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SYSTEMATIC REVIEW

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Family history and risk of miscarriage: A systematic review and meta-analysis of observational studies

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Abstract

Introduction: Miscarriage, a spontaneous pregnancy loss at <24 weeks' gestation, is a common complication of pregnancy but the etiologies of miscarriage and recurrent miscarriage are not fully understood. Other obstetric conditions such as preeclampsia and preterm birth, which may share similar pathophysiology to miscarriage, exhibit familial patterns, suggesting inherited predisposition to these conditions. Parental genetic polymorphisms have been associated with unexplained miscarriage, suggesting there could be a genetically inherited predisposition to miscarriage. This systematic review and meta-analysis of observational studies aimed to assess the association between family history of miscarriage and the risk of miscarriage in women.

Material and methods: A systematic review and meta-analysis of observational studies was carried out in accordance with Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Electronic searches using databases (MEDLINE, EMBASE and CINAHL) were carried out to identify eligible studies from 1946 until 2019. Observational studies (cohort or case-control) were included. Human studies only were included. Participants were women of reproductive age. Exposure was a family history of one or more miscarriage(s). The primary outcome was miscarriage in women. Abstracts were screened and data were extracted by two independent reviewers. Study quality was assessed using Critical Appraisal Skills Program (CASP) tools. Data were pooled from individual studies using the Mantel-Haenszel method to produce pooled odds ratios (ORs) with 95% confidence intervals (95% CI). Systematic review registration number (PROSPERO): CRD42019127950.

Results: Thirteen studies were identified in the systematic review; 10 were eligible for inclusion in the meta-analysis. Twelve studies reported an association between family history of miscarriage and miscarriage in women. In all, 41 287 women were included in the meta-analysis. Women who miscarried were more likely to report a family history of miscarriage (pooled unadjusted OR 1.90, 95% CI 1.37-2.63). Overall study quality and size varied, with few adjusting for confounding factors. Results

Abbreviations: CASP, Critical Appraisal Skills Program; OR, odds ratio.

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should be interpreted with caution as the associations presented are based on unadjusted analyses only.

Conclusions: Women who miscarry may be more likely to have a family history of miscarriage. Further research is required to confirm or refute the findings.

KEYWORDS

familial, family history, inherited, miscarriage, predisposition, recurrent miscarriage

1 | INTRODUCTION

Miscarriage, the loss of a pregnancy prior to 24 weeks' gestation,[1] is the most common complication of pregnancy. Approximately 1 in 5-6 pregnancies end prior to 12 weeks' gestation.[2-4] Around half of miscarriages are thought to be secondary to fetal chromosomal abnormalities;[5] however, many remain unexplained. Furthermore, some couples face repeated losses, with 1%-2% of couples diagnosed with recurrent miscarriage (defined as three or more consecutive miscarriages in the UK).[6,7]

Parental genetic polymorphisms related to immunity, coagulation, metabolism and angiogenesis have been associated with unexplained miscarriage or recurrent miscarriage.[8-10] Over 5% of couples with recurrent miscarriage are also thought to personally carry chromosomal abnormalities which may increase the risk of chromosomal abnormalities in the fetus causing miscarriage or recurrent miscarriage.[11] If genetic factors have a role in miscarriage or recurrent miscarriage, either through specific gene polymorphisms or via chromosomal translocations, it is possible that such a genetic predisposition could be inherited through families. Many environmental and lifestyle factors are also associated with miscarriage, such as ionizing radiation,[12] exposure to environmental heavy metals and chemicals,[13] smoking, caffeine intake, extremes of body mass index and illegal drugs.[14-18] It is also possible that such factors could descend through generations of the same family and could be responsible for familial patterns of miscarriage among family members.

Family history of miscarriage is not a universally accepted predictor for miscarriage currently, but there is growing evidence that there may be a familial association.[19-21] The objective of this systematic review and meta-analysis of observational studies was to determine whether there is an association between a woman's family history of miscarriage and the risk of miscarriage. To our knowledge, this is the first systematic review to appraise the evidence on familial predisposition to miscarriage.

Key message

Women who miscarry are more likely to report a family history of miscarriage. More research is needed to determine whether there are heritable risk factors for miscarriage or recurrent miscarriage.

2 | MATERIAL AND METHODS

A protocol was developed a priori and the systematic review was registered on the PROSPERO website (registration number: CRD42019127950) and reported in accordance with MOOSE guidelines.[22] No funding was received to undertake this review.

2.1 | Eligibility criteria

Observational studies which investigated the association between a family history of miscarriage and miscarriage in women of reproductive age were included. Cohort (retrospective or prospective) and case-control studies were included. The population included were women who had at least one pregnancy and information of their family's reproductive history. Miscarriage was defined as one or more spontaneous pregnancy losses prior to viability. Studies which investigated spontaneous miscarriage in first or second trimester, excluding stillbirths, were eligible for inclusion. The risk factor studied was a family history of one or more miscarriages. A family history was any reported history of miscarriage in the women's family, including first-, second- or third-degree relatives. Women with no family history of miscarriage were the comparators for cohort studies and women with no history of miscarriage were the controls for case-control studies. Primary or secondary outcomes were miscarriage or recurrent miscarriage. Studies were included where outcomes and exposure status were collected from national or local data registries, hospital records or self-reported via questionnaires or interviews. Studies were excluded if they were descriptive/ecological/cross-sectional studies, animal studies, studies where the outcome was stillbirth or ectopic pregnancy or where the outcome was not a family history of miscarriage.

2.2 | Search strategy

Electronic searches using MEDLINE, EMBASE and CINAHL were carried out. Searches were performed from 1946 to the present. The search strategy was developed in MEDLINE and modified for other databases (Table S1). The initial search was carried out on 23 February 2018 and a final search was carried out on 20 April 2020. Systematic

searches were carried out using defined keywords and mapping to Mesh or Emtree headings where applicable. Search tools such as Boolean operators (AND/OR), truncation and searching using text words were used to optimize results. The search strategy was refined by an Information Consultant and Librarian (Mel Bickerton, University of Aberdeen). Citation lists of relevant studies and reviews were handsearched. Two researchers (A.W. and P.N.) independently conducted the literature searches. The same two researchers screened abstracts and study titles confirming their eligibility. Any disagreement was resolved by discussion with a third researcher. There were no limits set for language, year of publication or publication status.

2.3 | Data collection

Authors were contacted where additional data were required, with the exception of those studies published more than 30 years ago. Authors were sent two reminder emails and given a minimum of 4 weeks to reply from the final reminder, thereafter it was deemed that no further information was available. Quality of studies were assessed using the Critical Appraisal Skills Program (CASP)[23] tools for cohort and case-control studies as appropriate.

Primary analysis and data aggregation were performed on eligible studies in which a family history of a miscarriage or recurrent miscarriage was the exposure, and miscarriage or recurrent miscarriage in women was the outcome. Data extraction tables were created and used to report study characteristics and findings.

2.4 | Statistical analyses

Data were pooled from individual studies using Mantel-Haenszel method to produce pooled odds ratios (ORs) with 95% confidence intervals (95% CI). Data were pooled from studies where clinical heterogeneity was deemed moderate to low and where adequate data were available on exposures and outcomes. Raw data were used to calculate unadjusted ORs and 95% CI for women with pregnancy loss to determine any association with a family history of pregnancy loss on the outcome of pregnancy loss in women (both miscarriage and stillbirth). Where data were available for women with primary and secondary recurrent miscarriage as two separate groups of cases within the same study,[24,25] the data for the two groups of cases were combined to create a single group of cases (primary or secondary miscarriage).

Statistical heterogeneity was estimated using I^2. Where I^2 was greater than 50% (moderate to high statistical heterogeneity), random effects models were used to present the results of the meta-analysis. Where I^2 was less than 50% (low statistical heterogeneity), fixed effects models were presented. A P value of $<.05$ was considered statistically significant. REVMAN version 5.3 software (Review Manager [RevMan] [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane center, The Cochrane Collaboration) was used to perform meta-analyses.

Studies which investigated recurrent miscarriage in women and the association with a family history of miscarriage were included in a subgroup analysis. A further subgroup analysis was carried out including only studies published in the last 20 years (2000-2020) to determine any difference in the results according to differing diagnostic criteria over time for miscarriage. A sensitivity analysis was carried out where studies presented significantly outlying results compared with other included studies. A funnel plot was used to assess risk of publication bias.

3 | RESULTS

Thirteen studies met the eligibility criteria (Figure 1).[20,21,24-34] Study characteristics are summarized in Table 1 and study findings in Table 2. Excluded studies are detailed in Table S2.

Included studies defined family history as:

any family history of miscarriage;[29]
any family history of miscarriage within the last 5 years in either first- or second-degree relatives;[30]
any family history in first- or second-degree relatives;[26]
any family history in first-, second- or third-degree relatives;[32,34]
any family history of recurrent miscarriage;[24,25]
a family history of recurrent miscarriage in first-degree relatives;[21,28,33]
mother's history of miscarriage.[20,27,31]

There was a degree of clinical heterogeneity between studies including differences in the study aims, definition of family history, gestational threshold for defining miscarriage and definitions of cases and controls. Miscarriage was universally defined as spontaneous pregnancy loss or abortion, but definitions varied in terms of the gestational threshold for diagnosing miscarriage: at <20 weeks' gestation,[27] <16 weeks,[32] <24 weeks,[20,29] <12 weeks,[24,28] in the first or second trimester,[33] at more than 6 weeks' gestation and less than 28 weeks' gestation.[21] Five studies[25,26,30,31,34] did not provide a gestational age threshold for defining miscarriage. Eight[21,24-26,28,30,33,34] studies specifically investigated recurrent miscarriage (either two or more[20,25,26,28] or three or more[21,24,30,33] miscarriages) as the outcome. Seven studies[20,21,24,25,28,33,34] investigated a family history of recurrent miscarriage as the exposure.

Three studies investigated primary recurrent miscarriage (history of miscarriages and no live births) and secondary recurrent miscarriages (women with history of miscarriage as well as prior live births) as two separate groups and compared them to the same controls.[24,25,34] Two studies[21,33] included women with a history of either primary or secondary miscarriage as one group of cases.

Ten studies (41 287 women)[20,24-31,33] were eligible for inclusion in a meta-analysis. Unpublished data were obtained from Pouta et al.[31] Two studies were excluded from the meta-analysis as there was no exposure status available for their control groups.[21,32]

All but one study reported that women with miscarriage or recurrent miscarriage were more likely to have a family history

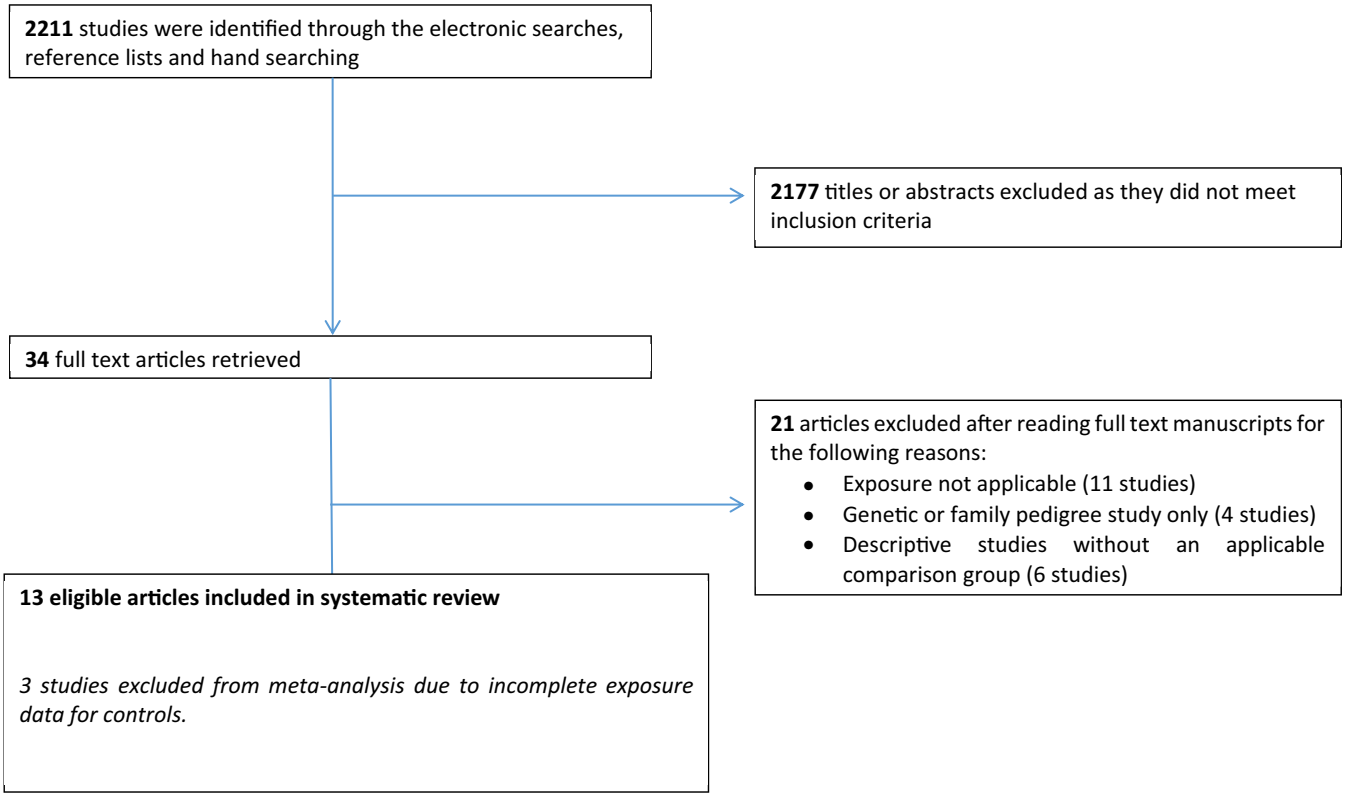

FIGURE 1 Flow diagram of study selection process for systematic review [Color figure can be viewed at wileyonlinelibrary.com]

of miscarriage or recurrent miscarriage. Pouta et al[31] found no statistically significant association between a mother's history of miscarriage and a daughter's history of miscarriage. Women with a history of miscarriage were significantly more likely to have a family history of miscarriage (pooled unadjusted OR 1.90, 95% CI 1.37-2.63) (Figure 2), though statistical heterogeneity was high at 83%. Three studies[24,25,33] reported that women were more likely to report a family history of recurrent miscarriage; however, results were not statistically significant. Three studies[20,27,31] specifically investigated a maternal history of miscarriage and risk of miscarriage in daughters; two reported an association between a mother's history of miscarriage and an increased risk of miscarriage in daughters. A subgroup analysis was carried out including studies including women with primary miscarriage only[24,25] (pooled unadjusted OR 1.95, 95% CI 1.40-2.71, I^2 = 83%, using random effects model). Women with two or more recurrent miscarriages (pooled unadjusted OR 1.83, 95% CI 1.21-2.77, I^2 = 67%; Figure 3) and three or more recurrent miscarriages[24,30,33] (OR 2.20, 95% CI 1.46-3.33, I^2 = 5%) were more likely to have a family history of miscarriage. Finally, a subgroup analysis was carried out including only studies published in the preceding 20 years (2000-2020) which again found there was an association between a family history of miscarriage in women who miscarry (OR 1.51, 95% CI 1.09-2.07, I^2 = 86%).

Most studies did not include adjustment for confounding factors; therefore, we were only able to produce unadjusted estimates of effect.

3.1 | Risk of bias assessment

In summary, 38% of included studies were deemed of moderate to high quality and 62% were of poor quality using the CASP checklist tools.[23] Risk of bias assessment is summarized in Figure S2.

3.1.1 | Cohort studies

As Zhou et al[27] and Pouta et al[31] were prospective cohort studies, they should not be subject to recall bias. Although Zhou et al[27] used self-reported questionnaires and telephone interviews for their baseline data collection and follow-up, data collection took place prior to the daughters' pregnancies, to determine pre-pregnancy risk factors for miscarriage thereby reducing recall bias. The risk of selection bias is low in Pouta et al[31], as they were able to collect 96% of eligible mothers. as well as in Zhou et al,[27] where all women trying to conceive were selected randomly from communities in a defined geographic area. As with most cohort studies, both studies were subject to follow-up bias, whereby at various points in the data collection there were daughters lost to follow-up.

3.1.2 | Case-control studies

All of the case-control studies due to their retrospective design were subject to recall bias, with the exception of Woolner et al,[20]

TABLE 1 Study characteristics–studies eligible for inclusion in the systematic review which investigated family history of miscarriage and the outcome of miscarriage in women

Study[Ref]	Aim	Setting	Study design	Population	Data sources	Statistics used	Measurement of outcome
Woolner et al[20]	To investigate whether there is an association with maternal history of miscarriage and miscarriage in daughters	Hospital recorded pregnancies, Aberdeen, UK	Nested case-control in intergenerational cohort	Mother and daughter pairs who each have at least 1 pregnancy recorded	Aberdeen Maternity and Neonatal databank	Generalized estimating equations	Odds ratio and 95% CI
Zhou et al[27]	To assess pre-pregnancy risks for miscarriage	Communities and villages in Anhui, China	Prospective cohort	Married women residing in Anhui, China, not using fertility treatment and trying for a pregnancy followed for 2 y	Self-reported questionnaires and telephone interview	Poisson regression	Relative risks and 95% CI
Rasti et al[26]	To investigate genetic polymorphism (+49 A/G CTLA4) and predisposition to recurrent miscarriage; association of positive family history on miscarriage	Clinics, Southwest Iran	Case-control	Women with history of at least two recurrent miscarriage (cases); controls were postmenopausal women with at least two live births and no history of miscarriage	Interview	Logistic regression	Odds ratio and 95% CI
Miskovic et al[32]	To evaluate the relation between recurrent miscarriage, parental and fetal chromosomal status and association with recurrent miscarriage	Genetic Counseling Unit, Split, Croatia	Case-control	Women (couples) with one or more miscarriages (cases); women with no history of miscarriage or complicated pregnancies with healthy offspring (controls)	Retrospective case note review	Kruskal-Wallis test and Bonferroni test	Proportions and *P* values
Zhang et al[30]	To determine risk factors for recurrent miscarriage	Hospitals in Guangzhou, China	Case-control	Women with three or more miscarriages (cases); Pregnant or women with one previous live birth (controls)	Self-reported questionnaire	Logistic regression	Odds ratio and 95% CI
Pouta et al[31]	To assess intergenerational patterns of reproduction from mother to daughter	Two provinces in Finland	Prospective cohort	Pregnant women (mothers) with expected dates of delivery in 1966 whose pregnancy resulted in a daughter	Self-reported questionnaires	Spearman correlation coefficient	Unpublished proportions obtained
Al-Ansary et al[29]	To identify risk factors for miscarriage	Hospital in Riyadh, Saudi Arabia	Case-control	Women admitted to hospital for miscarriage (cases); women in hospital with live births (controls)	Structured interviews	Logistic regression	Relative risks and 95% CI
Berkowitz et al[25]	To assess the association between an estrogen receptor gene variant and risk of spontaneous miscarriage and evaluate other risk factors for recurrent miscarriage including family history	Private medical centers associated with Mount Sinai Medical Center, USA	Case-control	Women with a history of at least two miscarriages and no live births (cases); women who had at least two live births and no history of miscarriage. Included women with primary or secondary recurrent miscarriage	Telephone interviews	Logistic regression	Odds ratio and 95% CI

(Continues)

TABLE 1 (Continued)

Study[Ref]	Aim	Setting	Study design	Population	Data sources	Statistics used	Measurement of outcome
Parazzini et al[28]	To evaluate risk factors for miscarriage	Hospital and clinic setting in Northern Italy	Case-control	Women with recurrent miscarriages (two or more unexplained) and no previous term deliveries (cases); Women admitted for normal delivery without history of miscarriage (controls)	Structured interviews	χ^2 test Mantel-Haenszel test	Relative risks and 95% CI
Ho et al[34]	To determine the prevalence of recurrent miscarriage, cancer and congenital anomalies in the first-, second- and third-degree relatives of couples with gestational trophoblastic tumors or recurrent spontaneous abortion	Obstetrics Clinic, National Taiwan University Hospital, Taiwan	Case-control	Couples with recurrent miscarriage (cases); definition of recurrent miscarriage not clear; and fertile couples (controls)	Interview and questionnaire to relatives of husbands and wives	2×2 contingency test	Proportions and *P* values only
Christiansen et al[21]	1. To investigate partner specificity on pregnancy outcome 2. To investigate familial predisposition to miscarriage	Hospital Department of Obstetrics and gynecology, Denmark	Case-control	Participants in RCT women with recurrent miscarriage (RCT investigating leukocyte immunization for prevention of recurrent miscarriage); controls were Danish women with at least one conception	Interview; self-reported questionnaires from relatives; hospital records	χ^2 test	Lifetime abortion incidence rates per 100
Johnson et al[24]	1. To identify immunologic markers of recurrent miscarriage 2. To investigate family history in women with primary and secondary recurrent miscarriage	Liverpool Maternity Hospital, UK	Case-control	Women with primary recurrent miscarriage and secondary recurrent miscarriage (cases) and women with a term live birth (controls)	Women surveyed – method not disclosed	χ^2 test	Proportions and *P* value only
Alexander et al[33]	To investigate immunization with paternal lymphocytes for women with recurrent miscarriage	Obstetric clinics in Brussels, Belgium	Case-control	Women with recurrent miscarriage (at least three miscarriages, cases); antenatal women (controls) definition of controls not clear	Not described	None	Proportions only

TABLE 2 Study findings–studies eligible for inclusion in the systematic review which investigated family history of miscarriage and the outcome of miscarriage in women

Study	Total population	Family history of miscarriage or recurrent miscarriage	Outcome of miscarriage or recurrent miscarriage	Results reported
Woolner et al[20]	31 565	4284	758	OR 1.11 (95% CI 1.01-1.22)
Zhou et al[27]	3062	39	229 (miscarriage)	Adjusted RR (miscarriage all losses <20 wk) 1.96 (95% CI 1.22-3.14) Adjusted RR (miscarriage <10 wk) 1.9 (95% CI 0.96-3.75) Adjusted RR (miscarriage 10-20 wk) 2.16 (95% CI 1.37-3.41)
Rasti et al[26]	240	66	120 (recurrent miscarriage)	OR 1.80 (95% CI 1.01-3.20)
Miskovic et al[32]	632	Unable to determine	567 (miscarriage)	48% of first, second and third generation relatives of the women had history of miscarriage for the cases; however, reproductive history of the controls is not available
Zhang et al[30]	726	86	52 (recurrent miscarriage)	Adjusted OR 2.12 (95% CI 1.28-3.49)
Pouta et al[31]	4442	820	117 (miscarriage)	No association reported in intergenerational analysis (Spearman correlation coefficient 0.0001) between mother and daughter pairs Proportions obtained from unpublished data received from authors are presented in the meta-analysis
Al-Ansary et al[29]	452	58	226 (miscarriage)	RR 4.6 (95% CI 2.3-9.4)
Berkowitz et al[25]	164	27	121 (including both primary or secondary recurrent miscarriage)	20% (primary recurrent miscarriage) 18% (secondary recurrent miscarriage) had a family history of recurrent miscarriage compared to with 9.3% of controls. OR 2.4 (95% CI 0.7-8.1) including only primary recurrent miscarriage vs controls
Parazzini et al[28]	270	20	12 (recurrent miscarriage)	RR 3.2 (95% CI 1.3-8.1)
Ho et al[34]	624	Unable to determine	218 (including both primary or secondary recurrent miscarriage)	Couples with recurrent miscarriage more likely to have first, second or third-degree relatives with recurrent miscarriage than controls ($P < .0001$)
Christiansen et al[21]	721	Unable to determine	90 (recurrent miscarriage)	The sisters of cases had a higher rate of spontaneous abortion (25.3%, 95% CI 18.5-33.2) compared with controls rate of spontaneous abortion. No statistical comparisons carried out for mothers and daughters; no data on unexposed controls for sisters or mothers
Johnson et al[24]	166	17	12 (including both primary or secondary recurrent miscarriage)	11/67 (16.4%) women with primary recurrent miscarriage had a positive family history of recurrent miscarriage (3 or more), $P < .01$
Alexander et al[33]	200	7	100 (recurrent miscarriage)	7% of cases with a mother or sister with history of recurrent miscarriage; 0% of controls have history of recurrent miscarriage

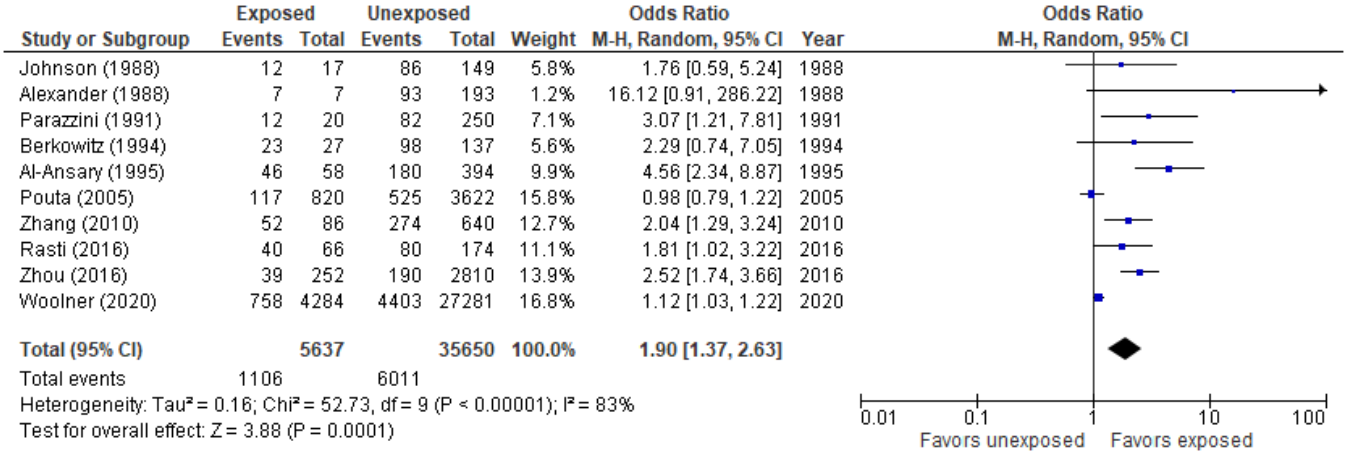

FIGURE 2 Forest plot: pooled estimate of the effect of a family history of miscarriage on a woman's risk of miscarriage (unadjusted OR [95% CI]) including the results generated in the intergenerational case-control study [Color figure can be viewed at wileyonlinelibrary.com]

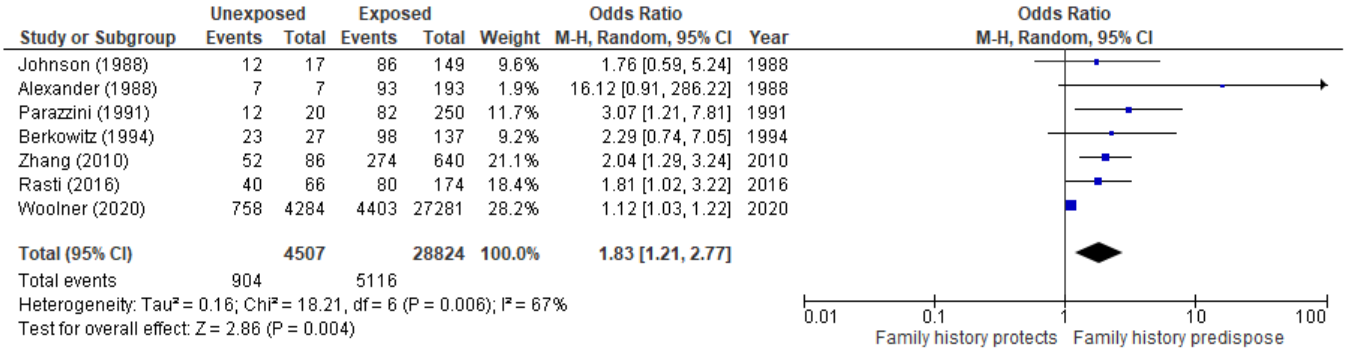

FIGURE 3 Forest plot: pooled estimate of effect of a family history of miscarriage on a woman's risk of recurrent miscarriage (unadjusted OR [95% CI]) including the results generated in the intergenerational case-control study [Color figure can be viewed at wileyonlinelibrary.com]

as that study used routinely collected registry-based data. There is a risk of observer bias in studies which utilized interviews to collect data. There could be selection bias in all of the case-control studies whereby women were selected based on their attendance at hospital. In all except one study,[20] women with no knowledge of their family history were excluded, thereby creating selection bias. Alexander et al[33] did not report their method of control selection. In all the other case-control studies, control selection was deemed appropriate, though it varied between studies.

A funnel plot (Figure S1) shows a largely asymmetric funnel suggesting that there is a risk of publication bias. The lower portion of the funnel is essentially empty, which suggests that small studies that do not report an association, may be missing.

4 | DISCUSSION

The pooled data from observational studies suggest that women who miscarry may be more likely to have a family history of miscarriage. There also appears to be a familial predisposition to recurrent miscarriage, as evidenced in both analyses. However, results need to be interpreted with caution, as pooled estimates are based on unadjusted analyses, most studies not adjusting for confounding factors. Also, as many studies used self-reported exposure and outcome data, it is possible that women with a history of miscarriage are simply more likely to report a history of miscarriage due to the risks of recall bias. Furthermore, there is a risk of publication bias.

This is the first paper to synthesize the current evidence on the association of a family history of miscarriage and risk of miscarriage in women. Data extraction and reviews were conducted by two reviewers and disagreements settled by a third reviewer. No language, date or publication status limits were set. A subgroup analysis was performed to determine any effect on the results due to changing miscarriage definitions over time by including only studies published from 2000 to 2020.

There are limitations to this review. There was high statistical heterogeneity between studies (I^2 = 83%) and random effect models were used to account for this. Including a heterogeneous group of women may have contributed to the heterogeneity seen in the results. Ideally, subgroup analysis including only women with spontaneous conception, without co-morbidities which may increase

miscarriage risk, and stratification of the results according to increased maternal age could have improved the results.

There is a significant risk of selection and recall bias for most of the studies identified. Nine of the studies are case-control and so at high risk of bias. Given the numerous potential confounding factors which could affect a woman's risk of miscarriage, such as maternal age, it must be noted that the significant associations presented from the results of the meta-analysis are based on unadjusted analyses. Many included studies did not adjust for potential confounding factors in the individual study results. Grey literature was not searched and therefore this is a potential limitation of this review. The definition of family history of miscarriage was generalized in this review with little clarification of what constituted a positive family history within some individual studies. By including generalized definitions of exposure or outcomes, this could mean that the associations found relate solely to the aforementioned recall bias, for example, women with a miscarriage being more likely to report family history even if that is in a more distant relative. This could falsely inflate the association seen. Furthermore, the biological plausibility for a familial association is more likely for first-generation relatives. It is possible by including generalized definitions that specific lineages of familial predisposition could be missed. This means that although a significant association was found, more research is needed to delineate further the specific routes of transmission of familial risk, such as from mothers, grandmothers or other female relatives, as well as paternal influence. Using a more stringent definition of outcome led to a stronger association for primary recurrent miscarriage.

Furthermore, given the differences in defining miscarriage as well as recurrent miscarriage, caution must be exercised when interpreting our results. Although a stronger association was found when a subgroup analysis was performed with a more stringent inclusion of only studies with primary recurrent miscarriage, this also entailed inclusion of a much smaller sample size and the exclusion of several studies, which in itself could lead to bias. This is another example of where a consensus in clinical definitions would improve research on miscarriage. It could also be argued it was inappropriate to perform a meta-analysis or to include studies with varying definitions of miscarriage and recurrent miscarriage. We have detailed the study characteristics and differences in definitions for exposure and outcomes for each study. Nonetheless, this is a potential limitation of this review.

The results from this review of epidemiological studies would suggest that there is an association with family history of miscarriage and miscarriage. However, these results need to be interpreted with caution. As the results are based on pooled unadjusted analyses, as most studies did not adjust for confounding factors the results may not be precise as many other factors, such as maternal age, can affect the risk of miscarriage.[3,14,15] However, one study previously published by our group[20] adjusted for smoking, deprivation, age and year of delivery in daughters when investigating the association of a maternal history of miscarriage. A much more conservative association was found, which likely reflects the robust statistical methods used. Nonetheless, an association was found which suggests that familial predisposition may have a role in the etiology of miscarriage. At present, there is insufficient evidence to inform practice, but this review highlights the need to understand the potential shared factors associated with miscarriage, whether genetic, environmental or lifestyle.

Obstetric conditions other than miscarriage, such as preeclampsia, preterm birth and growth restriction,[35-41] are thought to be at least partially inherited through families. A Danish cohort study also found that daughters were at higher risk of an ectopic pregnancy if their mother had experienced an ectopic (rate ratio 1.50, 95% CI 1.19-1.88).[42] This suggests the possibility that underlying pathophysiological mechanisms common to these, such as placental dysfunction or aberrant immunological responses, could be genetically inherited. Over 50 maternal genetic polymorphisms have been found to be associated with recurrent miscarriage.[9] It is possible that many genes are involved, or indeed that differences in gene expression or signaling may contribute to the risk of miscarriage.

Due to the observational nature of the included studies, causation cannot be proved. Much of the bias reported is inherent to study design. However, the results of this review provide a basis to generate hypotheses and an impetus to conduct basic science and large population-based studies using routinely collected data to confirm or refute the findings of a familial association with miscarriage and recurrent miscarriage. Furthermore, more research is needed on the potential impact that shared environmental or lifestyle factors have on the risk of miscarriage and whether this affects any association between family members. Future research may take the form of Cornelius et al,[43] who quantified the extent to which family history of type 2 diabetes originated from genetic or environmental factors. Given the pathophysiology may be different for primary vs secondary miscarriage, fetal chromosomal abnormalities vs chromosomally normal fetus miscarriages, and recurrent vs non-recurrent miscarriage, future research must ideally ensure clear and consistent definitions of miscarriages well as core outcome sets.

5 | CONCLUSION

Women who miscarry appear more likely to have a family history of miscarriage; however, results should be interpreted with caution as most of the eligible studies were of poor quality and at high risk of bias. Further epidemiological research using high-quality, routinely collected population data is needed to confirm or refute this association.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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