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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

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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

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3 of placenta previa with PAS and the incidence of PAS in the placenta previa cohort. The
4
5 high heterogeneity between studies emphasizing the need to implement standardized
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7 protocols for the diagnoses of both placenta previa and PAS, including the type of
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9 placenta previa on ultrasound imaging and grading of villous invasiveness at delivery.
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15 **Strengths and limitations of this study**

- 16
17 ⇒ This is the first study providing a comprehensive evaluation of the prevalence of
18 placenta previa complicated by PAS and the incidence of PAS in women
19 presenting with a placenta previa.
20
21 ⇒ Large amounts of heterogeneity for the prevalence and incidence of placenta
22 previa accreta highlight the effect of the absence of standardisation in reporting
23 on both placenta previa and placenta previa accreta in many cohort studies.
24
25 ⇒ Thirteen out of 20 studies included in the analysis were retrospective with
26 considerable variation between studies in both the prenatal diagnosis of placenta
27 previa and the confirmation of the diagnosis of accreta placentation at births.
28
29 ⇒ The lack of accurate data on the depth of accreta placentation in most studies
30 limits the evaluation of differences in outcome between the adherent and
31 invasive accreta previa placentation.
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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 Hertig¹ 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 al² 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

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3 10,000 births in women with both a previous caesarean delivery and placenta previa.⁸
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5 Both abnormal adherence and invasion of villous tissue into the myometrium
6 results in failure of the placenta to separate spontaneously from the uterine wall at
7 delivery.²⁻⁴ When unsuspected at the time of delivery, attempts to manually remove
8 accreta villous tissue typically provoke rapid bleeding from the utero-placental
9 circulation.^{5,11} In invasive cases, this can lead to massive obstetric hemorrhage due to
10 the disruption of the deep uterine vasculature of the increta or percreta area.^{4,5} Not
11 surprisingly, prenatal diagnosis of PAS has been shown to decrease maternal morbidity
12 and mortality, and has thus become essential in improving its management.^{12,13} Tabsh et
13 al were the first in 1982 to report on the prenatal ultrasound diagnosis of a case of
14 placenta increta.¹⁴ A recent systematic review and meta-analysis of prenatal ultrasound
15 diagnosis of placenta previa with PAS in women with a history of caesarean delivery has
16 found that the overall diagnostic accuracy of ultrasound in specialist units is in 90.9%.¹⁵
17 However, even in countries with well-established screening programs for fetal anomalies,
18 over half the cases of PAS are not diagnosed before delivery.^{8,10}
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38 Accreta placentation and in particular its invasive forms are impacting maternal
39 health outcomes globally and its prevalence is likely to increase. Women with a history
40 of previous caesarean delivery presenting with placenta previa accreta in an ongoing
41 pregnancy are now the cohort of obstetric patients with the highest risk of delivery
42 complications¹⁶, however, their epidemiology has not been comprehensively reviewed
43 yet. Health provision for the development of maternity centres with specialist teams,
44 equipment, drugs, blood bank and intensive care infrastructure to safely manage
45 women presenting with placenta previa accreta requires an accurate evaluation of its
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3 epidemiology. The objective of this meta-analysis is to review the epidemiology of
4 women presenting with placenta previa and to examine the different diagnostic criteria
5 used by the authors of cohort studies to diagnose placenta previa prenatally and PAS
6 and confirmed the diagnosis of PAS at birth.
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14 **MATERIALS AND METHODS**

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17 A systematic review was performed for articles providing data on prevalence and
18 incidence of PAS in women presenting with a placenta previa where the populations
19 sampled was defined. Embase, PubMed, Google Scholar, clinicalTrials.gov and
20 MEDLINE were searched for studies published between the first prenatal ultrasound
21 description of placenta accreta in August 1982 by Tabsh¹⁴ et al and September 2018.
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23 The search protocol was designed a priori and registered on PROSPERO
24 (CRD42017068589) (<http://www.crd.york.ac.uk/PROSPERO>). The overall search
25 strategy was inclusive of MeSH headings for “placenta accreta, placenta increta,
26 placenta percreta, abnormally invasive placenta, morbidly adherent placenta, low-lying
27 placenta, minor placenta previa, major placenta previa” which were combined with
28 terms including “prevalence, incidence, obstetric hysterectomy and caesarean
29 hysterectomy”. Title, abstracts and full-text were independently assessed by the authors
30 for content, data extraction and analysis. Additional relevant studies were identified from
31 reference lists of reviews and editorials and by hand-searching key journals and
32 websites. All search results were combined in a reference database. Duplicates were
33 removed by hand. The search was limited to articles published in English.
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3 Two independent authors (EJ and LG) selected studies in two stages. The
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5 abstracts of all potentially relevant papers were individually examined for suitability.
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7 Papers were only ruled out at this stage if they obviously did not meet the inclusion
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9 criteria. The remainder were obtained in full text and were independently assessed
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11 for content, data extraction and analysis. Disagreements between the two original
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13 reviewers were resolved by discussion with the third reviewer (JLR). Articles were
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15 excluded if; they were published before August 1982, contained no data on the study
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17 population such as the overall pregnancies, births and/or deliveries numbers, were case
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19 reports or were overlapping.
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24 Study characteristics were extracted using a predesigned data extraction
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26 protocol including: author institution, year of publication, country of origin, study period,
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28 study type (retrospective, single institution, multiple institutions), total number of cases
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30 in the study population, type of placenta previa, diagnosis of PAS at birth. The need to
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32 perform a peripartum hysterectomy, direct maternal mortality and prior surgical history
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34 were also recorded. The reference standard for differential diagnosis between minor
35
36 and major placenta previa was the evaluation of the placental position inside the uterine
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38 cavity on transvaginal ultrasound with relation to the internal cervical os. For the
39
40 diagnosis of accreta placentation, we referred to the clinical grading based on surgical
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42 findings at delivery as previously described¹⁷ and to histopathologic findings when a
43
44 caesarean hysterectomy was performed i.e. placental villi directly attached to the
45
46 myometrium without interposing decidua or invading the uterine wall.
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51 Two independent reviewers (EJ and LG) undertook the quality assessment with
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53 difference agreed by consensus. The Newcastle-Ottawa scale for observational studies
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3 was used to establish the risk of bias in selection, comparability, and outcome
4 assessment.¹⁸ Studies that scored four stars for selection, two stars for comparability,
5 and three stars for ascertainment of the outcome were regarded to have a low risk of
6 bias. Studies with two or three stars for selection, one for comparability, and two for
7 outcome ascertainment were considered to have a medium risk of bias. We deemed
8 any study with a score of one for selection or outcome ascertainment, or zero for any of
9 the three domains, to have a high risk of bias. No study was excluded based on the risk
10 of bias assessment.
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21 Analyses were conducted using STATA software (version 15; StataCorp, College
22 Station, TX). Standard Kurtosis analysis indicated that some values were not normally
23 distributed and are therefore presented as median and interquartile range (IQR). A
24 random effects model was used to combine the studies while incorporating variations
25 among studies unless there were three or less studies contributing to the meta-analysis
26 in which case a fixed effect model was used. Statistical heterogeneity was assessed
27 with the Cochran's Q-test and the I^2 statistic (the proportion of variation in study
28 estimates because of heterogeneity rather than sampling error). Forest plots are
29 presented to graphically summarize the study results and the pooled results. A test for
30 heterogeneity between sub-groups (i.e. study types) was conducted.
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47 **RESULTS**

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49 The initial search provided 256 records with cross-referencing providing an additional
50 two studies, making a total of 258 potentially relevant articles. After exclusion of
51 duplicates and the two which were not available (Figure 1), 220 remained. On screening
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3 the titles and abstracts, a further 162 were excluded as the reported outcomes were not
4 relevant, leaving 58 studies which were obtained for full text review. An additional 38
5 articles were excluded after full review including letters (n=16), narrative reviews (n= 10)
6 commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another
7 publication (n=1).
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14 The quality of the studies is shown in Figure 2. Eighteen of the 20 included
15 studies included in the final review had low or medium risk of bias for sample selection,
16 nine had low risk of bias for outcome assessment, and six had low risk of bias for
17 comparability of cohorts. Overall, 18 studies had low or medium risk of bias.
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24 Table 1 presents the study characteristics and epidemiology data of the 20
25 studies. There were 13 retrospective^{19,20,23,25-27,29-31,33-35,38} and 7
26 prospective^{21,22,24,28,32,36,37} studies including a total of 1,197,296 births and 23,864
27 pregnancies. There were 15 studies from a single institution^{19-24,27-30,32-34,37,38} and five
28 from multiple institutions^{25,31} or a geographical region.^{26,35,36} These studies included 587
29 women with placenta previa complicated by PAS out of 6,628 cases of placenta previa.
30 The median prevalence of placenta previa in the 20 studies was 0.56% (IQR 0.39;1.24)
31 whereas the median prevalence of placenta previa with PAS was 0.07% (IQR
32 0.05;0.16). The median incidence of PAS in women with a placenta previa was 11.10%
33 (IQR 7.65;17.35).
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46 All authors except two^{29,33} reported on the criteria used for the prenatal
47 ultrasound diagnosis of placenta previa. Six studies^{24,26,30,32,37,38} only included major
48 placenta previa in their cohort as defined as the placenta completely covering or
49 partially covering the internal os of the cervix. The others included both major and minor
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3 placenta previa. The definition of minor placenta previa varied with two studies^{31,36} using
4 the placental edge being <2cm from the internal os, two studies using < 3cm^{22,23} and
5 one study using <3 cm or <5 cm if associated with abnormal fetal presentation.²¹ The
6 gestational age at confirmation of the prenatal diagnosis of placenta previa was
7 reported in six studies^{22,23,24,28,32,37} and ranged between 20 weeks and 34 weeks and in
8 one study the diagnosis of placenta previa was confirmed at birth when the placenta
9 was found to be inserted in the lower segment.¹⁹

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19 The ultrasound diagnostic signs for PAS were reported in six studies^{24,28,30,32,36,37}
20 with two studies also reporting on the use of magnetic resonance imaging.^{29,38} The
21 clinical criteria used for the diagnosis of PAS at birth were reported by nine
22 studies^{19,20,23,27,28,30,33,36,37} and included a difficult delivery of the placenta without easy
23 separation uterine wall or requiring a “piecemeal removal” associated with heavy
24 bleeding and excessive bleeding from the placental bed after placental delivery. One
25 author described the presence of invasive villous tissue at delivery²⁷ and one the need
26 to suture the placental bed.²³ None of the other authors reported on the gross
27 appearance of the uterus or surgical findings at the time of caesarean delivery. In 12
28 studies^{19,23,24,27-31,33,34,36,37} the prenatal and/or clinical diagnosis was confirmed by
29 histopathological examination with detailed description of the microscopic criterion only
30 reported in six^{19,27,28,30,31,37}. Detailed histopathological findings on the depth of villous
31 invasiveness were reported in nine studies^{24,27-29,31,33,34,36,37} out of the 20 studies. These
32 included 283 cases of placenta previa accreta graded for 171 (60.4%) as placenta creta
33 (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta percreta.
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3 All authors but two^{22,23} reported on prior surgical history including caesarean
4 section^{19-21,24-38}, uterine curettage^{28,30-32,34,37,38} and myomectomy.^{28,36,37} Data on surgical
5 management was available in 14 out of the 20 studies^{19,20,23,27-31,33-38} with 314 out of 441
6 women presenting with a placenta previa complicated by PAS. The median peri-partum
7 hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal mortality were available
8 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}
9 out of 387 (1.3%) cases of placenta previa with PAS.

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

22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 **DISCUSSION**

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49 This study provides a comprehensive evaluation of the prevalence of placenta previa
50 complicated by PAS and the incidence of PAS in women presenting with a placenta
51 previa. Women with a prior history of caesarean delivery presenting with a low-
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3 lying/placenta previa represent more than 90% of the cases of PAS.^{8,10,16} The meta-
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5 analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa
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7 and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the
8
9 need to use international standardized clinical protocols for the screening and
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11 management of this complex obstetric condition. The current situation limits the capacity
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13 building of healthcare providers on improvements in training, implementation of
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15 guidelines and changes in clinical practice behaviour.
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19 Defining the position of the placenta inside the uterus was one of the first aims of
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21 obstetric ultrasound examination.^{39,40} Following the development of real-time ultrasound
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23 imaging, placental location became an integral part of the mid-pregnancy ultrasound
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25 examination.⁴¹ Placenta previa was initially described with transabdominal scan as a
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27 placenta developing within the lower uterine segment and classified according to the
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29 relationship and/or the distance between the lower placental edge and the internal os of
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31 the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine
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33 segment down to the internal os and major placenta previa when the placenta covers the
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35 cervix. Minor placenta previa can be further subdivided into low-lying placenta when the
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37 lower edge does not reach the internal os and marginal placenta previa when it does.
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39 Major placenta previa can also be described as partial or complete depending on the
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41 amount of placental tissue covering the cervix. The use of transvaginal scanning has
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43 allowed for a more precise evaluation of the distance between the placental edge and the
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45 internal os^{42,43} but as demonstrated in our meta-analysis, the reporting of the ultrasound
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47 criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we
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49 found also wide variation in the gestational age at diagnosis. The timing of the
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3 confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of
4 minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.^{44,45} An
5 expert panel of the American Institute of Ultrasound in Medicine⁴⁶ has recently
6 recommended ceasing the use of the terms 'partial' and 'marginal' and using the term
7 'placenta previa' only when the placenta lies directly over the internal os. The placenta
8 should be reported as 'low lying' when the placental edge is less than 2 cm from the
9 internal os and as normal when the placental edge is more than 2 cm from the internal
10 os. The findings of our meta-analysis highlight the need for the use of such a classification
11 in further studies.
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24 Only six of the 20 studies included in the present meta-analysis provided data on
25 the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included
26 in the systematic review all studies published since the first ultrasound description of
27 PAS by Tabsh et al in 1982.¹⁴ We found no studies between 1982 and 1993 (Table 1)
28 which corresponds to the time when high-resolution grey-scale ultrasound imaging
29 became widely available. Colour-Doppler imaging was introduced for the diagnosis of
30 PAS in 1992⁴⁷, however the sensitivity and specificity of grey-scale imaging alone in
31 diagnosing for placenta previa accreta are high when performed by experience
32 operators.¹⁵ These findings indicate that the prenatal diagnosis of PAS can be
33 performed using standard ultrasound equipment. Unlike placenta previa which is
34 routinely screened for at the time of the fetal anomaly scan, PAS is currently not
35 screened for and the data available on the prenatal diagnosis of the condition come
36 exclusively from specialist centres.¹⁶ In these centres, the diagnostic accuracy of
37 ultrasound imaging is over 90%, but similarly, to placenta previa, the description of the
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3 ultrasound signs used for the diagnosis of PAS, over the last two decades, has also
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5 been highly variable.^{47,48} The European Working Group on Abnormally Invasive
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7 Placenta and the Abnormally Invasive Placenta international expert group have recently
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9 proposed a standardised description of ultrasound signs used for the prenatal diagnosis
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11 and a proforma protocol for the ultrasound assessment of PAS.^{49,50} The use of these
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13 protocols in prospective studies should also facilitate the screening of patients at high
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15 risk of PAS and in particular those with multiple prior caesarean deliveries presenting
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17 with a low-lying or placenta previa.⁵¹
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22 We found significant heterogeneity in the qualitative definition and diagnosis of
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24 PAS at birth among the nine studies that provided a description of the clinical
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26 findings.^{19,20,23,27,28,30,33,36,37} Only one of these studies described the invasive
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28 appearance of placental tissue at delivery²⁷ whereas the others reported a difficult
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30 delivery of the placenta without easy separation from the uterine wall or requiring a
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32 “piecemeal removal” associated with heavy bleeding as diagnostic of PAS. These
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34 clinical criteria were first described by Irving and Hertig⁴ in 1937 who did not have
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36 invasive cases in their cohort and thus their definition only applies to abnormally
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38 adherent placenta and not to placenta increta or percreta. This definition also fails to
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40 clearly differentiate between abnormal adherence and placental retention as both
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42 present with similar clinical symptoms and etiology⁵² leading to possible over diagnosis
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44 of placenta previa accreta. Similarly, the finding of excessive bleeding from the
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46 placental bed after delivery of the placenta is a common complication of non-accreta
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48 placenta previa due to the implantation of the placenta in the lower uterine segment
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50 which contains less muscular fibers than the upper segment and is often thinner and
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3 dehiscent after multiple caesarean deliveries.
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5 Detailed histopathologic reports can only be obtained in those patients who have
6 a hysterectomy or a partial myometrial resection and thus in many studies there is not
7 histopathologic confirmation of the clinical diagnosis. The main histological diagnostic
8 criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi
9 and the superficial myometrium, is found with increasing incidence with advancing
10 gestation in pregnancies with no clinical evidence of PAS.⁵ Thus the combination of
11 clinical criteria that do not differentiate between placenta retention and adherent accreta
12 and the use of non-diagnostic criteria of villous invasiveness may result in the over-
13 diagnosis of the adherent grade of PAS, in particular in those studies reporting a low
14 rate of caesarean hysterectomy.^{28,36} Overall, this can explain the wide range in the
15 prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to 71.6%) of
16 PAS in women presenting with placenta previa (Figures 3 and 4).
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33 Overall, management strategies and outcomes will vary depending on the
34 accuracy of prenatal diagnosis, local surgical expertise and more recently access to a
35 centre of excellence with multidisciplinary team approach.^{53,54} In cases of high suspicion
36 of PAS during cesarean delivery, 60-70% of obstetricians gynecologists proceed with a
37 peripartum hysterectomy.^{55,56} By contrast with a conservative management approach,
38 radical surgery is often considered to be safer, in particular in cases of invasive
39 placentation.⁵⁷ The association between a placenta previa and a PAS increases the
40 risks of both maternal morbidity and mortality. In the present study we found that a
41 caesarean hysterectomy was the primary management option in around 70% of the
42 patients presenting with a placenta previa and PAS. The inter-study range was wide
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3 with four studies^{19,21,29,37} reporting peripartum hysterectomy rates < 50%, five^{28,31,32,34,36}
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5 had rates between 50-99% and four^{22,30,35,38} had rates of 100%. This may be due to
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7 difference in study protocols, local expertise and the impact of prenatal diagnosis on
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9 management strategies but also as suggested by our analysis to difference in the rates
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11 of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed
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13 histopathologic examination confirming the diagnosis.
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17 The main limitations of this review are the quality of the published data. Thirteen
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19 out of 20 studies included in the analysis studies were retrospective and there was wide
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21 variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta
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23 previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed
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25 histopathology data to confirm the clinical diagnosis. This is hampering the analysis of
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27 the secondary outcome in particular the incidence of major hemorrhage at delivery and
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29 the need and amount of blood transfusion but also the choice in management protocols
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31 and in particular the use of conservative management procedures. We would not,
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33 therefore, recommend the use of the pooled estimates beyond as a driver towards the
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35 development of standardized diagnostic protocols.
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40 The prevalence of PAS in the general population of women giving birth varies
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42 widely.^{8,10,58,59} This may be due to several factors including national and local caesarean
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44 delivery rates, expertise in diagnosing the condition antenatally and access to perinatal
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46 pathologist to confirm the diagnosis at birth. There is a need for further prospective multi-
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48 centre studies with participatory methodologies involving local service providers and
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50 facility management to accurately evaluate the consequences of high caesarean sections
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52 rates on maternal health within a particular population. Within this context, accurate
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3 epidemiologic data on PAS disorders are essential in planning screening programs and
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5 in making provision for the development of centres of excellence for the management of
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7 this increasingly common complex obstetric condition. Whilst the concept of core outcome
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9 measures within clinical trials is now well recognised and championed, greater efforts to
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11 disseminate this approach in epidemiological research to facilitate global estimation and
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13 recognition of problems emerging on a global scale. Our study supports implementation,
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15 in both clinical practice and in reporting data on placenta previa accreta in the medical
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17 literature, of standardized protocols for prenatal diagnosis of both placenta previa and
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19 PAS, for the clinical diagnosis of PAS at birth and for the histopathologic confirmation
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21 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)
Ascioglu 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.

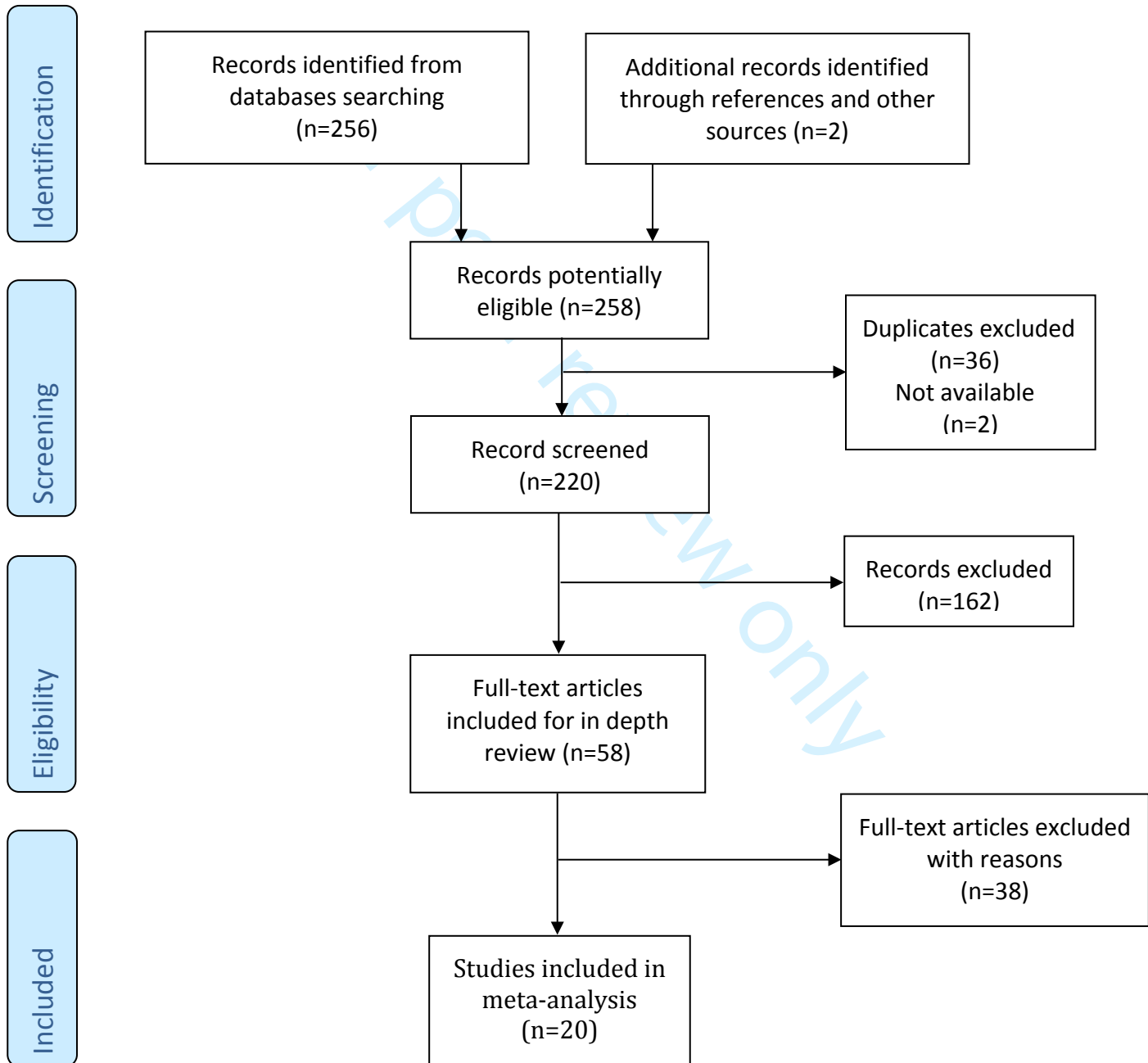
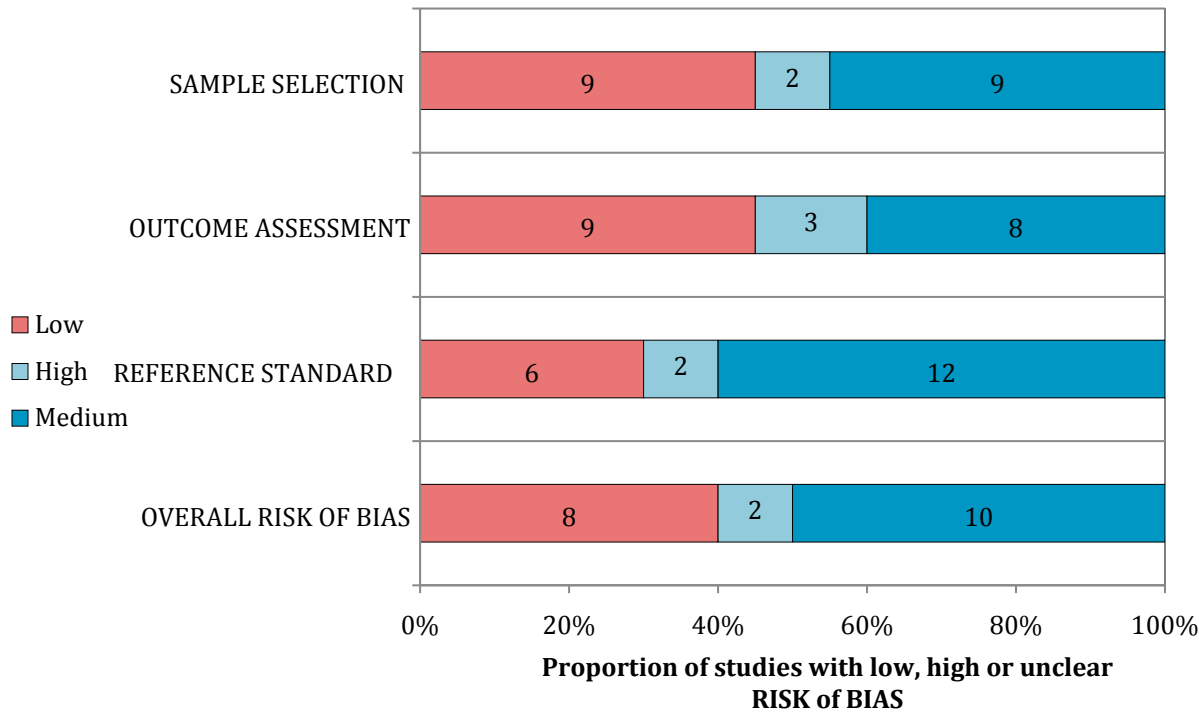


Fig 2: Quality assessment using the Newcastle-Ottawa Scale for cohort studies.



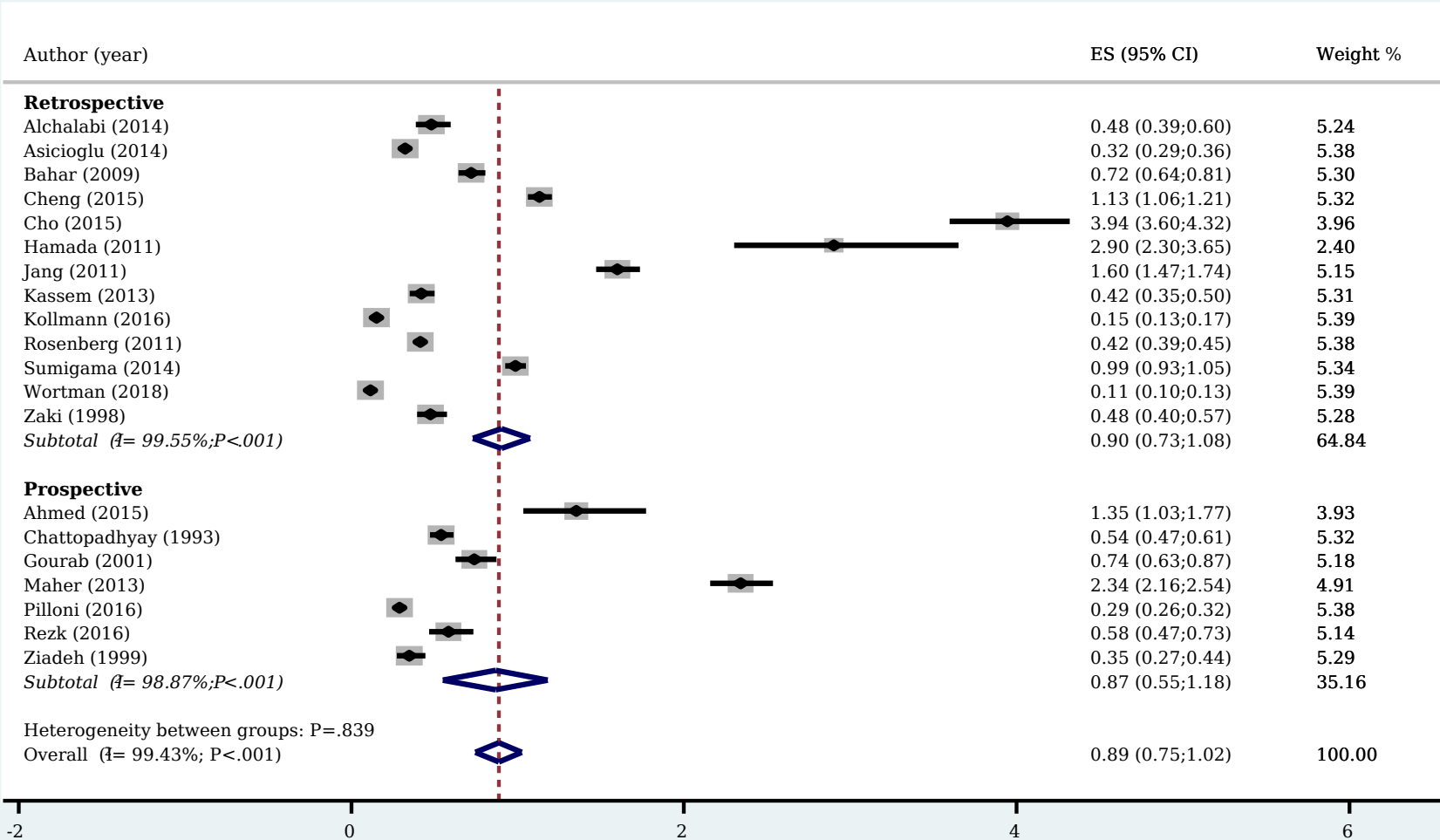
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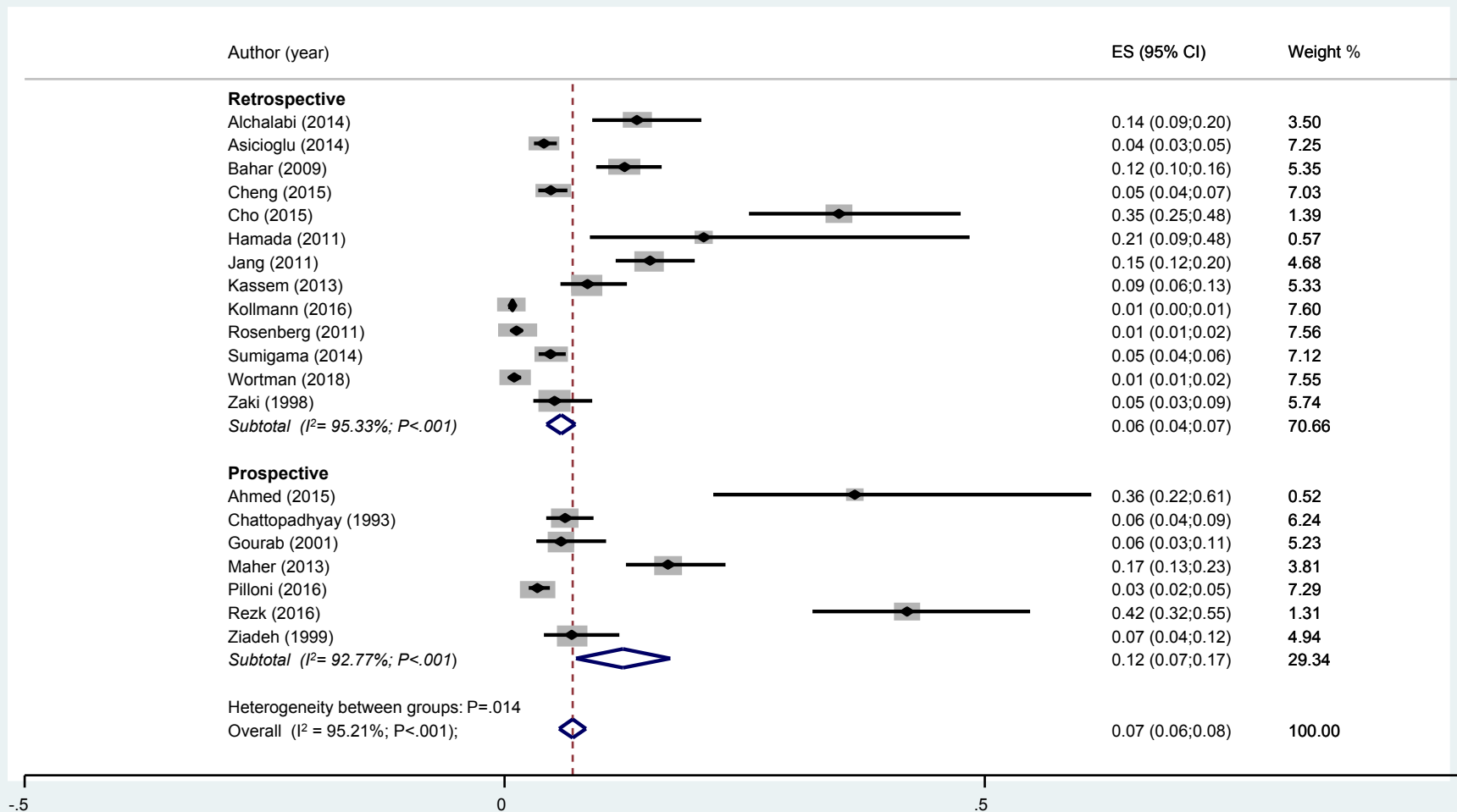
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3 **Fig 3:** Forest plots showing the heterogeneity of prevalence data in prospective and
4 retrospective cohort studies of women presenting with a placenta previa. Only first
5 author's name is given for each reference.
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7
8 **Fig 4:** Forest plots showing heterogeneity in the prevalence data for prospective and
9 retrospective cohort studies of women diagnosed with placenta previa and PAS. Only
10 first author's name is given for each reference.
11

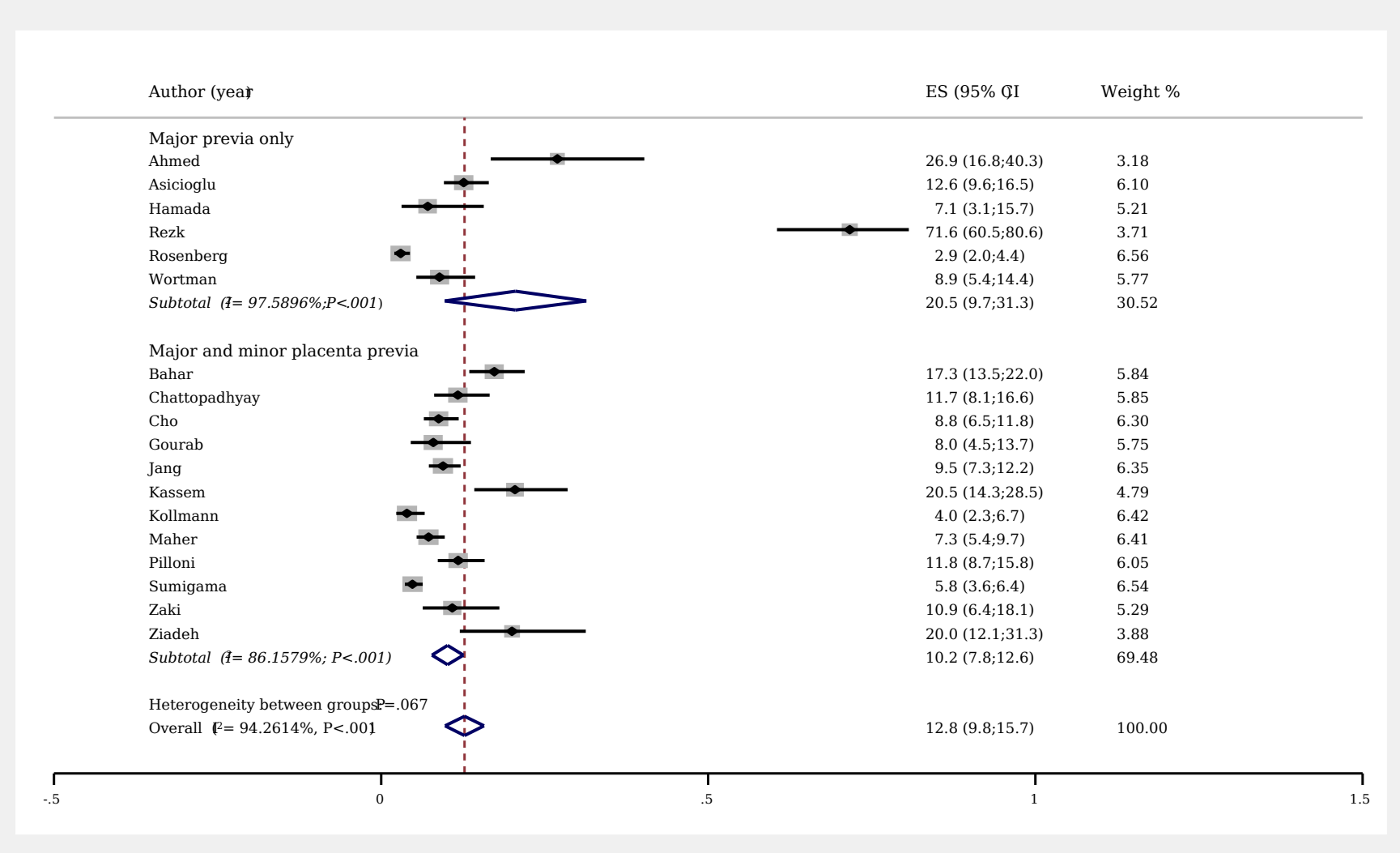
12 **Fig 5:** Forest plots showing the heterogeneity in cohort studies reporting incidence data
13 for women diagnosed with placenta previa major and PAS and those with either
14 placenta previa minor or major and PAS.
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PRISMA 2009 Checklist

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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

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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

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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

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Competing interest

The authors report no conflict of interest.

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

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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

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3 prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of
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5 PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).
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7 **Conclusions** The high heterogeneity in qualitative and diagnostic data between studies
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9 emphasizes the need to implement standardized protocols for the diagnoses of both
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11 placenta previa and PAS, including the type of placenta previa and grade of villous
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13 invasiveness.
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19 PROSPERO Registration CRD42017068589
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23 **Strengths and limitations of this study**

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26 • This study provides the first comprehensive evaluation of the epidemiology of
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28 placenta previa complicated by PAS.
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32 • The search was performed using predetermined eligibility criteria in a defined
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34 obstetric population.
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37 • Thirteen out of 20 studies included in the study were retrospective limiting the
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39 overall quality of the analysis.
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42 • Only six studies provided data on the prenatal ultrasound diagnosis of PAS in
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44 patients with placenta previa and nine studies on detailed histopathological
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46 findings.
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- 48
49 • High level of inconsistency between estimates in prevalence and incidence did
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51 not allow for full meta-analysis of the clinical outcomes.
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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 Hertig¹ 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 al² 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

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3 10,000 births in women with both a previous caesarean delivery and placenta previa.⁸
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5 Both abnormal adherence and invasion of villous tissue into the myometrium
6 results in failure of the placenta to separate spontaneously from the uterine wall at
7 delivery.²⁻⁴ When unsuspected at the time of delivery, attempts to manually remove
8 accreta villous tissue typically provoke rapid bleeding from the utero-placental
9 circulation.^{5,11} In invasive cases, this can lead to massive obstetric hemorrhage due to
10 the disruption of the deep uterine vasculature of the increta or percreta area.^{4,5} Not
11 surprisingly, prenatal diagnosis of PAS has been shown to decrease maternal morbidity
12 and mortality, and has thus become essential in improving its management.^{12,13} Tabsh et
13 al were the first in 1982 to report on the prenatal ultrasound diagnosis of a case of
14 placenta increta.¹⁴ A recent systematic review and meta-analysis of prenatal ultrasound
15 diagnosis of placenta previa with PAS in women with a history of caesarean delivery has
16 found that the overall diagnostic accuracy of ultrasound in specialist units is in 90.9%.¹⁵
17 However, even in countries with well-established screening programs for fetal anomalies,
18 over half the cases of PAS are not diagnosed before delivery.^{8,10}
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38 Accreta placentation and in particular its invasive forms are impacting maternal
39 health outcomes globally and its prevalence is likely to increase. Women with a history
40 of previous caesarean delivery presenting with placenta previa complicated by PAS in
41 an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of
42 delivery complications¹⁶, however, their epidemiology has not been comprehensively
43 reviewed yet. Health provision for the development of maternity centres with specialist
44 teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage
45 women presenting with placenta previa and PAS requires an accurate evaluation of its
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3 epidemiology. The objective of this meta-analysis is to review the epidemiology of
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5 women presenting with placenta previa and to examine the different criteria used by the
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7 authors of cohort studies to diagnose placenta previa and PAS prenatally and to confirm
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9 the diagnosis of PAS at birth.
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14 **MATERIALS AND METHODS**

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17 A systematic review was undertaken of articles providing data on prevalence and
18
19 incidence of PAS in women presenting with a placenta previa where the populations
20
21 sampled were defined. PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were
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23 searched for studies published between the first prenatal ultrasound description of
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25 placenta accreta in August 1982 by Tabsh¹⁴ et al and September 2018. The search
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27 protocol was designed *a priori* and registered on PROSPERO (CRD42017068589). The
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29 overall search strategy was inclusive of MeSH headings for “placenta accreta, placenta
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31 increta, placenta percreta, abnormally invasive placenta, morbidly adherent placenta
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33 and major placenta previa” which were combined with terms including “prevalence,
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35 incidence, obstetric hysterectomy and caesarean hysterectomy”. Title, abstracts and
36
37 full-text were independently assessed by the authors for content, data extraction and
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39 analysis. Additional relevant studies were identified from reference lists of reviews and
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41 editorials and by hand-searching key journals and websites. All search results were
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43 combined in a reference database. Duplicates were removed by hand. The search was
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45 limited to articles published in English.
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52 Two independent investigators (EJ and LG) selected studies in two stages. The
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54 abstracts of all potentially relevant papers were individually examined for suitability.
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3 Papers were only ruled out at this stage if they obviously did not meet the inclusion
4 criteria. The remainder were obtained in full text and were independently assessed
5 for content, data extraction and analysis. Disagreements between the two original
6 reviewers were resolved by discussion with the third investigator (JLR). Articles were
7 excluded if; they were published before August 1982, contained no data on the study
8 population such as the overall pregnancies, births and/or deliveries numbers, were case
9 reports or were overlapping.
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19 Study characteristics were extracted using a predesigned data extraction
20 protocol including: author institution, year of publication, country of origin, study period,
21 study type (retrospective, single institution, multiple institutions), total number of cases
22 in the study population, type of placenta previa, diagnosis of PAS at birth (Appendix 1).
23 Outcome measures included the need to perform a peripartum hysterectomy and direct
24 maternal mortality. Prior surgical history was also recorded. The reference standard for
25 differential diagnosis between minor and major placenta previa was recorded based on
26 the placental position inside the uterine cavity on transvaginal ultrasound with relation to
27 the internal cervical os. For the diagnosis of accreta placentation, we referred to the
28 clinical grading based on surgical findings at delivery as previously described¹⁷ and to
29 histopathologic findings when a caesarean hysterectomy was performed i.e. placental
30 villi directly attached to the myometrium without interposing decidua or invading the
31 uterine wall.
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49 Two independent reviewers (EJ and LG) undertook the quality assessment with
50 difference agreed by consensus. The Newcastle-Ottawa scale for observational studies
51 was used to establish the risk of bias in selection, comparability, and outcome
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3 assessment.¹⁸ Studies that scored four stars for selection, two stars for comparability,
4 and three stars for ascertainment of the outcome were regarded to have a low risk of
5 bias. Studies with two or three stars for selection, one for comparability, and two for
6 outcome ascertainment were considered to have a medium risk of bias. We deemed
7 any study with a score of one for selection or outcome ascertainment, or zero for any of
8 the three domains, to have a high risk of bias. No study was excluded based on the risk
9 of bias assessment.

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11 Analyses were conducted using STATA software (version 15; StataCorp, College
12 Station, TX). Standard Kurtosis analysis indicated that some values were not normally
13 distributed and study specific estimates are therefore presented as median and
14 interquartile range (IQR). A random effects model was used to combine the studies
15 while incorporating variations among studies unless there were three or less studies
16 contributing to the meta-analysis in which case a fixed effect model was used. Statistical
17 heterogeneity was assessed with the Cochran's Q-test and the I² statistic (the
18 proportion of variation in study estimates because of heterogeneity rather than sampling
19 error). Forest plots are presented to graphically summarize the study results and the
20 pooled results. A test for heterogeneity between sub-groups (i.e. study types) was
21 conducted.

22 **Patients and public involvement**

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

24 **RESULTS**

25 The initial search provided 256 records with cross-referencing providing an additional
26 two studies, making a total of 258 potentially relevant articles. After exclusion of
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3 duplicates and the two which were not available (Figure 1), 220 remained. On screening
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5 the titles and abstracts, a further 162 were excluded as the reported outcomes were not
6
7 relevant, leaving 58 studies which were obtained for full text review. An additional 38
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9 articles were excluded after full review including letters (n=16), narrative reviews (n= 10)
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11 commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another
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13 publication (n=1), leaving 20 articles for the final analysis.¹⁹⁻³⁸
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17 The characteristics and the results of the quality assessment are displayed in
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19 table 1. There were 13 retrospective^{19,20,23,25-27,29-31,33-35,38} and 7
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21 prospective^{21,22,24,28,32,36,37} studies including a total of 1,207,296 births and 23,864 cases
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23 referred as pregnancies. There were 15 studies from a single institution^{19-24,27-30,32-34,37,38}
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25 and five from multiple institutions^{25,31} or a geographical region.^{26,35,36} Overall, 18 studies
26
27 had low or medium risk of bias.
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31 Table 2 presents the epidemiology data of the 20 studies. These studies included
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33 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta
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35 previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR
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37 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07%
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39 (IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was
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41 11.10% (IQR 7.65;17.35).
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45 All authors except two^{29,33} reported on the criteria used for the prenatal
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47 ultrasound diagnosis of placenta previa. Six studies^{24,26,30,32,37,38} only included major
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49 placenta previa in their cohort as defined as the placenta completely covering or
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51 partially covering the internal os of the cervix. The others included both major and minor
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53 placenta previa. The definition of minor placenta previa varied with two studies^{31,36} using
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3 the placental edge being <2cm from the internal os, two studies using < 3cm^{22,23} and
4 one study using <3 cm or <5 cm if associated with abnormal fetal presentation.²¹ The
5 gestational age at confirmation of the prenatal diagnosis of placenta previa was
6 reported in six studies ^{22,23,24,28,32,37} and ranged between 20 weeks and 34 weeks and in
7 one study the diagnosis of placenta previa was confirmed at birth when the placenta
8 was found to be inserted in the lower segment.¹⁹

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17 The ultrasound diagnostic signs for PAS were reported in six studies^{24,28,30,32,36,37}
18 with two studies also reporting on the use of magnetic resonance imaging.^{29,38} The
19 clinical criteria used for the diagnosis of PAS at birth were reported by nine
20 studies^{19,20,23,27,28,30,33,36,37} and included a difficult delivery of the placenta without easy
21 separation uterine wall or requiring a “piecemeal removal” associated with heavy
22 bleeding and excessive bleeding from the placental bed after placental delivery. One
23 author described the presence of invasive villous tissue at delivery²⁷ and one the need
24 to suture the placental bed.²³ None of the other authors reported on the gross
25 appearance of the uterus or surgical findings at the time of caesarean delivery. In 12
26 studies^{19,23,24,27-31,33,34,36,37} the prenatal and/or clinical diagnosis was confirmed by
27 histopathological examination with detailed description of the microscopic criterion only
28 reported in six^{19,27,28,30,31,37}. Detailed histopathological findings on the depth of villous
29 invasiveness were reported in nine studies^{24,27-29,31,33,34,36,37} out of the 20 studies. These
30 included 283 cases of placenta previa accreta graded for 171 (60.4%) as placenta creta
31 (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta percreta.

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

12
13 All authors but two^{22,23} reported on prior surgical history including
14 caesarean section^{19-21,24-38}, uterine curettage^{28,30-32,34,37,38} and myomectomy.^{28,36,37} Data
15 on surgical management was available in 14 out of the 20 studies^{19,20,23,27-31,33-38} with
16 314 out of 441 women presenting with a placenta previa complicated by PAS. The
17 median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal
18 mortality were available in 13 studies^{19-21,23,25,27-30,32,35,37,38} and PAS accounted for 5
19 maternal deaths^{19,20,25,29,30} out of 387 (1.3%) cases of placenta previa with PAS.

20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 **DISCUSSION**

43
44 This study provides a comprehensive evaluation of the prevalence of placenta previa
45 complicated by PAS and the incidence of PAS in women presenting with a placenta
46 previa. Women with a prior history of caesarean delivery presenting with a low-
47 lying/placenta previa represent more than 90% of the cases of PAS.^{8,10,16} The meta-
48 analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa
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3 and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the
4 need to use international standardized clinical protocols for the screening and
5 management of this complex obstetric condition. The current situation limits the capacity
6 building of healthcare providers on improvements in training, implementation of
7 guidelines and changes in clinical practice behaviour.
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15 Defining the position of the placenta inside the uterus was one of the first aims of
16 obstetric ultrasound examination.^{39,40} Following the development of real-time ultrasound
17 imaging, placental location became an integral part of the mid-pregnancy ultrasound
18 examination.⁴¹ Placenta previa was initially described with transabdominal scan as a
19 placenta developing within the lower uterine segment and classified according to the
20 relationship and/or the distance between the lower placental edge and the internal os of
21 the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine
22 segment down to the internal os and major placenta previa when the placenta covers the
23 cervix. Minor placenta previa can be further subdivided into low-lying placenta when the
24 lower edge does not reach the internal os and marginal placenta previa when it does.
25 Major placenta previa can also be described as partial or complete depending on the
26 amount of placental tissue covering the cervix. The use of transvaginal scanning has
27 allowed for a more precise evaluation of the distance between the placental edge and the
28 internal os^{42,43} but as demonstrated in our meta-analysis, the reporting of the ultrasound
29 criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we
30 found also wide variation in the gestational age at diagnosis. The timing of the
31 confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of
32 minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.^{44,45} An
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3 expert panel of the American Institute of Ultrasound in Medicine⁴⁶ has recently
4 recommended ceasing the use of the terms 'partial' and 'marginal' and using the term
5 'placenta previa' only when the placenta lies directly over the internal os. The placenta
6 should be reported as 'low lying' when the placental edge is less than 2 cm from the
7 internal os and as normal when the placental edge is more than 2 cm from the internal
8 os. The findings of our meta-analysis highlight the need for the use of such a classification
9 in further studies.
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19 Only six of the 20 studies included in the present meta-analysis provided data on
20 the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included
21 in the systematic review all studies published since the first ultrasound description of
22 PAS by Tabsh et al in 1982.¹⁴ We found no studies between 1982 and 1993 (Table 1)
23 which corresponds to the time when high-resolution grey-scale ultrasound imaging
24 became widely available. Colour-Doppler imaging was introduced for the diagnosis of
25 PAS in 1992⁴⁷, however the sensitivity and specificity of grey-scale imaging alone in
26 diagnosing for placenta previa accreta are high when performed by experience
27 operators.¹⁵ These findings indicate that the prenatal diagnosis of PAS can be
28 performed using standard ultrasound equipment. Unlike placenta previa which is
29 routinely screened for at the time of the fetal anomaly scan, PAS is currently not
30 screened for and the data available on the prenatal diagnosis of the condition come
31 exclusively from specialist centres.¹⁶ In these centres, the diagnostic accuracy of
32 ultrasound imaging is over 90%, but similar to placenta previa, the description of the
33 ultrasound signs used for the diagnosis of PAS has also been highly variable over the
34 last two decades.^{47,48} The European Working Group on Abnormally Invasive Placenta
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3 and the Abnormally Invasive Placenta international expert group have recently
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5 proposed standardised descriptions of the ultrasound signs used for the prenatal
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7 diagnosis and a protocol for the ultrasound assessment of PAS.^{49,50} The use of these
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9 protocols in prospective studies should also facilitate the screening of patients at high
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11 risk of PAS and in particular those with multiple prior caesarean deliveries presenting
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13 with a low-lying or placenta previa.⁵¹
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17 We found significant heterogeneity in the qualitative definition and diagnosis of
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19 PAS at birth among the nine studies that provided a description of the clinical
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21 findings.^{19,20,23,27,28,30,33,36,37} Only one of these studies described the invasive
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23 appearance of placental tissue at delivery²⁷ whereas the others reported a difficult
24
25 delivery of the placenta without easy separation from the uterine wall or requiring a
26
27 “piecemeal removal” associated with heavy bleeding as diagnostic of PAS. These
28
29 clinical criteria were first described by Irving and Hertig¹ in 1937 who did not have
30
31 invasive cases in their cohort and thus their definition only applies to abnormally
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33 adherent placenta and not to placenta increta or percreta. This definition also fails to
34
35 clearly differentiate between abnormal adherence and placental retention as both
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37 present with similar clinical symptoms and etiology⁵² leading to possible over diagnosis
38
39 of placenta previa accreta. Similarly, the finding of excessive bleeding from the
40
41 placental bed after delivery of the placenta is a common complication of non-accreta
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43 placenta previa due to the implantation of the placenta in the lower uterine segment
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45 which contains less muscular fibers than the upper segment and is often thinner and
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47 dehiscent after multiple caesarean deliveries.
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54 Detailed histopathologic reports can only be obtained in those patients who have
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3 a hysterectomy or a partial myometrial resection and thus in many studies there is not
4
5 histopathologic confirmation of the clinical diagnosis. The main histological diagnostic
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7 criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi
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9 and the superficial myometrium, is found with increasing incidence with advancing
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11 gestation in pregnancies with no clinical evidence of PAS.⁵ Thus the combination of
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13 clinical criteria that do not differentiate between placenta retention and adherent accreta
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15 and the use of non-diagnostic criteria of villous invasiveness may result in the over-
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17 diagnosis of the adherent grade of PAS, in particular in those studies reporting a low
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19 rate of caesarean hysterectomy.^{28,36} Overall, this can explain the wide range in the
20
21 prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to 71.6%) of
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23 PAS in women presenting with placenta previa (Figures 3 and 4).

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28 Overall, management strategies and outcomes will vary depending on the
29
30 accuracy of prenatal diagnosis, local surgical expertise and more recently access to a
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32 centre of excellence with multidisciplinary team approach.^{53,54} In cases of high suspicion
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34 of PAS during cesarean delivery, 60-70% of obstetricians gynecologists proceed with a
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36 peripartum hysterectomy.^{55,56} By contrast with a conservative management approach,
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38 radical surgery is often considered to be safer, in particular in cases of invasive
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40 placentation.⁵⁷ The association between a placenta previa and a PAS increases the
41
42 risks of both maternal morbidity and mortality. In the present study we found that a
43
44 caesarean hysterectomy was the primary management option in around 70% of the
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46 patients presenting with a placenta previa and PAS. The inter-study range was wide
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48 with four studies^{19,21,29,37} reporting peripartum hysterectomy rates < 50%, five^{28,31,32,34,36}
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50 had rates between 50-99% and four^{22,30,35,38} had rates of 100%. This may be due to
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3 difference in study protocols, local expertise and the impact of prenatal diagnosis on
4 management strategies but also as suggested by our analysis to difference in the rates
5 of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed
6 histopathologic examination confirming the diagnosis.
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12 The main limitations of this review are the quality of the published data. Thirteen
13 out of 20 studies included in the analysis studies were retrospective and there was wide
14 variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta
15 previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed
16 histopathology data to confirm the clinical diagnosis. This is hampering the meta-
17 analysis of the clinical outcomes in particular the incidence of major hemorrhage at
18 delivery and the need and amount of blood transfusion but also the choice in
19 management protocols and in particular the use of conservative management
20 procedures. We would not, therefore, recommend the use of the pooled estimates
21 beyond that of a driver towards the development of standardized diagnostic protocols.
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35 The prevalence of PAS in the general population of women giving birth varies
36 widely.^{8,10,58,59} A systematic review and meta-analysis of the prevalence of placenta
37 praevia has found evidence suggestive of regional variation.⁶⁰ As both conditions are
38 often associated with prior caesarean sections it is likely that national and local caesarean
39 delivery rates, expertise in diagnosing both conditions antenatally and access to perinatal
40 pathologist to confirm the diagnosis of PAS at birth will influence these epidemiology data.
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49 There is a need for further prospective multi-centre studies with participatory
50 methodologies involving local service providers and facility management to accurately
51 evaluate the consequences of high caesarean sections rates on maternal health within a
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3 particular population. Within this context, accurate epidemiologic data on PAS disorders
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5 are essential in planning screening programs and in making provision for the development
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7 of centres of excellence for the management of this increasingly common complex
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9 obstetric condition. Whilst the concept of core outcome measures within clinical trials is
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11 now well recognised and championed, greater efforts are required to disseminate this
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13 approach in epidemiological research to facilitate global estimation and recognition of
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15 problems emerging on a worldwide scale. Our study supports implementation, in both
16
17 clinical practice and in reporting data on placenta previa accreta in the medical literature,
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19 of standardized protocols for prenatal diagnosis of both placenta previa and PAS, for the
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21 clinical diagnosis of PAS at birth and for the histopathologic confirmation examination.
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31 **Author contributions**

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33 EJ, CB and JLR contributed equally to the study design. EJ, LG and JLR collected the
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35 data and carried out the qualitative analysis. CB and EJ carried out the quantitative
36
37 analysis. EJ, JLR and SC drafted the manuscript. All authors were involved in the critical
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39 discussion and approved this final version for publication. EJ is the guarantor of the study.
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45 **Data sharing statement**

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

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49 doi:10.5061/dryad.5ds4833
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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)
Ascioglu 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)

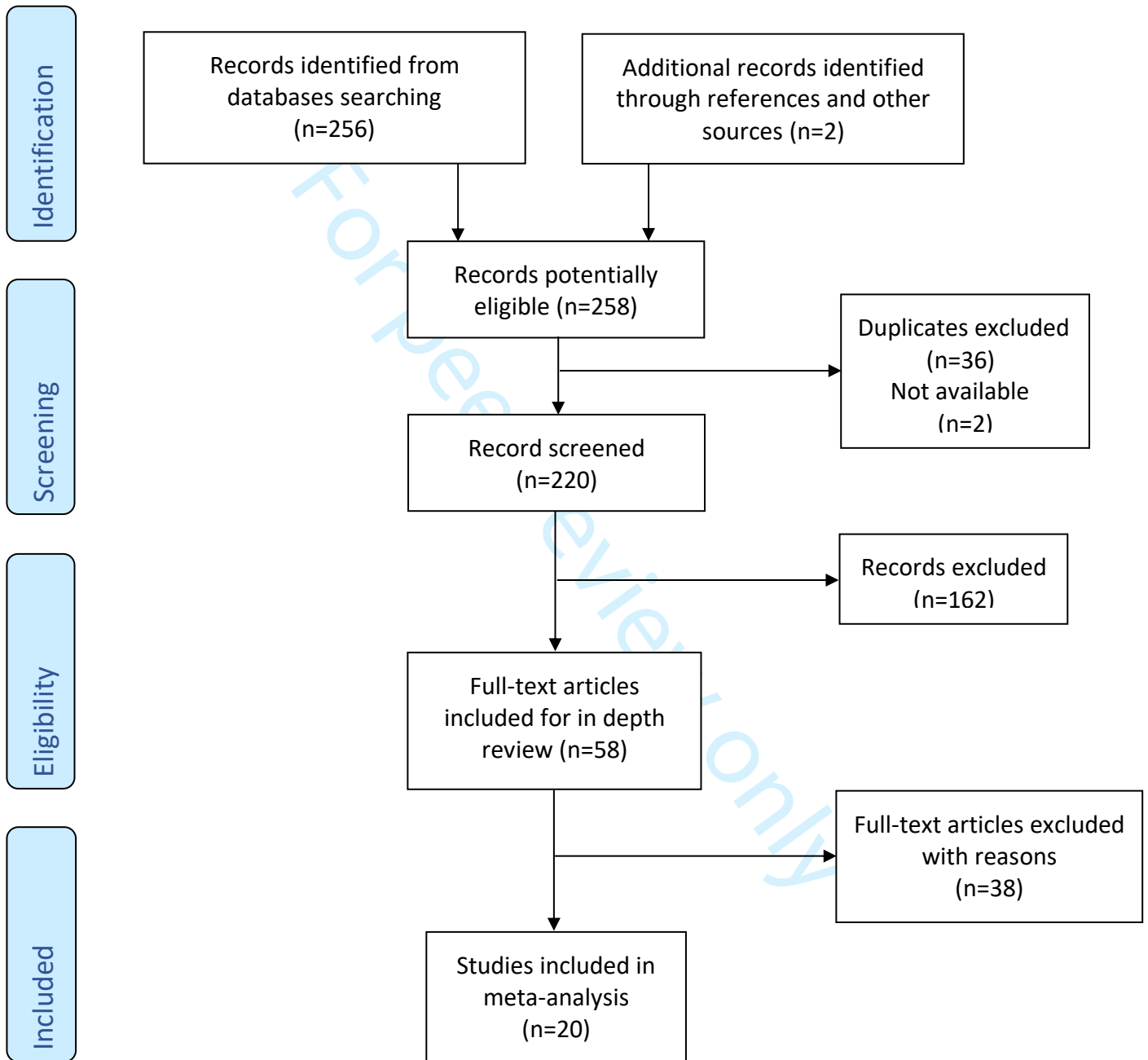
Figure legends

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*



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Author (year) ES (95% CI) Weight %

Retrospective

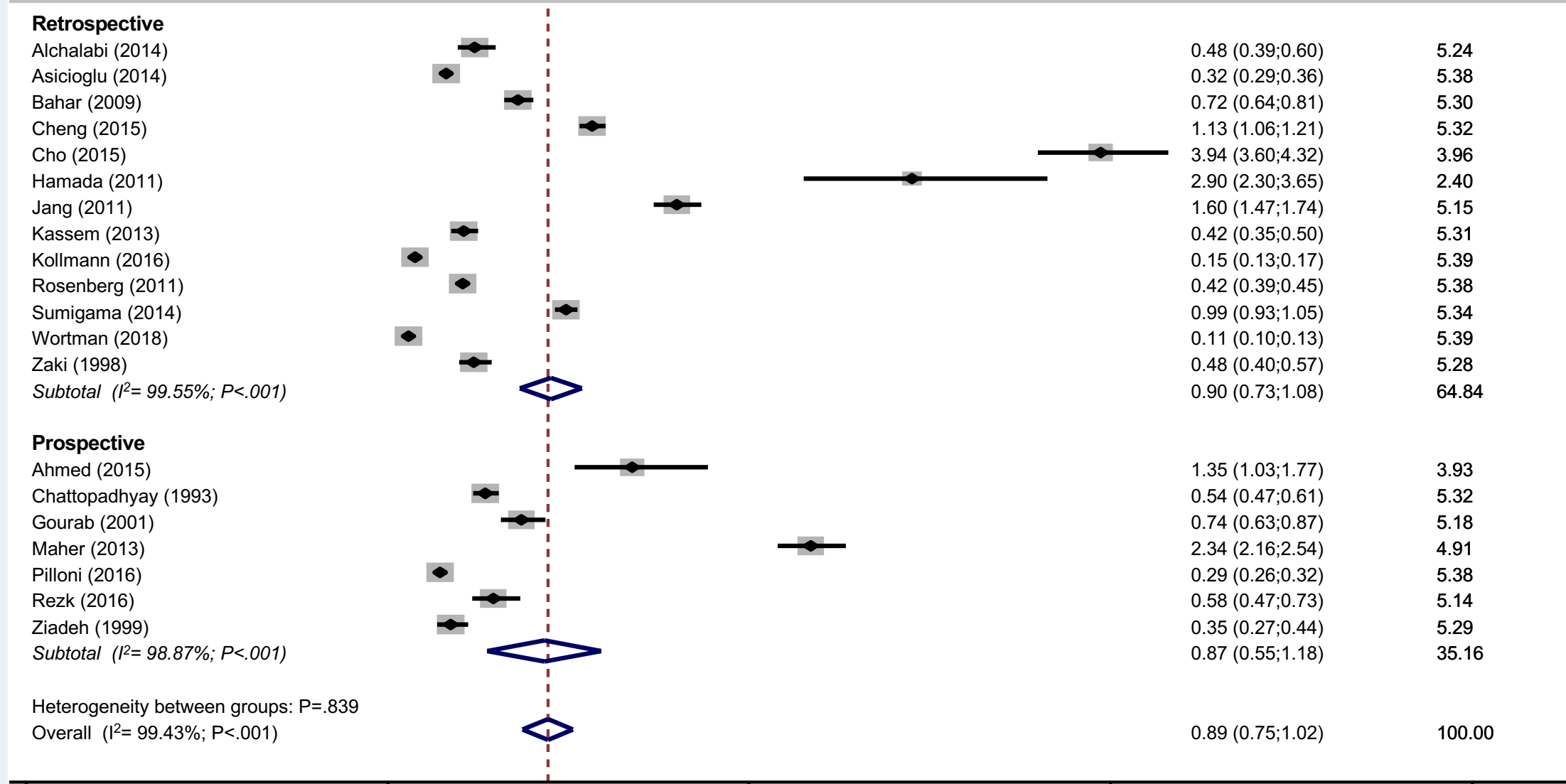
Alchalabi (2014)	0.48 (0.39;0.60)	5.24
Ascioglu (2014)	0.32 (0.29;0.36)	5.38
Bahar (2009)	0.72 (0.64;0.81)	5.30
Cheng (2015)	1.13 (1.06;1.21)	5.32
Cho (2015)	3.94 (3.60;4.32)	3.96
Hamada (2011)	2.90 (2.30;3.65)	2.40
Jang (2011)	1.60 (1.47;1.74)	5.15
Kassem (2013)	0.42 (0.35;0.50)	5.31
Kollmann (2016)	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
<i>Subtotal (I²= 99.55%; P<.001)</i>	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
<i>Subtotal (I²= 98.87%; P<.001)</i>	0.87 (0.55;1.18)	35.16

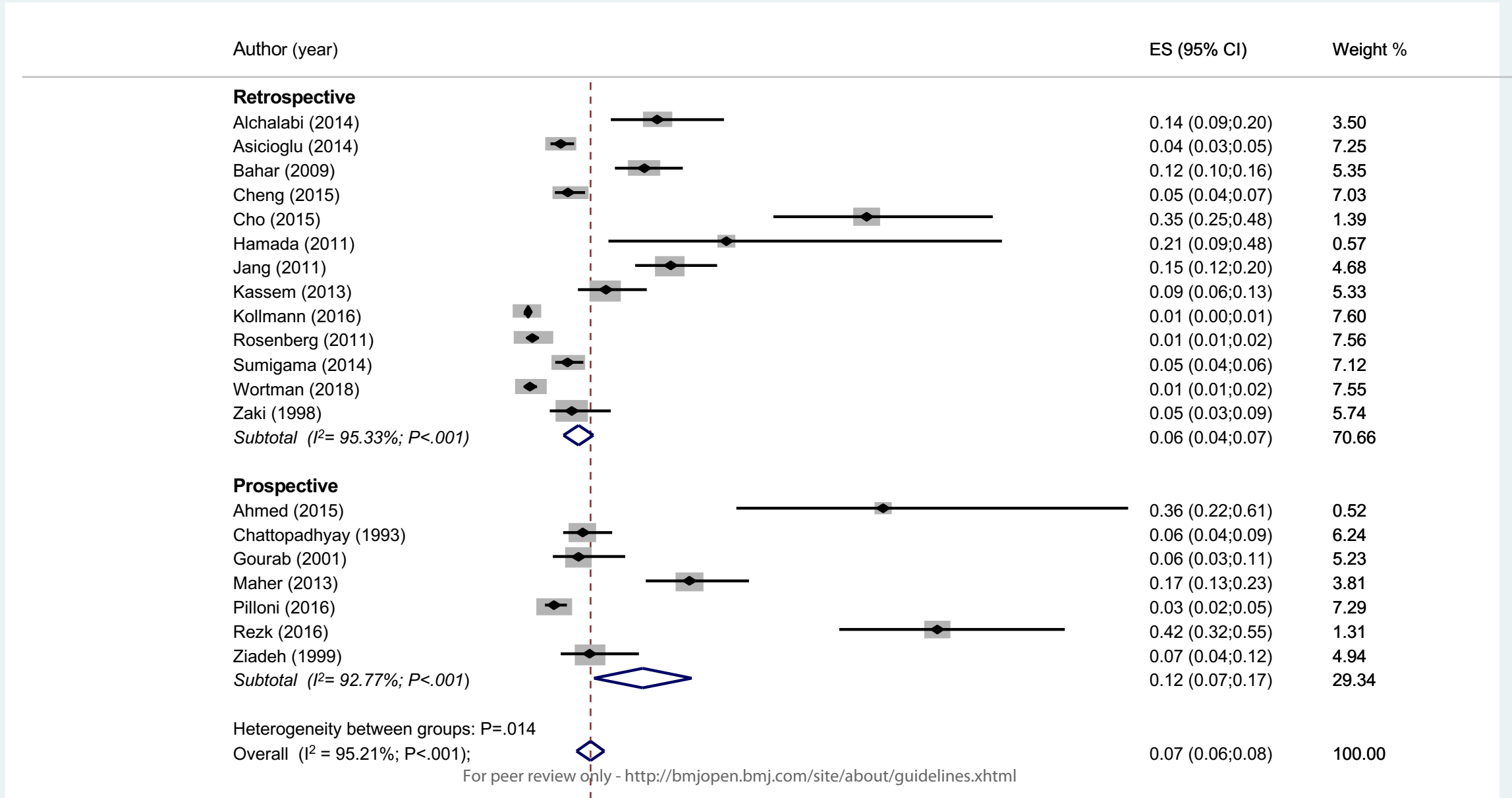
Heterogeneity between groups: P=.839

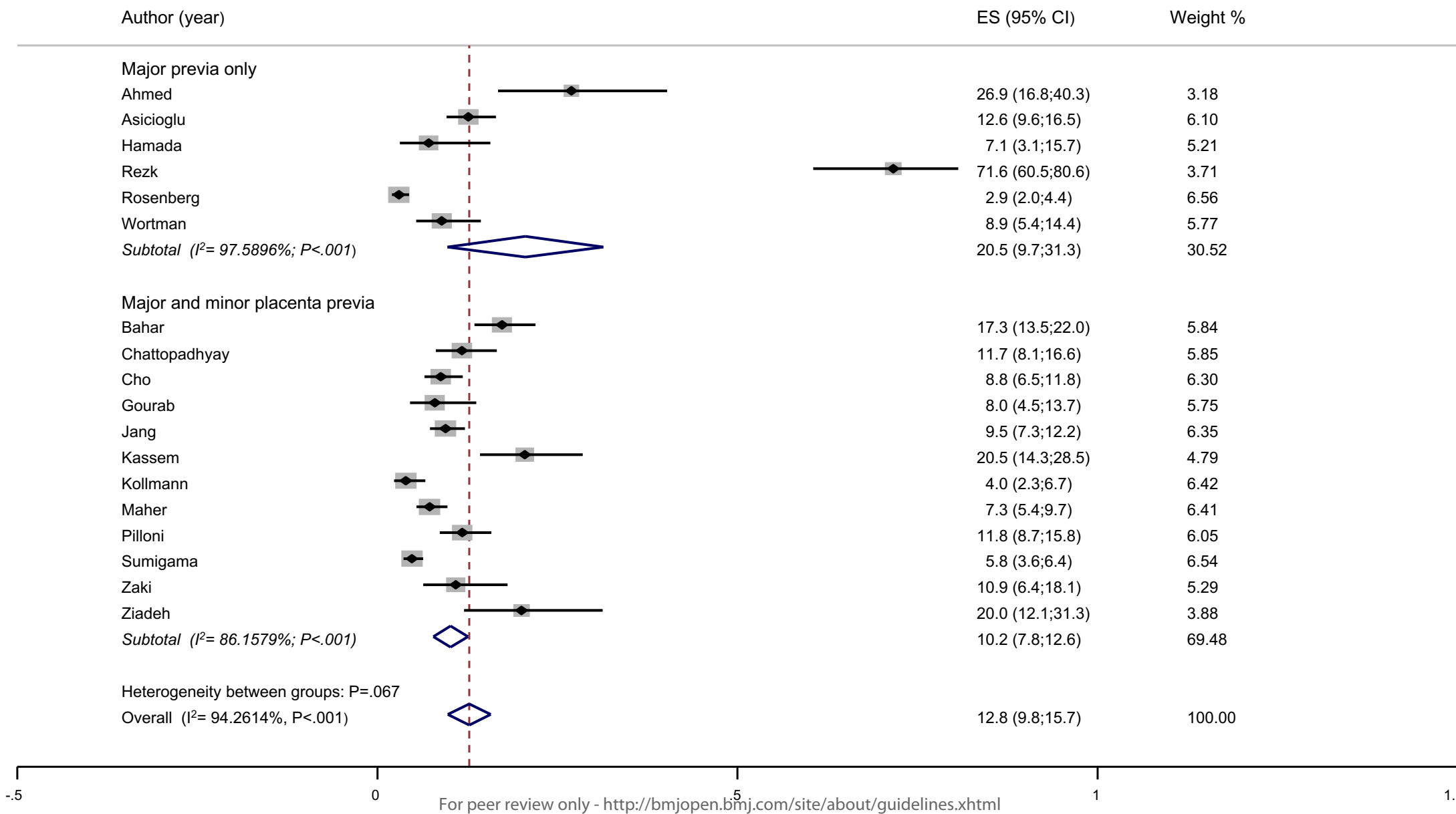
Overall (I²= 99.43%; P<.001) 0.89 (0.75;1.02) 100.00



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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		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)		

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		
Assessment of heterogeneity		
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		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non-English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

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.

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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

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

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Competing interest

The authors report no conflict of interest.

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

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

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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

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2
3 prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of
4
5 PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).
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7 **Conclusions** The high heterogeneity in qualitative and diagnostic data between studies
8
9 emphasizes the need to implement standardized protocols for the diagnoses of both
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11 placenta previa and PAS, including the type of placenta previa and grade of villous
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13 invasiveness.
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19 PROSPERO Registration CRD42017068589
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23 24 **Strengths and limitations of this study**

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26 • This study provides the first comprehensive evaluation of the epidemiology of
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28 placenta previa complicated by PAS.
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32 • The search was performed using predetermined eligibility criteria in a defined
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34 obstetric population.
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37 • Thirteen out of 20 studies included in the study were retrospective limiting the
38
39 overall quality of the analysis.
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- 41
42 • Only six studies provided data on the prenatal ultrasound diagnosis of PAS in
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44 patients with placenta previa and nine studies on detailed histopathological
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46 findings.
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- 48
49 • High level of inconsistency between estimates in prevalence and incidence did
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51 not allow for full meta-analysis of the clinical outcomes.
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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 Hertig¹ 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 al² 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

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3 10,000 births in women with both a previous caesarean delivery and placenta previa.⁸
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5 Both abnormal adherence and invasion of villous tissue into the myometrium result
6 in failure of the placenta to separate spontaneously from the uterine wall at delivery.²⁻⁴
7
8 When unsuspected at the time of delivery, attempts to manually remove accreta villous
9 tissue typically provoke rapid bleeding from the utero-placental circulation.^{5,11} In invasive
10 cases, this can lead to massive obstetric hemorrhage due to the disruption of the deep
11 uterine vasculature of the increta or percreta area.^{4,5} Not surprisingly, prenatal diagnosis
12 of PAS has been shown to decrease maternal morbidity and mortality, and has thus
13 become essential in improving its management.^{12,13} Tabsh et al were the first in 1982 to
14 report on the prenatal ultrasound diagnosis of a case of placenta increta.¹⁴ A recent
15 systematic review and meta-analysis of prenatal ultrasound diagnosis of placenta previa
16 with PAS in women with a history of caesarean delivery has found that the overall
17 diagnostic accuracy of ultrasound in specialist units is in 90.9%.¹⁵ However, in countries
18 with well-established screening programs for fetal anomalies, over half the cases of PAS
19 are not diagnosed before delivery.^{8,10}
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37 Accreta placentation and in particular its invasive forms are impacting maternal
38 health outcomes globally and its prevalence is likely to increase. Women with a history
39 of previous caesarean delivery presenting with placenta previa complicated by PAS in
40 an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of
41 delivery complications¹⁶, however, their epidemiology has not been comprehensively
42 reviewed yet. Health provision for the development of maternity centres with specialist
43 teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage
44 women presenting with placenta previa and PAS requires an accurate evaluation of its
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3 epidemiology. The objective of this meta-analysis is to review the epidemiology of
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5 women presenting with placenta previa and to examine the different criteria used by the
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7 authors of cohort studies to diagnose placenta previa and PAS prenatally and to confirm
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9 the diagnosis of PAS at birth.
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14 **MATERIALS AND METHODS**

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17 A systematic review was undertaken of articles providing data on prevalence and
18
19 incidence of PAS in women presenting with a placenta previa where the populations
20
21 sampled were defined. PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were
22
23 searched for studies published between the first prenatal ultrasound description of
24
25 placenta accreta in August 1982 by Tabsh¹⁴ et al and September 2018. The search
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27 protocol was designed *a priori* and registered on PROSPERO (CRD42017068589). The
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29 overall search strategy was inclusive of MeSH headings for “placenta accreta, placenta
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31 increta, placenta percreta, abnormally invasive placenta, morbidly adherent placenta
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33 and major placenta previa” which were combined with terms including “prevalence,
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35 incidence, obstetric hysterectomy and caesarean hysterectomy”. Title, abstracts and
36
37 full-text were independently assessed by the authors for content, data extraction and
38
39 analysis. Additional relevant studies were identified from reference lists of reviews and
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41 editorials and by hand-searching key journals and websites. All search results were
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43 combined in a reference database. Duplicates were removed by hand. The search was
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45 limited to articles published in English.
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52 Two independent investigators (EJ and LG) selected studies in two stages. The
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54 abstracts of all potentially relevant papers were individually examined for suitability.
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3 Papers were only ruled out at this stage if they obviously did not meet the inclusion
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5 criteria. The remainder were obtained in full text and were independently assessed
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7 for content, data extraction and analysis. Disagreements between the two original
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9 reviewers were resolved by discussion with the third investigator (JLR). Articles were
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11 excluded if; they were published before August 1982, contained no data on the study
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13 population such as the overall pregnancies, births and/or deliveries numbers, were case
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15 reports or were overlapping.
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19 Study characteristics were extracted using a predesigned data extraction
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21 protocol including: author institution, year of publication, country of origin, study period,
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23 study type (retrospective, single institution, multiple institutions), total number of cases
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25 in the study population, type of placenta previa, diagnosis of PAS at birth (Appendix 1).
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27 Outcome measures included the need to perform a peripartum hysterectomy and direct
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29 maternal mortality. Prior surgical history was also recorded. The reference standard for
30
31 differential diagnosis between minor and major placenta previa was recorded based on
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33 the placental position inside the uterine cavity on transvaginal ultrasound with relation to
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35 the internal cervical os. For the diagnosis of accreta placentation, we referred to the
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37 clinical grading based on surgical findings at delivery as previously described¹⁷ and to
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39 histopathologic findings when a caesarean hysterectomy was performed i.e. placental
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41 villi directly attached to the myometrium without interposing decidua or invading the
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43 uterine wall.
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49 Two independent reviewers (EJ and LG) undertook the quality assessment with
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51 difference agreed by consensus. The Newcastle-Ottawa scale for observational studies
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53 was used to establish the risk of bias in selection (representativeness of the exposed
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3 cohort, ascertainment of exposure and the demonstration that the outcome of interest
4 was not present at the start of the study), comparability (evaluation of the cohorts
5 based on the design or analysis), and outcome assessment.¹⁸ These included
6 retrospective versus prospective studies, single versus multiple institutions studies,
7 prenatal ultrasound description of low-lying/placenta previa and PAS, histopathologic
8 confirmation of the diagnosis of the PAS and corresponding grade of invasiveness and
9 detailed data on management and maternal outcomes. Studies that scored four stars for
10 selection, two stars for comparability, and three stars for ascertainment of the outcome
11 were regarded to have a low risk of bias. Studies with two or three stars for selection,
12 one for comparability, and two for outcome ascertainment were considered to have a
13 medium risk of bias. We deemed any study with a score of one for selection or outcome
14 ascertainment, or zero for any of the three domains, to have a high risk of bias. No
15 study was excluded based on the risk of bias assessment.

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

4 5 **Patients and public involvement**

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8 Patients and the public were not involved in the design or planning of the study.
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10 11 **RESULTS**

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14 The initial search provided 256 records with cross-referencing providing an additional
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16 two studies, making a total of 258 potentially relevant articles. After exclusion of
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18 duplicates and the two which were not available (Figure 1), 220 remained. On screening
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20 the titles and abstracts, a further 162 were excluded as the reported outcomes were not
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22 relevant, leaving 58 studies which were obtained for full text review. An additional 38
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24 articles were excluded after full review including letters (n=16), narrative reviews (n= 10)
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26 commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another
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28 publication (n=1), leaving 20 articles for the final analysis.¹⁹⁻³⁸
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33 The characteristics and the results of the quality assessment are displayed in
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35 table 1. There were 13 retrospective^{19,20,23,25-27,29-31,33-35,38} and 7
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37 prospective^{21,22,24,28,32,36,37} studies including a total of 1,207,296 births and 23,864 cases
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39 referred as pregnancies. There were 15 studies from a single institution^{19-24,27-30,32-34,37,38}
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41 and five from multiple institutions^{25,31} or a geographical region.^{26,35,36} Overall, 18 studies
42
43 had low or medium risk of bias.
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46
47 Table 2 presents the epidemiology data of the 20 studies. These studies included
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49 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta
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51 previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR
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53 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07%
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3 (IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was
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5 11.10% (IQR 7.65;17.35).
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8 All authors except two^{29,33} reported on the criteria used for the prenatal
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10 ultrasound diagnosis of placenta previa. Six studies^{24,26,30,32,37,38} only included major
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12 placenta previa in their cohort as defined as the placenta completely covering or
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14 partially covering the internal os of the cervix. The others included both major and minor
15
16 placenta previa. The definition of minor placenta previa varied with two studies^{31,36} using
17
18 the placental edge being <2cm from the internal os, two studies using < 3cm^{22,23} and
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20 one study using <3 cm or <5 cm if associated with abnormal fetal presentation.²¹ The
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22 gestational age at confirmation of the prenatal diagnosis of placenta previa was
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24 reported in six studies^{22,23,24,28,32,37} and ranged between 20 weeks and 34 weeks and in
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26 one study the diagnosis of placenta previa was confirmed at birth when the placenta
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28 was found to be inserted in the lower segment.¹⁹
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33 The ultrasound diagnostic signs for PAS were reported in six studies^{24,28,30,32,36,37}
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35 with two studies also reporting on the use of magnetic resonance imaging.^{29,38} The
36
37 clinical criteria used for the diagnosis of PAS at birth were reported by nine
38
39 studies^{19,20,23,27,28,30,33,36,37} and included a difficult delivery of the placenta without easy
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41 separation uterine wall or requiring a “piecemeal removal” associated with heavy
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43 bleeding and excessive bleeding from the placental bed after placental delivery. One
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45 author described the presence of invasive villous tissue at delivery²⁷ and one the need
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47 to suture the placental bed.²³ None of the other authors reported on the gross
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49 appearance of the uterus or surgical findings at the time of caesarean delivery. In 12
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51 studies^{19,23,24,27-31,33,34,36,37} the prenatal and/or clinical diagnosis was confirmed by
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3 histopathological examination with detailed description of the microscopic criterion only
4 reported in six^{19,27,28,30,31,37}. Detailed histopathological findings on the depth of villous
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6 invasiveness were reported in nine studies^{24,27-29,31,33,34,36,37} out of the 20 studies (Table
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8 3). These included 283 cases of placenta previa accreta graded for 171 (60.4%) as
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10 placenta creta (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta
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12 percreta.
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17 The meta-analysis indicated statistically significant ($P<.001$) level of overall
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19 heterogeneity between study estimates for the prevalence of placenta previa (Figure 2),
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21 the prevalence of placenta previa with PAS (Figure 3) and the incidence of PAS in the
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23 placenta previa cohort (Figure 4). There was strong evidence of inconsistency between
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25 study types with I^2 values greater 85%. The difference in heterogeneity between
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27 prospective versus retrospective studies was not statistically significantly ($P=.839$)
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29 different (Figure 2) whereas it was significant ($P=.014$) for the prevalence of placenta
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31 previa accreta (Figure 3). Adjusting for type of study (prospective versus retrospective)
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33 did not reduce inconsistency between studies. The in-between placenta previa major
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35 only versus minor and major placental previa was not significant ($P=.067$) for the
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37 incidence of PAS in patient with placenta previa (Figure 4).
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42 All authors but two^{22,23} reported on prior surgical history including
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44 caesarean section^{19-21,24-38}, uterine curettage^{28,30-32,34,37,38} and myomectomy.^{28,36,37} Data
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46 on surgical management was available in 14 out of the 20 studies^{19,20,23,27-31,33-38} with
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48 314 out of 441 women presenting with a placenta previa complicated by PAS. The
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50 median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal
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3 mortality were available in 13 studies^{19-21,23,25,27-30,32,35,37,38} and PAS accounted for 5
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5 maternal deaths^{19,20,25,29,30} out of 387 (1.3%) cases of placenta previa with PAS.
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10 **DISCUSSION**

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12 This study provides a comprehensive evaluation of the prevalence of placenta previa
13 complicated by PAS and the incidence of PAS in women presenting with a placenta
14 previa. Women with a prior history of caesarean delivery presenting with a low-
15 lying/placenta previa represent more than 90% of the cases of PAS.^{8,10,16} The meta-
16
17 analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa
18 and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the
19 need to use international standardized clinical protocols for the screening and
20 management of this complex obstetric condition. The current situation limits the capacity
21 building of healthcare providers on improvements in training, implementation of
22 guidelines and changes in clinical practice behaviour.
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36 Defining the position of the placenta inside the uterus was one of the first aims of
37 obstetric ultrasound examination.^{39,40} Following the development of real-time ultrasound
38 imaging, placental location became an integral part of the mid-pregnancy ultrasound
39 examination.⁴¹ Placenta previa was initially described with transabdominal scan as a
40 placenta developing within the lower uterine segment and classified according to the
41 relationship and/or the distance between the lower placental edge and the internal os of
42 the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine
43 segment down to the internal os and major placenta previa when the placenta covers the
44 cervix. Minor placenta previa can be further subdivided into low-lying placenta when the
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3 lower edge does not reach the internal os and marginal placenta previa when it does.
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5 Major placenta previa can also be described as partial or complete depending on the
6
7 amount of placental tissue covering the cervix. The use of transvaginal scanning has
8
9 allowed for a more precise evaluation of the distance between the placental edge and the
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11 internal os^{42,43} but as demonstrated in our meta-analysis, the reporting of the ultrasound
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13 criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we
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15 found also wide variation in the gestational age at diagnosis. The timing of the
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17 confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of
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19 minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.^{44,45} An
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21 expert panel of the American Institute of Ultrasound in Medicine⁴⁶ has recently
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23 recommended ceasing the use of the terms 'partial' and 'marginal' and using the term
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25 'placenta previa' only when the placenta lies directly over the internal os. The placenta
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27 should be reported as 'low lying' when the placental edge is less than 2 cm from the
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29 internal os and as normal when the placental edge is more than 2 cm from the internal
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31 os. The findings of our meta-analysis highlight the need for the use of such a classification
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33 in further studies.
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40 Only six of the 20 studies included in the present meta-analysis provided data on
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42 the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included
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44 in the systematic review all studies published since the first ultrasound description of
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46 PAS by Tabsh et al in 1982.¹⁴ We found no studies between 1982 and 1993 (Table 1)
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48 which corresponds to the time when high-resolution grey-scale ultrasound imaging
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50 became widely available. Colour-Doppler imaging was introduced for the diagnosis of
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52 PAS in 1992⁴⁷, however the sensitivity and specificity of grey-scale imaging alone in
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3 diagnosing for placenta previa accreta are high when performed by experience
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5 operators.¹⁵ These findings indicate that the prenatal diagnosis of PAS can be
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7 performed using standard ultrasound equipment. Unlike placenta previa which is
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9 routinely screened for at the time of the fetal anomaly scan, PAS is currently not
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11 screened for and the data available on the prenatal diagnosis of the condition come
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13 exclusively from specialist centres.¹⁶ In these centres, the diagnostic accuracy of
14
15 ultrasound imaging is over 90%, but similar to placenta previa, the description of the
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17 ultrasound signs used for the diagnosis of PAS has also been highly variable over the
18
19 last two decades.^{47,48} The European Working Group on Abnormally Invasive Placenta
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21 and the Abnormally Invasive Placenta international expert group have recently
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23 proposed standardised descriptions of the ultrasound signs used for the prenatal
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25 diagnosis and a protocol for the ultrasound assessment of PAS.^{49,50} The use of these
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27 protocols in prospective studies should also facilitate the screening of patients at high
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29 risk of PAS and in particular those with multiple prior caesarean deliveries presenting
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31 with a low-lying or placenta previa.⁵¹

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38 We found significant heterogeneity in the qualitative definition and diagnosis of
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40 PAS at birth among the nine studies that provided a description of the clinical
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42 findings.^{19,20,23,27,28,30,33,36,37} Only one of these studies described the invasive
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44 appearance of placental tissue at delivery²⁷ whereas the others reported a difficult
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46 delivery of the placenta without easy separation from the uterine wall or requiring a
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48 “piecemeal removal” associated with heavy bleeding as diagnostic of PAS. These
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50 clinical criteria were first described by Irving and Hertig¹ in 1937 who did not have
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52 invasive cases in their cohort limiting their definition to abnormally adherent placenta
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3 and not to placenta increta or percreta. This definition also fails to clearly differentiate
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5 between abnormal adherence and placental retention as both present with similar
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7 clinical symptoms and etiology⁵² leading to possible over diagnosis of placenta previa
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9 accreta. Similarly, the finding of excessive bleeding from the placental bed after delivery
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11 of the placenta is a common complication of non-accreta placenta previa due to the
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13 implantation of the placenta in the lower uterine segment which contains less muscular
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15 fibers than the upper segment and is often thinner and dehiscent after multiple
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17 caesarean deliveries.
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22 Detailed histopathologic reports can only be obtained in those patients who have
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24 a hysterectomy or a partial myometrial resection and thus in many studies there is not
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26 histopathologic confirmation of the clinical diagnosis. The main histological diagnostic
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28 criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi
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30 and the superficial myometrium, is found with increasing incidence with advancing
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32 gestation in pregnancies with no clinical evidence of PAS.⁵ Thus the combination of
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34 clinical criteria that do not differentiate between placenta retention and adherent accreta
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36 and the use of non-diagnostic criteria of villous invasiveness may result in the over-
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38 diagnosis of the adherent grade of PAS (Table 3), in particular in those studies reporting
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40 a low rate of caesarean hysterectomy.^{28,36} Overall, this can explain the wide range in
41
42 the prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to
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44 71.6%) of PAS in women presenting with placenta previa (Figures 3 and 4).
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50 Overall, management strategies and outcomes will vary depending on the
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52 accuracy of prenatal diagnosis, local surgical expertise and more recently access to a
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54 centre of excellence with multidisciplinary team approach.^{53,54} In cases of high suspicion
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3 of PAS during cesarean delivery, 60-70% of obstetricians-gynecologists proceed with a
4 peripartum hysterectomy.^{55,56} By contrast with a conservative management approach,
5 radical surgery is often considered to be safer, in particular in cases of invasive
6 placentation.⁵⁷ The association between a placenta previa and a PAS increases the
7 risks of both maternal morbidity and mortality. In the present study we found that a
8 caesarean hysterectomy was the primary management option in around 70% of the
9 patients presenting with a placenta previa and PAS. The inter-study range was wide
10 with four studies^{19,21,29,37} reporting peripartum hysterectomy rates < 50%, five^{28,31,32,34,36}
11 had rates between 50-99% and four^{22,30,35,38} had rates of 100%. This may be due to
12 difference in study protocols, local expertise and the impact of prenatal diagnosis on
13 management strategies but also as suggested by our analysis to difference in the rates
14 of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed
15 histopathologic examination confirming the diagnosis.

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

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3 The prevalence of PAS in the general population of women giving birth varies
4 widely.^{8,10,58,59} A systematic review and meta-analysis of the prevalence of placenta
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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

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3 analysis. EJ, JLR and SC drafted the manuscript. All authors were involved in the critical
4 discussion and approved this final version for publication. EJ is the guarantor of the study.
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10 **Data sharing statement**

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

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15 doi:10.5061/dryad.5ds4833
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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
Ascioglu 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)
Ascioglu 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.

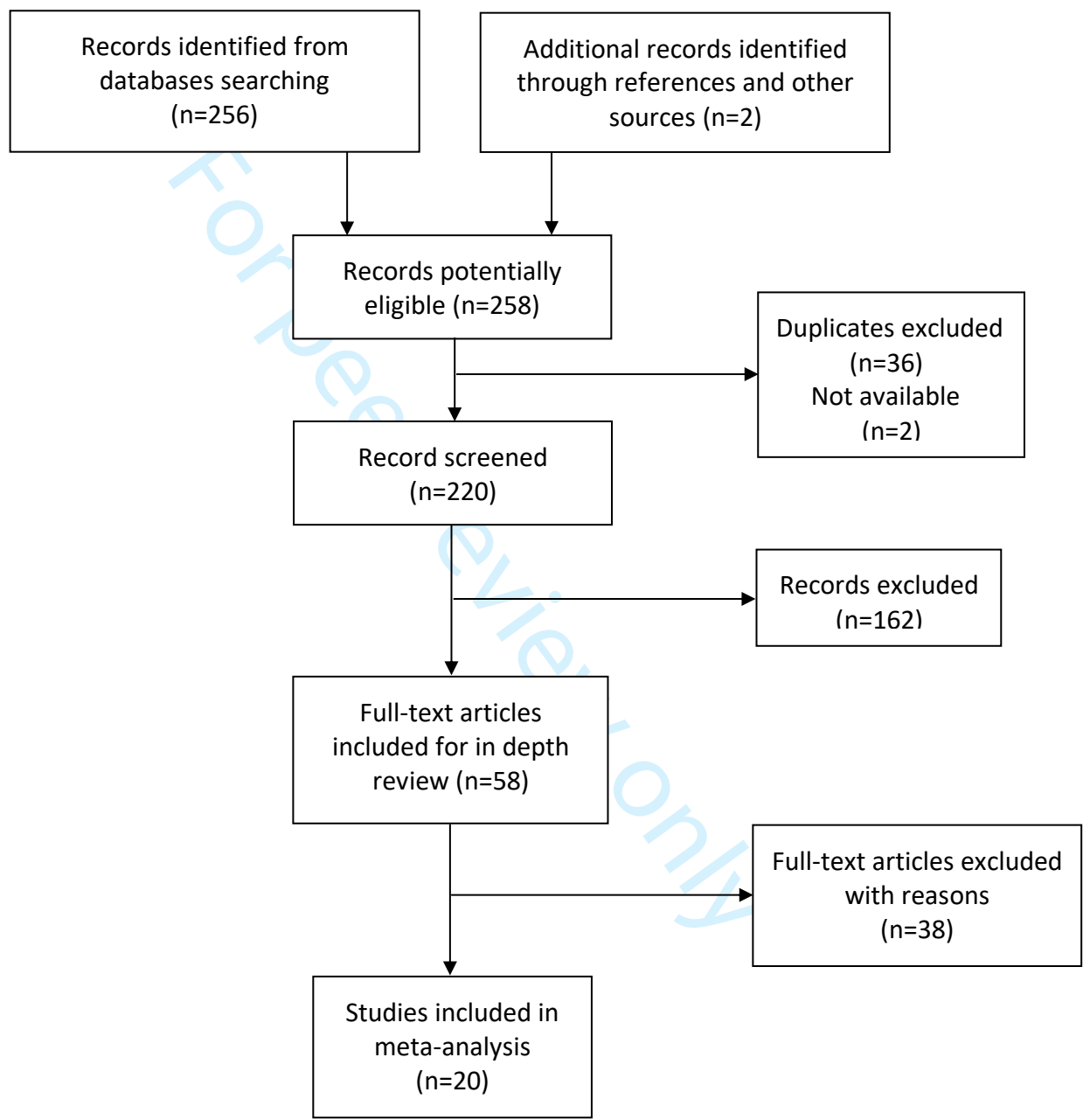
Fig 2: Forest plots showing the heterogeneity of prevalence data in prospective and retrospective cohort studies of women presenting with a placenta previa. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

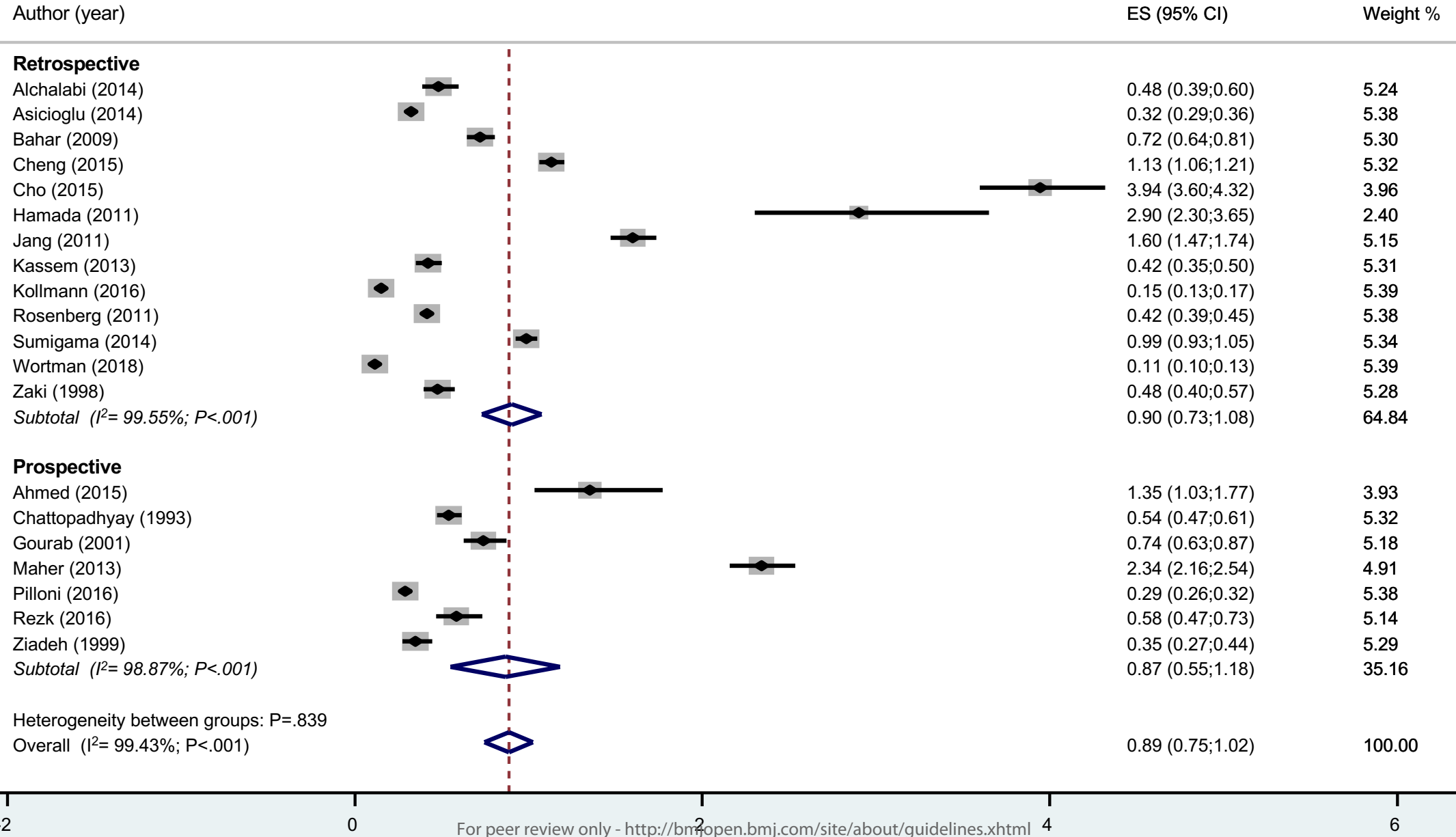
Fig 3: Forest plots showing heterogeneity in the prevalence data for prospective and retrospective cohort studies of women diagnosed with placenta previa accreta. Only first author's name is given for each reference. *ES, effect size. CI, confidence interval*

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*

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Identification
Screening
Eligibility
Included





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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
<i>Subtotal (I²= 95.33%; P<.001)</i>	0.06 (0.04;0.07)	70.66

Prospective

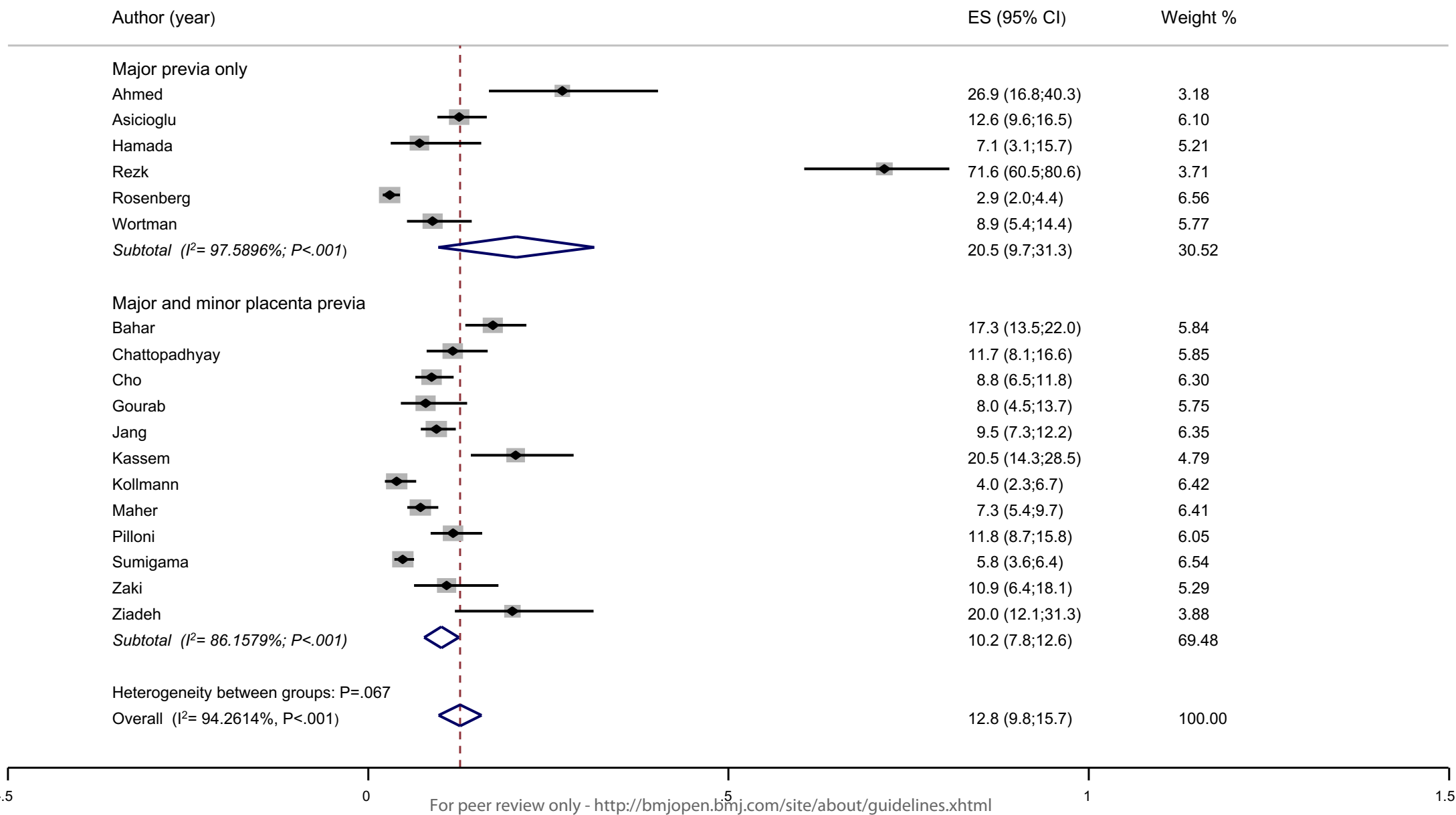
Ahmed (2015)	0.36 (0.22;0.61)	0.52
Chattopadhyay (1993)	0.06 (0.04;0.09)	6.24
Gourab (2001)	0.06 (0.03;0.11)	5.23
Maher (2013)	0.17 (0.13;0.23)	3.81
Pilloni (2016)	0.03 (0.02;0.05)	7.29
Rezk (2016)	0.42 (0.32;0.55)	1.31
Ziadeh (1999)	0.07 (0.04;0.12)	4.94
<i>Subtotal (I²= 92.77%; P<.001)</i>	0.12 (0.07;0.17)	29.34

Heterogeneity between groups: P=.014

Overall (I² = 95.21%; P<.001);



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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		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)		

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		
Assessment of heterogeneity		
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		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non-English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

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

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

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Competing interest

The authors report no conflict of interest.

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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

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3 prevalence of placenta previa with PAS was 0.07% (IQR 0.05;0.16). The incidence of
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5 PAS in women with a placenta previa was 11.10% (IQR 7.65;17.35).
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7 **Conclusions** The high heterogeneity in qualitative and diagnostic data between studies
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9 emphasizes the need to implement standardized protocols for the diagnoses of both
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11 placenta previa and PAS, including the type of placenta previa and grade of villous
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13 invasiveness.
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19 PROSPERO Registration CRD42017068589
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23 **Strengths and limitations of this study**

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26 • This study provides the first comprehensive evaluation of the epidemiology of
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28 placenta previa complicated by PAS.
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32 • The search was performed using predetermined eligibility criteria in a defined
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34 obstetric population.
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37 • Thirteen out of 20 studies included in the study were retrospective limiting the
38
39 overall quality of the analysis.
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42 • Only six studies provided data on the prenatal ultrasound diagnosis of PAS in
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44 patients with placenta previa and nine studies on detailed histopathological
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46 findings.
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49 • High level of inconsistency between estimates in prevalence and incidence did
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51 not allow for full meta-analysis of the clinical outcomes.
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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 Hertig¹ 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 al² 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

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3 10,000 births in women with both a previous caesarean delivery and placenta previa.⁸
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5 Both abnormal adherence and invasion of villous tissue into the myometrium result
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7 in failure of the placenta to separate spontaneously from the uterine wall at delivery.²⁻⁴
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9 When unsuspected at the time of delivery, attempts to manually remove accreta villous
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11 tissue typically provoke rapid bleeding from the utero-placental circulation.^{5,11} In invasive
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13 cases, this can lead to massive obstetric hemorrhage due to the disruption of the deep
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15 uterine vasculature of the increta or percreta area.^{4,5} Not surprisingly, prenatal diagnosis
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17 of PAS has been shown to decrease maternal morbidity and mortality, and has thus
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19 become essential in improving its management.^{12,13} Tabsh et al were the first in 1982 to
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21 report on the prenatal ultrasound diagnosis of a case of placenta increta.¹⁴ A recent
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23 systematic review and meta-analysis of prenatal ultrasound diagnosis of placenta previa
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25 with PAS in women with a history of caesarean delivery has found that the overall
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27 diagnostic accuracy of ultrasound in specialist units is in 90.9%.¹⁵ However, in countries
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29 with well-established screening programs for fetal anomalies, over half the cases of PAS
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31 are not diagnosed before delivery.^{8,10}
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37 Accreta placentation and in particular its invasive forms are impacting maternal
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39 health outcomes globally and its prevalence is likely to increase. Women with a history
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41 of previous caesarean delivery presenting with placenta previa complicated by PAS in
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43 an ongoing pregnancy are now the cohort of obstetric patients with the highest risk of
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45 delivery complications¹⁶, however, their epidemiology has not been comprehensively
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47 reviewed yet. Health provision for the development of maternity centres with specialist
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49 teams, equipment, drugs, blood bank and intensive care infrastructure to safely manage
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51 women presenting with placenta previa and PAS requires an accurate evaluation of its
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3 epidemiology. The objective of this meta-analysis is to review the epidemiology of
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5 women presenting with placenta previa and to examine the different criteria used by the
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7 authors of cohort studies to diagnose placenta previa and PAS prenatally and to confirm
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9 the diagnosis of PAS at birth.
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14 **MATERIALS AND METHODS**

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17 A systematic review was undertaken of articles providing data on prevalence and
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19 incidence of PAS in women presenting with a placenta previa where the populations
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21 sampled were defined. PubMed, Google Scholar, clinicalTrials.gov and MEDLINE were
22
23 searched for studies published between the first prenatal ultrasound description of
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25 placenta accreta in August 1982 by Tabsh¹⁴ et al and September 2018. The search
26
27 protocol was designed *a priori* and registered on PROSPERO (CRD42017068589). The
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29 overall search strategy was inclusive of MeSH headings for the following terms
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31 “placenta accreta, placenta increta, placenta percreta, abnormally invasive placenta,
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33 morbidly adherent placenta and major placenta previa” (search strategy in online
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35 supplementary data 1). Title, abstracts and full-text were independently assessed by the
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37 authors for content, data extraction and analysis. Additional relevant studies were
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39 identified from reference lists of reviews and editorials and by hand-searching key
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41 journals and websites. All search results were combined in a reference database.
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43 Duplicates were removed by hand. The search was limited to articles published in
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45 English.
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52 Two independent investigators (EJ and LG) selected studies in two stages. The
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54 abstracts of all potentially relevant papers were individually examined for suitability.
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3 Papers were only ruled out at this stage if they obviously did not meet the inclusion
4 criteria. The remainder were obtained in full text and were independently assessed
5 for content, data extraction and analysis. Disagreements between the two original
6 reviewers were resolved by discussion with the third investigator (JLR). Articles were
7 excluded if; they were published before August 1982, contained no data on the study
8 population such as the overall pregnancies, births and/or deliveries numbers, were case
9 reports or were overlapping.
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19 Study characteristics were extracted using a predesigned data extraction
20 protocol including: author institution, year of publication, country of origin, study period,
21 study type (retrospective, single institution, multiple institutions), total number of cases
22 in the study population, type of placenta previa, diagnosis of PAS at birth (search
23 strategy in online supplementary data 2). Outcome measures included the need to
24 perform a peripartum hysterectomy and direct maternal mortality. Prior surgical history
25 was also recorded. The reference standard for differential diagnosis between minor and
26 major placenta previa was recorded based on the placental position inside the uterine
27 cavity on transvaginal ultrasound with relation to the internal cervical os. For the
28 diagnosis of accreta placentation, we referred to the clinical grading based on surgical
29 findings at delivery as previously described¹⁷ and to histopathologic findings when a
30 caesarean hysterectomy was performed i.e. placental villi directly attached to the
31 myometrium without interposing decidua or invading the uterine wall.
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49 Two independent reviewers (EJ and LG) undertook the quality assessment with
50 difference agreed by consensus. The Newcastle-Ottawa scale for observational studies
51 was used to establish the risk of bias in selection (representativeness of the exposed
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3 cohort, ascertainment of exposure and the demonstration that the outcome of interest
4 was not present at the start of the study), comparability (evaluation of the cohorts
5 based on the design or analysis), and outcome assessment.¹⁸ These included
6 retrospective versus prospective studies, single versus multiple institutions studies,
7 prenatal ultrasound description of low-lying/placenta previa and PAS, histopathologic
8 confirmation of the diagnosis of the PAS and corresponding grade of invasiveness and
9 detailed data on management and maternal outcomes. Studies that scored four stars for
10 selection, two stars for comparability, and three stars for ascertainment of the outcome
11 were regarded to have a low risk of bias. Studies with two or three stars for selection,
12 one for comparability, and two for outcome ascertainment were considered to have a
13 medium risk of bias. We deemed any study with a score of one for selection or outcome
14 ascertainment, or zero for any of the three domains, to have a high risk of bias. No
15 study was excluded based on the risk of bias assessment.

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33 Analyses were conducted using STATA software (version 15; StataCorp, College
34 Station, TX). Standard Kurtosis analysis indicated that some values were not normally
35 distributed and study specific estimates are therefore presented as median and
36 interquartile range (IQR). A random effects model was used to combine the studies
37 while incorporating variations among studies unless there were three or less studies
38 contributing to the meta-analysis in which case a fixed effect model was used. Statistical
39 heterogeneity was assessed with the Cochran's Q-test and the I^2 statistic (the
40 proportion of variation in study estimates because of heterogeneity rather than sampling
41 error). Forest plots are presented to graphically summarize the study results and the
42 pooled results. A test for heterogeneity between sub-groups (i.e. study types) was
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4 5 **Patients and public involvement**

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8 Patients and the public were not involved in the design or planning of the study.
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10 11 **RESULTS**

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14 The initial search provided 256 records with cross-referencing providing an additional
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16 two studies, making a total of 258 potentially relevant articles. After exclusion of
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18 duplicates and the two which were not available (Figure 1), 220 remained. On screening
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20 the titles and abstracts, a further 162 were excluded as the reported outcomes were not
21
22 relevant, leaving 58 studies which were obtained for full text review. An additional 38
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24 articles were excluded after full review including letters (n=16), narrative reviews (n= 10)
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26 commentaries (n= 9), conference proceedings (n= 2) and duplication of data in another
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28 publication (n=1), leaving 20 articles for the final analysis.¹⁹⁻³⁸

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33 There were 13 retrospective^{19,20,23,25-27,29-31,33-35,38} and 7
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35 prospective^{21,22,24,28,32,36,37} studies including a total of 1,207,296 births and 23,864 cases
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37 referred as pregnancies. There were 15 studies from a single institution^{19-24,27-30,32-34,37,38}
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39 and five from multiple institutions^{25,31} or a geographical region.^{26,35,36} Overall, 18 studies
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41 had low or medium risk of bias (Full data in online supplementary data 3).
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45 Table 1 presents the epidemiology data of the 20 studies. These studies included
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47 587 women with placenta previa complicated by PAS out of 6,628 cases of placenta
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49 previa. The median prevalence of placenta previa in the 20 studies was 0.56% (IQR
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51 0.39;1.24) whereas the median prevalence of placenta previa with PAS was 0.07%
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53 (IQR 0.05;0.16). The median incidence of PAS in women with a placenta previa was
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55 11.10% (IQR 7.65;17.35).
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3 All authors except two^{29,33} reported on the criteria used for the prenatal
4 ultrasound diagnosis of placenta previa. Six studies^{24,26,30,32,37,38} only included major
5 placenta previa in their cohort as defined as the placenta completely covering or
6 partially covering the internal os of the cervix. The others included both major and minor
7 placenta previa. The definition of minor placenta previa varied with two studies^{31,36} using
8 the placental edge being <2cm from the internal os, two studies using < 3cm^{22,23} and
9 one study using <3 cm or <5 cm if associated with abnormal fetal presentation.²¹ The
10 gestational age at confirmation of the prenatal diagnosis of placenta previa was
11 reported in six studies^{22,23,24,28,32,37} and ranged between 20 weeks and 34 weeks and in
12 one study the diagnosis of placenta previa was confirmed at birth when the placenta
13 was found to be inserted in the lower segment.¹⁹

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28 The ultrasound diagnostic signs for PAS were reported in six studies^{24,28,30,32,36,37}
29 with two studies also reporting on the use of magnetic resonance imaging.^{29,38} The
30 clinical criteria used for the diagnosis of PAS at birth were reported by nine
31 studies^{19,20,23,27,28,30,33,36,37} and included a difficult delivery of the placenta without easy
32 separation uterine wall or requiring a “piecemeal removal” associated with heavy
33 bleeding and excessive bleeding from the placental bed after placental delivery. One
34 author described the presence of invasive villous tissue at delivery²⁷ and one the need
35 to suture the placental bed.²³ None of the other authors reported on the gross
36 appearance of the uterus or surgical findings at the time of caesarean delivery. In 12
37 studies^{19,23,24,27-31,33,34,36,37} the prenatal and/or clinical diagnosis was confirmed by
38 histopathological examination with detailed description of the microscopic criterion only
39 reported in six^{19,27,28,30,31,37}. Detailed histopathological findings on the depth of villous
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3 invasiveness were reported in nine studies^{24,27-29,31,33,34,36,37} out of the 20 studies (Table
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5 2). These included 283 cases of placenta previa accreta graded for 171 (60.4%) as
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7 placenta creta (adherent), 74 (26.2%) as placenta increta and 38 (13.4%) as placenta
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9 percreta. These studies included a total of 383,003 pregnancies or births and the
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11 prevalence for the different grades of placenta previa accreta was 0.05%, 0.02% and
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13 0.01% for creta, increta and percreta, respectively.
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17 The meta-analysis indicated statistically significant ($P<.001$) level of overall
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19 heterogeneity between study estimates for the prevalence of placenta previa (Figure 2),
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21 the prevalence of placenta previa with PAS (Figure 3) and the incidence of PAS in the
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23 placenta previa cohort (Figure 4). There was strong evidence of inconsistency between
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25 study types with I^2 values greater 85%. The difference in heterogeneity between
26
27 prospective versus retrospective studies was not statistically significantly ($P=.839$)
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29 different (Figure 2) whereas it was significant ($P=.014$) for the prevalence of placenta
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31 previa accreta (Figure 3). Adjusting for type of study (prospective versus retrospective)
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33 did not reduce inconsistency between studies. The in-between placenta previa major
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35 only versus minor and major placental previa was not significant ($P=.067$) for the
36
37 incidence of PAS in patient with placenta previa (Figure 4).
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42 All authors but two^{22,23} reported on prior surgical history including
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44 caesarean section^{19-21,24-38}, uterine curettage^{28,30-32,34,37,38} and myomectomy.^{28,36,37} Data
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46 on surgical management was available in 14 out of the 20 studies^{19,20,23,27-31,33-38} with
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48 314 out of 441 women presenting with a placenta previa complicated by PAS. The
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50 median peri-partum hysterectomy rate of 69.2% (IQR 50.0;84.0). Data on maternal
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3 mortality were available in 13 studies^{19-21,23,25,27-30,32,35,37,38} and PAS accounted for 5
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5 maternal deaths^{19,20,25,29,30} out of 387 (1.3%) cases of placenta previa with PAS.
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10 **DISCUSSION**

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12 This study provides a comprehensive evaluation of the prevalence of placenta previa
13 complicated by PAS and the incidence of PAS in women presenting with a placenta
14 previa. Women with a prior history of caesarean delivery presenting with a low-
15 lying/placenta previa represent more than 90% of the cases of PAS.^{8,10,16} The meta-
16
17 analysis indicates high heterogeneity for both the prenatal diagnosis of placenta previa
18 and for the confirmation of the diagnosis of PAS at delivery. These findings highlight the
19 need to use international standardized clinical protocols for the screening and
20 management of this complex obstetric condition. The current situation limits the capacity
21 building of healthcare providers on improvements in training, implementation of
22 guidelines and changes in clinical practice behaviour.
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36 Defining the position of the placenta inside the uterus was one of the first aims of
37 obstetric ultrasound examination.^{39,40} Following the development of real-time ultrasound
38 imaging, placental location became an integral part of the mid-pregnancy ultrasound
39 examination.⁴¹ Placenta previa was initially described with transabdominal scan as a
40 placenta developing within the lower uterine segment and classified according to the
41 relationship and/or the distance between the lower placental edge and the internal os of
42 the uterine cervix i.e. minor placenta previa when lower edge is inside the lower uterine
43 segment down to the internal os and major placenta previa when the placenta covers the
44 cervix. Minor placenta previa can be further subdivided into low-lying placenta when the
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3 lower edge does not reach the internal os and marginal placenta previa when it does.
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5 Major placenta previa can also be described as partial or complete depending on the
6
7 amount of placental tissue covering the cervix. The use of transvaginal scanning has
8
9 allowed for a more precise evaluation of the distance between the placental edge and the
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11 internal os^{42,43} but as demonstrated in our meta-analysis, the reporting of the ultrasound
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13 criteria used for the diagnosis of placenta previa has been heterogenous. In addition, we
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15 found also wide variation in the gestational age at diagnosis. The timing of the
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17 confirmation of the diagnosis has a direct impact on epidemiology data as up to 70% of
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19 minor placenta previa at 20-23 weeks of gestation will resolve by 32-35 weeks.^{44,45} An
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21 expert panel of the American Institute of Ultrasound in Medicine⁴⁶ has recently
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23 recommended ceasing the use of the terms 'partial' and 'marginal' and using the term
24
25 'placenta previa' only when the placenta lies directly over the internal os. The placenta
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27 should be reported as 'low lying' when the placental edge is less than 2 cm from the
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29 internal os and as normal when the placental edge is more than 2 cm from the internal
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31 os. The findings of our meta-analysis highlight the need for the use of such a classification
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33 in further studies.
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40 Only six of the 20 studies included in the present meta-analysis provided data on
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42 the prenatal ultrasound diagnosis of PAS in patients with placenta previa. We included
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44 in the systematic review all studies published since the first ultrasound description of
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46 PAS by Tabsh et al in 1982.¹⁴ We found no studies between 1982 and 1993 (Table 1)
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48 which corresponds to the time when high-resolution grey-scale ultrasound imaging
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50 became widely available. Colour-Doppler imaging was introduced for the diagnosis of
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52 PAS in 1992⁴⁷, however the sensitivity and specificity of grey-scale imaging alone in
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3 diagnosing for placenta previa accreta are high when performed by experience
4 operators.¹⁵ These findings indicate that the prenatal diagnosis of PAS can be
5 performed using standard ultrasound equipment. Unlike placenta previa which is
6 routinely screened for at the time of the fetal anomaly scan, PAS is currently not
7 screened for and the data available on the prenatal diagnosis of the condition come
8 exclusively from specialist centres.¹⁶ In these centres, the diagnostic accuracy of
9 ultrasound imaging is over 90%, but similar to placenta previa, the description of the
10 ultrasound signs used for the diagnosis of PAS has also been highly variable over the
11 last two decades.^{47,48} The European Working Group on Abnormally Invasive Placenta
12 and the Abnormally Invasive Placenta international expert group have recently
13 proposed standardised descriptions of the ultrasound signs used for the prenatal
14 diagnosis and a protocol for the ultrasound assessment of PAS.^{49,50} The use of these
15 protocols in prospective studies should also facilitate the screening of patients at high
16 risk of PAS and in particular those with multiple prior caesarean deliveries presenting
17 with a low-lying or placenta previa.⁵¹

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19 We found significant heterogeneity in the qualitative definition and diagnosis of
20 PAS at birth among the nine studies that provided a description of the clinical
21 findings.^{19,20,23,27,28,30,33,36,37} Only one of these studies described the invasive
22 appearance of placental tissue at delivery²⁷ whereas the others reported a difficult
23 delivery of the placenta without easy separation from the uterine wall or requiring a
24 “piecemeal removal” associated with heavy bleeding as diagnostic of PAS. These
25 clinical criteria were first described by Irving and Hertig¹ in 1937 who did not have
26 invasive cases in their cohort limiting their definition to abnormally adherent placenta

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3 and not to placenta increta or percreta. This definition also fails to clearly differentiate
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5 between abnormal adherence and placental retention as both present with similar
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7 clinical symptoms and etiology⁵² leading to possible over diagnosis of placenta previa
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9 accreta. Similarly, the finding of excessive bleeding from the placental bed after delivery
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11 of the placenta is a common complication of non-accreta placenta previa due to the
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13 implantation of the placenta in the lower uterine segment which contains less muscular
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15 fibers than the upper segment and is often thinner and dehiscent after multiple
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17 caesarean deliveries.
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22 Detailed histopathologic reports can only be obtained in those patients who have
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24 a hysterectomy or a partial myometrial resection and thus in many studies there is not
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26 histopathologic confirmation of the clinical diagnosis. The main histological diagnostic
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28 criteria of accreta placentation i.e. absence of decidua between the tip of anchoring villi
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30 and the superficial myometrium, is found with increasing incidence with advancing
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32 gestation in pregnancies with no clinical evidence of PAS.⁵ Thus the combination of
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34 clinical criteria that do not differentiate between placenta retention and adherent accreta
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36 and the use of non-diagnostic criteria of villous invasiveness may result in the over-
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38 diagnosis of the adherent grade of PAS (Table 2), in particular in those studies reporting
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40 a low rate of caesarean hysterectomy.^{28,36} Overall, this can explain the wide range in
41
42 the prevalence (0.04 to 0.42%) of placenta previa with PAS and incidence (2.9 to
43
44 71.6%) of PAS in women presenting with placenta previa (Figures 3 and 4).
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50 Overall, management strategies and outcomes will vary depending on the
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52 accuracy of prenatal diagnosis, local surgical expertise and more recently access to a
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54 centre of excellence with multidisciplinary team approach.^{53,54} In cases of high suspicion
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3 of PAS during cesarean delivery, 60-70% of obstetricians-gynecologists proceed with a
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5 peripartum hysterectomy.^{55,56} By contrast with a conservative management approach,
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7 radical surgery is often considered to be safer, in particular in cases of invasive
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9 placentation.⁵⁷ The association between a placenta previa and a PAS increases the
10
11 risks of both maternal morbidity and mortality. In the present study we found that a
12
13 caesarean hysterectomy was the primary management option in around 70% of the
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15 patients presenting with a placenta previa and PAS. The inter-study range was wide
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17 with four studies^{19,21,29,37} reporting peripartum hysterectomy rates < 50%, five^{28,31,32,34,36}
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19 had rates between 50-99% and four^{22,30,35,38} had rates of 100%. This may be due to
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21 difference in study protocols, local expertise and the impact of prenatal diagnosis on
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23 management strategies but also as suggested by our analysis to difference in the rates
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25 of the different grades of PAS and the accuracy of clinical diagnosis at birth and detailed
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27 histopathologic examination confirming the diagnosis.
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33 The main limitations of this review are the quality of the published data. Thirteen
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35 out of 20 studies included in the analysis studies were retrospective and there was wide
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37 variation in the use of different ultrasound criteria for the prenatal diagnosis of placenta
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39 previa, in the clinical diagnosis of PAS at delivery and in the authors providing detailed
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41 histopathology data to confirm the clinical diagnosis. This is hampering the meta-
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43 analysis of the clinical outcomes in particular the incidence of major hemorrhage at
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45 delivery and the need and amount of blood transfusion but also the choice in
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47 management protocols and in particular the use of conservative management
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49 procedures. We would not, therefore, recommend the use of the pooled estimates
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51 beyond that of a support towards the development of standardized diagnostic protocols.
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3 The prevalence of PAS in the general population of women giving birth varies
4 widely.^{8,10,58,59} A systematic review and meta-analysis of the prevalence of placenta
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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

1
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3 analysis. EJ, JLR and SC drafted the manuscript. All authors were involved in the critical
4 discussion and approved this final version for publication. EJ is the guarantor of the study.
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10 **Data sharing statement**

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12 Extra data can be accessed via the Dryad data repository at <http://datadryad.org/> with the
13 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)
Ascioglu 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

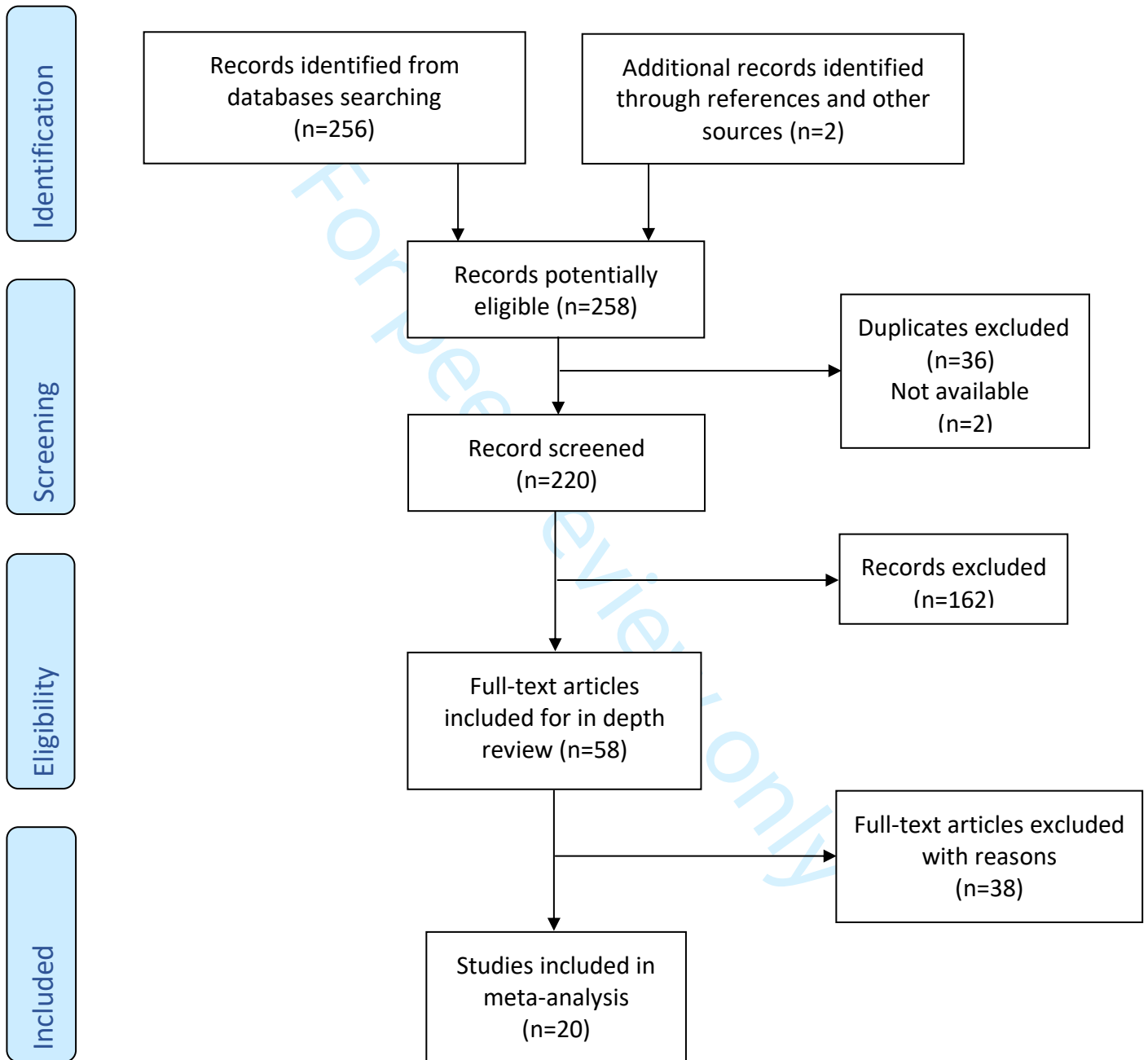
Figure legends

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*



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Author (year)

ES (95% CI)

Weight %

Retrospective

Alchalabi (2014)	0.48 (0.39;0.60)	5.24
Ascioglu (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
<i>Subtotal (I²= 99.55%; P<.001)</i>	<i>0.90 (0.73;1.08)</i>	<i>64.84</i>

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
<i>Subtotal (I²= 98.87%; P<.001)</i>	<i>0.87 (0.55;1.18)</i>	<i>35.16</i>

Heterogeneity between groups: P=.839

Overall (I²= 99.43%; P<.001) 0.89 (0.75;1.02) 100.00

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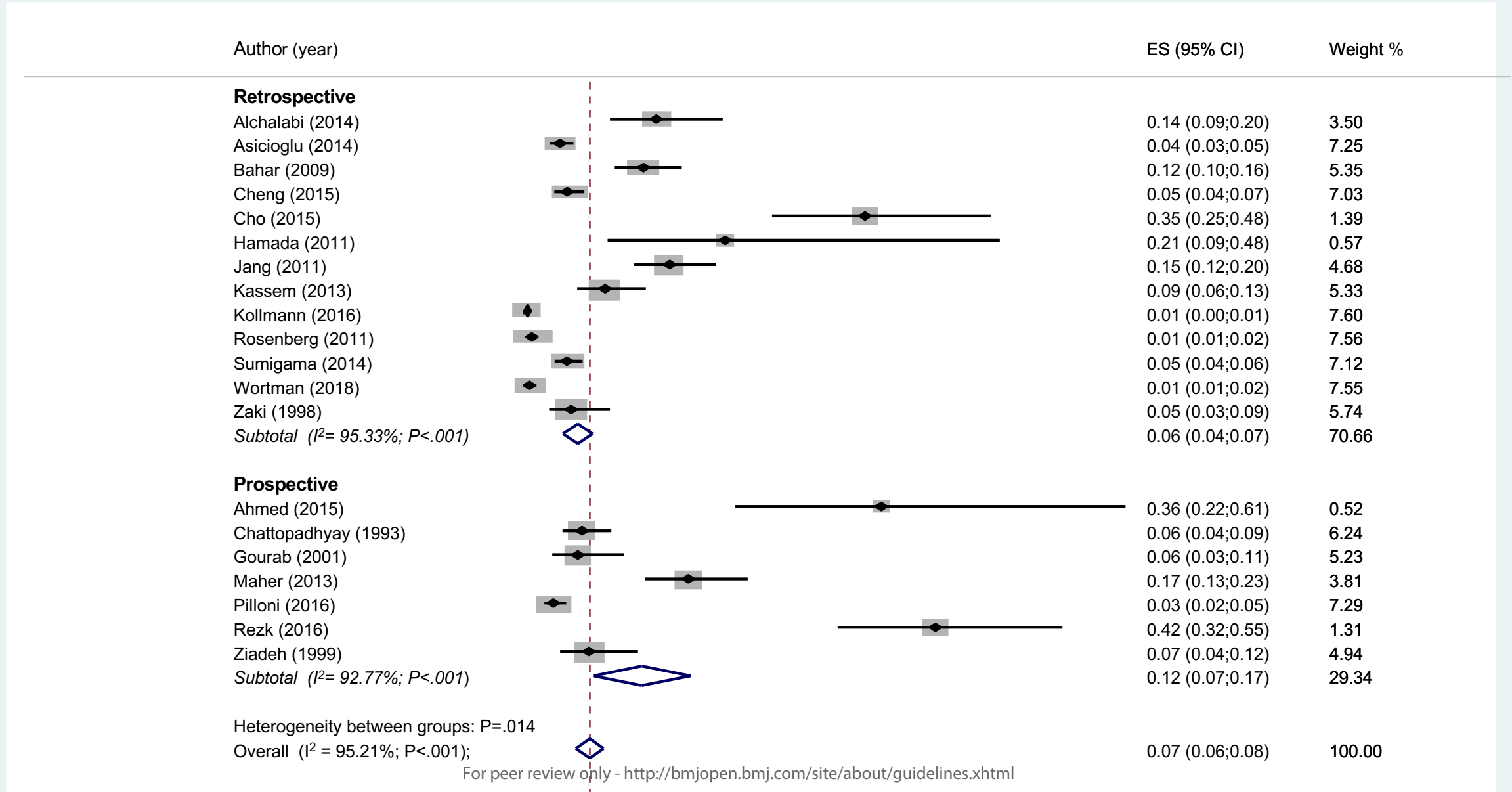
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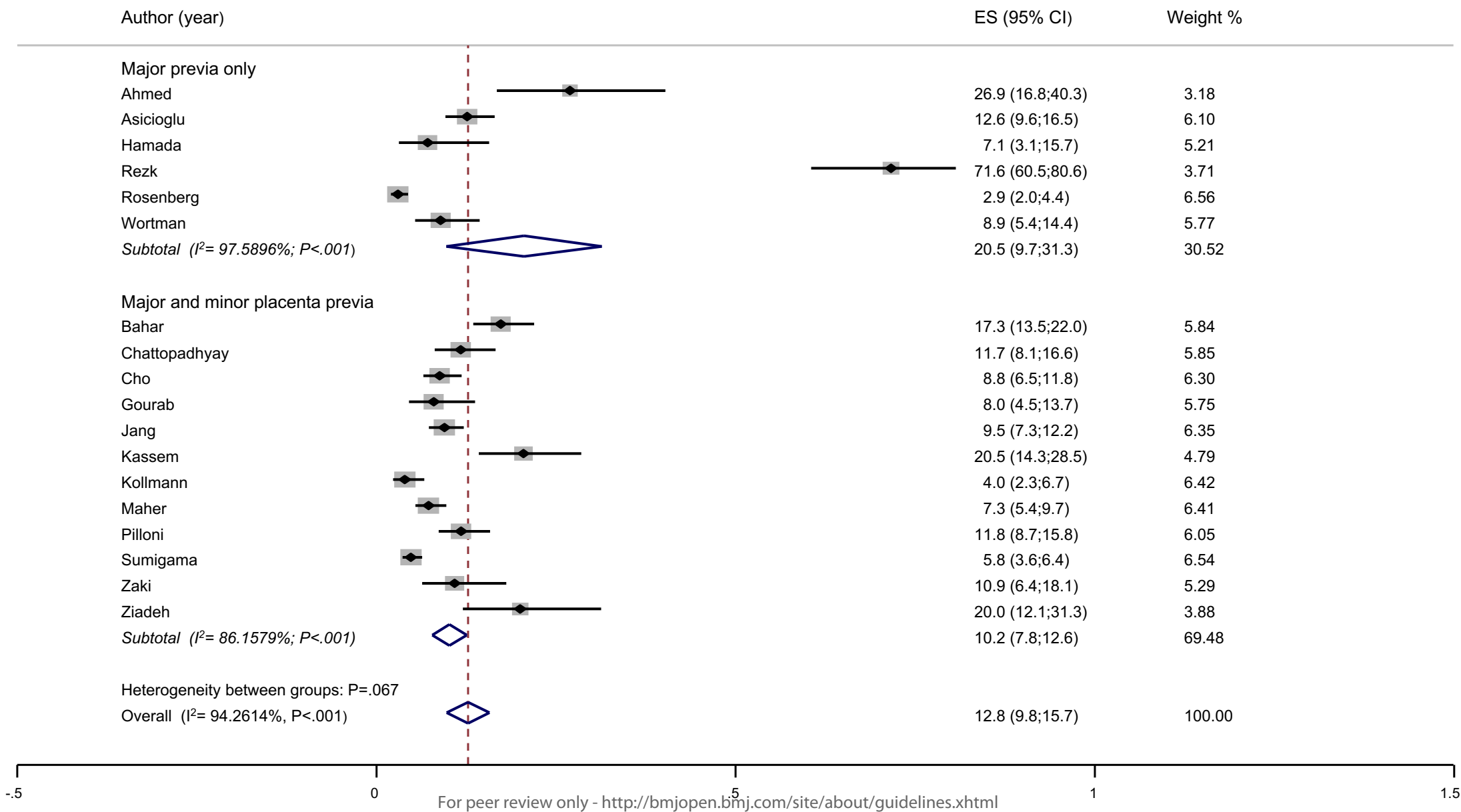
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Supplementary data 1: Search strategy for PubMed

(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.

For peer review only

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			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
Ascioglu 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		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies		
Description of any contact with authors		
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested		
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)		
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)		
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)		

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		
Assessment of heterogeneity		
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		
Provision of appropriate tables and graphics		
Reporting of Results		
Table giving descriptive information for each study included		
Results of sensitivity testing (eg, subgroup analysis)		
Indication of statistical uncertainty of findings		
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)		
Justification for exclusion (eg, exclusion of non-English-language citations)		
Assessment of quality of included studies		
Reporting of Conclusions		
Consideration of alternative explanations for observed results		
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)		
Guidelines for future research		
Disclosure of funding source		

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.