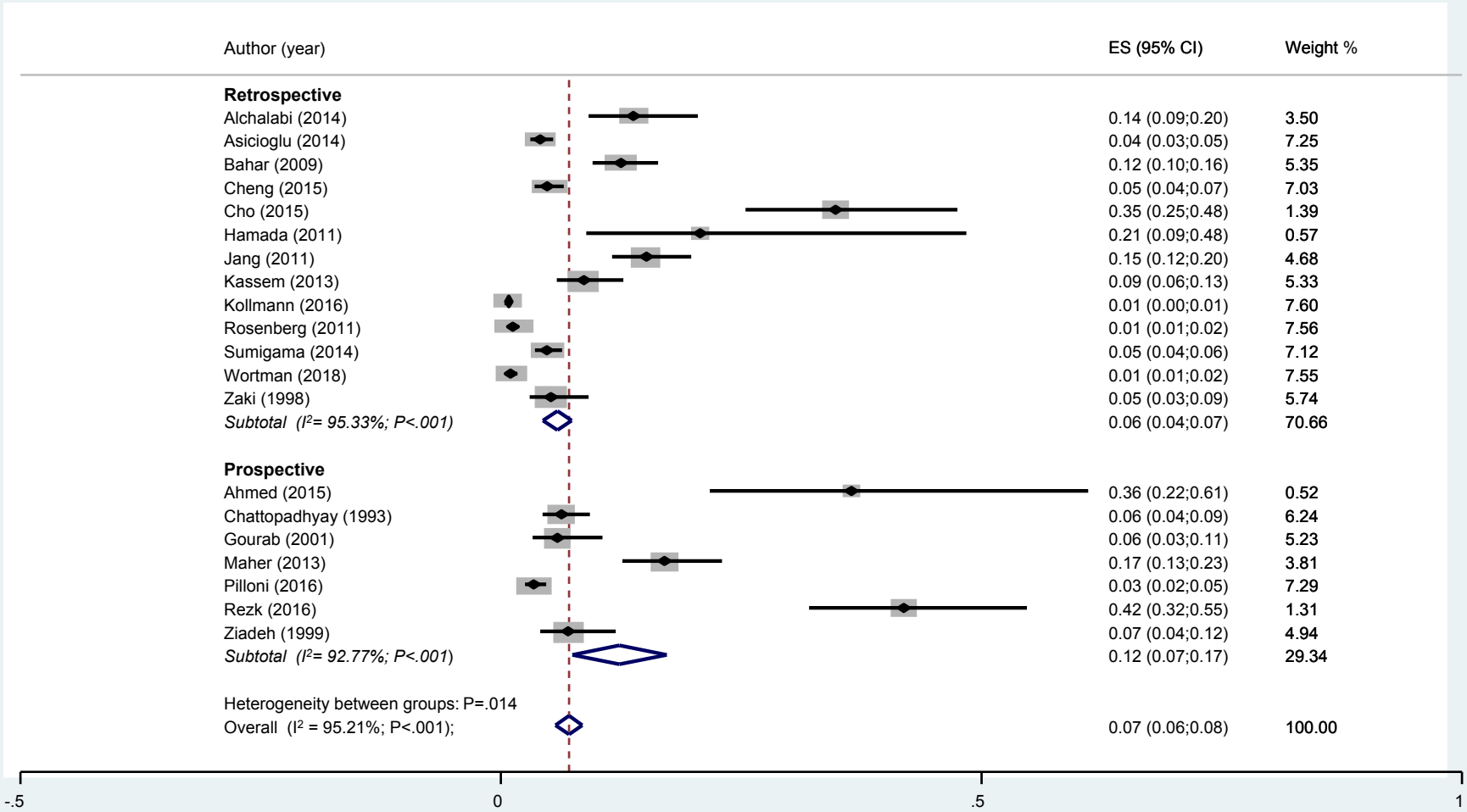
Author (year)
ES (95% CI)
Weight %
Retrospective
Alchalabi (2014) 0.14 (0.09;0.20) 3.50
Asicioglu (2014) 0.04 (0.03;0.05) 7.25
Bahar (2009) 0.12 (0.10;0.16) 5.35
Cheng (2015) 0.05 (0.04;0.07) 7.03
Cho (2015) 0.35 (0.25;0.48) 1.39
Hamada (2011) 0.21 (0.09;0.48) 0.57
Jang (2011) 0.15 (0.12;0.20) 4.68
Kassem (2013) 0.09 (0.06;0.13) 5.33
Kollmann (2016) 0.01 (0.00;0.01) 7.60
Rosenberg (2011) 0.01 (0.01;0.02) 7.56
Sumigama (2014) 0.05 (0.04;0.06) 7.12
Wortman (2018) 0.01 (0.01;0.02) 7.55
Zaki (1998) 0.05 (0.03;0.09) 5.74
Subtotal (I²= 95.33%; P<.001) 0.06 (0.04;0.07) 70.66
Prospective
Ahmed (2015) 0.36 (0.22;0.61) 0.52
Chattopadhyay (1993) 0.06 (0.04;0.09) 6.24
Gourab (2001) 0.06 (0.03;0.11) 5.23
Maher (2013) 0.17 (0.13;0.23) 3.81
Pilloni (2016) 0.03 (0.02;0.05) 7.29
Rezk (2016) 0.42 (0.32;0.55) 1.31
Ziadeh (1999) 0.07 (0.04;0.12) 4.94
Subtotal (I²= 92.77%; P<.001) 0.12 (0.07;0.17) 29.34
Heterogeneity between groups: P=.014
Overall (I² = 95.21%; P<.001); 0.07 (0.06;0.08) 100.00
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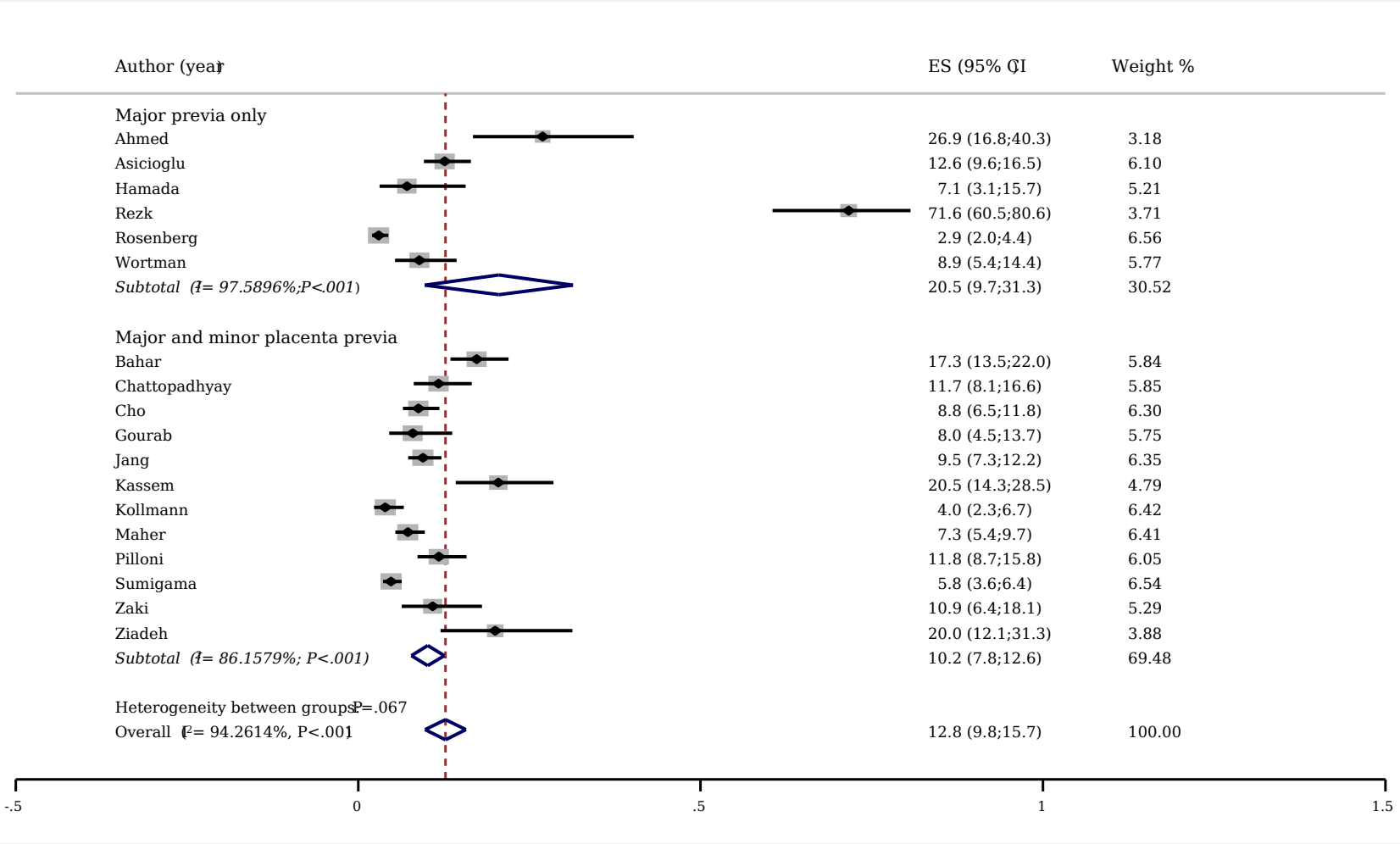
Author (year)
ES (95% CI)
Weight %
Major previa only
Ahmed 26.9 (16.8;40.3) 3.18
Asicioglu 12.6 (9.6;16.5) 6.10
Hamada 7.1 (3.1;15.7) 5.21
Rezk 71.6 (60.5;80.6) 3.71
Rosenberg 2.9 (2.0;4.4) 6.56
Wortman 8.9 (5.4;14.4) 5.77
Subtotal (I² = 97.5896%;P<.001) 20.5 (9.7;31.3) 30.52
Major and minor placenta previa
Bahar 17.3 (13.5;22.0) 5.84
Chattopadhyay 11.7 (8.1;16.6) 5.85
Cho 8.8 (6.5;11.8) 6.30
Gourab 8.0 (4.5;13.7) 5.75
Jang 9.5 (7.3;12.2) 6.35
Kassem 20.5 (14.3;28.5) 4.79
Kollmann 4.0 (2.3;6.7) 6.42
Maher 7.3 (5.4;9.7) 6.41
Pilloni 11.8 (8.7;15.8) 6.05
Sumigama 5.8 (3.6;6.4) 6.54
Zaki 10.9 (6.4;18.1) 5.29
Ziadeh 20.0 (12.1;31.3) 3.88
Subtotal (I² = 86.1579%; P<.001) 10.2 (7.8;12.6) 69.48
Heterogeneity between groups P=.067
Overall (I² = 94.2614%, P<.001) 12.8 (9.8;15.7) 100.00
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.5
1
1.5

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 & 3 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 5 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6 & 7 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 & 7 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 & 8 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | N/A |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7 & 8 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 8 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 7 & 8 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8 & 9 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 9 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9-11 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 11 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 9 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 11-14 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 15 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 15 &16 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 1 |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis



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| Keywords: | Placenta previa accreta, Prevalence, Incidence, Low-lying placenta, Placenta previa |
| | |

# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis

Eric Jauniaux,[1] Lene Grønbeck,[2] Catey Bunce,[3] Jens Langhoff-Roos,[2] Sally L Collins[4]

**Author affiliations**

1. EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.
2. Department of Obstetrics, Rigshospitalet, University of Copenhagen, Denmark.
3. Statistic unit, School of Population Health and Environmental Sciences, Kings College London, London UK.
4. Nuffield Department of Women's and Reproductive Health, University of Oxford, UK

**Competing interest**
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**Corresponding author:** *Professor Eric Jauniaux,*
*EGA* Institute for Women's Health, *University College London,*
*86-96 Chenies Mews, London WC1E 6HX, UK.*
Telephone numbers: +44/207/3908113
Fax: +44/207/3908115
E-mail: e.jauniaux@ucl.ac.uk

# ABSTRACT

**Objective** To estimate the prevalence and incidence of placenta previa complicated by placenta accreta spectrum (PAS) and to examine the different criteria being used for the diagnosis.

**Design** Systematic review and meta-analysis.

**Data Sources** PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched between August 1982 and September 2018.

**Eligibility Criteria** Studies reporting on placenta previa complicated by PAS diagnosed in a defined obstetric population.

**Data extraction and synthesis** Two independent reviewers performed the data extraction using a predefined protocol and assessed the risk of bias using the Newcastle-Ottawa scale for observational studies, with difference agreed by consensus. The primary outcomes were overall prevalence of placenta previa, incidence of PAS according to the type of placenta previa and the reported clinical outcomes including number of peri-partum hysterectomies and direct maternal mortality. The secondary outcomes included the criteria used for the prenatal ultrasound diagnosis of placenta previa and the criteria used to diagnose and grade PAS at birth.

**Results** A total of 258 articles were reviewed and 13 retrospective and 7 prospective studies were included in the analysis which reported on 587 women with placenta previa and PAS. The meta-analysis indicated a significant (P<.001) heterogeneity between study estimates for the prevalence of placenta previa, the prevalence of placenta previa with PAS and the incidence of PAS in the placenta previa cohort. The median prevalence of placenta previa was 0.56% (IQR 0.39;1.24) whereas the median

prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

**Conclusions** The high heterogeneity in qualitative and diagnostic data between studies emphasizes the need to implement standardized protocols for the diagnoses of both placenta previa and PAS, including the type of placenta previa and grade of villous invasiveness.

PROSPERO Registration CRD42017068589

**Strengths and limitations of this study**

- This study provides the first comprehensive evaluation of the epidemiology of placenta previa complicated by PAS.
- The search was performed using predetermined eligibility criteria in a defined obstetric population.
- Thirteen out of 20 studies included in the study were retrospective limiting the overall quality of the analysis.
- Only six studies provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa and nine studies on detailed histopathological findings.
- High level of inconsistency between estimates in prevalence and incidence did not allow for full meta-analysis of the clinical outcomes.

# INTRODUCTION

Placenta accreta is a pathological condition of placentation associated with a high risk of massive obstetric hemorrhage during delivery. Initially described in 1937 by Irving and Hertig[1] as the abnormal adherence of the placenta to the myometrium due to the partial or complete absence of decidua basalis, it was subsequently redefined by Lukes et al[2] as a spectrum of abnormally adherent and invasive placentation disorders. Placenta accreta is now graded according to the depth of the villous penetration into the uterine wall starting with the abnormally adherent placenta or creta, where the villi attach directly to the surface of the myometrium without invading it, and extending to the invasive grades of placenta increta, where the villi penetrate deeply into the myometrium up to the uterine serosa, and placenta percreta, where the invasive villous tissue penetrates through the uterine serosa often entering the surrounding pelvic tissues.[3-5] The different grades of the placenta accreta spectrum (PAS) can co-exist in the same specimens and can be focal (just a small area of the placental bed) or extensive (including much of the placental bed).[2]

Over the last two decades, a growing body of epidemiology research has identified the effect of the rapid increase in caesarean delivery rates on the risks of PAS.[6-10] The main additional risk factor after a previous caesarean delivery is placenta previa. A large multicentric U.S. cohort study noted that for women presenting with placenta previa and prior caesarean delivery, the risk of PAS was 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more cesarean deliveries, respectively.[7] A national case-control study using the UK Obstetric Surveillance System found that the incidence of PAS increases from 1.7 per 10,000 births overall to 577 per

10,000 births in women with both a previous caesarean delivery and placenta previa.[8]

Both abnormal adherence and invasion of villous tissue into the myometrium results in failure of the placenta to separate spontaneously from the uterine wall at delivery.[2-4] When unsuspected at the time of delivery, attempts to manually remove accreta villous tissue typically provoke rapid bleeding from the utero-placental circulation.[5,11] In invasive cases, this can lead to massive obstetric hemorrhage due to the disruption of the deep uterine vasculature of the increta or percreta area.[4,5] Not surprisingly, prenatal diagnosis of PAS has been shown to decrease maternal morbidity and mortality, and has thus become essential in improving its management.[12,13] Tabsh et al were the first in 1982 to report on the prenatal ultrasound diagnosis of a case of placenta increta.[14] A recent systematic review and meta-analysis of prenatal ultrasound diagnosis of placenta previa with PAS in women with a history of caesarean delivery has found that the overall diagnostic accuracy of ultrasound in specialist units is in 90.9%.[15] However, even in countries with well-established screening programs for fetal anomalies, over half the cases of PAS are not diagnosed before delivery.[8,10]

Accreta placentation and in particular its invasive forms are impacting maternal health outcomes globally and its prevalence is likely to increase. Women with a history of previous caesarean delivery presenting with placenta previa complicated by PAS in an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of delivery complications[16], however, their epidemiology has not been comprehensively reviewed yet. Health provision for the development of maternity centres with specialist teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with placenta previa and PAS requires an accurate evaluation of its

epidemiology. The objective of this meta-analysis is to review the epidemiology of women presenting with placenta previa and to examine the different criteria used by the authors of cohort studies to diagnose placenta previa and PAS prenatally and to confirm the diagnosis of PAS at birth.

## MATERIALS AND METHODS

A systematic review was undertaken of articles providing data on prevalence and incidence of PAS in women presenting with a placenta previa where the populations sampled were defined. PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched for studies published between the first prenatal ultrasound description of placenta accreta in August 1982 by Tabsh[14] et al and September 2018. The search protocol was designed *a priori* and registered on PROSPERO (CRD42017068589). The overall search strategy was inclusive of MeSH headings for “placenta accreta, placenta increta, placenta percreta, abnormally invasive placenta, morbidly adherent placenta and major placenta previa” which were combined with terms including “prevalence, incidence, obstetric hysterectomy and caesarean hysterectomy”. Title, abstracts and full-text were independently assessed by the authors for content, data extraction and analysis. Additional relevant studies were identified from reference lists of reviews and editorials and by hand-searching key journals and websites. All search results were combined in a reference database. Duplicates were removed by hand. The search was limited to articles published in English.

Two independent investigators (EJ and LG) selected studies in two stages. The abstracts of all potentially relevant papers were individually examined for suitability.

Papers were only ruled out at this stage if they obviously did not meet the inclusion criteria. The remainder were obtained in full text and were independently assessed for content, data extraction and analysis. Disagreements between the two original reviewers were resolved by discussion with the third investigator (JLR). Articles were excluded if; they were published before August 1982, contained no data on the study population such as the overall pregnancies, births and/or deliveries numbers, were case reports or were overlapping.

Study characteristics were extracted using a predesigned data extraction protocol including: author institution, year of publication, country of origin, study period, study type (retrospective, single institution, multiple institutions), total number of cases in the study population, type of placenta previa, diagnosis of PAS at birth (Appendix 1). Outcome measures included the need to perform a peripartum hysterectomy and direct maternal mortality. Prior surgical history was also recorded. The reference standard for differential diagnosis between minor and major placenta previa was recorded based on the placental position inside the uterine cavity on transvaginal ultrasound with relation to the internal cervical os. For the diagnosis of accreta placentation, we referred to the clinical grading based on surgical findings at delivery as previously described[17] and to histopathologic findings when a caesarean hysterectomy was performed i.e. placental villi directly attached to the myometrium without interposing decidua or invading the uterine wall.

Two independent reviewers (EJ and LG) undertook the quality assessment with difference agreed by consensus. The Newcastle-Ottawa scale for observational studies was used to establish the risk of bias in selection, comparability, and outcome

assessment.[18] Studies that scored four stars for selection, two stars for comparability, and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias. We deemed any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, to have a high risk of bias. No study was excluded based on the risk of bias assessment.

Analyses were conducted using STATA software (version 15; StataCorp, College Station, TX). Standard Kurtosis analysis indicated that some values were not normally distributed and study specific estimates are therefore presented as median and interquartile range (IQR). A random effects model was used to combine the studies while incorporating variations among studies unless there were three or less studies contributing to the meta-analysis in which case a fixed effect model was used. Statistical heterogeneity was assessed with the Cochran's Q-test and the $I^2$ statistic (the proportion of variation in study estimates because of heterogeneity rather than sampling error). Forest plots are presented to graphically summarize the study results and the pooled results. A test for heterogeneity between sub-groups (i.e. study types) was conducted.

## Patients and public involvement

Patients and the public were not involved in the design or planning of the study.

## RESULTS

The initial search provided 256 records with cross-referencing providing an additional two studies, making a total of 258 potentially relevant articles. After exclusion of

duplicates and the two which were not available (Figure 1), 220 remained. On screening the titles and abstracts, a further 162 were excluded as the reported outcomes were not relevant, leaving 58 studies which were obtained for full text review. An additional 38 articles were excluded after full review including letters (n=16), narrative reviews (n= 10) commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another publication (n=1), leaving 20 articles for the final analysis.[19-38]

The characteristics and the results of the quality assessment are displayed in table 1. There were 13 retrospective[19,20,23,25-27,29-31,33-35,38] and 7 prospective[21,22,24,28,32,36,37] studies including a total of 1,207,296 births and 23,864 cases referred as pregnancies. There were 15 studies from a single institution[19-24,27-30,32-34,37,38] and five from multiple institutions[25,31] or a geographical region.[26,35,36] Overall, 18 studies had low or medium risk of bias.

Table 2 presents the epidemiology data of the 20 studies. These studies included 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

All authors except two[29,33] reported on the criteria used for the prenatal ultrasound diagnosis of placenta previa. Six studies[24,26,30,32,37,38] only included major placenta previa in their cohort as defined as the placenta completely covering or partially covering the internal os of the cervix. The others included both major and minor placenta previa. The definition of minor placenta previa varied with two studies[31,36] using

the placental edge being <2cm from the internal os, two studies using < 3cm[22,23] and one study using <3 cm or <5 cm if associated with abnormal fetal presentation.[21] The gestational age at confirmation of the prenatal diagnosis of placenta previa was reported in six studies [22,23,24,28,32,37] and ranged between 20 weeks and 34 weeks and in one study the diagnosis of placenta previa was confirmed at birth when the placenta was found to be inserted in the lower segment.[19]

The ultrasound diagnostic signs for PAS were reported in six studies[24,28,30,32,36,37] with two studies also reporting on the use of magnetic resonance imaging.[29,38] The clinical criteria used for the diagnosis of PAS at birth were reported by nine studies[19,20,23,27,28,30,33,36,37] and included a difficult delivery of the placenta without easy separation uterine wall or requiring a "piecemeal removal" associated with heavy bleeding and excessive bleeding from the placental bed after placental delivery. One author described the presence of invasive villous tissue at delivery[27] and one the need to suture the placental bed.[23] None of the other authors reported on the gross appearance of the uterus or surgical findings at the time of caesarean delivery. In 12 studies[19,23,24,27-31,33,34,36,37] the prenatal and/or clinical diagnosis was confirmed by histopathological examination with detailed description of the microscopic criterion only reported in six[19,27,28,30,31,37]. Detailed histopathological findings on the depth of villous invasiveness were reported in nine studies[24,27-29,31,33,34,36,37] out of the 20 studies. These included 283 cases of placenta previa accreta graded for 171 (60.4%) as placenta creta (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta percreta.

The meta-analysis indicated statistically significant (P<.001) level of overall heterogeneity between study estimates for the prevalence of placenta previa (Figure 2),

the prevalence of placenta previa with PAS (Figure 3) and the incidence of PAS in the placenta previa cohort (Figure 4). There was strong evidence of inconsistency between study types with $I^2$ values greater 85%. The difference in heterogeneity between prospective versus retrospective studies was not statistically significantly (P=.839) different (Figure 2) whereas it was significant (P=.014) for the prevalence of placenta previa accreta (Figure 3). Adjusting for type of study (prospective versus retrospective) did not reduce inconsistency between studies. The in-between placenta previa major only versus minor and major placental previa was not significant (P=.067) for the incidence of PAS in patient with placenta previa (Figure 4).

All authors but two[22,23] reported on prior surgical history including caesarean section[19-21,24-38], uterine curettage[28,30-32,34,37,38] and myomectomy.[28,36,37] Data on surgical management was available in 14 out of the 20 studies[19,20,23,27-31,33-38] with 314 out of 441 women presenting with a placenta previa complicated by PAS. The median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal mortality were available in 13 studies[19-21,23,25,27-30,32,35,37,38] and PAS accounted for 5 maternal deaths[19,20,25,29,30] out of 387 (1.3%) cases of placenta previa with PAS.

## DISCUSSION

This study provides a comprehensive evaluation of the prevalence of placenta previa complicated by PAS and the incidence of PAS in women presenting with a placenta previa. Women with a prior history of caesarean delivery presenting with a low-lying/placenta previa represent more than 90% of the cases of PAS.[8,10,16] The meta-analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa

and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the need to use international standardized clinical protocols for the screening and management of this complex obstetric condition. The current situation limits the capacity building of healthcare providers on improvements in training, implementation of guidelines and changes in clinical practice behaviour.

Defining the position of the placenta inside the uterus was one of the first aims of obstetric ultrasound examination.[39,40] Following the development of real-time ultrasound imaging, placental location became an integral part of the mid-pregnancy ultrasound examination.[41] Placenta previa was initially described with transabdominal scan as a placenta developing within the lower uterine segment and classified according to the relationship and/or the distance between the lower placental edge and the internal os of the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine segment down to the internal os and major placenta previa when the placenta covers the cervix. Minor placenta previa can be further subdivided into low-lying placenta when the lower edge does not reach the internal os and marginal placenta previa when it does. Major placenta previa can also be described as partial or complete depending on the amount of placental tissue covering the cervix. The use of transvaginal scanning has allowed for a more precise evaluation of the distance between the placental edge and the internal os[42,43] but as demonstrated in our meta-analysis, the reporting of the ultrasound criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we found also wide variation in the gestational age at diagnosis. The timing of the confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.[44,45] An

expert panel of the American Institute of Ultrasound in Medicine[46] has recently recommended ceasing the use of the terms 'partial' and 'marginal' and using the term 'placenta previa' only when the placenta lies directly over the internal os. The placenta should be reported as 'low lying' when the placental edge is less than 2 cm from the internal os and as normal when the placental edge is more than 2 cm from the internal os. The findings of our meta-analysis highlight the need for the use of such a classification in further studies.

Only six of the 20 studies included in the present meta-analysis provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included in the systematic review all studies published since the first ultrasound description of PAS by Tabsh et al in 1982.[14] We found no studies between 1982 and 1993 (Table 1) which corresponds to the time when high-resolution grey-scale ultrasound imaging became widely available. Colour-Doppler imaging was introduced for the diagnosis of PAS in 1992[47], however the sensitivity and specificity of grey-scale imaging alone in diagnosing for placenta previa accreta are high when performed by experience operators.[15] These findings indicate that the prenatal diagnosis of PAS can be performed using standard ultrasound equipment. Unlike placenta previa which is routinely screened for at the time of the fetal anomaly scan, PAS is currently not screened for and the data available on the prenatal diagnosis of the condition come exclusively from specialist centres.[16] In these centres, the diagnostic accuracy of ultrasound imaging is over 90%, but similar to placenta previa, the description of the ultrasound signs used for the diagnosis of PAS has also been highly variable over the last two decades.[47,48] The European Working Group on Abnormally Invasive Placenta

and the Abnormally Invasive Placenta international expert group have recently proposed standardised descriptions of the ultrasound signs used for the prenatal diagnosis and a protocol for the ultrasound assessment of PAS.[49,50] The use of these protocols in prospective studies should also facilitate the screening of patients at high risk of PAS and in particular those with multiple prior caesarean deliveries presenting with a low-lying or placenta previa.[51]

We found significant heterogeneity in the qualitative definition and diagnosis of PAS at birth among the nine studies that provided a description of the clinical findings.[19,20,23,27,28,30,33,36,37] Only one of these studies described the invasive appearance of placental tissue at delivery[27] whereas the others reported a difficult delivery of the placenta without easy separation from the uterine wall or requiring a "piecemeal removal" associated with heavy bleeding as diagnostic of PAS. These clinical criteria were first described by Irving and Hertig[1] in 1937 who did not have invasive cases in their cohort and thus their definition only applies to abnormally adherent placenta and not to placenta increta or percreta. This definition also fails to clearly differentiate between abnormal adherence and placental retention as both present with similar clinical symptoms and etiology[52] leading to possible over diagnosis of placenta previa accreta. Similarly, the finding of excessive bleeding from the placental bed after delivery of the placenta is a common complication of non-accreta placenta previa due to the implantation of the placenta in the lower uterine segment which contains less muscular fibers than the upper segment and is often thinner and dehiscent after multiple caesarean deliveries.

Detailed histopathologic reports can only be obtained in those patients who have

a hysterectomy or a partial myometrial resection and thus in many studies there is not histopathologic confirmation of the clinical diagnosis. The main histological diagnostic criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi and the superficial myometrium, is found with increasing incidence with advancing gestation in pregnancies with no clinical evidence of PAS.[5] Thus the combination of clinical criteria that do not differentiate between placenta retention and adherent accreta and the use of non-diagnostic criteria of villous invasiveness may result in the over-diagnosis of the adherent grade of PAS, in particular in those studies reporting a low rate of caesarean hysterectomy.[28,36] Overall, this can explain the wide range in the prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to 71.6%) of PAS in women presenting with placenta previa (Figures 3 and 4).

Overall, management strategies and outcomes will vary depending on the accuracy of prenatal diagnosis, local surgical expertise and more recently access to a centre of excellence with multidisciplinary team approach.[53,54] In cases of high suspicion of PAS during cesarean delivery, 60-70% of obstetricians gynecologists proceed with a peripartum hysterectomy.[55,56] By contrast with a conservative management approach, radical surgery is often considered to be safer, in particular in cases of invasive placentation.[57] The association between a placenta previa and a PAS increases the risks of both maternal morbidity and mortality. In the present study we found that a caesarean hysterectomy was the primary management option in around 70% of the patients presenting with a placenta previa and PAS. The inter-study range was wide with four studies[19,21,29,37] reporting peripartum hysterectomy rates < 50%, five[28,31,32,34,36] had rates between 50-99% and four[22,30,35,38] had rates of 100%. This may be due to

difference in study protocols, local expertise and the impact of prenatal diagnosis on management strategies but also as suggested by our analysis to difference in the rates of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed histopathologic examination confirming the diagnosis.

The main limitations of this review are the quality of the published data. Thirteen out of 20 studies included in the analysis studies were retrospective and there was wide variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed histopathology data to confirm the clinical diagnosis. This is hampering the meta-analysis of the clinical outcomes in particular the incidence of major hemorrhage at delivery and the need and amount of blood transfusion but also the choice in management protocols and in particular the use of conservative management procedures. We would not, therefore, recommend the use of the pooled estimates beyond that of a driver towards the development of standardized diagnostic protocols.

The prevalence of PAS in the general population of women giving birth varies widely.[8,10,58,59] A systematic review and meta-analysis of the prevalence of placenta praevia has found evidence suggestive of regional variation.[60] As both conditions are often associated with prior caesarean sections it is likely that national and local caesarean delivery rates, expertise in diagnosing both conditions antenatally and access to perinatal pathologist to confirm the diagnosis of PAS at birth will influence these epidemiology data. There is a need for further prospective multi-centre studies with participatory methodologies involving local service providers and facility management to accurately evaluate the consequences of high caesarean sections rates on maternal health within a

particular population. Within this context, accurate epidemiologic data on PAS disorders are essential in planning screening programs and in making provision for the development of centres of excellence for the management of this increasingly common complex obstetric condition. Whilst the concept of core outcome measures within clinical trials is now well recognised and championed, greater efforts are required to disseminate this approach in epidemiological research to facilitate global estimation and recognition of problems emerging on a worldwide scale. Our study supports implementation, in both clinical practice and in reporting data on placenta previa accreta in the medical literature, of standardized protocols for prenatal diagnosis of both placenta previa and PAS, for the clinical diagnosis of PAS at birth and for the histopathologic confirmation examination.

## Author contributions

EJ, CB and JLR contributed equally to the study design. EJ, LG and JLR collected the data and carried out the qualitative analysis. CB and EJ carried out the quantitative analysis. EJ, JLR and SC drafted the manuscript. All authors were involved in the critical discussion and approved this final version for publication. EJ is the guarantor of the study.

## Data sharing statement

Data relevant to the study are available from the Dryad digital repository

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**Table 1:** Characteristics and quality assessment of the 20 studies included in the review.

| | Country | Dates | Study type | Risk of bias Categories | | | Overall |
|---|---|---|---|---|---|---|---|
| | | | | Selection | Comparability | Outcome | |
| Chattopadhyay et al., 1993[19] | Saudi Arabia | 1988-1992 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Zaki et al., 1998[20] | Saudi Arabia | 1990-1996 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗ | High |
| Ziadeh et al., 1999[21] | Jordan | 1995-1996 | Prospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Gourab et al., 2001[22] | Saudi Arabia | 1995-2000 | Prospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Bahar et al., 2009[23] | Saudi Arabia | 1996-2005 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Hamada et al., 2011[24] | Japan | 2007-2009 | Prospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Jang et al., 2011[25] | South Korea | 1999-2009 | Retrospective/ 3 Institutions | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Rosenberg et al., 2011[26] | Israel | 1988-2009 | Retrospective/ Region¶ | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Kassem et al., 2013[27] | Saudi Arabia | 2009-2012 | Retrospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Maher et al., 2013[28] | Egypt | 2008-2011 | Prospective/ Single Institution | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Alchalabi et al., 2014[29] | Jordan | 2003-2012 | Retrospective/ Single Institution* | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Asicioglu et al., 2014[30] | Turkey | 2005-2010 | Retrospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Sumigama et al., 2014[31] | Japan | 1994-2012 | Retrospective/ 11 Institutions¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Ahmed et al., 2015[32] | Egypt | 2014 | Prospective/ Single Institution¶ | ⊗⊗ | ⊗ | ⊗ | High |
| Cheng et al., 2015[33] | China | 1999-2013 | Retrospective/ Single Institution* | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Cho et al., 2015[34] | South-Korea | 1991-2013 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Kollmann et al., 2016[35] | Austria | 1993-2012 | Retrospective/ Region | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Pilloni et al., 2016[36] | Italy | 2011-2014 | Prospective/ Region | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Rezk et al., 2016[37] | Egypt | 2012-2014 | Prospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Wortman et al., 2018[38] | US | 2002-2011 | Retrospective/ Single Institution¶ | ⊗⊗ | ⊗ | ⊗⊗ | Medium |

¶= Studies including major placenta previa only; * Studies with no description of the ultrasound diagnostic signs for PAS.

**Table 2:** Prevalence of placenta previa with placenta accreta spectrum (PAS) per pregnancies or births in the corresponding obstetric population and incidence of PAS per cohorts of placenta previa.

| | Obstetric population | Prevalence (%) | Incidence (%) |
|---|---|---|---|
| Chattopadhyay et al., 1993[19] | 41,206 births | 26 (0.063) | 26/222 (11.7) |
| Zaki et al., 1998[20] | 23,070 births | 12 (0.052) | 12/110 (10.9) |
| Ziadeh et al., 1999[21] | 18,651 births | 13 (0.070) | 13/65 (20.0) |
| Gourab et al., 2001[22] | 18,670 births | 11 (0.059) | 11/138 (8.0) |
| Bahar et al., 2009[23] | 42,487 births | 53 (0.125) | 53/306 (17.3) |
| Hamada et al., 2011[24] | 2,413 births | 5 (0.207) | 5/70 (7.1) |
| Jang et al., 2011[25] | 35,030 births | 53 (0.151) | 53/560 (9.5) |
| Rosenberg et al., 2011[26] | 185,476 births | 23 (0.012) | 23/779 (3.0) |
| Kassem et al., 2013[27] | 29,053 births | 25 (0.085) | 25/122 (20.5) |
| Maher et al., 2013[28] | 24,661 births | 42 (0.170) | 42/577 (7.3) |
| Alchalabi et al., 2014[29] | 16,845 births | 23 (0.137) | 23/81 (28.4) |
| Asicioglu et al., 2014[30] | 112,819 births | 46 (0.041) | 46/364 (12.6) |
| Sumigama et al., 2014[31] | 96,670 births | 46 (0.048) | 46/954 (4.8) |
| Ahmed et al., 2015[32] | 3,841 births | 14 (0.365) | 14/52 26.9 |
| Cheng et al., 2015[33] | 81,497 births | 39 (0.048) | 39/921 (4.2) |
| Cho et al., 2015[34] | 11,210 pregnancies | 39 (0.348) | 39/442 (8.8) |
| Kollmann et al., 2016[35] | 218,876 births | 13 (0.006) | 13/328 (4.0) |
| Pilloni et al., 2016[36] | 108,000 births | 37 (0.034) | 37/314 (11.8) |
| Rezk et al., 2016[37] | 12,654 pregnancies | 53 (0.419) | 53/74 (71.6) |
| Wortman et al., 2018[38] | 148,031 births | 14 (0.010) | 14/157 (8.9) |

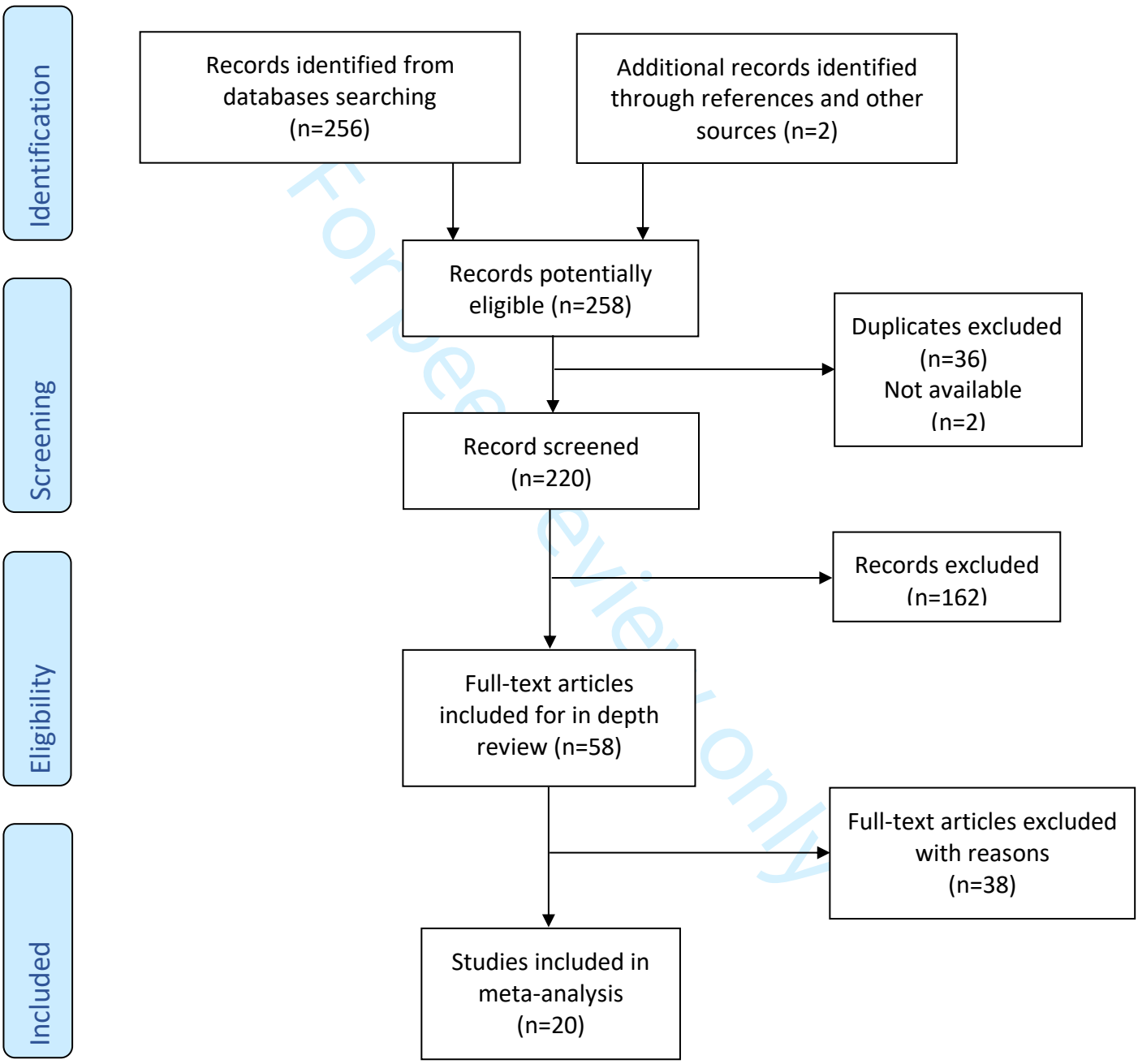
# Figure legends

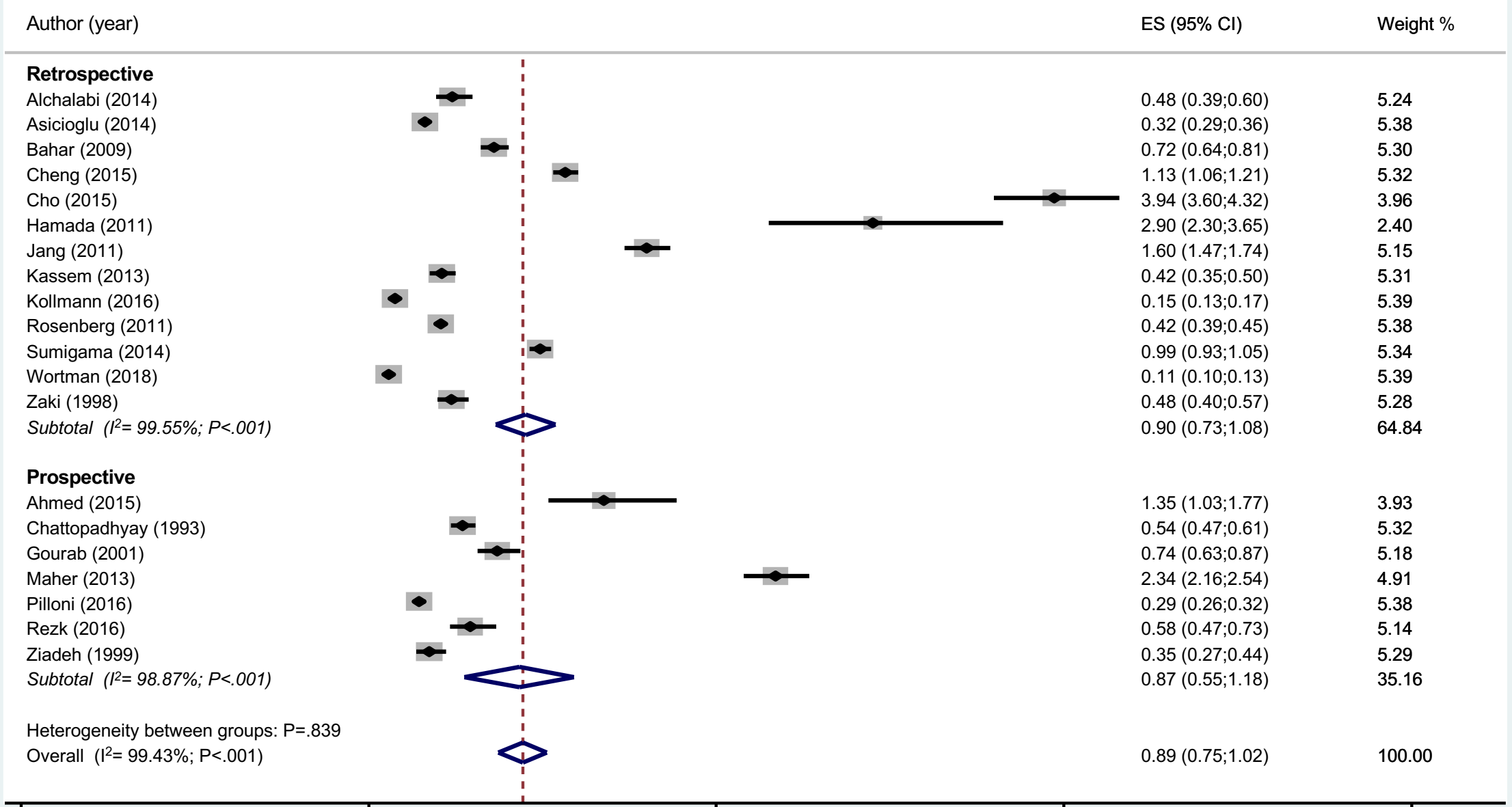
**Fig 1:** Flow diagram showing the selection of reports included in the review.

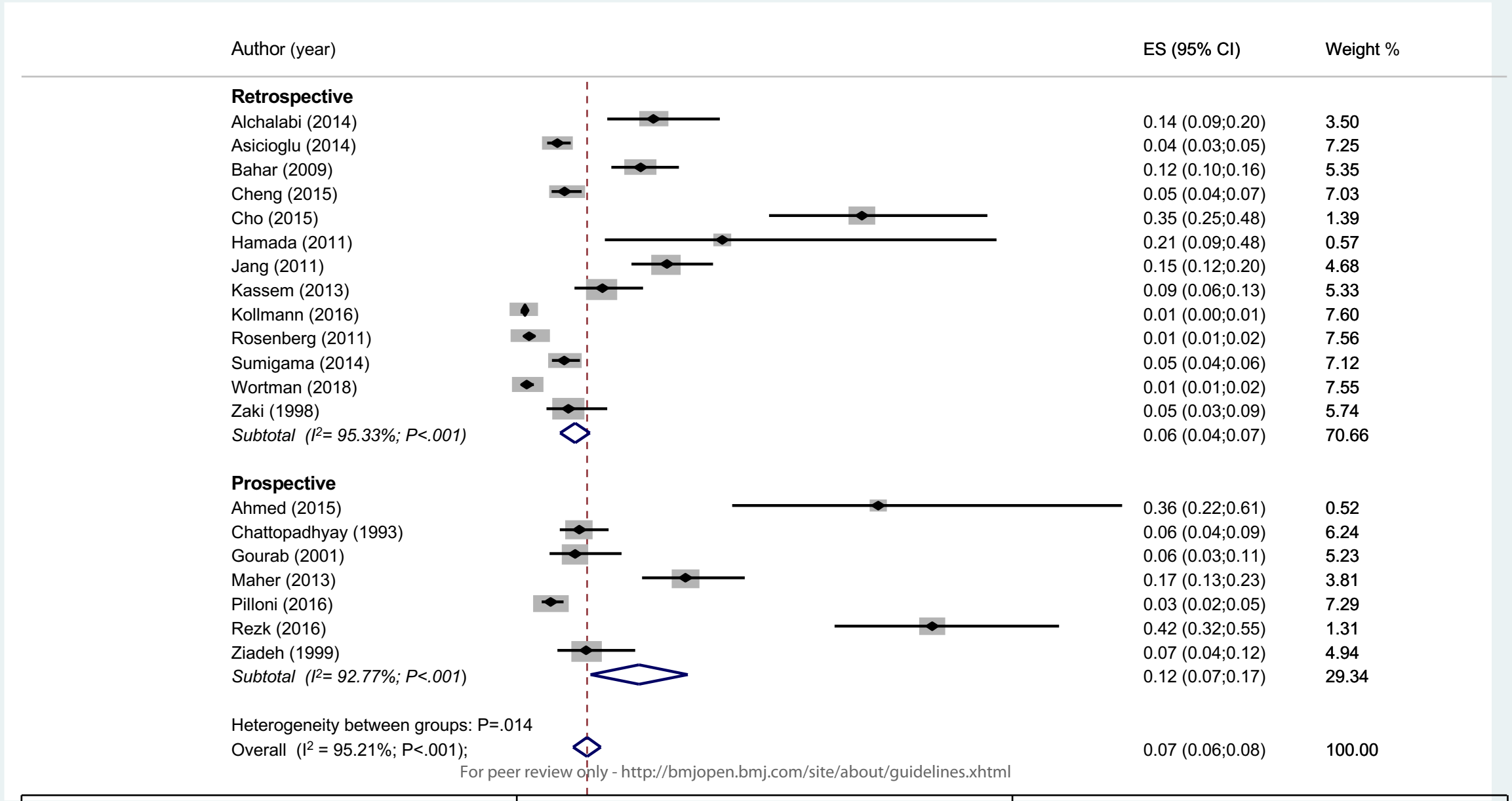
**Fig 2:** Forest plots showing the heterogeneity of prevalence data in prospective and retrospective cohort studies of women presenting with a placenta previa. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

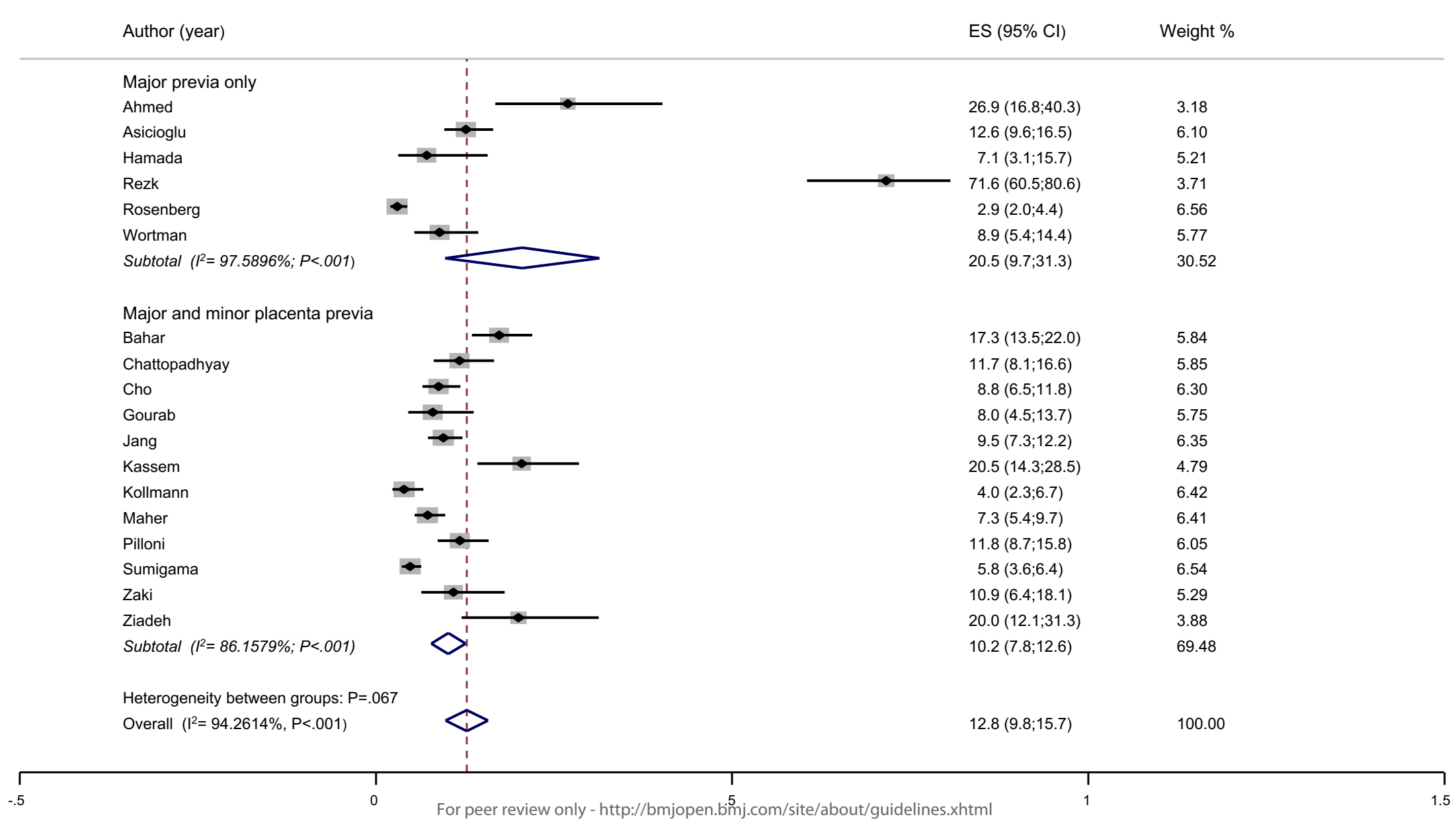
**Fig 3:** Forest plots showing heterogeneity in the prevalence data for prospective and retrospective cohort studies of women diagnosed with placenta previa accreta. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

**Fig 4:** Forest plots showing the heterogeneity in cohort studies reporting incidence data for women diagnosed with placenta previa major and PAS and those with either placenta previa minor or major and PAS. *ES, effect size. CI, confidence interval*









**Appendix** Electronic search strategy

***Time period*:** August 1982 and September 2018

***Inclusion Criteria***

- Cohort studies involving women presenting with a singleton pregnancy and placenta previa complicated by accreta placentation diagnosed during the second half of pregnancy and/or at birth.
- Original publication with data on the number of pregnancies, births and/or deliveries in the corresponding population.

***Exclusion Criteria***

- Reviews, opinions, letters, protocols and conference proceedings.
- Case series and cohorts of less than 50 cases of placenta previa.
- Articles published before 1982.
- Articles in languages other than English.
- Non-human studies.

## MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | Yes | 5 |
| Hypothesis statement | Yes | 6 & 7 |
| Description of Study Outcome(s) | Yes | 11 |
| Type of exposure or intervention used | No | N/A |
| Type of study design used | Yes | 10 |
| Study population | Yes | 10 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (eg, librarians and investigators) | No | 7 & 8 |
| Search strategy, including time period included in the synthesis and keywords | Yes | 7 |
| Effort to include all available studies, including contact with authors | Yes | 7 |
| Databases and registries searched | Yes | 7 |
| Search software used, name and version, including special features used (eg, explosion) | No | N/A |
| Use of hand searching (eg, reference lists of obtained articles) | Yes | 7 |
| List of citations located and those excluded, including justification | Yes | 7 |
| Method for addressing articles published in languages other than English | No | N/A |
| Method of handling abstracts and unpublished studies | Yes | 7 & 8 |
| Description of any contact with authors | No | N/A |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Yes | 8 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | No | N/A |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | No | N/A |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate | No | N/A |

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Yes | 7 & 8 |
| Assessment of heterogeneity | Yes | Figures 2-4 |
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | Yes | 9 |
| Provision of appropriate tables and graphics | Yes | 28 & 29 |
| **Reporting of Results** | | |
| Table giving descriptive information for each study included | Yes | Table 1 |
| Results of sensitivity testing (eg, subgroup analysis) | Yes | 12 |
| Indication of statistical uncertainty of findings | No | N/A |
| **Reporting of Discussion** | | |
| Quantitative assessment of bias (eg, publication bias) | Yes | Table 1 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | No | N/A |
| Assessment of quality of included studies | Yes | 14 & 15 |
| **Reporting of Conclusions** | | |
| Consideration of alternative explanations for observed results | Yes | 16 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | Yes | 17 |
| Guidelines for future research | Yes | 18 |
| Disclosure of funding source | Yes | 1 |

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# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis



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| | |

# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis

Eric Jauniaux,[1] Lene Grønbeck,[2] Catey Bunce,[3] Jens Langhoff-Roos,[2] Sally L Collins[4]

**Author affiliations**

1. EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.
2. Department of Obstetrics, Rigshospitalet, University of Copenhagen, Denmark.
3. Statistic unit, School of Population Health and Environmental Sciences, Kings College London, London UK.
4. Nuffield Department of Women's and Reproductive Health, University of Oxford, UK

**Competing interest**
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**Key Words:** Placenta accreta spectrum; prevalence; incidence; low-lying placenta; placenta previa.

**Word counts**: Abstract=294; Main text= 3786.

**Corresponding author:** *Professor Eric Jauniaux,*
*EGA* Institute for Women's Health, *University College London,*
*86-96 Chenies Mews, London WC1E 6HX, UK.*
Telephone numbers: +44/207/3908113
Fax: +44/207/3908115
E-mail: e.jauniaux@ucl.ac.uk

# ABSTRACT

**Objective** To estimate the prevalence and incidence of placenta previa complicated by placenta accreta spectrum (PAS) and to examine the different criteria being used for the diagnosis.

**Design** Systematic review and meta-analysis.

**Data Sources** PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched between August 1982 and September 2018.

**Eligibility Criteria** Studies reporting on placenta previa complicated by PAS diagnosed in a defined obstetric population.

**Data extraction and synthesis** Two independent reviewers performed the data extraction using a predefined protocol and assessed the risk of bias using the Newcastle-Ottawa scale for observational studies, with difference agreed by consensus. The primary outcomes were overall prevalence of placenta previa, incidence of PAS according to the type of placenta previa and the reported clinical outcomes including number of peri-partum hysterectomies and direct maternal mortality. The secondary outcomes included the criteria used for the prenatal ultrasound diagnosis of placenta previa and the criteria used to diagnose and grade PAS at birth.

**Results** A total of 258 articles were reviewed and 13 retrospective and 7 prospective studies were included in the analysis which reported on 587 women with placenta previa and PAS. The meta-analysis indicated a significant (P<.001) heterogeneity between study estimates for the prevalence of placenta previa, the prevalence of placenta previa with PAS and the incidence of PAS in the placenta previa cohort. The median prevalence of placenta previa was 0.56% (IQR 0.39;1.24) whereas the median

prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

**Conclusions** The high heterogeneity in qualitative and diagnostic data between studies emphasizes the need to implement standardized protocols for the diagnoses of both placenta previa and PAS, including the type of placenta previa and grade of villous invasiveness.

PROSPERO Registration CRD42017068589

**Strengths and limitations of this study**

- This study provides the first comprehensive evaluation of the epidemiology of placenta previa complicated by PAS.
- The search was performed using predetermined eligibility criteria in a defined obstetric population.
- Thirteen out of 20 studies included in the study were retrospective limiting the overall quality of the analysis.
- Only six studies provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa and nine studies on detailed histopathological findings.
- High level of inconsistency between estimates in prevalence and incidence did not allow for full meta-analysis of the clinical outcomes.

# INTRODUCTION

Placenta accreta is a pathological condition of placentation associated with a high risk of massive obstetric hemorrhage during delivery. Initially described in 1937 by Irving and Hertig[1] as the abnormal adherence of the placenta to the myometrium due to the partial or complete absence of decidua basalis, it was subsequently redefined by Lukes et al[2] as a spectrum of abnormally adherent and invasive placentation disorders. Placenta accreta is now graded according to the depth of the villous penetration into the uterine wall starting with the abnormally adherent placenta or creta, where the villi attach directly to the surface of the myometrium without invading it, and extending to the invasive grades of placenta increta, where the villi penetrate deeply into the myometrium up to the uterine serosa, and placenta percreta, where the invasive villous tissue penetrates through the uterine serosa often entering the surrounding pelvic tissues.[3-5] The different grades of the placenta accreta spectrum (PAS) can co-exist in the same specimen and can be focal (just a small area of the placental bed) or extensive (including much of the placental bed).[2]

Over the last two decades, a growing body of epidemiology research has identified the effect of the rapid increase in caesarean delivery rates on the risks of PAS.[6-10] The main additional risk factor after a previous caesarean delivery is placenta previa. A large multicentric U.S. cohort study noted that for women presenting with placenta previa and prior caesarean delivery, the risk of PAS was 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more cesarean deliveries, respectively.[7] A national case-control study using the UK Obstetric Surveillance System found that the incidence of PAS increases from 1.7 per 10,000 births overall to 577 per

10,000 births in women with both a previous caesarean delivery and placenta previa.[8]

Both abnormal adherence and invasion of villous tissue into the myometrium result in failure of the placenta to separate spontaneously from the uterine wall at delivery.[2-4] When unsuspected at the time of delivery, attempts to manually remove accreta villous tissue typically provoke rapid bleeding from the utero-placental circulation.[5,11] In invasive cases, this can lead to massive obstetric hemorrhage due to the disruption of the deep uterine vasculature of the increta or percreta area.[4,5] Not surprisingly, prenatal diagnosis of PAS has been shown to decrease maternal morbidity and mortality, and has thus become essential in improving its management.[12,13] Tabsh et al were the first in 1982 to report on the prenatal ultrasound diagnosis of a case of placenta increta.[14] A recent systematic review and meta-analysis of prenatal ultrasound diagnosis of placenta previa with PAS in women with a history of caesarean delivery has found that the overall diagnostic accuracy of ultrasound in specialist units is in 90.9%.[15] However, in countries with well-established screening programs for fetal anomalies, over half the cases of PAS are not diagnosed before delivery.[8,10]

Accreta placentation and in particular its invasive forms are impacting maternal health outcomes globally and its prevalence is likely to increase. Women with a history of previous caesarean delivery presenting with placenta previa complicated by PAS in an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of delivery complications[16], however, their epidemiology has not been comprehensively reviewed yet. Health provision for the development of maternity centres with specialist teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with placenta previa and PAS requires an accurate evaluation of its

epidemiology. The objective of this meta-analysis is to review the epidemiology of women presenting with placenta previa and to examine the different criteria used by the authors of cohort studies to diagnose placenta previa and PAS prenatally and to confirm the diagnosis of PAS at birth.

## MATERIALS AND METHODS

A systematic review was undertaken of articles providing data on prevalence and incidence of PAS in women presenting with a placenta previa where the populations sampled were defined. PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched for studies published between the first prenatal ultrasound description of placenta accreta in August 1982 by Tabsh[14] et al and September 2018. The search protocol was designed *a priori* and registered on PROSPERO (CRD42017068589). The overall search strategy was inclusive of MeSH headings for “placenta accreta, placenta increta, placenta percreta, abnormally invasive placenta, morbidly adherent placenta and major placenta previa” which were combined with terms including “prevalence, incidence, obstetric hysterectomy and caesarean hysterectomy”. Title, abstracts and full-text were independently assessed by the authors for content, data extraction and analysis. Additional relevant studies were identified from reference lists of reviews and editorials and by hand-searching key journals and websites. All search results were combined in a reference database. Duplicates were removed by hand. The search was limited to articles published in English.

Two independent investigators (EJ and LG) selected studies in two stages. The abstracts of all potentially relevant papers were individually examined for suitability.

Papers were only ruled out at this stage if they obviously did not meet the inclusion criteria. The remainder were obtained in full text and were independently assessed for content, data extraction and analysis. Disagreements between the two original reviewers were resolved by discussion with the third investigator (JLR). Articles were excluded if; they were published before August 1982, contained no data on the study population such as the overall pregnancies, births and/or deliveries numbers, were case reports or were overlapping.

Study characteristics were extracted using a predesigned data extraction protocol including: author institution, year of publication, country of origin, study period, study type (retrospective, single institution, multiple institutions), total number of cases in the study population, type of placenta previa, diagnosis of PAS at birth (Appendix 1). Outcome measures included the need to perform a peripartum hysterectomy and direct maternal mortality. Prior surgical history was also recorded. The reference standard for differential diagnosis between minor and major placenta previa was recorded based on the placental position inside the uterine cavity on transvaginal ultrasound with relation to the internal cervical os. For the diagnosis of accreta placentation, we referred to the clinical grading based on surgical findings at delivery as previously described[17] and to histopathologic findings when a caesarean hysterectomy was performed i.e. placental villi directly attached to the myometrium without interposing decidua or invading the uterine wall.

Two independent reviewers (EJ and LG) undertook the quality assessment with difference agreed by consensus. The Newcastle-Ottawa scale for observational studies was used to establish the risk of bias in selection (representativeness of the exposed

cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of the study), comparability (evaluation of the cohorts based on the design or analysis), and outcome assessment.[18] These included retrospective versus prospective studies, single versus multiple institutions studies, prenatal ultrasound description of low-lying/placenta previa and PAS, histopathologic confirmation of the diagnosis of the PAS and corresponding grade of invasiveness and detailed data on management and maternal outcomes. Studies that scored four stars for selection, two stars for comparability, and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias. We deemed any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, to have a high risk of bias. No study was excluded based on the risk of bias assessment.

Analyses were conducted using STATA software (version 15; StataCorp, College Station, TX). Standard Kurtosis analysis indicated that some values were not normally distributed and study specific estimates are therefore presented as median and interquartile range (IQR). A random effects model was used to combine the studies while incorporating variations among studies unless there were three or less studies contributing to the meta-analysis in which case a fixed effect model was used. Statistical heterogeneity was assessed with the Cochran's Q-test and the $I^2$ statistic (the proportion of variation in study estimates because of heterogeneity rather than sampling error). Forest plots are presented to graphically summarize the study results and the pooled results. A test for heterogeneity between sub-groups (i.e. study types) was

conducted.

## Patients and public involvement

Patients and the public were not involved in the design or planning of the study.

## RESULTS

The initial search provided 256 records with cross-referencing providing an additional two studies, making a total of 258 potentially relevant articles. After exclusion of duplicates and the two which were not available (Figure 1), 220 remained. On screening the titles and abstracts, a further 162 were excluded as the reported outcomes were not relevant, leaving 58 studies which were obtained for full text review. An additional 38 articles were excluded after full review including letters (n=16), narrative reviews (n= 10) commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another publication (n=1), leaving 20 articles for the final analysis.[19-38]

The characteristics and the results of the quality assessment are displayed in table 1. There were 13 retrospective[19,20,23,25-27,29-31,33-35,38] and 7 prospective[21,22,24,28,32,36,37] studies including a total of 1,207,296 births and 23,864 cases referred as pregnancies. There were 15 studies from a single institution[19-24,27-30,32-34,37,38] and five from multiple institutions[25,31] or a geographical region.[26,35,36] Overall, 18 studies had low or medium risk of bias.

Table 2 presents the epidemiology data of the 20 studies. These studies included 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07%

(IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

All authors except two[29,33] reported on the criteria used for the prenatal ultrasound diagnosis of placenta previa. Six studies[24,26,30,32,37,38] only included major placenta previa in their cohort as defined as the placenta completely covering or partially covering the internal os of the cervix. The others included both major and minor placenta previa. The definition of minor placenta previa varied with two studies[31,36] using the placental edge being <2cm from the internal os, two studies using < 3cm[22,23] and one study using <3 cm or <5 cm if associated with abnormal fetal presentation.[21] The gestational age at confirmation of the prenatal diagnosis of placenta previa was reported in six studies [22,23,24,28,32,37] and ranged between 20 weeks and 34 weeks and in one study the diagnosis of placenta previa was confirmed at birth when the placenta was found to be inserted in the lower segment.[19]

The ultrasound diagnostic signs for PAS were reported in six studies[24,28,30,32,36,37] with two studies also reporting on the use of magnetic resonance imaging.[29,38] The clinical criteria used for the diagnosis of PAS at birth were reported by nine studies[19,20,23,27,28,30,33,36,37] and included a difficult delivery of the placenta without easy separation uterine wall or requiring a “piecemeal removal” associated with heavy bleeding and excessive bleeding from the placental bed after placental delivery. One author described the presence of invasive villous tissue at delivery[27] and one the need to suture the placental bed.[23] None of the other authors reported on the gross appearance of the uterus or surgical findings at the time of caesarean delivery. In 12 studies[19,23,24,27-31,33,34,36,37] the prenatal and/or clinical diagnosis was confirmed by

histopathological examination with detailed description of the microscopic criterion only reported in six[19,27,28,30,31,37]. Detailed histopathological findings on the depth of villous invasiveness were reported in nine studies[24,27-29,31,33,34,36,37] out of the 20 studies (Table 3). These included 283 cases of placenta previa accreta graded for 171 (60.4%) as placenta creta (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta percreta.

The meta-analysis indicated statistically significant (P<.001) level of overall heterogeneity between study estimates for the prevalence of placenta previa (Figure 2), the prevalence of placenta previa with PAS (Figure 3) and the incidence of PAS in the placenta previa cohort (Figure 4). There was strong evidence of inconsistency between study types with $I^2$ values greater 85%. The difference in heterogeneity between prospective versus retrospective studies was not statistically significantly (P=.839) different (Figure 2) whereas it was significant (P=.014) for the prevalence of placenta previa accreta (Figure 3). Adjusting for type of study (prospective versus retrospective) did not reduce inconsistency between studies. The in-between placenta previa major only versus minor and major placental previa was not significant (P=.067) for the incidence of PAS in patient with placenta previa (Figure 4).

All authors but two[22,23] reported on prior surgical history including caesarean section[19-21,24-38], uterine curettage[28,30-32,34,37,38] and myomectomy.[28,36,37] Data on surgical management was available in 14 out of the 20 studies[19,20,23,27-31,33-38] with 314 out of 441 women presenting with a placenta previa complicated by PAS. The median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal

mortality were available in 13 studies[19-21,23,25,27-30,32,35,37,38] and PAS accounted for 5 maternal deaths[19,20,25,29,30] out of 387 (1.3%) cases of placenta previa with PAS.

## DISCUSSION

This study provides a comprehensive evaluation of the prevalence of placenta previa complicated by PAS and the incidence of PAS in women presenting with a placenta previa. Women with a prior history of caesarean delivery presenting with a low-lying/placenta previa represent more than 90% of the cases of PAS.[8,10,16] The meta-analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the need to use international standardized clinical protocols for the screening and management of this complex obstetric condition. The current situation limits the capacity building of healthcare providers on improvements in training, implementation of guidelines and changes in clinical practice behaviour.

Defining the position of the placenta inside the uterus was one of the first aims of obstetric ultrasound examination.[39,40] Following the development of real-time ultrasound imaging, placental location became an integral part of the mid-pregnancy ultrasound examination.[41] Placenta previa was initially described with transabdominal scan as a placenta developing within the lower uterine segment and classified according to the relationship and/or the distance between the lower placental edge and the internal os of the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine segment down to the internal os and major placenta previa when the placenta covers the cervix. Minor placenta previa can be further subdivided into low-lying placenta when the

lower edge does not reach the internal os and marginal placenta previa when it does. Major placenta previa can also be described as partial or complete depending on the amount of placental tissue covering the cervix. The use of transvaginal scanning has allowed for a more precise evaluation of the distance between the placental edge and the internal os[42,43] but as demonstrated in our meta-analysis, the reporting of the ultrasound criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we found also wide variation in the gestational age at diagnosis. The timing of the confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.[44,45] An expert panel of the American Institute of Ultrasound in Medicine[46] has recently recommended ceasing the use of the terms 'partial' and 'marginal' and using the term 'placenta previa' only when the placenta lies directly over the internal os. The placenta should be reported as 'low lying' when the placental edge is less than 2 cm from the internal os and as normal when the placental edge is more than 2 cm from the internal os. The findings of our meta-analysis highlight the need for the use of such a classification in further studies.

Only six of the 20 studies included in the present meta-analysis provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included in the systematic review all studies published since the first ultrasound description of PAS by Tabsh et al in 1982.[14] We found no studies between 1982 and 1993 (Table 1) which corresponds to the time when high-resolution grey-scale ultrasound imaging became widely available. Colour-Doppler imaging was introduced for the diagnosis of PAS in 1992[47], however the sensitivity and specificity of grey-scale imaging alone in

diagnosing for placenta previa accreta are high when performed by experience operators.[15] These findings indicate that the prenatal diagnosis of PAS can be performed using standard ultrasound equipment. Unlike placenta previa which is routinely screened for at the time of the fetal anomaly scan, PAS is currently not screened for and the data available on the prenatal diagnosis of the condition come exclusively from specialist centres.[16] In these centres, the diagnostic accuracy of ultrasound imaging is over 90%, but similar to placenta previa, the description of the ultrasound signs used for the diagnosis of PAS has also been highly variable over the last two decades.[47,48] The European Working Group on Abnormally Invasive Placenta and the Abnormally Invasive Placenta international expert group have recently proposed standardised descriptions of the ultrasound signs used for the prenatal diagnosis and a protocol for the ultrasound assessment of PAS.[49,50] The use of these protocols in prospective studies should also facilitate the screening of patients at high risk of PAS and in particular those with multiple prior caesarean deliveries presenting with a low-lying or placenta previa.[51]

We found significant heterogeneity in the qualitative definition and diagnosis of PAS at birth among the nine studies that provided a description of the clinical findings.[19,20,23,27,28,30,33,36,37] Only one of these studies described the invasive appearance of placental tissue at delivery[27] whereas the others reported a difficult delivery of the placenta without easy separation from the uterine wall or requiring a "piecemeal removal" associated with heavy bleeding as diagnostic of PAS. These clinical criteria were first described by Irving and Hertig[1] in 1937 who did not have invasive cases in their cohort limiting their definition to abnormally adherent placenta

and not to placenta increta or percreta. This definition also fails to clearly differentiate between abnormal adherence and placental retention as both present with similar clinical symptoms and etiology[52] leading to possible over diagnosis of placenta previa accreta. Similarly, the finding of excessive bleeding from the placental bed after delivery of the placenta is a common complication of non-accreta placenta previa due to the implantation of the placenta in the lower uterine segment which contains less muscular fibers than the upper segment and is often thinner and dehiscent after multiple caesarean deliveries.

Detailed histopathologic reports can only be obtained in those patients who have a hysterectomy or a partial myometrial resection and thus in many studies there is not histopathologic confirmation of the clinical diagnosis. The main histological diagnostic criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi and the superficial myometrium, is found with increasing incidence with advancing gestation in pregnancies with no clinical evidence of PAS.[5] Thus the combination of clinical criteria that do not differentiate between placenta retention and adherent accreta and the use of non-diagnostic criteria of villous invasiveness may result in the over-diagnosis of the adherent grade of PAS (Table 3), in particular in those studies reporting a low rate of caesarean hysterectomy.[28,36] Overall, this can explain the wide range in the prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to 71.6%) of PAS in women presenting with placenta previa (Figures 3 and 4).

Overall, management strategies and outcomes will vary depending on the accuracy of prenatal diagnosis, local surgical expertise and more recently access to a centre of excellence with multidisciplinary team approach.[53,54] In cases of high suspicion

of PAS during cesarean delivery, 60-70% of obstetricians-gynecologists proceed with a peripartum hysterectomy.[55,56] By contrast with a conservative management approach, radical surgery is often considered to be safer, in particular in cases of invasive placentation.[57] The association between a placenta previa and a PAS increases the risks of both maternal morbidity and mortality. In the present study we found that a caesarean hysterectomy was the primary management option in around 70% of the patients presenting with a placenta previa and PAS. The inter-study range was wide with four studies[19,21,29,37] reporting peripartum hysterectomy rates < 50%, five[28,31,32,34,36] had rates between 50-99% and four[22,30,35,38] had rates of 100%. This may be due to difference in study protocols, local expertise and the impact of prenatal diagnosis on management strategies but also as suggested by our analysis to difference in the rates of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed histopathologic examination confirming the diagnosis.

The main limitations of this review are the quality of the published data. Thirteen out of 20 studies included in the analysis studies were retrospective and there was wide variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed histopathology data to confirm the clinical diagnosis. This is hampering the meta-analysis of the clinical outcomes in particular the incidence of major hemorrhage at delivery and the need and amount of blood transfusion but also the choice in management protocols and in particular the use of conservative management procedures. We would not, therefore, recommend the use of the pooled estimates beyond that of a support towards the development of standardized diagnostic protocols.

The prevalence of PAS in the general population of women giving birth varies widely.[8,10,58,59] A systematic review and meta-analysis of the prevalence of placenta praevia has found evidence suggestive of regional variation.[60] As both conditions are often associated with prior caesarean sections it is likely that national and local caesarean delivery rates, expertise in diagnosing both conditions antenatally and access to perinatal pathologist to confirm the diagnosis of PAS at birth will influence these epidemiology data. There is a need for further prospective multi-centre studies with participatory methodologies involving local service providers and facility management to accurately evaluate the consequences of high caesarean sections rates on maternal health within a particular population. Within this context, accurate epidemiologic data on PAS disorders are essential in planning screening programs and in making provision for the development of centres of excellence for the management of this increasingly common complex obstetric condition. Whilst the concept of core outcome measures within clinical trials is now well recognised and championed, greater efforts are required to disseminate this approach in epidemiological research to facilitate global estimation and recognition of problems emerging on a worldwide scale. Our study supports implementation, in both clinical practice and in reporting data on placenta previa accreta in the medical literature, of standardized protocols for prenatal diagnosis of both placenta previa and PAS, for the clinical diagnosis of PAS at birth and for the histopathologic confirmation examination.

## Author contributions

EJ, CB and JLR contributed equally to the study design. EJ, LG and JLR collected the data and carried out the qualitative analysis. CB and EJ carried out the quantitative

analysis. EJ, JLR and SC drafted the manuscript. All authors were involved in the critical discussion and approved this final version for publication. EJ is the guarantor of the study.

## Data sharing statement

Data relevant to the study are available from the Dryad digital repository

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**Table 1:** Characteristics and quality assessment of the 20 studies included in the review.

| | Country | Dates | Study type | Risk of bias Categories | | | Overall |
|---|---|---|---|---|---|---|---|
| | | | | Selection | Comparability | Outcome | |
| Chattopadhyay et al., 1993[19] | Saudi Arabia | 1988-1992 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Zaki et al., 1998[20] | Saudi Arabia | 1990-1996 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗ | High |
| Ziadeh et al., 1999[21] | Jordan | 1995-1996 | Prospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Gourab et al., 2001[22] | Saudi Arabia | 1995-2000 | Prospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Bahar et al., 2009[23] | Saudi Arabia | 1996-2005 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Hamada et al., 2011[24] | Japan | 2007-2009 | Prospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Jang et al., 2011[25] | South Korea | 1999-2009 | Retrospective/ 3 Institutions | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Rosenberg et al., 2011[26] | Israel | 1988-2009 | Retrospective/ Region¶ | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Kassem et al., 2013[27] | Saudi Arabia | 2009-2012 | Retrospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Maher et al., 2013[28] | Egypt | 2008-2011 | Prospective/ Single Institution | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Alchalabi et al., 2014[29] | Jordan | 2003-2012 | Retrospective/ Single Institution* | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Asicioglu et al., 2014[30] | Turkey | 2005-2010 | Retrospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Sumigama et al., 2014[31] | Japan | 1994-2012 | Retrospective/ 11 Institutions¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Ahmed et al., 2015[32] | Egypt | 2014 | Prospective/ Single Institution¶ | ⊗⊗ | ⊗ | ⊗ | High |
| Cheng et al., 2015[33] | China | 1999-2013 | Retrospective/ Single Institution* | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Cho et al., 2015[34] | South-Korea | 1991-2013 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Kollmann et al., 2016[35] | Austria | 1993-2012 | Retrospective/ Region | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Pilloni et al., 2016[36] | Italy | 2011-2014 | Prospective/ Region | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Rezk et al., 2016[37] | Egypt | 2012-2014 | Prospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Wortman et al., 2018[38] | US | 2002-2011 | Retrospective/ Single Institution¶ | ⊗⊗ | ⊗ | ⊗⊗ | Medium |

¶= Studies including major placenta previa only; * Studies with no description of the ultrasound diagnostic signs for PAS.

**Table 2:** Prevalence of placenta previa with placenta accreta spectrum (PAS) per pregnancies or births in the corresponding obstetric population and incidence of PAS per cohorts of placenta previa.

| | Obstetric population | Prevalence (%) | Incidence (%) |
|---|---|---|---|
| Chattopadhyay et al., 1993[19] | 41,206 births | 26 (0.063) | 26/222 (11.7) |
| Zaki et al., 1998[20] | 23,070 births | 12 (0.052) | 12/110 (10.9) |
| Ziadeh et al., 1999[21] | 18,651 births | 13 (0.070) | 13/65 (20.0) |
| Gourab et al., 2001[22] | 18,670 births | 11 (0.059) | 11/138 (8.0) |
| Bahar et al., 2009[23] | 42,487 births | 53 (0.125) | 53/306 (17.3) |
| Hamada et al., 2011[24] | 2,413 births | 5 (0.207) | 5/70 (7.1) |
| Jang et al., 2011[25] | 35,030 births | 53 (0.151) | 53/560 (9.5) |
| Rosenberg et al., 2011[26] | 185,476 births | 23 (0.012) | 23/779 (3.0) |
| Kassem et al., 2013[27] | 29,053 births | 25 (0.085) | 25/122 (20.5) |
| Maher et al., 2013[28] | 24,661 births | 42 (0.170) | 42/577 (7.3) |
| Alchalabi et al., 2014[29] | 16,845 births | 23 (0.137) | 23/81 (28.4) |
| Asicioglu et al., 2014[30] | 112,819 births | 46 (0.041) | 46/364 (12.6) |
| Sumigama et al., 2014[31] | 96,670 births | 46 (0.048) | 46/954 (4.8) |
| Ahmed et al., 2015[32] | 3,841 births | 14 (0.365) | 14/52 26.9 |
| Cheng et al., 2015[33] | 81,497 births | 39 (0.048) | 39/921 (4.2) |
| Cho et al., 2015[34] | 11,210 pregnancies | 39 (0.348) | 39/442 (8.8) |
| Kollmann et al., 2016[35] | 218,876 births | 13 (0.006) | 13/328 (4.0) |
| Pilloni et al., 2016[36] | 108,000 births | 37 (0.034) | 37/314 (11.8) |
| Rezk et al., 2016[37] | 12,654 pregnancies | 53 (0.419) | 53/74 (71.6) |
| Wortman et al., 2018[38] | 148,031 births | 14 (0.010) | 14/157 (8.9) |

**Table 3:** Studies presenting detailed histopathologic data on the depth of villous invasiveness (PAS grades).

| Author/Year | No of cases analysed per No of cases included in the study | PAS grades PC (%) | PI (%) | PP (%) |
|---|---|---|---|---|
| Hamada et al, 2011[24] | 5/5 | 3 (60.0%) | 2 (40.0%) | -- |
| Kassem et al, 2013[27] | 19/25 | 13 (68.4%) | 5 (26.3%) | 1 (5.3%) |
| Maher et al, 2013[28] | 42/42 | 28 (66.6%) | 13 (31.0%) | 1 (2.4%) |
| Achalabi et al, 2014[29] | 23/23 | 15 (65.2%) | 4 (17.4%) | 4 (17.4%) |
| Sumigama et al, 2014[31] | 46/46 | 14 (30.4%) | 21 (45.7%) | 11 (23.9%) |
| Cheng et al, 2015[33] | 39/39 | 36 (92.3%) | -- | 3 (7.7%) |
| Cho et al, 2015[34] | 39/39 | 24 (37.4) | 11 (31.3%) | 4 (31.3%) |
| Pilloni et al, 2016[36] | 17/37 | 7 (41.2%) | 4 (23.5%) | 6 (35.3%) |
| Rezk et al, 2016[37] | 53/53 | 31 (58.5%) | 14 (26.4%) | 8 (15.1%) |
| **Total** | **283/309** | **171 (60.4%)** | **74 (26.2%)** | **38 (13.4%)** |

PAS= placenta accreta spectrum

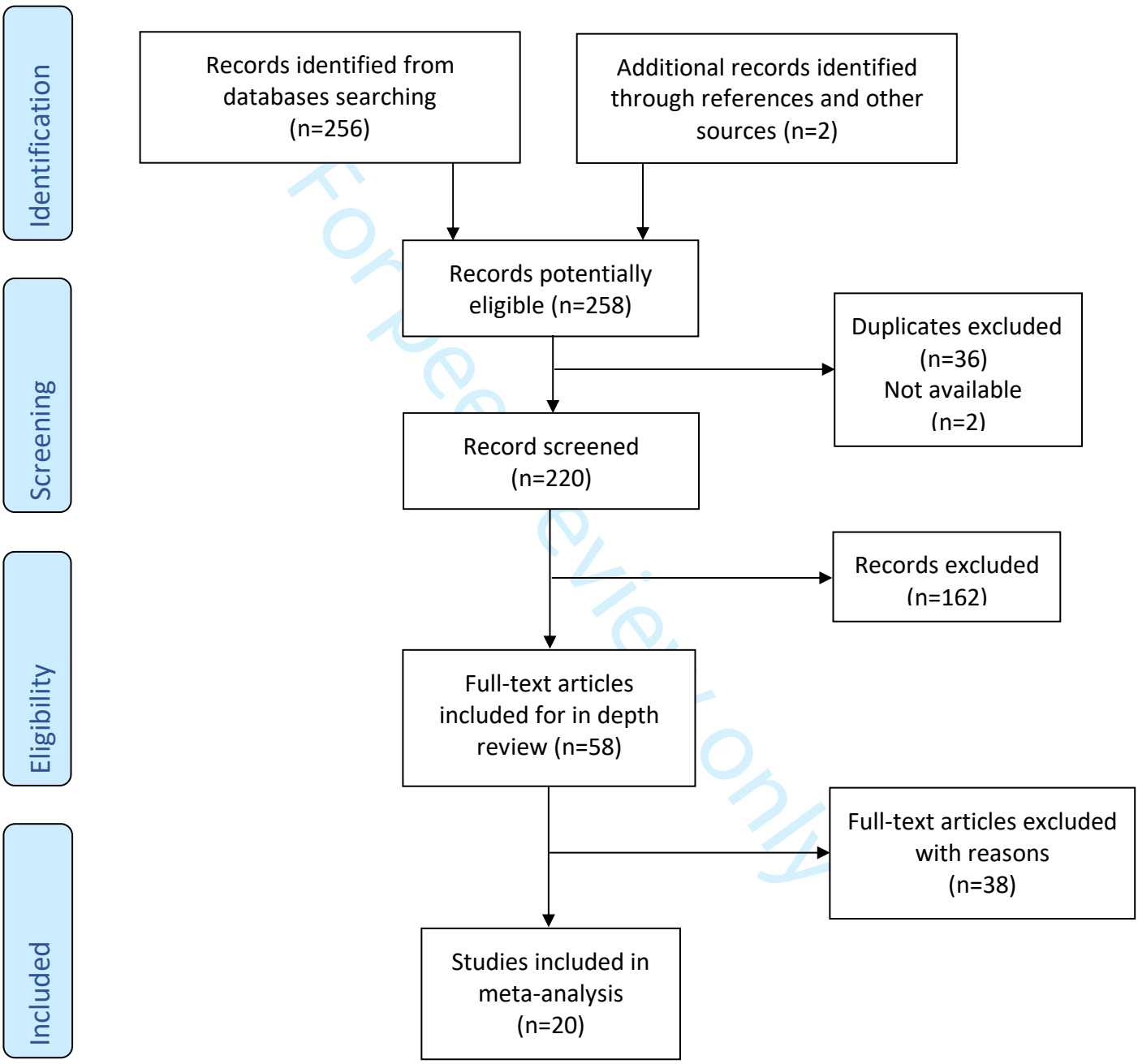
# Figure legends

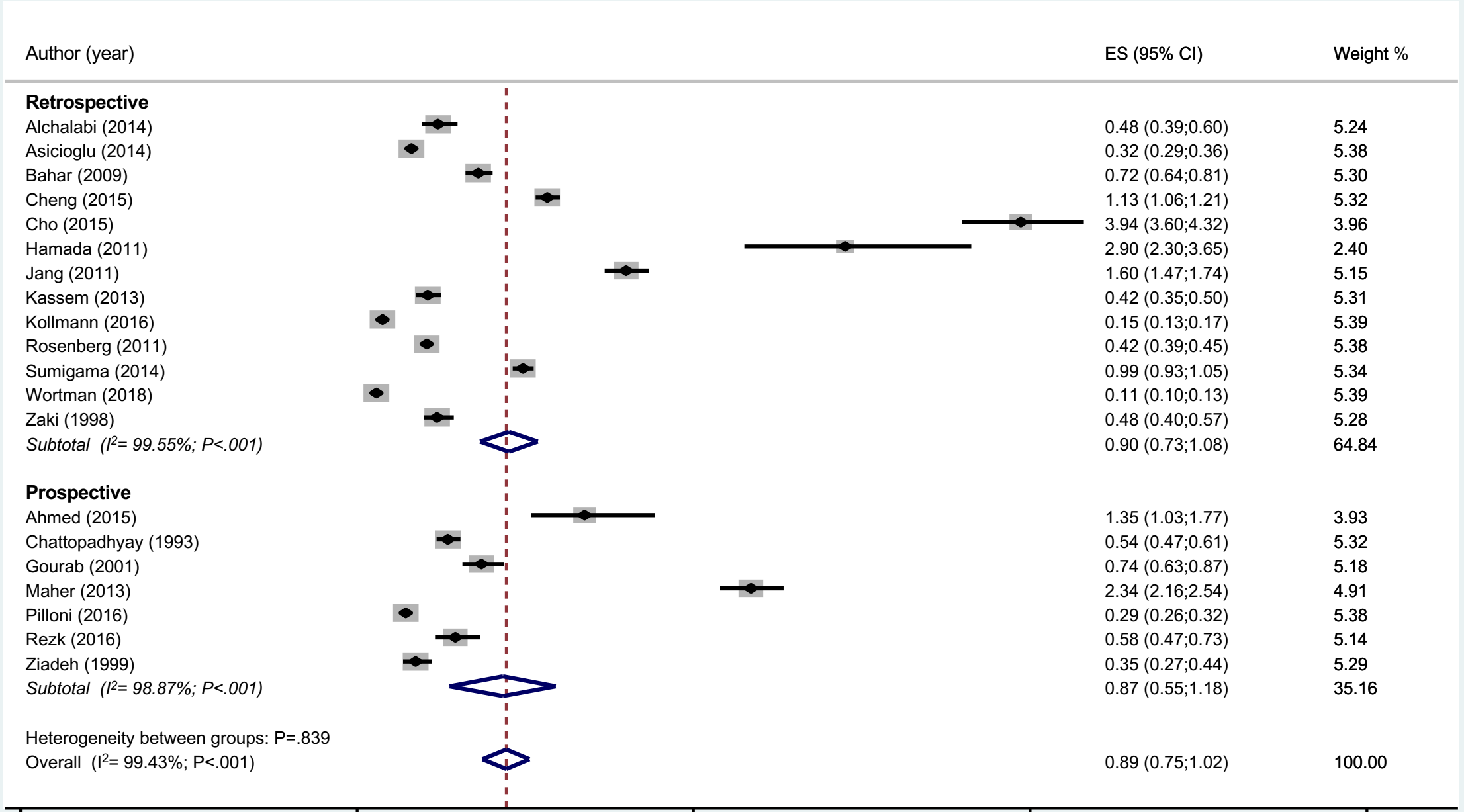
**Fig 1:** Flow diagram showing the selection of reports included in the review.

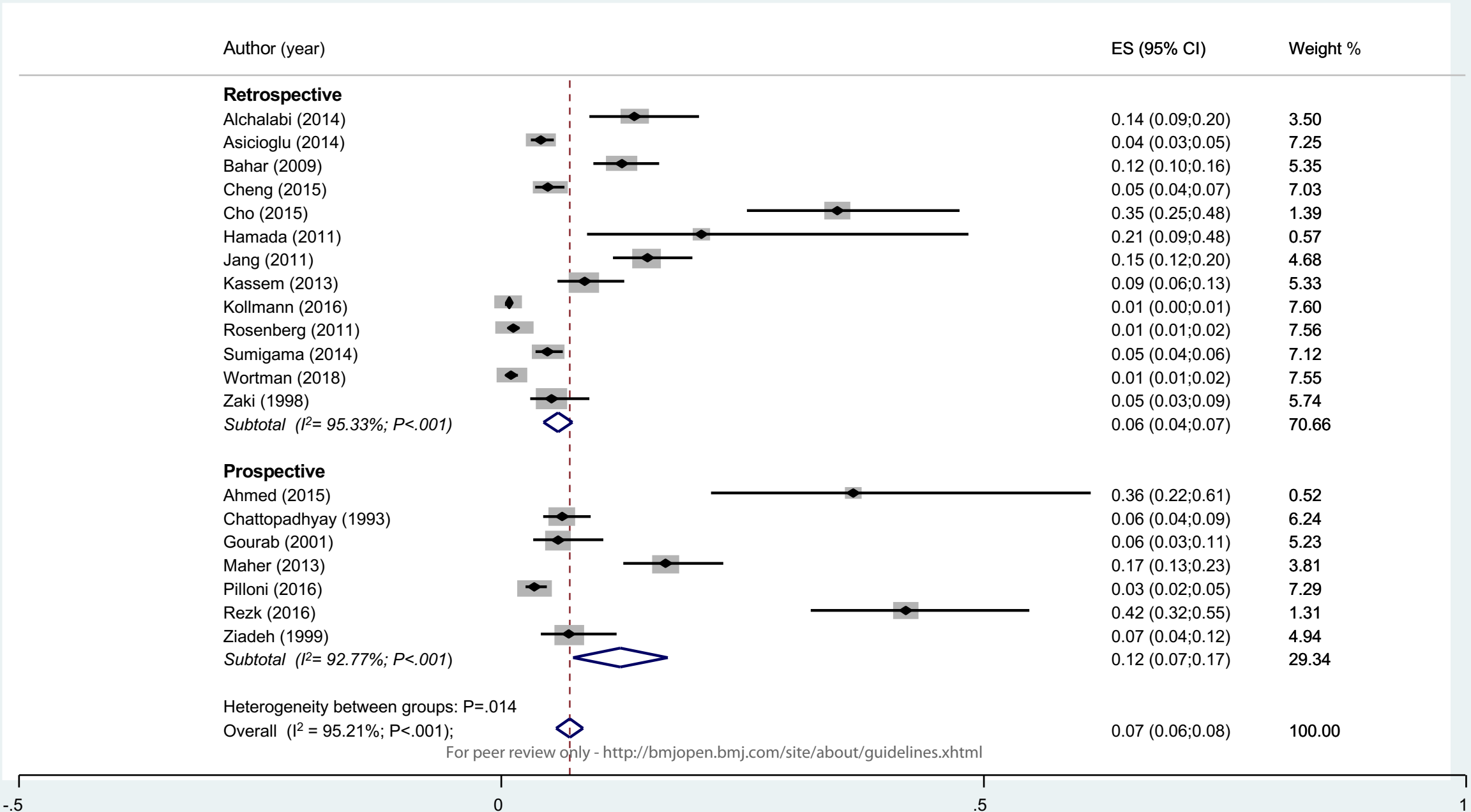
**Fig 2:** Forest plots showing the heterogeneity of prevalence data in prospective and retrospective cohort studies of women presenting with a placenta previa. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

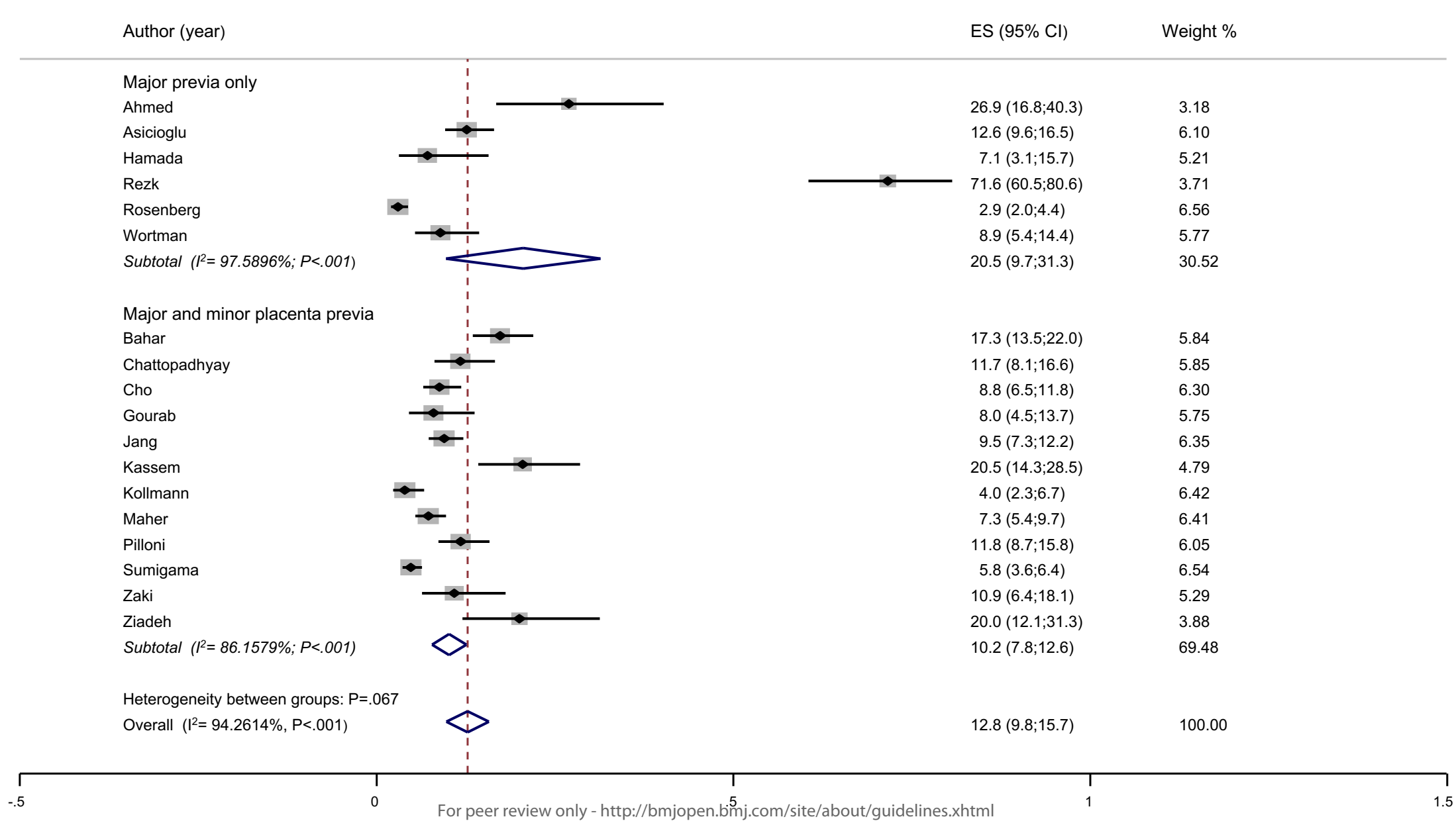
**Fig 3:** Forest plots showing heterogeneity in the prevalence data for prospective and retrospective cohort studies of women diagnosed with placenta previa accreta. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

**Fig 4:** Forest plots showing the heterogeneity in cohort studies reporting incidence data for women diagnosed with placenta previa major and PAS and those with either placenta previa minor or major and PAS. *ES, effect size. CI, confidence interval*









**Appendix** Electronic search strategy

***Time period*:** August 1982 and September 2018

***Inclusion Criteria***

- Cohort studies involving women presenting with a singleton pregnancy and placenta previa complicated by accreta placentation diagnosed during the second half of pregnancy and/or at birth.
- Original publication with data on the number of pregnancies, births and/or deliveries in the corresponding population.

***Exclusion Criteria***

- Reviews, opinions, letters, protocols and conference proceedings.
- Case series and cohorts of less than 50 cases of placenta previa.
- Articles published before 1982.
- Articles in languages other than English.
- Non-human studies.

## MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | Yes | 5 |
| Hypothesis statement | Yes | 6 & 7 |
| Description of Study Outcome(s) | Yes | 11 |
| Type of exposure or intervention used | No | N/A |
| Type of study design used | Yes | 10 |
| Study population | Yes | 10 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (eg, librarians and investigators) | No | 7 & 8 |
| Search strategy, including time period included in the synthesis and keywords | Yes | 7 |
| Effort to include all available studies, including contact with authors | Yes | 7 |
| Databases and registries searched | Yes | 7 |
| Search software used, name and version, including special features used (eg, explosion) | No | N/A |
| Use of hand searching (eg, reference lists of obtained articles) | Yes | 7 |
| List of citations located and those excluded, including justification | Yes | 7 |
| Method for addressing articles published in languages other than English | No | N/A |
| Method of handling abstracts and unpublished studies | Yes | 7 & 8 |
| Description of any contact with authors | No | N/A |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Yes | 8 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | No | N/A |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | No | N/A |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate | No | N/A |

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Yes | 7 & 8 |
| Assessment of heterogeneity | Yes | Figures 2-4 |
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | Yes | 9 |
| Provision of appropriate tables and graphics | Yes | 28 & 29 |
| **Reporting of Results** | | |
| Table giving descriptive information for each study included | Yes | Table 1 |
| Results of sensitivity testing (eg, subgroup analysis) | Yes | 12 |
| Indication of statistical uncertainty of findings | No | N/A |
| **Reporting of Discussion** | | |
| Quantitative assessment of bias (eg, publication bias) | Yes | Table 1 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | No | N/A |
| Assessment of quality of included studies | Yes | 14 & 15 |
| **Reporting of Conclusions** | | |
| Consideration of alternative explanations for observed results | Yes | 16 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | Yes | 17 |
| Guidelines for future research | Yes | 18 |
| Disclosure of funding source | Yes | 1 |

**Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**

BMJ Open

# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis



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# Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis

Eric Jauniaux,[1] Lene Grønbeck,[2] Catey Bunce,[3] Jens Langhoff-Roos,[2] Sally L Collins[4]

**Author affiliations**

1. EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.
2. Department of Obstetrics, Rigshospitalet, University of Copenhagen, Denmark.
3. Statistic unit, School of Population Health and Environmental Sciences, Kings College London, London UK.
4. Nuffield Department of Women's and Reproductive Health, University of Oxford, UK

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**Key Words:** Placenta accreta spectrum; prevalence; incidence; low-lying placenta; placenta previa.

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**Corresponding author:** *Professor Eric Jauniaux,*
*EGA* Institute for Women's Health, *University College London,*
*86-96 Chenies Mews, London WC1E 6HX, UK.*
Telephone numbers: +44/207/3908113
Fax: +44/207/3908115
E-mail: e.jauniaux@ucl.ac.uk

# ABSTRACT

**Objective** To estimate the prevalence and incidence of placenta previa complicated by placenta accreta spectrum (PAS) and to examine the different criteria being used for the diagnosis.

**Design** Systematic review and meta-analysis.

**Data Sources** PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched between August 1982 and September 2018.

**Eligibility Criteria** Studies reporting on placenta previa complicated by PAS diagnosed in a defined obstetric population.

**Data extraction and synthesis** Two independent reviewers performed the data extraction using a predefined protocol and assessed the risk of bias using the Newcastle-Ottawa scale for observational studies, with difference agreed by consensus. The primary outcomes were overall prevalence of placenta previa, incidence of PAS according to the type of placenta previa and the reported clinical outcomes including number of peri-partum hysterectomies and direct maternal mortality. The secondary outcomes included the criteria used for the prenatal ultrasound diagnosis of placenta previa and the criteria used to diagnose and grade PAS at birth.

**Results** A total of 258 articles were reviewed and 13 retrospective and 7 prospective studies were included in the analysis which reported on 587 women with placenta previa and PAS. The meta-analysis indicated a significant (P<.001) heterogeneity between study estimates for the prevalence of placenta previa, the prevalence of placenta previa with PAS and the incidence of PAS in the placenta previa cohort. The median prevalence of placenta previa was 0.56% (IQR 0.39;1.24) whereas the median

prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

**Conclusions** The high heterogeneity in qualitative and diagnostic data between studies emphasizes the need to implement standardized protocols for the diagnoses of both placenta previa and PAS, including the type of placenta previa and grade of villous invasiveness.

PROSPERO Registration CRD42017068589

**Strengths and limitations of this study**

- This study provides the first comprehensive evaluation of the epidemiology of placenta previa complicated by PAS.
- The search was performed using predetermined eligibility criteria in a defined obstetric population.
- Thirteen out of 20 studies included in the study were retrospective limiting the overall quality of the analysis.
- Only six studies provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa and nine studies on detailed histopathological findings.
- High level of inconsistency between estimates in prevalence and incidence did not allow for full meta-analysis of the clinical outcomes.

# INTRODUCTION

Placenta accreta is a pathological condition of placentation associated with a high risk of massive obstetric hemorrhage during delivery. Initially described in 1937 by Irving and Hertig[1] as the abnormal adherence of the placenta to the myometrium due to the partial or complete absence of decidua basalis, it was subsequently redefined by Lukes et al[2] as a spectrum of abnormally adherent and invasive placentation disorders. Placenta accreta is now graded according to the depth of the villous penetration into the uterine wall starting with the abnormally adherent placenta or creta, where the villi attach directly to the surface of the myometrium without invading it, and extending to the invasive grades of placenta increta, where the villi penetrate deeply into the myometrium up to the uterine serosa, and placenta percreta, where the invasive villous tissue penetrates through the uterine serosa often entering the surrounding pelvic tissues.[3-5] The different grades of the placenta accreta spectrum (PAS) can co-exist in the same specimen and can be focal (just a small area of the placental bed) or extensive (including much of the placental bed).[2]

Over the last two decades, a growing body of epidemiology research has identified the effect of the rapid increase in caesarean delivery rates on the risks of PAS.[6-10] The main additional risk factor after a previous caesarean delivery is placenta previa. A large multicentric U.S. cohort study noted that for women presenting with placenta previa and prior caesarean delivery, the risk of PAS was 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more cesarean deliveries, respectively.[7] A national case-control study using the UK Obstetric Surveillance System found that the incidence of PAS increases from 1.7 per 10,000 births overall to 577 per

10,000 births in women with both a previous caesarean delivery and placenta previa.[8]

Both abnormal adherence and invasion of villous tissue into the myometrium result in failure of the placenta to separate spontaneously from the uterine wall at delivery.[2-4] When unsuspected at the time of delivery, attempts to manually remove accreta villous tissue typically provoke rapid bleeding from the utero-placental circulation.[5,11] In invasive cases, this can lead to massive obstetric hemorrhage due to the disruption of the deep uterine vasculature of the increta or percreta area.[4,5] Not surprisingly, prenatal diagnosis of PAS has been shown to decrease maternal morbidity and mortality, and has thus become essential in improving its management.[12,13] Tabsh et al were the first in 1982 to report on the prenatal ultrasound diagnosis of a case of placenta increta.[14] A recent systematic review and meta-analysis of prenatal ultrasound diagnosis of placenta previa with PAS in women with a history of caesarean delivery has found that the overall diagnostic accuracy of ultrasound in specialist units is in 90.9%.[15] However, in countries with well-established screening programs for fetal anomalies, over half the cases of PAS are not diagnosed before delivery.[8,10]

Accreta placentation and in particular its invasive forms are impacting maternal health outcomes globally and its prevalence is likely to increase. Women with a history of previous caesarean delivery presenting with placenta previa complicated by PAS in an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of delivery complications[16], however, their epidemiology has not been comprehensively reviewed yet. Health provision for the development of maternity centres with specialist teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage women presenting with placenta previa and PAS requires an accurate evaluation of its

epidemiology. The objective of this meta-analysis is to review the epidemiology of women presenting with placenta previa and to examine the different criteria used by the authors of cohort studies to diagnose placenta previa and PAS prenatally and to confirm the diagnosis of PAS at birth.

## MATERIALS AND METHODS

A systematic review was undertaken of articles providing data on prevalence and incidence of PAS in women presenting with a placenta previa where the populations sampled were defined. PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were searched for studies published between the first prenatal ultrasound description of placenta accreta in August 1982 by Tabsh[14] et al and September 2018. The search protocol was designed *a priori* and registered on PROSPERO (CRD42017068589). The overall search strategy was inclusive of MeSH headings for the following terms "placenta accreta, placenta increta, placenta percreta, abnormally invasive placenta, morbidly adherent placenta and major placenta previa" (search strategy in online supplementary data 1). Title, abstracts and full-text were independently assessed by the authors for content, data extraction and analysis. Additional relevant studies were identified from reference lists of reviews and editorials and by hand-searching key journals and websites. All search results were combined in a reference database. Duplicates were removed by hand. The search was limited to articles published in English.

Two independent investigators (EJ and LG) selected studies in two stages. The abstracts of all potentially relevant papers were individually examined for suitability.

Papers were only ruled out at this stage if they obviously did not meet the inclusion criteria. The remainder were obtained in full text and were independently assessed for content, data extraction and analysis. Disagreements between the two original reviewers were resolved by discussion with the third investigator (JLR). Articles were excluded if; they were published before August 1982, contained no data on the study population such as the overall pregnancies, births and/or deliveries numbers, were case reports or were overlapping.

Study characteristics were extracted using a predesigned data extraction protocol including: author institution, year of publication, country of origin, study period, study type (retrospective, single institution, multiple institutions), total number of cases in the study population, type of placenta previa, diagnosis of PAS at birth (search strategy in online supplementary data 2). Outcome measures included the need to perform a peripartum hysterectomy and direct maternal mortality. Prior surgical history was also recorded. The reference standard for differential diagnosis between minor and major placenta previa was recorded based on the placental position inside the uterine cavity on transvaginal ultrasound with relation to the internal cervical os. For the diagnosis of accreta placentation, we referred to the clinical grading based on surgical findings at delivery as previously described[17] and to histopathologic findings when a caesarean hysterectomy was performed i.e. placental villi directly attached to the myometrium without interposing decidua or invading the uterine wall.

Two independent reviewers (EJ and LG) undertook the quality assessment with difference agreed by consensus. The Newcastle-Ottawa scale for observational studies was used to establish the risk of bias in selection (representativeness of the exposed

cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of the study), comparability (evaluation of the cohorts based on the design or analysis), and outcome assessment.[18] These included retrospective versus prospective studies, single versus multiple institutions studies, prenatal ultrasound description of low-lying/placenta previa and PAS, histopathologic confirmation of the diagnosis of the PAS and corresponding grade of invasiveness and detailed data on management and maternal outcomes. Studies that scored four stars for selection, two stars for comparability, and three stars for ascertainment of the outcome were regarded to have a low risk of bias. Studies with two or three stars for selection, one for comparability, and two for outcome ascertainment were considered to have a medium risk of bias. We deemed any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains, to have a high risk of bias. No study was excluded based on the risk of bias assessment.

Analyses were conducted using STATA software (version 15; StataCorp, College Station, TX). Standard Kurtosis analysis indicated that some values were not normally distributed and study specific estimates are therefore presented as median and interquartile range (IQR). A random effects model was used to combine the studies while incorporating variations among studies unless there were three or less studies contributing to the meta-analysis in which case a fixed effect model was used. Statistical heterogeneity was assessed with the Cochran's Q-test and the $I^2$ statistic (the proportion of variation in study estimates because of heterogeneity rather than sampling error). Forest plots are presented to graphically summarize the study results and the pooled results. A test for heterogeneity between sub-groups (i.e. study types) was

conducted.

## Patients and public involvement

Patients and the public were not involved in the design or planning of the study.

## RESULTS

The initial search provided 256 records with cross-referencing providing an additional two studies, making a total of 258 potentially relevant articles. After exclusion of duplicates and the two which were not available (Figure 1), 220 remained. On screening the titles and abstracts, a further 162 were excluded as the reported outcomes were not relevant, leaving 58 studies which were obtained for full text review. An additional 38 articles were excluded after full review including letters (n=16), narrative reviews (n= 10) commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another publication (n=1), leaving 20 articles for the final analysis.[19-38]

There were 13 retrospective[19,20,23,25-27,29-31,33-35,38] and 7 prospective[21,22,24,28,32,36,37] studies including a total of 1,207,296 births and 23,864 cases referred as pregnancies. There were 15 studies from a single institution[19-24,27-30,32-34,37,38] and five from multiple institutions[25,31] or a geographical region.[26,35,36] Overall, 18 studies had low or medium risk of bias (Full data in online supplementary data 3).

Table 1 presents the epidemiology data of the 20 studies. These studies included 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).

All authors except two[29,33] reported on the criteria used for the prenatal ultrasound diagnosis of placenta previa. Six studies[24,26,30,32,37,38] only included major placenta previa in their cohort as defined as the placenta completely covering or partially covering the internal os of the cervix. The others included both major and minor placenta previa. The definition of minor placenta previa varied with two studies[31,36] using the placental edge being <2cm from the internal os, two studies using < 3cm[22,23] and one study using <3 cm or <5 cm if associated with abnormal fetal presentation.[21] The gestational age at confirmation of the prenatal diagnosis of placenta previa was reported in six studies [22,23,24,28,32,37] and ranged between 20 weeks and 34 weeks and in one study the diagnosis of placenta previa was confirmed at birth when the placenta was found to be inserted in the lower segment.[19]

The ultrasound diagnostic signs for PAS were reported in six studies[24,28,30,32,36,37] with two studies also reporting on the use of magnetic resonance imaging.[29,38] The clinical criteria used for the diagnosis of PAS at birth were reported by nine studies[19,20,23,27,28,30,33,36,37] and included a difficult delivery of the placenta without easy separation uterine wall or requiring a “piecemeal removal” associated with heavy bleeding and excessive bleeding from the placental bed after placental delivery. One author described the presence of invasive villous tissue at delivery[27] and one the need to suture the placental bed.[23] None of the other authors reported on the gross appearance of the uterus or surgical findings at the time of caesarean delivery. In 12 studies[19,23,24,27-31,33,34,36,37] the prenatal and/or clinical diagnosis was confirmed by histopathological examination with detailed description of the microscopic criterion only reported in six[19,27,28,30,31,37]. Detailed histopathological findings on the depth of villous

invasiveness were reported in nine studies[24,27-29,31,33,34,36,37] out of the 20 studies (Table 2). These included 283 cases of placenta previa accreta graded for 171 (60.4%) as placenta creta (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta percreta. These studies included a total of 383,003 pregnancies or births and the prevalence for the different grades of placenta previa accreta was 0.05%, 0.02% and 0.01% for creta, increta and percreta, respectively.

The meta-analysis indicated statistically significant (P<.001) level of overall heterogeneity between study estimates for the prevalence of placenta previa (Figure 2), the prevalence of placenta previa with PAS (Figure 3) and the incidence of PAS in the placenta previa cohort (Figure 4). There was strong evidence of inconsistency between study types with $I^2$ values greater 85%. The difference in heterogeneity between prospective versus retrospective studies was not statistically significantly (P=.839) different (Figure 2) whereas it was significant (P=.014) for the prevalence of placenta previa accreta (Figure 3). Adjusting for type of study (prospective versus retrospective) did not reduce inconsistency between studies. The in-between placenta previa major only versus minor and major placental previa was not significant (P=.067) for the incidence of PAS in patient with placenta previa (Figure 4).

All authors but two[22,23] reported on prior surgical history including caesarean section[19-21,24-38], uterine curettage[28,30-32,34,37,38] and myomectomy.[28,36,37] Data on surgical management was available in 14 out of the 20 studies[19,20,23,27-31,33-38] with 314 out of 441 women presenting with a placenta previa complicated by PAS. The median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal

mortality were available in 13 studies[19-21,23,25,27-30,32,35,37,38] and PAS accounted for 5 maternal deaths[19,20,25,29,30] out of 387 (1.3%) cases of placenta previa with PAS.

## DISCUSSION

This study provides a comprehensive evaluation of the prevalence of placenta previa complicated by PAS and the incidence of PAS in women presenting with a placenta previa. Women with a prior history of caesarean delivery presenting with a low-lying/placenta previa represent more than 90% of the cases of PAS.[8,10,16] The meta-analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the need to use international standardized clinical protocols for the screening and management of this complex obstetric condition. The current situation limits the capacity building of healthcare providers on improvements in training, implementation of guidelines and changes in clinical practice behaviour.

Defining the position of the placenta inside the uterus was one of the first aims of obstetric ultrasound examination.[39,40] Following the development of real-time ultrasound imaging, placental location became an integral part of the mid-pregnancy ultrasound examination.[41] Placenta previa was initially described with transabdominal scan as a placenta developing within the lower uterine segment and classified according to the relationship and/or the distance between the lower placental edge and the internal os of the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine segment down to the internal os and major placenta previa when the placenta covers the cervix. Minor placenta previa can be further subdivided into low-lying placenta when the

lower edge does not reach the internal os and marginal placenta previa when it does. Major placenta previa can also be described as partial or complete depending on the amount of placental tissue covering the cervix. The use of transvaginal scanning has allowed for a more precise evaluation of the distance between the placental edge and the internal os[42,43] but as demonstrated in our meta-analysis, the reporting of the ultrasound criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we found also wide variation in the gestational age at diagnosis. The timing of the confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.[44,45] An expert panel of the American Institute of Ultrasound in Medicine[46] has recently recommended ceasing the use of the terms 'partial' and 'marginal' and using the term 'placenta previa' only when the placenta lies directly over the internal os. The placenta should be reported as 'low lying' when the placental edge is less than 2 cm from the internal os and as normal when the placental edge is more than 2 cm from the internal os. The findings of our meta-analysis highlight the need for the use of such a classification in further studies.

Only six of the 20 studies included in the present meta-analysis provided data on the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included in the systematic review all studies published since the first ultrasound description of PAS by Tabsh et al in 1982.[14] We found no studies between 1982 and 1993 (Table 1) which corresponds to the time when high-resolution grey-scale ultrasound imaging became widely available. Colour-Doppler imaging was introduced for the diagnosis of PAS in 1992[47], however the sensitivity and specificity of grey-scale imaging alone in

diagnosing for placenta previa accreta are high when performed by experience operators.[15] These findings indicate that the prenatal diagnosis of PAS can be performed using standard ultrasound equipment. Unlike placenta previa which is routinely screened for at the time of the fetal anomaly scan, PAS is currently not screened for and the data available on the prenatal diagnosis of the condition come exclusively from specialist centres.[16] In these centres, the diagnostic accuracy of ultrasound imaging is over 90%, but similar to placenta previa, the description of the ultrasound signs used for the diagnosis of PAS has also been highly variable over the last two decades.[47,48] The European Working Group on Abnormally Invasive Placenta and the Abnormally Invasive Placenta international expert group have recently proposed standardised descriptions of the ultrasound signs used for the prenatal diagnosis and a protocol for the ultrasound assessment of PAS.[49,50] The use of these protocols in prospective studies should also facilitate the screening of patients at high risk of PAS and in particular those with multiple prior caesarean deliveries presenting with a low-lying or placenta previa.[51]

We found significant heterogeneity in the qualitative definition and diagnosis of PAS at birth among the nine studies that provided a description of the clinical findings.[19,20,23,27,28,30,33,36,37] Only one of these studies described the invasive appearance of placental tissue at delivery[27] whereas the others reported a difficult delivery of the placenta without easy separation from the uterine wall or requiring a "piecemeal removal" associated with heavy bleeding as diagnostic of PAS. These clinical criteria were first described by Irving and Hertig[1] in 1937 who did not have invasive cases in their cohort limiting their definition to abnormally adherent placenta

and not to placenta increta or percreta. This definition also fails to clearly differentiate between abnormal adherence and placental retention as both present with similar clinical symptoms and etiology[52] leading to possible over diagnosis of placenta previa accreta. Similarly, the finding of excessive bleeding from the placental bed after delivery of the placenta is a common complication of non-accreta placenta previa due to the implantation of the placenta in the lower uterine segment which contains less muscular fibers than the upper segment and is often thinner and dehiscent after multiple caesarean deliveries.

Detailed histopathologic reports can only be obtained in those patients who have a hysterectomy or a partial myometrial resection and thus in many studies there is not histopathologic confirmation of the clinical diagnosis. The main histological diagnostic criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi and the superficial myometrium, is found with increasing incidence with advancing gestation in pregnancies with no clinical evidence of PAS.[5] Thus the combination of clinical criteria that do not differentiate between placenta retention and adherent accreta and the use of non-diagnostic criteria of villous invasiveness may result in the over-diagnosis of the adherent grade of PAS (Table 2), in particular in those studies reporting a low rate of caesarean hysterectomy.[28,36] Overall, this can explain the wide range in the prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to 71.6%) of PAS in women presenting with placenta previa (Figures 3 and 4).

Overall, management strategies and outcomes will vary depending on the accuracy of prenatal diagnosis, local surgical expertise and more recently access to a centre of excellence with multidisciplinary team approach.[53,54] In cases of high suspicion

of PAS during cesarean delivery, 60-70% of obstetricians-gynecologists proceed with a peripartum hysterectomy.[55,56] By contrast with a conservative management approach, radical surgery is often considered to be safer, in particular in cases of invasive placentation.[57] The association between a placenta previa and a PAS increases the risks of both maternal morbidity and mortality. In the present study we found that a caesarean hysterectomy was the primary management option in around 70% of the patients presenting with a placenta previa and PAS. The inter-study range was wide with four studies[19,21,29,37] reporting peripartum hysterectomy rates < 50%, five[28,31,32,34,36] had rates between 50-99% and four[22,30,35,38] had rates of 100%. This may be due to difference in study protocols, local expertise and the impact of prenatal diagnosis on management strategies but also as suggested by our analysis to difference in the rates of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed histopathologic examination confirming the diagnosis.

The main limitations of this review are the quality of the published data. Thirteen out of 20 studies included in the analysis studies were retrospective and there was wide variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed histopathology data to confirm the clinical diagnosis. This is hampering the meta-analysis of the clinical outcomes in particular the incidence of major hemorrhage at delivery and the need and amount of blood transfusion but also the choice in management protocols and in particular the use of conservative management procedures. We would not, therefore, recommend the use of the pooled estimates beyond that of a support towards the development of standardized diagnostic protocols.

The prevalence of PAS in the general population of women giving birth varies widely.[8,10,58,59] A systematic review and meta-analysis of the prevalence of placenta praevia has found evidence suggestive of regional variation.[60] As both conditions are often associated with prior caesarean sections it is likely that national and local caesarean delivery rates, expertise in diagnosing both conditions antenatally and access to perinatal pathologist to confirm the diagnosis of PAS at birth will influence these epidemiology data. There is a need for further prospective multi-centre studies with participatory methodologies involving local service providers and facility management to accurately evaluate the consequences of high caesarean sections rates on maternal health within a particular population. Within this context, accurate epidemiologic data on PAS disorders are essential in planning screening programs and in making provision for the development of centres of excellence for the management of this increasingly common complex obstetric condition. Whilst the concept of core outcome measures within clinical trials is now well recognised and championed, greater efforts are required to disseminate this approach in epidemiological research to facilitate global estimation and recognition of problems emerging on a worldwide scale. Our study supports implementation, in both clinical practice and in reporting data on placenta previa accreta in the medical literature, of standardized protocols for prenatal diagnosis of both placenta previa and PAS, for the clinical diagnosis of PAS at birth and for the histopathologic confirmation examination.

## Author contributions

EJ, CB and JLR contributed equally to the study design. EJ, LG and JLR collected the data and carried out the qualitative analysis. CB and EJ carried out the quantitative

analysis. EJ, JLR and SC drafted the manuscript. All authors were involved in the critical discussion and approved this final version for publication. EJ is the guarantor of the study.

## Data sharing statement

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.5ds4833

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**Table 1:** Prevalence of placenta previa with placenta accreta spectrum (PAS) per pregnancies or births in the corresponding obstetric population and incidence of PAS per cohorts of placenta previa.

| | Obstetric population | Prevalence (%) | Incidence (%) |
|---|---|---|---|
| Chattopadhyay et al., 1993[19] | 41,206 births | 26 (0.063) | 26/222 (11.7) |
| Zaki et al., 1998[20] | 23,070 births | 12 (0.052) | 12/110 (10.9) |
| Ziadeh et al., 1999[21] | 18,651 births | 13 (0.070) | 13/65 (20.0) |
| Gourab et al., 2001[22] | 18,670 births | 11 (0.059) | 11/138 (8.0) |
| Bahar et al., 2009[23] | 42,487 births | 53 (0.125) | 53/306 (17.3) |
| Hamada et al., 2011[24] | 2,413 births | 5 (0.207) | 5/70 (7.1) |
| Jang et al., 2011[25] | 35,030 births | 53 (0.151) | 53/560 (9.5) |
| Rosenberg et al., 2011[26] | 185,476 births | 23 (0.012) | 23/779 (3.0) |
| Kassem et al., 2013[27] | 29,053 births | 25 (0.085) | 25/122 (20.5) |
| Maher et al., 2013[28] | 24,661 births | 42 (0.170) | 42/577 (7.3) |
| Alchalabi et al., 2014[29] | 16,845 births | 23 (0.137) | 23/81 (28.4) |
| Asicioglu et al., 2014[30] | 112,819 births | 46 (0.041) | 46/364 (12.6) |
| Sumigama et al., 2014[31] | 96,670 births | 46 (0.048) | 46/954 (4.8) |
| Ahmed et al., 2015[32] | 3,841 births | 14 (0.365) | 14/52 26.9 |
| Cheng et al., 2015[33] | 81,497 births | 39 (0.048) | 39/921 (4.2) |
| Cho et al., 2015[34] | 11,210 pregnancies | 39 (0.348) | 39/442 (8.8) |
| Kollmann et al., 2016[35] | 218,876 births | 13 (0.006) | 13/328 (4.0) |
| Pilloni et al., 2016[36] | 108,000 births | 37 (0.034) | 37/314 (11.8) |
| Rezk et al., 2016[37] | 12,654 pregnancies | 53 (0.419) | 53/74 (71.6) |
| Wortman et al., 2018[38] | 148,031 births | 14 (0.010) | 14/157 (8.9) |

**Table 2:** Studies presenting detailed histopathologic data on the depth of villous invasiveness (PAS grades).

| Author/Year | No of cases Analysed/ No of cases included in the study | PAS grades PC (%) | PI (%) | PP (%) |
|---|---|---|---|---|
| Hamada et al, 2011[24] | 5/5 | 3 (60.0%) | 2 (40.0%) | -- |
| Kassem et al, 2013[27] | 19/25 | 13 (68.4%) | 5 (26.3%) | 1 (5.3%) |
| Maher et al, 2013[28] | 42/42 | 28 (66.6%) | 13 (31.0%) | 1 (2.4%) |
| Achalabi et al, 2014[29] | 23/23 | 15 (65.2%) | 4 (17.4%) | 4 (17.4%) |
| Sumigama et al, 2014[31] | 46/46 | 14 (30.4%) | 21 (45.7%) | 11 (23.9%) |
| Cheng et al, 2015[33] | 39/39 | 36 (92.3%) | -- | 3 (7.7%) |
| Cho et al, 2015[34] | 39/39 | 24 (37.4) | 11 (31.3%) | 4 (31.3%) |
| Pilloni et al, 2016[36] | 17/37 | 7 (41.2%) | 4 (23.5%) | 6 (35.3%) |
| Rezk et al, 2016[37] | 53/53 | 31 (58.5%) | 14 (26.4%) | 8 (15.1%) |
| **Total** | **283/309** | **171 (60.4%)** | **74 (26.2%)** | **38 (13.4%)** |

PAS= placenta accreta spectrum

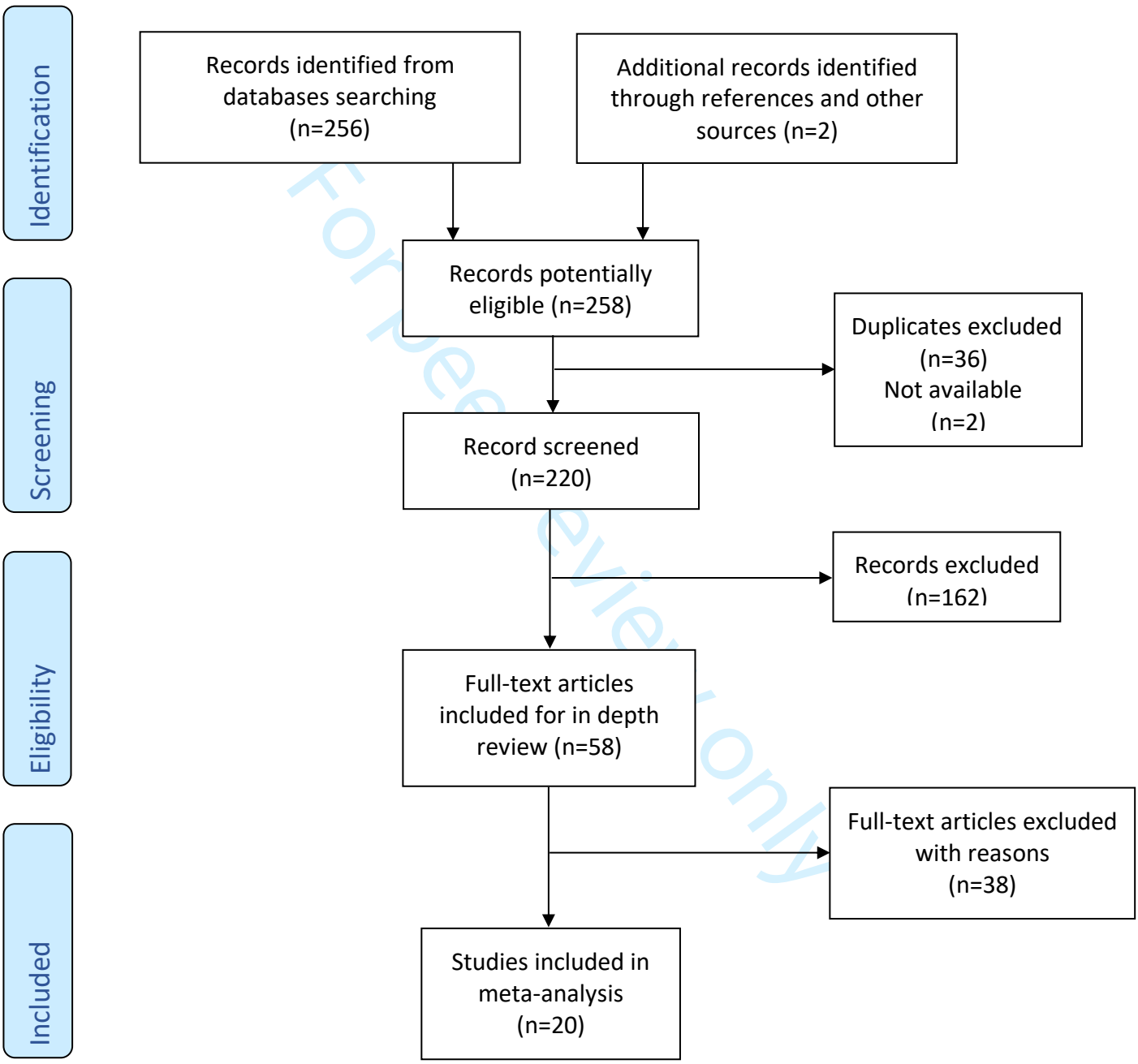
# Figure legends

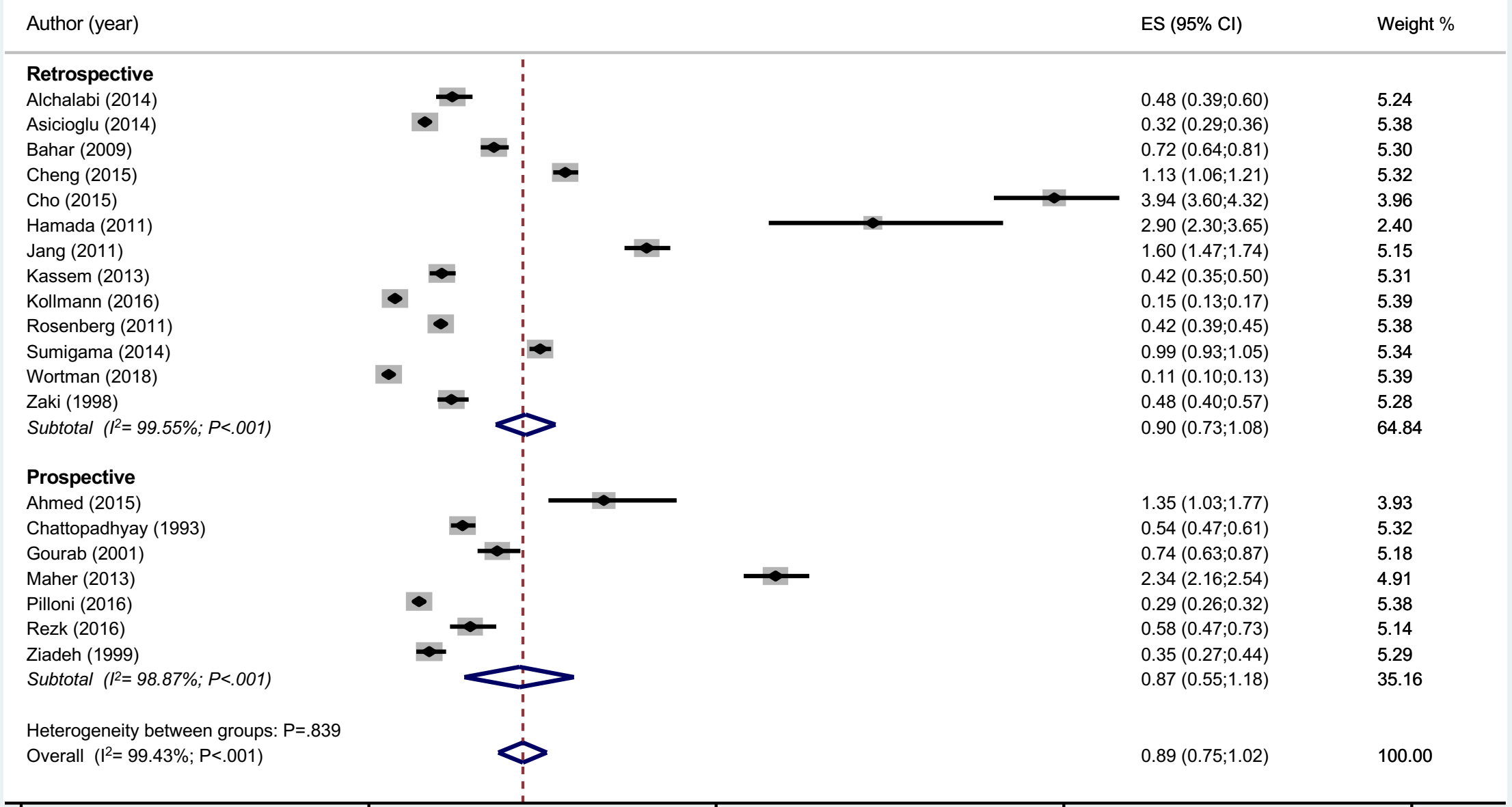
**Fig 1:** Flow diagram showing the selection of reports included in the review.

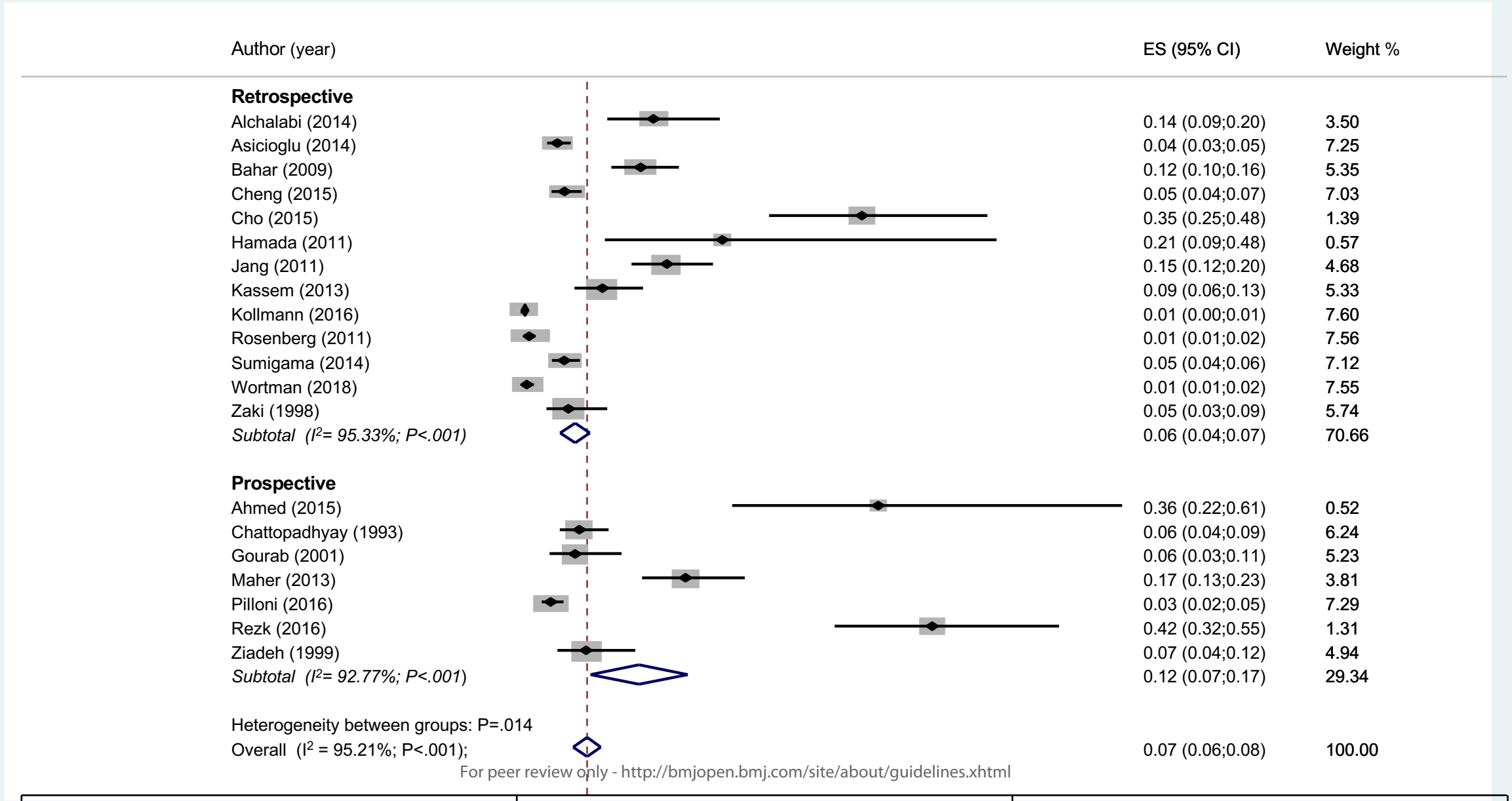
**Fig 2:** Forest plots showing the heterogeneity of prevalence data in prospective and retrospective cohort studies of women presenting with a placenta previa. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

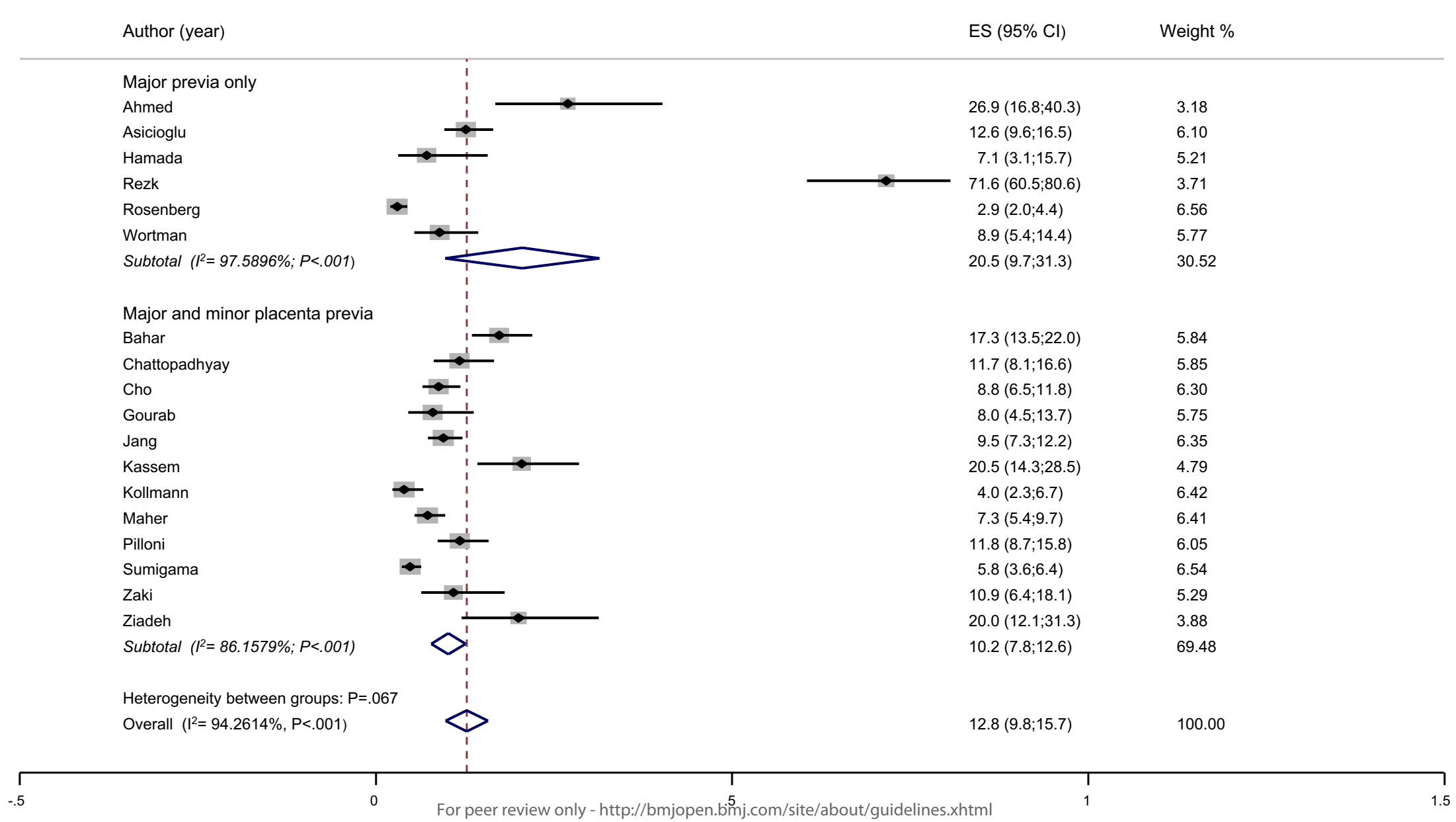
**Fig 3:** Forest plots showing heterogeneity in the prevalence data for prospective and retrospective cohort studies of women diagnosed with placenta previa accreta. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

**Fig 4:** Forest plots showing the heterogeneity in cohort studies reporting incidence data for women diagnosed with placenta previa major and PAS and those with either placenta previa minor or major and PAS. *ES, effect size. CI, confidence interval*









**Supplementary data 1: Search strategy for PubMed**

(placenta accreta*.tw OR placenta increta*.tw OR placenta percreta*.tw OR abnormally invasive placenta*.tw OR morbidly adherent placenta*.tw)
AND
(placenta previa*.tw OR major placenta previa*.tw OR minor placenta previa*.tw OR low-lying placenta*.tw)
AND
(prevalence*.tw OR incidence*.tw OR obstetric hysterectomy*.tw OR caesarean hysterectomy*.tw OR maternal mortality*.tw OR)

The search was limited to articles published in English.

**Supplementary Data 2 Electronic search strategy**

***Time period*:** August 1982 and September 2018

***Inclusion Criteria***

- Cohort studies involving women presenting with a singleton pregnancy and placenta previa complicated by accreta placentation diagnosed during the second half of pregnancy and/or at birth.
- Original publication with data on the number of pregnancies, births and/or deliveries in the corresponding population.

***Exclusion Criteria***

- Reviews, opinions, letters, protocols and conference proceedings.
- Case series and cohorts of less than 50 cases of placenta previa.
- Articles published before 1982.
- Articles in languages other than English.
- Non-human studies.

**Supplementary data 3:** Characteristics and quality assessment of the 20 studies included in the review.

| | Country | Dates | Study type | Risk of bias Categories Selection | Comparability | Outcome | Overall |
|---|---|---|---|---|---|---|---|
| Chattopadhyay et al., 1993[19] | Saudi Arabia | 1988-1992 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Zaki et al., 1998[20] | Saudi Arabia | 1990-1996 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗ | High |
| Ziadeh et al., 1999[21] | Jordan | 1995-1996 | Prospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Gourab et al., 2001[22] | Saudi Arabia | 1995-2000 | Prospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Bahar et al., 2009[23] | Saudi Arabia | 1996-2005 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Hamada et al., 2011[24] | Japan | 2007-2009 | Prospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Jang et al., 2011[25] | South Korea | 1999-2009 | Retrospective/ 3 Institutions | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Rosenberg et al., 2011[26] | Israel | 1988-2009 | Retrospective/ Region¶ | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Kassem et al., 2013[27] | Saudi Arabia | 2009-2012 | Retrospective/ Single Institution | ⊗⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Maher et al., 2013[28] | Egypt | 2008-2011 | Prospective/ Single Institution | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Alchalabi et al., 2014[29] | Jordan | 2003-2012 | Retrospective/ Single Institution* | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Asicioglu et al., 2014[30] | Turkey | 2005-2010 | Retrospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Sumigama et al., 2014[31] | Japan | 1994-2012 | Retrospective/ 11 Institutions¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Ahmed et al., 2015[32] | Egypt | 2014 | Prospective/ Single Institution¶ | ⊗⊗ | ⊗ | ⊗ | High |
| Cheng et al., 2015[33] | China | 1999-2013 | Retrospective/ Single Institution* | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Cho et al., 2015[34] | South-Korea | 1991-2013 | Retrospective/ Single Institution | ⊗⊗ | ⊗ | ⊗⊗ | Medium |
| Kollmann et al., 2016[35] | Austria | 1993-2012 | Retrospective/ Region | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Pilloni et al., 2016[36] | Italy | 2011-2014 | Prospective/ Region | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Rezk et al., 2016[37] | Egypt | 2012-2014 | Prospective/ Single Institution¶ | ⊗⊗⊗⊗ | ⊗⊗ | ⊗⊗⊗ | Low |
| Wortman et al., 2018[38] | US | 2002-2011 | Retrospective/ Single Institution¶ | ⊗⊗ | ⊗ | ⊗⊗ | Medium |

¶= Studies including major placenta previa only; * Studies with no description of the ultrasound diagnostic signs for PAS.

## MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| **Reporting of Background** | | |
| Problem definition | Yes | 5 |
| Hypothesis statement | Yes | 6 & 7 |
| Description of Study Outcome(s) | Yes | 11 |
| Type of exposure or intervention used | No | N/A |
| Type of study design used | Yes | 10 |
| Study population | Yes | 10 |
| **Reporting of Search Strategy** | | |
| Qualifications of searchers (eg, librarians and investigators) | No | 7 & 8 |
| Search strategy, including time period included in the synthesis and keywords | Yes | 7 |
| Effort to include all available studies, including contact with authors | Yes | 7 |
| Databases and registries searched | Yes | 7 |
| Search software used, name and version, including special features used (eg, explosion) | No | N/A |
| Use of hand searching (eg, reference lists of obtained articles) | Yes | 7 |
| List of citations located and those excluded, including justification | Yes | 7 |
| Method for addressing articles published in languages other than English | No | N/A |
| Method of handling abstracts and unpublished studies | Yes | 7 & 8 |
| Description of any contact with authors | No | N/A |
| **Reporting of Methods** | | |
| Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Yes | 8 |
| Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | No | N/A |
| Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) | No | N/A |
| Assessment of confounding (eg, comparability of cases and controls in studies where appropriate | No | N/A |

| Reporting Criteria | Reported (Yes/No) | Reported on Page No. |
|---|---|---|
| Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Yes | 7 & 8 |
| Assessment of heterogeneity | Yes | Figures 2-4 |
| Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | Yes | 9 |
| Provision of appropriate tables and graphics | Yes | 28 & 29 |
| **Reporting of Results** | | |
| Table giving descriptive information for each study included | Yes | Table 1 |
| Results of sensitivity testing (eg, subgroup analysis) | Yes | 12 |
| Indication of statistical uncertainty of findings | No | N/A |
| **Reporting of Discussion** | | |
| Quantitative assessment of bias (eg, publication bias) | Yes | Table 1 |
| Justification for exclusion (eg, exclusion of non–English-language citations) | No | N/A |
| Assessment of quality of included studies | Yes | 14 & 15 |
| **Reporting of Conclusions** | | |
| Consideration of alternative explanations for observed results | Yes | 16 |
| Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) | Yes | 17 |
| Guidelines for future research | Yes | 18 |
| Disclosure of funding source | Yes | 1 |

**Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.**