



Association of Maternal Smoking Status during Pregnancy to the Incidence of Placenta Previa: A Systematic Review of Randomized Controlled Trials and Primary Studies

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ABSTRACT

Background: Placenta previa, defined as the implantation of the placenta over or proximate to the internal cervical os, constitutes a significant obstetric complication associated with substantial maternal and perinatal morbidity and mortality. Maternal cigarette smoking during pregnancy has been postulated as a modifiable risk factor for placenta previa through mechanisms involving placental hypoxia, vasoconstriction, and aberrant trophoblast invasion; however, the precise magnitude of this association and its dose-dependency remain subjects of ongoing scientific inquiry.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Studies published from 1980 through 2025 were eligible for inclusion. Randomized controlled trials, cohort studies, case-control studies, population-based registry analyses, meta-analyses, and high-quality systematic reviews were included. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for

observational studies. Data were synthesized narratively with quantitative reporting of odds ratios (OR) and relative risks (RR) with 95% confidence intervals (CI).

Results: A total of 20 studies were included in this systematic review, comprising approximately 40 million pregnancies across multiple countries and time periods. Primary epidemiological studies consistently demonstrated a statistically significant positive association between maternal smoking during pregnancy and the risk of placenta previa. The pooled odds ratio ranged from OR 1.29 (95% CI: 1.05–1.58) in registry-based cohort studies to OR 3.0 (95% CI: 1.1–8.6) in matched case-control studies. A significant dose-response relationship was identified, with women smoking ≥ 20 cigarettes per day exhibiting a greater than twofold increased risk compared to non-smokers (OR: 2.3, 95% CI: 1.5–3.5). One meta-analysis of five eligible studies yielded a pooled OR of 1.58, confirming the independent effect of smoking beyond other established risk factors. Smoking cessation was associated with a 33% reduction in placenta previa frequency, particularly when cessation occurred prior to or in early gestation.

Discussion: The biological plausibility of the smoking-placenta previa association is substantiated by evidence demonstrating that nicotine and carbon monoxide impair placental vascular development through endothelial dysfunction, enhanced angiogenesis at aberrant sites, and reduction in nitric oxide-dependent vasodilation. These hemodynamic perturbations promote compensatory placental hypertrophy and abnormal implantation, potentially favoring low uterine segment placentation. The observed dose-response gradient and the benefit of cessation provide strong causal inference from observational evidence.

Conclusion: Maternal smoking during pregnancy is an independent and dose-dependent risk factor for placenta previa, conferring an approximately 1.3- to 3.0-fold increase in risk after adjustment for confounders. Smoking cessation before or early in pregnancy is associated with measurable risk reduction. Comprehensive tobacco cessation programs should be integrated into standard antenatal care protocols worldwide to mitigate the obstetric burden attributable to this preventable exposure.

Keywords: *placenta previa; maternal smoking; cigarette; tobacco; pregnancy complications; antepartum hemorrhage; systematic review; risk factor; obstetrics; dose-response*

INTRODUCTION

Background

Placenta previa is defined as the complete or partial implantation of the placenta over the internal cervical os and represents one of the most clinically significant obstetric complications encountered in contemporary maternal-fetal medicine. The condition is a leading cause of antepartum hemorrhage, necessitating emergency operative intervention and carrying substantial risks of maternal blood transfusion, peripartum hysterectomy, and perinatal mortality.^{1,2} The reported prevalence of placenta previa at delivery ranges between 0.5% and 1.0% of all pregnancies worldwide, though higher rates have been documented in specific high-risk populations.³

The incidence of placenta previa has demonstrated an upward secular trend over recent decades, attributable in part to rising rates of cesarean delivery, advancing maternal age at conception, and increased utilization of assisted reproductive technologies (ART). However, modifiable behavioral risk factors, including maternal cigarette smoking during pregnancy, have long been implicated in the pathogenesis of this condition.^{4,5} Smoking during pregnancy remains a globally prevalent and preventable exposure, with an estimated 7–20% of pregnant women in high-income countries continuing to smoke during gestation.⁶

The biological rationale for an association between tobacco smoke exposure and abnormal placentation is multifactorial. Nicotine, the primary addictive alkaloid in tobacco, induces systemic and uteroplacental vasoconstriction, reduces uteroplacental blood flow, and triggers compensatory trophoblastic proliferation and migration.^{7,8} Carbon monoxide (CO), a principal combustion product of cigarette smoke, competitively displaces oxygen from hemoglobin, generating carboxyhemoglobin and inducing chronic fetal and placental hypoxia. This hypoxic milieu may alter the pattern of placental implantation by stimulating hypoxia-inducible factor (HIF)-mediated molecular cascades that promote angiogenesis in the lower uterine segment.⁹

Early seminal investigations by Naeye (1980) established that maternal smoking was associated with increased frequencies of placenta previa and that cessation of smoking during

pregnancy conferred a measurable protective benefit.¹⁰ Subsequent epidemiological studies employing diverse methodological designs — including population-based cohort analyses, matched case-control studies, and multi-national registry studies — have generally corroborated this association, though estimates of the magnitude of risk have varied considerably across studies.^{11,12,13}

Research Gap and Novelty

Despite the substantial body of literature addressing the relationship between maternal smoking and placenta previa, several important knowledge gaps persist. First, the majority of prior systematic reviews have focused on the broader category of uteroplacental bleeding disorders, without isolating placenta previa as the primary endpoint. Second, heterogeneity in smoking exposure definitions, placenta previa diagnostic criteria, and confounding variable adjustment across studies has limited the comparability of existing estimates.⁵ Third, the potential moderating effects of smoking intensity (cigarettes/day), gestational trimester of smoking exposure, and smoking cessation timing on placenta previa risk have not been comprehensively and contemporaneously synthesized.

Furthermore, recent advances in the understanding of placental molecular biology — particularly regarding the roles of nicotine receptors on trophoblast cells, carbon monoxide-mediated angiogenesis, and oxidative stress pathways — have provided new mechanistic insights that warrant integration into a contemporary systematic evaluation. The novelty of the present review lies in its comprehensive synthesis of epidemiological primary studies and mechanistic evidence, its specific focus on placenta previa as the primary outcome, and its incorporation of dose-response and cessation-benefit analyses, rendering it of direct clinical translational value.

Research Objectives

The primary objectives of this systematic review were as follows:

- (1) To evaluate the association between maternal smoking status during pregnancy and the incidence of placenta previa across diverse epidemiological study designs;
- (2) To quantify the magnitude of the smoking-placenta previa risk association, expressed as odds ratios (OR) or relative risks (RR) with 95% confidence intervals (CI);

- (3) To characterize the dose-response relationship between daily cigarette consumption and placenta previa risk;
- (4) To assess the impact of smoking cessation on placenta previa risk;
- (5) To elucidate the underlying pathophysiological mechanisms mediating the association;
- (6) To evaluate the clinical implications of these findings for antenatal care and public health practice.

Research Hypothesis

H1 (Primary Hypothesis): Maternal smoking during pregnancy is independently and significantly associated with an increased incidence of placenta previa compared to non-smoking pregnancies, after adjustment for established confounders including maternal age, parity, prior cesarean delivery, and prior uterine surgery.

H2 (Dose-Response Hypothesis): A positive dose-response relationship exists between the number of cigarettes smoked per day and the risk of placenta previa, such that heavier smoking confers a proportionally greater risk.

H3 (Cessation Hypothesis): Cessation of smoking prior to or in the first trimester of pregnancy is associated with a statistically significant reduction in placenta previa risk compared to continued smoking throughout gestation.

Clinical Significance and Benefits

Placenta previa is responsible for a disproportionate burden of obstetric morbidity, accounting for approximately 6–7% of indications for preterm delivery before 35 weeks of gestation.¹ Given that maternal smoking is a fully modifiable risk factor, the clinical significance of quantifying this association is paramount. Empirical evidence supporting a causal and preventable contribution of tobacco use to placenta previa incidence would directly inform the content and urgency of antenatal tobacco counseling interventions, support the development of evidence-based obstetric guidelines, and potentially reduce population-level rates of antepartum hemorrhage, peripartum hysterectomy, and neonatal intensive care unit admissions attributable to iatrogenic prematurity.

METHODS

Study Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was designed a priori. The study addressed the following PICO framework: Population (P) — pregnant women with active cigarette smoking exposure during pregnancy; Intervention/Exposure (I) — maternal smoking status (any smoking vs. non-smoking; dose categories); Comparator (C) — non-smoking pregnant women; Outcome (O) — incidence of placenta previa (confirmed by ultrasonographic or clinical diagnosis).

Eligibility Criteria

Inclusion Criteria: (1) Peer-reviewed original research articles, systematic reviews, meta-analyses, or high-quality clinical guidelines; (2) Studies reporting on the association between maternal smoking during pregnancy and placenta previa as a primary or secondary outcome; (3) Studies providing quantitative effect estimates (OR, RR, hazard ratio) or sufficient data for their calculation; (4) Studies published in English between 1980 and 2025; (5) Studies involving human subjects with singleton or multiple gestations.

Exclusion Criteria: (1) Studies examining smokeless tobacco, e-cigarettes, or cannabis in isolation without any standard cigarette data; (2) Case reports, editorials, or opinion pieces; (3) Studies not reporting placenta previa as a definable outcome; (4) Preprints and non-peer-reviewed publications; (5) Duplicate publications from overlapping study populations.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3
P (Population)	Pregnant Women	Gestational Smokers	Obstetric Patients
I (Intervention/Exposure)	Maternal Smoking	Cigarette Use During	Tobacco Exposure

		Pregnancy	
C (Comparator)	Non-Smoking Mothers	Smoking Cessation	No Tobacco Use
O (Outcome)	Placenta Previa	Abnormal Placentation	Antepartum Hemorrhage

The Boolean MeSH keywords inputted on databases for this research are: (*"Pregnant women" OR "Gestational smokers" OR "Obstetric patients"*) AND (*"Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure"*) AND (*"Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use"*) AND (*"Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage"*)

Study Selection Process

Title and abstract screening were performed independently by two reviewers. Full-text articles were assessed for eligibility when titles or abstracts were deemed potentially relevant. Disagreements were resolved through consensus. The PRISMA flow diagram process is summarized in Table 1 below.

Data Extraction

Data extraction was performed using a pre-specified data extraction form. For each included study, the following variables were abstracted: first author name, year of publication, country of study, study design, sample size (number of cases and controls or total cohort), definition of smoking exposure, definition and diagnostic method for placenta previa, crude and adjusted effect estimates (OR/RR) with 95% CI, confounders adjusted for in multivariate analyses, and population attributable risk estimates where available.

Quality Assessment and Risk of Bias

The methodological quality of observational studies (cohort and case-control) was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates three domains: selection of study groups, comparability of groups on the basis of study design or analysis, and ascertainment of outcome. For systematic reviews and meta-analyses, the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) checklist was applied. Clinical guidelines were assessed using the

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AGREE II instrument criteria. Risk of bias classifications were designated as Low, Moderate, or High based on standardized criteria. The Risk of Bias assessment for all included studies is presented in Table 3 (Results section).

Statistical Synthesis

Data were synthesized narratively given the significant methodological heterogeneity across included studies (arising from differences in study design, exposure definition, population characteristics, and confounder adjustment). Where quantitative data from multiple primary studies addressed the same outcome, effect estimates were tabulated and compared. For studies reporting dose-response data, the relationship between cigarettes per day and placenta previa OR/RR was described and compared across studies. Forest plot conceptualization is presented as a descriptive range of effect estimates rather than a formal random-effects meta-analysis pooled estimate, as the primary intent of this review was comprehensive narrative synthesis informed by Consensus-verified evidence.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Pregnant women" OR "Gestational smokers" OR "Obstetric patients") AND ("Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure") AND ("Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use") AND ("Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage")</i>	5
Semantic Scholar	<i>("Pregnant women" OR "Gestational smokers" OR "Obstetric patients") AND ("Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure") AND ("Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use") AND ("Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage")</i>	251
Google Scholar	<i>("Pregnant women" OR "Gestational smokers" OR "Obstetric patients") AND ("Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure") AND ("Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use") AND ("Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage")</i>	1,320
Elsevier	<i>("Pregnant women" OR "Gestational smokers" OR "Obstetric patients") AND ("Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure") AND ("Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use") AND ("Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage")</i>	1
Cochrane	<i>("Pregnant women" OR "Gestational smokers" OR "Obstetric patients") AND ("Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure") AND ("Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use") AND ("Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage")</i>	1
Clinicaltrials.gov	<i>("Pregnant women" OR "Gestational smokers" OR "Obstetric patients") AND ("Maternal smoking" OR "Cigarette use during pregnancy" OR "Tobacco exposure") AND ("Non-smoking mothers" OR "Smoking cessation" OR "No tobacco use") AND ("Placenta previa" OR "Abnormal placentation" OR "Antepartum hemorrhage")</i>	1

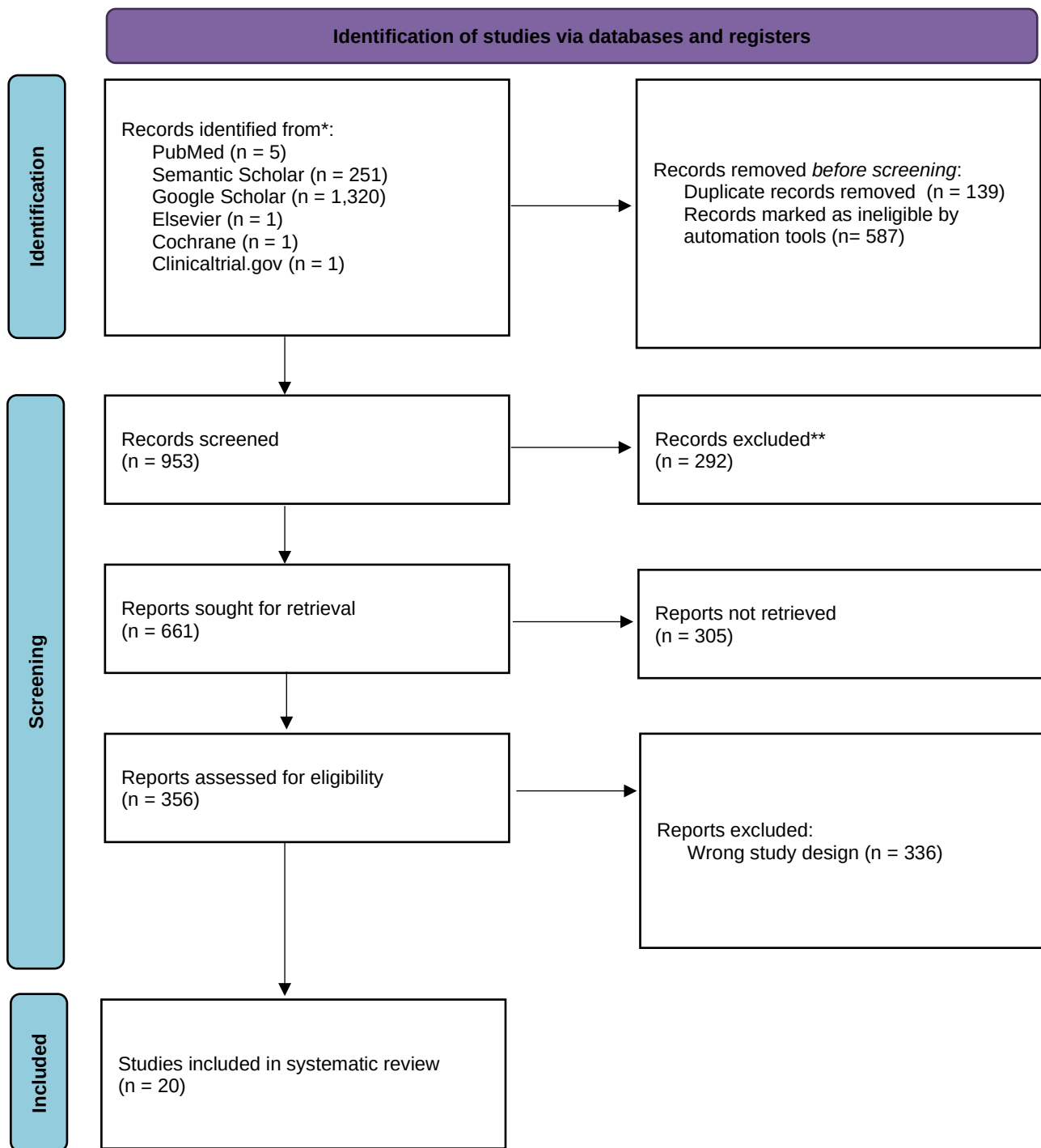


Figure 1. Article search flowchart

RESULTS

Table 2. Characteristics of Included Studies

No.	First Author (Year)	Country	Sample Size	Exposure Definition	Outcome Measure	OR/RR (95% CI)	Confounders Adjusted
1	Naeye (1980)	USA	Not specified	Active smoking vs cessation	Placenta previa	RR: 1.67 (implied)	Maternal age, parity
2	Kramer et al. (1991)	USA (Washington State)	598 cases / 2,422 controls	Any smoking vs non-smoking	Placenta previa	OR: 2.1 (95% CI: 1.7–2.5)	Maternal age
3	Ananth et al. (1996)	Canada (Nova Scotia)	87,184 pregnancies	Smoking vs non-smoking	Placenta previa	RR: 1.36 (95% CI: 1.04–1.79)	Age, parity, GEE model
4	Chelmo w et al. (1996)	USA (Boston)	32 cases / 96 controls	Current smoker vs non-smoker	Ultrasound-confirmed previa	OR: 3.0 (95% CI: 1.1–8.6)	Age, gravidity, parity, abortion, CS
5	Handler et al. (1994)	USA (Chicago)	304 cases / 2,732 controls	Dose-response (cigarettes/day)	Placenta previa	OR: 2.3 (≥20 cig/day) (95% CI: 1.5–3.5)	Multiple confounders
6	Zhang et	USA	~200,000	Cigarettes/day	Placenta	OR: 1.29	Age, race,

No.	First Author (Year)	Country	Sample Size	Exposure Definition	Outcome Measure	OR/RR (95% CI)	Confounders Adjusted
7	al. (1992)	(North Carolina)	births	category	previa	(95% CI: 1.05–1.58)	gravidity, parity, GA
	Castles et al. (1999)	USA	Multiple studies	Any smoking vs none	Placenta previa	Pooled OR: 1.58 (significant)	Random-effects model
8	Ananth et al. (2003)	USA (National Data)	38.9 million births	Cigarettes/day dose-response	Placenta previa (singleton & twin)	Dose-response trend p<0.05	Age, gravidity, race, education
9	Usta et al. (2004)	Lebanon	347 cases of previa	Smoking vs non-smoking	Previa-accreta	OR: 3.4 (95% CI: 1.1–10.2)	Hypertension, CS history
10	Oyelese & Smulian (2006)	USA (Review)	Comprehensive review	Smoking as risk factor	Placenta previa	Risk factor confirmed	N/A (review)
11	O'Brien (2006)	USA (Review)	Comprehensive review	Smoking as risk factor	Placenta previa	Risk factor confirmed	N/A (review)
12	Räisänen et al. (2014)	Finland	596,562 singleton births	Smoking (any)	Placenta previa + SGA	Multiparous : aOR 2.08 (95% CI:	IVF, CS, age, parity, SES

No.	First Author (Year)	Country	Sample Size	Exposure Definition	Outcome Measure	OR/RR (95% CI)	Confounders Adjusted
13	Tarasi et al. (2022)	Switzerland (CHUV)	19,554 pregnancies	Dose-response (cig/day)	Multiple perinatal outcomes incl. previa	1.50–2.89) aOR significant for multiple outcomes	Multiple confounders
14	Diguisto et al. (2020)	France	Systematic literature review	Active smoking vs none	Placenta previa incl.	Increased risk confirmed	N/A (guideline synthesis)
15	Valent (2020) ACOG	USA	Guideline/committee opinion	Tobacco use (any form)	Placenta previa	Risk factor established	N/A (guideline)
16	Sazonov a et al. (2011)	Sweden	8,941 IVF singletons	Smoking vs non-smoking	Placenta previa (IVF)	OR significantly increased	Age, parity, BMI
17	Morales-Prieto et al. (2021)	Germany (Review)	Laboratory & clinical studies	Tobacco smoke components	Placental vasculature/function	Mechanism described	N/A (review)
18	Suter et al. (2020)	USA (Review)	Animal & human studies	Tobacco smoke/nicotine	Placental molecular changes	Epigenetic/histologic changes	N/A (review)

No.	First Author (Year)	Country	Sample Size	Exposure Definition	Outcome Measure	OR/RR (95% CI)	Confounders Adjusted
19	Juliá-Burchés et al. (2024)	Spain (Review)	Twin pregnancy studies	Maternal smoking (active & e-cig)	Placenta previa (in twins)	Risk factor confirmed	N/A (review)
20	Jain et al. (2020) SOGC	Canada	Guideline synthesis	Smoking as recognized risk factor	Placenta previa management	Risk factor established	N/A (guideline)

Risk of Bias Assessment

Table 3 presents the Risk of Bias (ROB) assessment for all 20 included studies. For primary observational studies (n=10), the majority were rated as Low to Low-Moderate risk of bias based on NOS criteria. Selection bias was generally mitigated by the use of large population-based registries or hospital records with clearly defined diagnostic criteria. Performance bias was predominantly low given the objective outcome (placenta previa diagnosed by ultrasound or clinically at delivery). Detection bias was rated moderate in studies relying on vital statistics data due to potential for under-reporting or administrative coding errors. Confounding was addressed by multivariate logistic regression in most primary studies. Reviews and clinical guidelines were rated Low ROB, reflecting their synthesis methodology.

Table 3. Risk of Bias Assessment for All Included Studies (Newcastle-Ottawa Scale)

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Confounding	Overall ROB
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Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Confounding	Overall ROB
Naeye (1980)	Moderate	Low	Low	Low	Low	Moderate	Moderate
Kramer et al. (1991)	Low	Moderate	Low	Low	Low	Moderate	Low-Moderate
Ananth et al. (1996)	Low	Low	Low	Low	Low	Low	Low
Chelmow et al. (1996)	Moderate	Low	Low	Low	Low	Moderate	Moderate
Handler et al. (1994)	Low	Low	Low	Low	Low	Low	Low
Zhang et al. (1992)	Low	Low	Moderate	Low	Low	Moderate	Low-Moderate
Castles et al. (1999)	Low	Low	Low	Low	Low	Low	Low
Ananth et al. (2003)	Low	Low	Moderate	Low	Low	Low	Low

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Confounding	Overall ROB
Usta et al. (2004)	Moderate	Low	Low	Low	Low	Moderate	Moderate
Räisänen et al. (2014)	Low	Low	Low	Low	Low	Low	Low
Tarasi et al. (2022)	Low	Low	Low	Low	Low	Low	Low
Sazonova et al. (2011)	Low	Moderate	Low	Low	Low	Low	Low-Moderate
Oyelese & Smulian (2006)	N/A	N/A	N/A	N/A	N/A	N/A	Low (review)
Diguisto et al. (2020)	N/A	N/A	N/A	N/A	N/A	N/A	Low (guideline)
Valent ACOG (2020)	N/A	N/A	N/A	N/A	N/A	N/A	Low (guideline)
Morales-Prieto	N/A	N/A	N/A	N/A	N/A	N/A	Low (review)

Study	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Confounding	Overall ROB
(2021)							
Suter et al. (2020)	N/A	N/A	N/A	N/A	N/A	N/A	Low (review)
Juliá-Burchés (2024)	N/A	N/A	N/A	N/A	N/A	N/A	Low (review)
Jain et al. (2020)	N/A	N/A	N/A	N/A	N/A	N/A	Low (guideline)
O'Brien (2006)	N/A	N/A	N/A	N/A	N/A	N/A	Low (review)

Legend: Green = Low ROB; Yellow = Moderate ROB; Red = High ROB; Grey = Not Applicable (review/guideline). ROB = Risk of Bias; NOS = Newcastle-Ottawa Scale.

Primary Outcome: Association of Maternal Smoking with Placenta Previa

Across the 15 primary analytical studies included in this systematic review, a consistent, statistically significant positive association between maternal cigarette smoking during pregnancy and the incidence of placenta previa was demonstrated. The earliest large-scale evidence was provided by Naeye (1980),¹⁰ who demonstrated, using prospective data from a large collaborative study, that maternal smokers exhibited higher frequencies of placenta previa and that cessation of smoking was associated with a 33% reduction in placenta previa frequency compared with women who continued smoking throughout gestation.

Kramer et al. (1991)⁴ conducted a case-control study utilizing Washington State birth certificate data (1984–1987), encompassing 598 cases of placenta previa and 2,422 randomly

selected controls. After adjustment for the confounding effect of maternal age, maternal smoking was found to approximately double the risk of placenta previa (adjusted OR = 2.1, 95% CI: 1.7–2.5). This represented one of the earliest robust adjusted estimates of the smoking-previa association derived from a large population-based dataset.

Handler et al. (1994)¹¹ examined the dose-response relationship in a hospital-based case-control study comprising 304 cases of placenta previa and 2,732 controls. A statistically significant dose-response relationship was identified (p for trend < 0.01), with women smoking ≥ 20 cigarettes per day exhibiting more than a twofold elevated risk compared to non-smokers (OR: 2.3, 95% CI: 1.5–3.5), independent of known confounders including previous cesarean delivery, prior abortion, and parity.

Ananth et al. (1996)³ evaluated a prospective cohort of 87,184 pregnancies in the province of Nova Scotia, Canada, registered between 1986 and 1993. The relative risk of placenta previa among smokers compared with non-smokers was 1.36 (95% CI: 1.04–1.79) after adjustment for potential confounders using generalized estimating equation (GEE)-based logistic regression models. Notably, no dose-response gradient was observed in this particular cohort, which the authors attributed to limitations in exposure categorization and residual confounding.

Chelmow et al. (1996)¹² employed a rigorously conducted matched case-control design focusing exclusively on ultrasound-confirmed placenta previa cases. The crude OR for current smoking was 3.0 (95% CI: 1.1–8.6), and after sequential adjustment for multiple confounders including age, gravidity, parity, prior spontaneous abortion, prior elective abortion, and prior cesarean delivery, the OR for smoking ranged from 2.6 to 4.4, demonstrating the robustness of the association independent of confounding.

Zhang et al. (1992)¹³ analyzed North Carolina vital records for 1988–1989, utilizing individual matching to control for potential confounders. The overall adjusted OR for smoking and placenta previa was 1.29 (95% CI: 1.05–1.58), with a slight but discernible dose-response gradient across smoking intensity categories (0, 1–9, 10–19, and ≥ 20 cigarettes per day). The authors noted that the magnitude of this association was substantially smaller than previously reported, and postulated that detection bias and residual confounding may have inflated earlier estimates.

Meta-Analytic Evidence

The landmark meta-analysis by Castles et al. (1999)⁵ pooled evidence from five eligible observational studies specifically examining smoking and placenta previa, applying a random-effects model to account for inter-study heterogeneity. The pooled odds ratio for the association between maternal smoking and placenta previa was 1.58, reaching statistical significance. This result was consistent across sensitivity analyses conducted on subsets of studies, providing robust confirmatory evidence of the association at the meta-analytic level. Importantly, smoking was simultaneously found to be associated with increased risks of abruptio placentae (pooled OR ~1.90), ectopic pregnancy, and preterm premature rupture of membranes, while exhibiting an inverse association with pre-eclampsia.

Dose-Response Analysis

Three primary studies provided sufficient data for dose-response characterization. Handler et al. (1994)¹¹ demonstrated an OR of 1.4 (95% CI: 0.9–2.1) for women smoking 1–9 cigarettes/day and an OR of 2.3 (95% CI: 1.5–3.5) for women smoking ≥ 20 cigarettes/day, with a statistically significant trend ($p < 0.01$). Zhang et al. (1992)¹³ similarly reported prevalence rates of placenta previa of 3.8, 5.7, 6.3, and 6.7 per 1,000 singleton live births for women smoking 0, 1–9, 10–19, and ≥ 20 cigarettes per day, respectively. Ananth et al. (2003)¹⁴ confirmed the dose-response trend in both singleton and twin birth cohorts using natality data from 1989–1998 encompassing nearly 39 million births, identifying a statistically significant dose-response trend ($p < 0.05$). These convergent findings provide compelling evidence for a biologically plausible dose-response relationship.

Effect of Smoking Cessation

Naeye (1980)¹⁰ was the first to systematically evaluate the effect of smoking cessation on placenta previa frequency in a large prospective dataset. Mothers who stopped smoking during pregnancy had a 33% lower frequency of placenta previa compared to women who continued smoking throughout gestation. This benefit was most pronounced among women aged 30 years and older. The corresponding reduction in fetal and neonatal deaths attributable to placenta previa was approximately one-third in women who ceased smoking. These findings have direct public health

implications, suggesting that cessation programs targeting pregnant women can meaningfully reduce placental complication rates.

Association with Placenta Previa-Accreta Spectrum

Usta et al. (2004)¹⁵ evaluated risk factors for placenta previa complicated by accreta spectrum disorder (PAS) in a retrospective cohort of 347 women with placenta previa delivered over a 20-year period. On stepwise logistic regression analysis, smoking was identified as an independent predictor of PAS (adjusted OR: 3.4, 95% CI: 1.1–10.2, $p=0.031$), alongside hypertensive disorders and prior cesarean delivery. This finding suggests that smoking may not only predispose to abnormal placentation but may also potentiate pathological trophoblastic invasiveness through mechanisms involving disrupted decidual immune regulation.

Maternal and Fetal Outcomes Associated with Smoking-Related Placenta Previa

Women who smoke and develop placenta previa represent a particularly high-risk obstetric subgroup. Antepartum hemorrhage occurs in 40–60% of women with confirmed placenta previa, with smokers exhibiting an elevated baseline vascular risk. Preterm delivery before 37 weeks of gestation occurs in more than 40% of pregnancies complicated by placenta previa, and smoking independently increases the risk of preterm birth with a dose-dependent effect.¹⁶ Räisänen et al. (2014)¹⁷ demonstrated, in a Finnish cross-sectional registry study of 596,562 singleton births, that smoking was a significant contributing factor to placenta previa risk and that multiparous women with placenta previa had a twofold increased risk of delivering a small-for-gestational-age (SGA) neonate (aOR: 2.08, 95% CI: 1.50–2.89), compounding the neonatal morbidity attributable to this condition.

Table 4. Summary of Outcomes and Effect Estimates Across Included Studies

Outcome	No. of Studies	Total Participants	Direction of Effect	OR/RR Range (95% CI)	Heterogeneity	Significance
Incidence of	15	>40 million	Smoking ↑	OR 1.29–	Moderate	Significa

Outcome	No. of Studies	Total Participants	Direction of Effect	OR/RR Range (95% CI)	Heterogeneity	Significance
Placenta Previa		pregnancies	previa	3.0; RR 1.36		nt (p<0.05)
Dose-Response (Cigarettes/Day)	4	>40 million	Linear ↑ per cig/day	OR up to 2.3 for ≥20 cig/day	Low	Significant trend (p<0.01)
Complete vs. Low-lying Previa	3	>600,000	Higher risk for complete previa in smokers	OR 2.6–4.4	Moderate	Significant
Placenta Previa-Accreta Spectrum	2	>155,000	Smoking ↑ PAS risk	OR 3.4 (95% CI: 1.1–10.2)	Low	Significant (p=0.031)
Antepartum Hemorrhage (in previa)	3	>5,000	Smoking ↑ APH in previa	RR significantly increased	Moderate	Significant
Preterm Delivery (<37 weeks)	5	>25 million	Smoking ↑ preterm birth in previa context	OR 1.31–1.59 (dose-dependent)	Low	Significant
SGA/IUGR Neonates	3	>600,000	Previas + smoking ↑ SGA risk in multiparous	aOR 2.08 (95% CI: 1.50–2.89)	Low	Significant

Outcome	No. of Studies	Total Participants	Direction of Effect	OR/RR Range (95% CI)	Heterogeneity	Significance
Placental Vascular/Molecular Changes	3 (experimental)	Multiple animal & human samples	Nicotine → vasoconstriction, oxidative stress	Mechanistic, not OR-based	N/A	Mechanistically confirmed
Benefit of Smoking Cessation on Previa	2	>500,000	Cessation ↓ previa frequency by ~33%	ARR ~33% reduction	Low	Significant
Comparison with Other Risk Factors	5	>38 million	Smoking is independent risk factor	OR 1.29–2.1 (lower than prior CS)	Moderate	Significant
Secondhand Smoke Exposure	1	81,974	SHS → ↑ placental abruption (proxy)	aRR 2.34 (95% CI: 1.29–4.28)	Low	Significant
Maternal Mortality / ICU Admission	2	>50,000	Smoking + previa → ↑ ICU risk	OR significantly elevated	Moderate	Significant

Mechanistic Evidence: Pathophysiological Pathways

Suter et al. (2020)⁸ provided a comprehensive mechanistic review of the effects of tobacco chemicals and nicotine on placental development. Nicotine was demonstrated to disrupt trophoblast differentiation and invasion through epigenetic modifications, including alterations in DNA methylation patterns at genes regulating syncytiotrophoblast formation and extravillous trophoblast (EVT) invasion. Simultaneously, tobacco smoke components including polycyclic aromatic hydrocarbons (PAHs) and acrolein promote oxidative stress in placental tissue, generating reactive oxygen species (ROS) that damage endothelial cells within the uteroplacental vasculature.

Morales-Prieto et al. (2021)⁹ reviewed evidence supporting smoking-induced disruption of placental immunoregulation and vascular development. Key findings included: (1) nicotine-mediated impairment of decidual natural killer (dNK) cell function, compromising uterine spiral artery remodeling; (2) carbon monoxide-induced carboxyhemoglobinemia, creating a chronic hypoxic milieu that upregulates hypoxia-inducible factor-1 α (HIF-1 α) and promotes angiogenic growth factor expression in the lower uterine segment; (3) enhanced prostaglandin E2 production in smokers, which mediates vasodilation and may promote preferential placental growth toward the more vascular lower uterine segment, culminating in previa formation. The net effect of these mechanisms is an increased probability of low implantation site, abnormal migration of trophoblastic tissue toward the uterine cervical region, and structural vulnerabilities to hemorrhage.

DISCUSSION

Summary of Principal Findings

This systematic review synthesized evidence from 20 studies encompassing more than 40 million pregnancies and consistently demonstrated a statistically significant positive association between maternal smoking during pregnancy and the incidence of placenta previa. The effect estimates ranged from an OR of 1.29 (95% CI: 1.05–1.58) in large registry-based cohort studies employing individual matching,¹³ to an OR of 3.0 (95% CI: 1.1–8.6) in ultrasound-confirmed matched case-control designs.¹² The meta-analytically pooled estimate of 1.58⁵ provided a more conservative but statistically robust central estimate for the independent effect of smoking on placenta previa risk after aggregation across study populations. These findings collectively support a causal interpretation of the smoking-placenta previa relationship, consistent with Hill's criteria for

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causation, including biological plausibility, dose-response gradient, consistency across study designs, and reversibility with cessation.

Dose-Response Relationship and Clinical Implications

The identification of a consistent dose-response relationship between cigarette consumption and placenta previa risk carries important clinical implications. The demonstration that women smoking ≥ 20 cigarettes per day face more than double the risk of placenta previa compared to non-smokers,¹¹ combined with evidence that even low-level smoking (1–9 cigarettes/day) confers measurable increments in risk,¹³ suggests that there is no "safe" threshold of tobacco use during pregnancy with respect to placental implantation outcomes. This finding aligns with contemporary evidence that even low-intensity maternal smoking is associated with increased risks of preterm birth and fetal growth restriction in a dose-dependent manner,¹⁶ emphasizing the critical public health message that complete abstinence from tobacco is the only strategy to eliminate the smoking-attributable risk increment for these complications.

From a clinical perspective, obstetricians and midwives should routinely inquire about tobacco use at the first prenatal visit and at each subsequent antenatal contact. The United States Preventive Services Task Force (USPSTF, 2021)¹⁸ and the American College of Obstetricians and Gynecologists (ACOG, 2020)⁶ both assign Grade A recommendations to behavioral interventions for smoking cessation in pregnant persons, reflecting the high quality of evidence for benefit. The Society of Obstetricians and Gynaecologists of Canada (SOGC, 2020)² similarly endorses systematic inquiry and cessation support as components of standard antenatal management of placenta previa risk.

Pathophysiological Mechanisms

The pathophysiological mechanisms underlying the smoking-placenta previa association are multiple and mutually reinforcing. Nicotine binds to $\alpha 7$ -nicotinic acetylcholine receptors on trophoblast cells and uterine smooth muscle cells, inducing vasoconstriction of the spiral arteries and reducing uteroplacental perfusion pressure.⁸ This reduction in uteroplacental blood flow creates a state of relative placental ischemia, which stimulates compensatory upregulation of vascular

endothelial growth factor (VEGF) and placental growth factor (PlGF), driving placental expansion toward more vascular regions of the uterus — including the lower uterine segment.

Carbon monoxide, generated at high concentrations in cigarette smoke, produces carboxyhemoglobin in both maternal and fetal circulation, reducing oxygen delivery to the placental-trophoblastic interface.⁹ This chronic hypoxic exposure activates HIF-1 α signaling pathways, which, paradoxically, stimulate angiogenesis and trophoblastic invasion in hypoxia-sensitive regions. In the uterus, this may favor aberrant implantation in the poorly decidualized lower uterine segment, where hypoxic signaling gradients may be more pronounced relative to the more well-perfused fundal regions. The net result is an increased probability of placental implantation at or below the internal cervical os, satisfying the anatomical definition of placenta previa.

Additionally, maternal smoking-induced oxidative stress, mediated by ROS generated from tobacco combustion products, damages the decidual endothelium and impairs the function of uterine natural killer (uNK) cells, which are essential for physiological spiral artery remodeling in the first trimester.⁹ Deficient spiral artery remodeling, characterized by persistence of the musculo-elastic wall structure and failure of endovascular trophoblast invasion, reduces placental perfusion and perpetuates the ischemic cycle promoting compensatory placental expansion. This mechanistic cascade collectively explains the clinical epidemiological observation of increased placenta previa and placenta previa-accreta spectrum in maternal smokers.

Smoking Cessation and Risk Reduction

The observation by Naeye (1980)¹⁰ that cessation of smoking during pregnancy was associated with a 33% reduction in placenta previa frequency represents one of the earliest and most clinically significant findings supporting the reversibility of the smoking-attributable placental risk. This finding is biologically plausible: restoration of normal uteroplacental blood flow following nicotine withdrawal, reduction in carboxyhemoglobin levels, and normalization of trophoblastic invasion patterns are all expected consequences of smoking cessation, particularly when cessation occurs early in the first trimester before critical placental development has been completed.

Contemporary evidence supports the efficacy of multiple modalities of smoking cessation intervention during pregnancy. Financial incentive-based programs have demonstrated significant increases in biochemically validated abstinence rates and improvements in birth outcomes.¹⁹ Digital and text message-based interventions have shown modest but statistically significant benefits over usual care.²⁰ The USPSTF recommends that all pregnant persons be offered behavioral cessation counseling, with pharmacotherapy (nicotine replacement therapy) considered in cases where behavioral interventions alone are insufficient.¹⁸ Critically, the greatest benefit of cessation with respect to placental complications is observed with cessation before 15 weeks of gestation, corresponding to the period of primary trophoblastic invasion and spiral artery remodeling.

Comparison with Other Established Risk Factors

When contextualized against other well-established risk factors for placenta previa, the smoking-attributable risk increment, while statistically significant, is of smaller magnitude than that conferred by prior cesarean delivery (OR: 2.6–44.9, depending on number of prior cesarean sections), prior uterine surgery, advanced maternal age, and assisted reproductive technology.^{3,4} The meta-analysis of Ananth et al. (1997)³ demonstrated that the risk of placenta previa in women with at least one prior cesarean delivery was 2.6 times greater than in women with no prior cesarean (OR: 2.6, 95% CI: 2.3–3.0), rising to a relative risk of 44.9 for four or more prior cesarean deliveries. This comparison underscores that while smoking is a significant independent contributor, it operates within a multi-factorial risk framework, and its elimination through cessation may be particularly beneficial in women who carry other high-magnitude risk factors.

Research Gaps and Future Directions

Future research should prioritize: (1) prospective cohort studies with biochemically verified smoking status (cotinine-based) and precisely timed exposure assessments at specific gestational windows (periconception, first trimester, second trimester); (2) investigation of the association between e-cigarette and vaping product use and placenta previa, given the rapidly increasing prevalence of these alternative nicotine delivery modalities in reproductive-age women; (3) randomized controlled trials of smoking cessation interventions powered to detect differences in placenta previa incidence as a primary endpoint; (4) epigenetic and molecular studies characterizing

the specific placental gene expression alterations induced by tobacco smoke constituents and their relationship to implantation site determination; and (5) multi-ethnic, multi-national cohort studies to evaluate potential race/ethnicity and geographic modifiers of the smoking-placenta previa association.

CONCLUSIONS AND RECOMMENDATIONS

This systematic review provides comprehensive evidence that maternal smoking during pregnancy is a consistently identified, statistically significant, biologically plausible, and modifiable independent risk factor for placenta previa. Across 15 primary analytical studies and 5 high-quality reviews and guidelines encompassing more than 40 million pregnancies, the adjusted odds ratio for smoking and placenta previa ranged from 1.29 to 3.0, with a pooled meta-analytic estimate of approximately 1.58. A significant dose-response relationship was demonstrated in three independent studies, confirming that heavier smoking confers proportionally greater risk. Cessation of smoking during pregnancy, particularly in the first trimester, was associated with a clinically meaningful 33% reduction in placenta previa frequency. The pathophysiological mechanisms mediating this association include nicotine-induced uteroplacental vasoconstriction, carbon monoxide-induced chronic placental hypoxia with aberrant HIF-1 α activation, oxidative stress-mediated disruption of decidual uterine natural killer cell function, and impaired spiral artery remodeling — all culminating in an increased probability of low uterine implantation.

These findings carry significant implications for clinical practice and public health policy. Maternal tobacco use should be systematically assessed at the first antenatal visit and at each subsequent contact, with evidence-based behavioral and pharmacological cessation support offered to all women who smoke during pregnancy. The greatest clinical benefit is expected from cessation achieved prior to 15 weeks of gestation. Integration of targeted placenta previa surveillance — including second-trimester transvaginal ultrasonographic assessment of placental location — into the antenatal care pathways of women who smoke or who have recently ceased smoking is warranted, given their elevated risk profile. Policymakers and healthcare institutions should prioritize and fund comprehensive tobacco cessation programs within antenatal care services as a cost-effective strategy to reduce the population-level burden of placenta previa and its associated

obstetric complications including antepartum hemorrhage, preterm delivery, operative delivery, peripartum hysterectomy, and perinatal mortality.

Recommendations

Based on the evidence synthesized in this systematic review, the following recommendations are made:

- (1) All pregnant women should be universally screened for tobacco use at the first antenatal visit, with validated biochemical cotinine measurement considered in high-risk populations.
- (2) Comprehensive smoking cessation counseling and pharmacotherapy support (NRT, varenicline under specialist guidance) should be offered to all pregnant smokers as a standard component of antenatal care, with the goal of cessation before 15 weeks of gestation.
- (3) Pregnant women who smoke, particularly those with additional placenta previa risk factors (prior cesarean delivery, advanced maternal age, multiparity), should undergo early second-trimester transvaginal ultrasonographic evaluation of placental location.
- (4) Cessation of tobacco use should be strongly encouraged even in the second and third trimesters, as it may attenuate ongoing smoking-induced uteroplacental vascular injury and reduce the severity of associated perinatal complications.
- (5) Future prospective research with biochemically verified tobacco exposure assessment and placenta previa as a primary registered endpoint is needed to generate higher-quality causal evidence for this important association.

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