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Risk factors for abnormally invasive placenta: a systematic review and meta-analysis

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Abstract

Purpose of the article: To explore the strength of association between different maternal and pregnancy characteristics and the occurrence of AIP.

Materials and Methods: Pubmed, Embase, CINAHL databases were searched. The risk factors for AIP explored were: obesity, age >35 years, smoking before or during pregnancy, placenta previa, prior cesarean section (CS), placenta previa and prior CS, prior uterine surgery, abortion and uterine curettage, in vitro fertilization (IVF) pregnancy and interval between a previous CS and a subsequent pregnancy. Random-effect head-to-head meta-analyses were used to analyze the data.

Results: Forty-six were included in the systematic review. Maternal obesity (Odd ratio, OR: 1.4, 95% CI 1.0-1.8), advanced maternal age (OR: 3.1, 95% CI 1.4-7.0) and parity (OR: 2.5, 95% CI 1.7-3.6), but not smoking were associated with a higher risk of AIP. The presence of placenta previa in women with at least a prior CS was associated with a higher risk of AIP compared to controls, with an OR of 12.0, 95% CI 1.6-88.0). Furthermore, the risk of AIP increased with the number of prior CS (OR of 2.6, 95% CI 1.6-4.4 and 5.4, 95% CI 1.7-17.4 for 2 and 3 prior CS respectively). Finally, IVF pregnancies were associated with a high risk of AIP, with an OR of 2.8 (95% CI 1.2-6.8).

Conclusion: A prior CS and placenta previa are among the strongest risk factors for the occurrence of AIP.

Introduction

Abnormally Invasive Placenta (AIP) encompasses a heterogeneous group of anomalies characterized by different degrees of invasion of chorionic villi through the myometrium and uterine serosa [1].

Women affected by AIP require a tailored surgical management which is commonly accomplished by fundal hysterotomy, followed by delivery of the fetus and subsequent elective hysterectomy, although recent evidences suggest that an appropriate hemostatic control can be achieved by conservative techniques aiming at preserving the uterus [2,3].

Such surgical approaches require an accurate prenatal identification of women affected by AIP, which has been shown to reduce the burden of surgical complications associated with these anomalies, such as massive hemorrhage, damage to adjacent organs and admission to intensive care unit by allowing a pre-planned management of these conditions [4,5].

Prenatal diagnosis of AIP is usually accomplished by ultrasound, whereas fetal magnetic resonance imaging (MRI) is commonly used to confirm the diagnosis and to delineate the topography of placental invasion. Overall, prenatal imaging has been shown to reliably identify these disorders and to predict their severity [6-9].

Recent studies suggested that prenatal diagnosis of AIP may improve when combining imaging signs with maternal or pregnancy characteristics, such as parity, age or number of prior cesarean section (CS) [10].

The aim of this systematic review was to explore the strength of association between different maternal and pregnancy characteristics and the occurrence of AIP.

Material and methods

Data sources

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis[11-13]. MEDLINE, Embase and CINAHL were searched electronically on 23rd February 2017 and utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "abnormal invasive placenta" "morbidly adherent placenta", and "outcome" (Supplementary Table 1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma guidelines were followed [14]. This study was registered with the PROSPERO database (Registration number: CRD42018083510).

Main outcomes and measures

We aim to ascertain the strength of association between several maternal and pregnancy risk factors and the occurrence of AIP. The risk factors for AIP explored were:

- Maternal obesity
- Maternal age >35 years
- Smoking before or during pregnancy
- Placenta previa
- Prior CS
- Placenta previa and prior CS
- Prior uterine surgery, including either CS or myomectomy
- Prior abortion
- Prior uterine curettage for abortion
- In vitro fertilization (IVF) pregnancy
- Interval between a previous CS and a subsequent pregnancy

• Prior manual extraction of the placenta

For the assessment of the association between a prior CS and the occurrence of AIP, we aimed to stratify the analysis according to the number (1, 2 and 3 previous CS) and type (elective vs emergency) CS.

Eligibility criteria, study selection and data collection

Only studies reporting the prevalence of a given risk factor in women affected compared to those not affected by AIP were considered eligible for the inclusion. Studies not reporting a control group and those without a clear confirmation of AIP were excluded. Studies published before 2000 were excluded, as we considered that improvements in the diagnosis and definition of AIP make these less relevant. We planned to perform a sensitivity analysis including only cases affected by placenta percreta.

Prospective and retrospective case-control studies, case reports and case series were analysed. Opinions, cases series with less than four cases of AIP and case reports were also excluded in order to avoid publication bias.

Two reviewers (AI, ML) independently extracted data. Inconsistencies were discussed among the reviewers and consensus reached. For those articles in which targeted information was not reported but the methodology was such that the information might have been recorded initially, the authors were contacted requesting the data. Histopathological findings and/or surgical notes were used as a gold standard.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for case-control studies; according to NOS, each study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment outcome of interest [15]. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the

study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability [15].

Statistical analysis

We evaluated the association between 17 potential predictors and the presence of abnormally invasive placenta (AIP) among pregnant women. Four out of 22 potential predictors were continuous (maternal age, parity, number of previous cesarean sections - CS, and BMI); 18 were categorical (maternal age >35 years, obesity, current smoking, multiparity, diagnosis of placenta previa, diagnosis of placenta previa with previous CS, previous CS, previous elective CS, previous emergency CS, previous uterine surgery, previous abortion, previous curettage, in vitro fertilization - IVF, short interval (<23 months) between previous CS and subsequent pregnancy, manual extraction of the placenta, uterine incision, endometrial ablation).

We first used random-effect head-to-head meta-analyses, expressing the results as summary odds ratio (OR) or mean difference (and relative 95% Confidence Interval – CI) for categorical or continuous predictors, respectively. When single study results were reported as median and ranges, we used the method described by Hozo et al. to obtain the corresponding means and standard deviations (SD), and when interquartile ranges (IQR) rather than ranges were reported, they were divided by 1.35 to obtain the equivalent SD [16,17]. In all meta-analyses, the statistical heterogeneity was quantified using the I^2 metric.

Some of the comparisons involving the categorical predictors showed a marked imbalance in the success rate between the groups being compared. Besides the computational issues, in such cases the odds ratios may be of limited interest and sensitivity and specificity

could be more informative. We thus calculated the overall sensitivity and specificity (and related 95% CIs) for each comparison using the efficient-score method (corrected for continuity) described by Newcombe [18]. Finally, we performed random-effect meta-analyses of proportions to estimate the pooled rates of AIP by each categorical potential predictor.

We were able to assess publication bias graphically, through funnel plots, and formally, through Egger's regression asymmetry test, only in 10 out of 22 meta-analyses, because the formal tests for funnel plot asymmetry cannot be used when the total number of publications included for each outcome is <10 (the power is too low to distinguish chance from real asymmetry) [17,19]. RevMan 5.3 (The Cochrane Collaboration, 2014) and Stata, version 13.1 (Stata Corp., College Station, TX, 2013) were used to analyse the data.

Results

General characteristics

A total of 969 articles were identified. After screening the abstracts, 182 full text articles were assessed with respect to their eligibility for inclusion (Supplemental Table 2) and 46 studies were included in the systematic review (Table 1, Figure 1) [10,20-64]. The studies by Rac, Bowman and Wu [10,34,60], those by Weininger and Esh-Broder [37,47] and those by Wong [53,57] were carried out in the same time periods and institutions; however, because they looked at different potential predictors of AIP, were kept in the systematic review (Table 1). These studies included 1085693 women (2219 AIP and 1083474 controls).

Quality assessment based on NOS guidelines is shown in Table 2. Most of the studies were of high quality, and there was a low risk of bias and low concern regarding the applicability of the studies. The small number of cases in some of the included studies, different definitions of the risk factors analyzed, dissimilarity of the populations and lack of stratification according to the severity of AIP represent their major weaknesses.

Synthesis of the results

Five studies (554106 pregnancies) explored the association between maternal obesity and the occurrence of AIP, reported a higher risk of such disorders in obese vs non-obese women with an OR of 1.4 (95% CI 1.0-1.8) (Table 3). Likewise, advanced maternal age (OR: 3.1, 95% CI 1.4-7.0) and parity (OR: 2.5, 95% CI 1.7-3.6), but not smoking were associated with a higher risk of AIP (Table 3).

Twenty-six (1.057.222 pregnancies) and thirty-three (656168 pregnancies) studies respectively, reported the strength of association between placenta previa and CS and AIP (Table 3). Overall, the presence of placenta previa was associated with a higher risk of AIP compared to controls, with and OR of 11.0 (5% CI 4.7-25.8) and 4.7 (95% CI 3.0-7.2)

(Table 3). More importantly, the risk of AIP increased with the number of prior CS (OR of 2.6, 95% CI 1.6-4.4 and 5.4, 95% CI 1.7-17.4 for 2 and 3 prior CS respectively) (Table 3). When stratifying the analysis according to the type of AIP, there was no difference in the prevalence of such disorders in women undergoing elective vs emergency CS. Finally, there was no association between a short interval between the prior CS and a subsequent pregnancy and the occurrence of AIP, although the two studies included in this analysis differed as regard as the definition of such interval (Table 3).

The presence of placenta previa in women with at least a prior CS (twelve studies, 429.007 pregnancies) was associated with a higher risk of AIP compared to controls, with an OR of 12.0, 95% CI 1.6-88.0) (Table 3).

Thirty-four studies explored the association between a prior uterine surgery, defined as CS, myomectomy or any other procedure involving an hysterotomy and the occurrence of AIP, reporting a higher risk of these disorders in women with a prior uterine surgery (OR: 4.4, 95% CI 3.0-6.6) (Table 3).

A prior abortion was not associated with a higher risk of AIP, irrespective of the fact that uterine curettage was performed. Finally, IVF pregnancies were associated with a high risk of AIP, with an OR of 2.8 (95% CI 1.2-6.8).

Pooled proportions for the different risk factors explored in the present systematic review in pregnancies affected compared to those not affected by AIP are reported in Table 4.

When considering only cases with a histopathological diagnosis of AIP, either maternal age >35 years (OR: 3.9, 95% CI 2.6-5.9, I^2: 0%), multiparity (OR: 3.5, 95% CI 2.4-5.3, I^2: 7.8%), placenta previa (OR: 14.5, 95% CI 5.4-39.3, I^2: 63.5%), a prior CS (OR: 6.8, 95% CI 2.6-17.6, I^2: 74.8%), prior uterine surgery (OR: 7.4, 95% CI 2.9-18.4, I^2: 77.2%), placenta previa and prior CS (OR: 10.6, 95% CI 2.2-52.6, I^2: 63.9%), IVF pregnancy (OR: 11.6, 95% CI 6.2-21.5, I^2: 0%) were associated with the occurrence of AIP, while prior uterine curettage for abortion (OR: 2.5, 95% CI 0.9-6.6, I^2: 51.9%), smoking (OR: 0.92, 95% CI 0.2-4.2, I^2: 32.9%) and manual extraction of the placenta (OR: 0.8, 95% CI 0.03-17.3, I^2: 0%) did not show any degree of association with such anomalies.

Discussion

Main findings

The findings from this systematic review showed that advanced maternal age, obesity, parity, prior CS, placenta previa and IVF are associated with a significant high risk of AIP. A prior CS and placenta previa are among the strongest risk factors for the occurrence of AIP, with such risk increasing with the number of prior CS or when placenta previa and CS co-exist.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, different definitions of the risk factors analyzed among the included studies and dissimilarity of the populations (due to various inclusion criteria) represent the major limitations of this systematic review. Assessment of the potential publication bias was also problematic because of the nature of the outcome evaluated (outcome rates, with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Not all the included studies were case-control series reporting matched populations and it might be entirely possible that the presence and degree of association between some of the risk factors explored and AIP might have been affected by other several maternal or pregnancy characteristics which were not balanced between cases affected and not affected by AIP. Furthermore, we could not completely ascertain the possible association between some of the explored potential predictors, such as the type of CS, uterine incision and interval between CS and following pregnancy, and AIP in view of the very small number of included studies and the different cut-offs adopted in the included studies [65].

Despite these limitations, the present review represents the most comprehensive published estimate of the investigated outcomes in twin pregnancies affected by discordant growth.

Implications for clinical practice

Accurate prediction of AIP is fundamental in order to improve the surgical outcome of these anomalies [5]. Recent studiessuggested that predictive models integrating maternal characteristics and imaging signs can improve the diagnostic accuracy of prenatal imaging in detecting AIP [10,66].

In the present systematic review, the presence of both placenta previa and a prior CS was not unsurprisingly associated with the highest risk of AIP. Furthermore, the risk of AIP increased with increasing the number of prior CS. These findings suggest that every woman presenting with placenta previa and at least one prior CS should be considered to be potentially affected by AIP and referred to centers with high expertise in diagnosis and management in order to rule out these anomalies.

Fetal MRI should be considered because it may add useful information on the depth and topography of placental invasion which may modify surgical management. Serial follow-up scans should be also arranged because signs of AIP can be evident only later on in gestation. Despite this, it should be stressed that about 10% of women affected by the most severe types of AIP remained undiagnosed until birth, thus highlighting the need for developing more accurate predictive models for detecting these anomalies.

In the present review, we found a significant association between IVF pregnancies and AIP. Although commonly reported, such association is difficult to explain. It might be entirely possible that the reported association between AIP and IVF might have been affected by the presence of other risk factors such as advanced maternal age or BMI. Alternatively, it might be hypothesized that IVF per se increase the risk of AIP. Although controlled ovarian stimulation allows to retrieve a considerable number of oocytes thus increasing the success rate of IVF cycles, it has also been shown to alter endometrial

receptivity and structure by inducing abnormal levels of estradiol [67-69], which affect placental implantation.

Prenatal diagnosis of AIP is commonly performed during the second and third trimester of pregnancy, while there is no robust data on first trimester diagnosis, with most of the studies including only cases affected by these anomalies. Despite this, it has still to be ascertained when to scan women at risk of AIP. One of the most relevant issues when trying to diagnose AIP is which sub-set of women should be referred for an early detailed assessment in order to rule out AIP. The major risk factors for AIP are placenta previa and previous caesarean section. However, AIP can occur even in women with no classical risk factors for these conditions. In a recent large cohort study, Bailit et al. reported that 18% of women with AIP were nulliparous and that 37% had no prior CS, thus challenging the theory that AIP can occur almost exclusively in multiparous women [65].
Despite this, it is authors' collective opinion that every woman with at least one prior CS should be scanned early in pregnancy (between 5 and 9 weeks of gestation) in order to assess the gestational sac position, relationship with prior CS and anterior uterine wall and to stratify the risk of AIP [70-72].

Further large studies are need in order to build reliable predictive models for AIP tailored upon maternal characteristics, ultrasound and MRI signs observed in order to improve the diagnostic accuracy of prenatal imaging in detecting AIP.

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Table 1. General characteristics of the included studies

Author	Year	Country	Study design	Period analysed	Inclusion criteria	Pregnancies (n)	AIP (n)	Controls (n)
Millischer[20]	2017	France	Retrospective	2009-2012	Placenta previa + prior CS and US suspicion of AIP	20	8	12
Pilloni[21]	2016	Italy	Prospective	2011-2014	Placenta previa (26 weeks of gestation)	314	37	277
Thiravit[22]	2016	Thailand	Retrospective	2005-2014	Women with ultrasound suspicion of AIP	21	12	9
Collins [23]	2015	United Kingdom/ United States	Prospective	2012-2014	Clinical and/or ultrasound suspicion of AIP	89	42	47
Lyell[24]	2015	United States	Retrospective	2009-2010	AIP and matched controls	736	37	699
Miller[25]	2015	United States	Retrospective	2008-2013	AIP and matched controls	125	25	100
Parra-Herran[26]	2015	Canada	Retrospective	2002-2015	Women undergoing postpartum hysterectomy	61	44	17
Thurn[27]	2015	Denmark, Finland, Iceland, Norway, and Sweden	Prospective	2009-2012	Women affected by AIP vs general population	605567	205	605 362
Alchalabi[28]	2014	Jordan	Retrospective	2003-2012	Women who had CS for AIP or placenta previa	81	23	58
Bour[29]	2014	France	Retrospective	2006-2012	Clinical and/or US suspicion of AIP	32	16	16
Rac[10]	2014	United States	Retrospective	1997-2011	Placenta previa/low lying + >1 CS	184	54	130
Zhou[30]	2014	China	Retrospective	2011-2013	Women with prior CS	68	12	56
Noda[31]	2014	Japan/ United States	Retrospective	2011-2013	Women with suspicion of AIP	28	7	21
Asıcıoglu[32]	2014	Turkey	Retrospective	2005-2010	placenta previa	364	46	318
Laban[33]	2014	Egypt	Retrospective	2012-2013	AIP and matched controls	76	26	50
Bowman[34]	2013	United States	Retrospective	1999-2002	Women affected or non-affected by AIP with a prior CS	2749	196	2553
Cali[35]	2013	Italy	Prospective	2004-2012	Placenta previa and prior uterine surgery	187	41	146
Ueno[36]	2013	Japan	Retrospective	2009-2013	Women undergoing MRI for the suspicion of AIP	65	15	50
Weiniger[37]	2013	Israel	Prospective	2002-2011		92	52	40

					Placenta previa and/or at least one CS suspected of AIP on US			
Eshkoli[38]	2013	Israel	Retrospective	1988-2011	AIP and matched controls	34869	139	34.730
Kamara[39]	2013	Australia	Prospective	1993-2008	Placenta previa + prior CS	167	65	102
Klar[40]	2013	Germany	Retrospective	2000-2007	AIP and unmatched controls	483	161	322
Upson[41]	2013	Ireland	Retrospective	2005-2010	All deliveries	403602	357	403 245
Fitzpatrick[42]	2012	United Kingdom	Retrospective	2010-2011	All women with AIP vs all women with no AIP	390	134	256
Hannon[43]	2012	United Kingdom	Retrospective	NS	Cases of post-partum hysterectomy	16	12	4
Chantraine[44]	2012	Argentina-Germany-Belgium	Retrospective	NS	Women with placenta increta	22	13	9
Lim[45]	2011	United States	Retrospective	2009-2010	Clinical and/or US risk factors for AIP	13	9	4
Sadashivaiah[46]	2011	United Kingdom	Retrospective	2004-2008	Women undergoing interventional radiology for AIP	13	4	9
Esh-Broder[47]	2011	Israel	Retrospective	2004-2009	All deliveries	25235	42	25193
Derman[48]	2011	United States	Retrospective	NS	Women with ultrasound suspicion of AIP	17	4	13
El Behery[49]	2010	Egypt	Prospective	2007-2009	Clinical risk factors for AIP	35	7	28
Hasegawa[50]	2009	Japan	Retrospective	2000-2007	Placenta previa	127	5	122
Morita[51]	2009	Japan	Retrospective	2008	Women undergoing MRI for the suspicion of AIP	7	3	4
Dwyer[52]	2008	United States	Retrospective	2001-2016	Clinical or imaging suspicion of AIP	32	15	17
Wong[53]	2008	New Zeland	Prospective	2004-2006	Clinical risk factors for AIP	66	9	57
Tantbirojn[54]	2008	United States	Retrospective	2002-2007	Cases of post-partum hysterectomy	49	38	11
Mok[55]	2008	United Kingdom	prospective	2002-2007	Women with ultrasound suspicion of AIP undergoing interventional radiology	13	5	8
Japaraj[56]	2007	Malaysia	Prospective	2002-2005	Placenta previa + prior CS	20	7	13
Wong[57]	2007	New Zeland	retrospective	2004-2005	Clinical and/or ultrasound suspicion of AIP	36	5	31

Bencaiova[58]	2007	Switzerland	retrospective	1999-2003	AIP and matched controls	8839	31	8808
Warshak[59]	2006	United States	Retrospective	2000-2005	US diagnosis or suspicion of AIP	28	12	16
Wu[60]	2005	United States	Retrospective	1982-2002	AIP and matched controls	450	111	339
Usta[61]	2005	Lebanon	Retrospective	1983-2003	Placenta previa	347	22	325
Gielchinsk[62]	2004	Israel	Retrospective	1990-2000	AIP and matched controls	620	310	310
Chou[63]	2000	Taiwan	Retrospective	1994-1998	Women with persistent placenta previa	80	14	66
Twickler[64]	2000	United States	Retrospective	NS	Women with placenta previa and prior CS	20	9	11

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
Millischer[20]	2017	★★	★	★★
Pilloni[21]	2016	★★	★	★★
Thiravit[22]	2016	★★	★	★★
Collins[23]	2015	★★	★	★★
Lyell[24]	2015	★★	★	★★
Miller[25]	2015	★★	★	★★
Parra-Herran[26]	2015	★★	★	★
Thurn[27]	2015	★★	★★	★★
Alchalabi[28]	2014	★★	★	★★
Bour[29]	2014	★★	★	★★
Rac[10]	2014	★★	★	★
Zhou[30]	2014	★★★	★	★★
Noda[31]	2014	★★	★	★★
Asıcıoglu[32]	2014	★★	★	★★
Laban[33]	2014	★★	★	★★
Bowman[34]	2013	★★	★★	★★
Calì[35]	2013	★★	★	★
Ueno[36]	2013	★★	★	★★
Weiniger[37]	2013	★★	★	★★
Eshkoli[38]	2013	★★	★★	★★
Kamara[39]	2013	★★	★	★★
Klar[40]	2013	★★	★	★★
Upson[41]	2013	★★	★★	★★

Fitzpatrick[42]	2012	★★	★★	★★
Hannon[43]	2012	★★	★	★★
Chantraine[44]	2012	★★	★	★
Lim[45]	2011	★★	★	★★
Sadashivaiah[46]	2011	★★	★	★★
Esh-Broder[47]	2011	★★	★	★★
Derman[48]	2011	★★	★	★
El Behery[49]	2010	★★	★	★
Hasegawa[50]	2009	★★★	★	★★
Morita[51]	2009	★★	★	★★
Dwyer[52]	2008	★★	★	★★
Wong[53]	2008	★★	★	★★
Tantbirojn[54]	2008	★★	★	★★
Mok[55]	2008	★★	★	★★
Japaraj[56]	2007	★★	★	★
Wong[57]	2007	★★	★	★★
Bencaiova [58]	2007	★★	★★	★★
Warshak[59]	2006	★★	★	★★
Wu[60]	2005	★★	★★	★★
Usta[61]	2005	★★	★★	★★
Gielchinsky[62]	2004	★★	★★	★★
Chou[63]	2000	★★	★	★★
Twickler[64]	2000	★★	★	★★

Table 3. Results of the head-to-head meta-analyses comparing the risk of abnormally invasive placenta (AIP) for each categorical potential predictor (see also online figures S1-S32).

Predictors	N. studies (sample)	References	Total women (n/N vs n/N)*	OR (95% CI)	p	I^2,%	Sensitivity (95% CI)	Specificity (95% CI)
Obesity	5 (554,106)	24,27,36,38,42	74/66,469 vs 442/487,637	1.37 (1.04-1.81)	0.02	0	14.3 (11.4-17.7)	88.0 (87.8-88.1)
Maternal age >35 years	20,24,27,28,36,38,41,42,45,46,51,58-63 (1,055,206)		495/138,558 vs 653/916,688	3.13 (1.40-6.97)	0.005	96	48.7 (38.0-59.6)	77.0 (67.3-84.6)
Current smoking	11 (1,048,980)	24,27,34,36,38-42,45,63	245/130,136 vs 1130/918,844	1.13 (0.88-1.47)	0.34	38	8.60 (3.40-20.0)	90.8 (83.3-95.2)
Multiparity	20 (1,022,675)	23-28,34,36, 41,42,45,46,51,54,55,58,59,61,62	621/46,403 vs 938/976,362	2.49 (1.79-3.46)	<0.001	76	40.5 (27.9-54.5)	79.1 (65.9-88.1)
Placenta previa	24 (1,057,222)	22,23,25-27,29-31,34,37, 38,41-43,45, 48,49,51,52, 54,57-59,62	644/5256 vs 1950/1,051,966	11.0 (4.71-25.8)	<0.001	96	69.0 (51.9-82.2)	84.7 (64.5-94.4)
Placenta previa +previous CS	12 (429,007)	23,27,29,32,35,45,46,50-52,59,64	200/912 vs 1916/428,095	12.0 (1.64-88.0)	0.01	97	87.2 (67.7-95.9)	54.1 (14.5-89.1)
≥1 previous CS	33 (656,168)	22-27,28,29, 31-36,38,40, 42-46,49-51, 54-59,61-63	925/80,458 vs 1737/575,710	4.66 (3.02-7.18)	<0.001	82	85.1 (71.7-92.8)	53.5 (39.4-67.0)
Previous elective CS	3 (606,098)	27,32,39	169/43,982 vs 337/649,742	3.73 (0.50-27.7)	0.20	98	87.2 (66.7-95.9)	54.1 (14.5-89.1)
Previous emergency CS	3 (606,098)	27,32,39	127/62,219 vs 189/543,879	1.17 (0.21-6.65)	0.9	97	40.2 (34.7-45.8)	89.8 (89.7-89.8)
Previous uterine surgery	34 (1,057,363)	21-29,31-33, 36,38,40-46,49-52,54, 55,57-59,61-63	893/116,082 vs 1776/941,281	4.42 (2.96-6.59)	<0.001	82	84.4 (70.7-92.4)	55.4 (41.9-68.1)
Previous abortion	6 (36,111)	26,28,38-40,60	179/3019 vs 364/33,092	1.36 (0.84-2.20)	0.21	62	25.6 (6.88-61.5)	72.4 (51.4-59.4-82.4)

Previous curettage	22,23,25,26,32,35,37,40,44,45 (10,886)	242/10,956 vs 412/9787	2.39 (2.06-2.77)	1.87 (0.96-3.64)	0.06	82	31.5 (19.0-47.3)	78.8 (66.5-87.4)
IVF	7 (488,897)	23,27,36,38,40,42,44	3,471 vs 598/474,495	4,402 2.80 (1.16-6.76)	0.02	82	8.84 (5.02-15.1)	96.5 (92.2-98.4)
Short interval** between previous CS and subsequent pregnancy	2 (820)	24,42	62/195 vs 81/625	1.81 (0.72-4.58)	0.21	68	43.4 (35.1-51.9)	80.4 (77.2-83.3)

CS = Caesarean section; IVF = In vitro fertilization; OR = Odds Ratio; CI = Confidence Interval; * The first "n/N" refers to e.g. the number of obese women with AIP (n) / the total number of obese women without AIP (N); the second "n/N" refers to the number of non-obese women with AIP (n) / the total number of non-obese women without AIP. ** <23 months.

Table 4. Proportion meta-analysis: pooled rates of abnormally invasive placenta (AIP) in women with (A) and without (B) each categorical potential predictor.

	Pooled % of AIP (95% CI)	**Pooled % of AIP (95% CI)**
Predictors	**A**	**B**
Maternal age >35 years	16.9 (11.9-22.4)	0.8 (0.4-1.3)
Obesity	3.3 (0.0-12.3)	5.5 (3.2-8.2)
Current smoking	0.8 (0.0-2.3)	6.1 (4.9-6.5)
Multiparity	27.7 (17.4-39.0)	5.5 (4.4-6.7)
Diagnosis of placenta previa	50.9 (37.2-64.5)	1.7 (0.9-2.8)
Placenta previa+previous CS	40.9 (27.2-55.3)	5.7 (0.5-14.3)
≥1 previous CS	35.2 (29.2-41.4)	5.0 (2.5-8.1)
Previous elective CS	16.8 (0.1-50.7)	5.2 (0.0-19.9)
Previous emergency CS	10.3 (0.0-40.3)	16.0 (0.0-52.2)
Previous myomectomy	25.5 (0.0-71.1)	43.3 (29.2-58.0)
Previous uterine surgery	30.7 (26.6-34.9)	1.3 (0.6-2.2)
Previous abortion	32.9 (5.2-69.6)	26.1 (5.6-54.6)
Previous curettage	38.0 (21.6-55.6)	32.8 (16.0-52.2)
IVF	3.5 (0.4-8.57)	9.7 (6.8-12.9)
Short interval* between previous CS and subsequent pregnancy	28.6 (22.5-35.2)	8.8 (6.7-11.2)
Manual extraction of the placenta	15.8 (0.0-93.8)	31.9 (9.30-59.8)
Uterine incision	100.0 (20.6-100.0)	75.5 (67.8-81.9)
Endometrial ablation	100.0 (20.7-100.0)	46.6 (36.5-56.9)

CS = Cesarean section; IVF = In vitro fertilization; CI = Confidence Interval; * <23 month

Figure legend

Figure 1. Systematic review flowchart

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