

Leiomyomas in Pregnancy and Spontaneous Abortion

A Systematic Review and Meta-analysis

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OBJECTIVE: To systematically review studies reporting the risk of spontaneous abortion among pregnant women of typical reproductive potential with and without uterine leiomyomas.

DATA SOURCES: We searched PubMed, EMBASE, Web of Science, and ClinicalTrials.gov for publications from January 1970 to December 2016.

METHODS OF STUDY SELECTION: We excluded studies that did not use imaging to uniformly document leiomyoma status of all participants, did not have a comparison group without leiomyomas, or primarily included women seeking care for recurrent miscarriage, infertility care, or assisted reproductive technologies.

TABULATION, INTEGRATION, AND RESULTS: Two authors independently reviewed eligibility, extracted data, and assigned overall quality ratings based on predetermined criteria. Of 1,469 articles identified, nine were eligible. Five enrolled general obstetric populations and four included women undergoing amniocentesis. In five

studies in general obstetric populations that included 21,829 pregnancies (1,394 women with leiomyomas and 20,435 without), only one adjusted for potential confounders. This meta-analysis revealed no increase in risk of spontaneous abortion among those with leiomyomas compared with those without (11.5% compared with 8.0%; risk ratio 1.16, 95% CI 0.80–1.52). When bias from confounding was estimated for nonadjusted studies, the aggregate calculated risk ratio was 0.83 (95% CI 0.68–0.98).

CONCLUSION: Leiomyoma presence was not associated with increased risk of spontaneous abortion in an analysis of more than 20,000 pregnant women. Failure of prior studies to adjust for confounders may have led to the common clinical belief that leiomyomas are a risk factor for spontaneous abortion.

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Uterine leiomyomas are benign smooth muscle tumors of the uterus estimated to be present in up to one in five women of reproductive age.^{1–3} Leiomyomas are commonly implicated by patients and clinicians as a cause of spontaneous abortion. However, a Cochrane systematic review and meta-analysis failed to demonstrate any difference in spontaneous abortion risk between women randomized to myomectomy compared with no leiomyoma surgery before conception.⁴ Three systematic reviews since 2000 suggest leiomyoma status is associated with spontaneous abortion risk.^{5–7} These reviews are restricted to or dominated by studies of women seeking reproductive assistance. Because it is understood that women seeking fertility treatment differ in spontaneous abortion risk and rates of successful pregnancy from the average woman, it may not be appropriate to base general understanding of risk associated with leiomyomas on studies of special populations. These considerations provide grounds for

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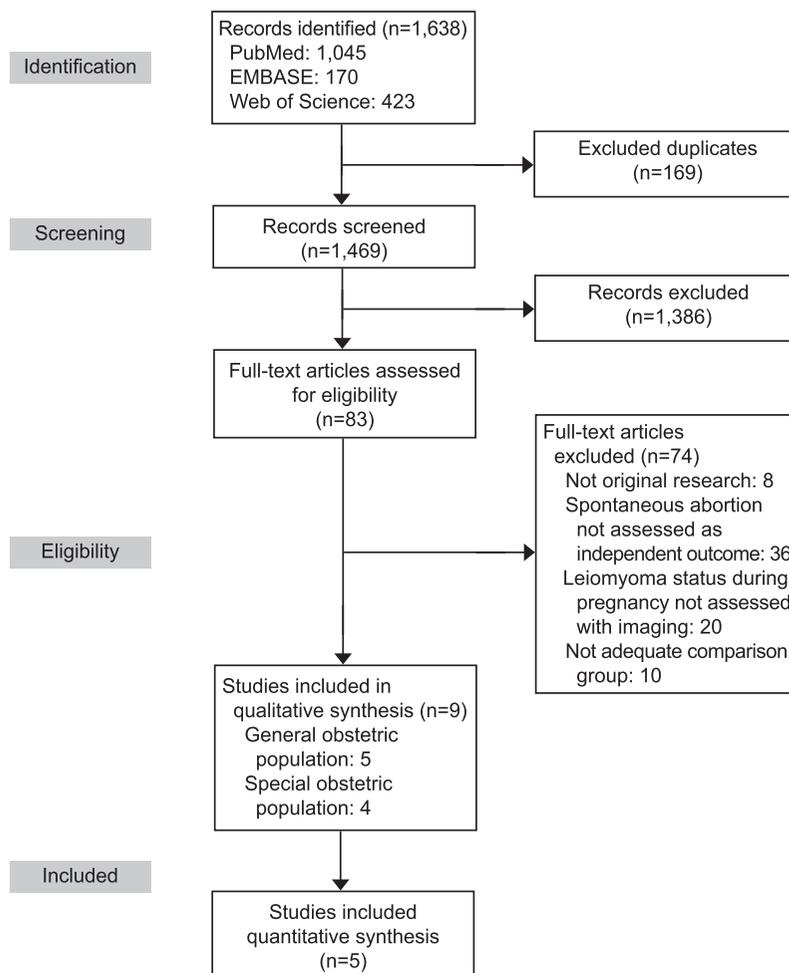


Fig. 1. Flow diagram of studies identified in the systematic review.

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Table 1. Characteristics of Studies From General Obstetric Populations

Study	Study Years	Study Design	No. of Participants*	Population
Exacoustòs and Rosati, ¹⁷ 1993, Italy	1984–1990	Retrospective cohort	12,708 (492/12,216)	Exposed and unexposed reportedly matched by age and parity
Mollica et al, ¹⁶ 1996, Italy	1983–1994	Retrospective cohort	2,551 (88/2,463)	Exposed randomized to clinical protocol and matched with unexposed receiving routine obstetric care
Benson et al, ¹⁵ 2001, U.S.	1991–1993	Retrospective cohort	858 (143/715)	Exposed and unexposed matched 1:5 by age and parity
Majeed et al, ¹⁸ 2011, Pakistan	2008–2010	Retrospective cohort	200 (100/100)	Exposed matched with random sample of unexposed
Hartmann et al, ¹⁹ 2017, U.S.	2000–2012	Prospective cohort	5,512 (571/4,941)	Women enrolled before conception or before 12 wk of gestation

—, not reported.

* Reported as total (with leiomyomas/without leiomyomas).

† Proportion of pregnancies ending in spontaneous abortion exposed compared with unexposed.

‡ Grading based on the Newcastle-Ottawa Scale.



reexamining uterine leiomyomas during pregnancy as risk factors for spontaneous abortion in populations more representative of all reproductive-aged women.

The purpose of this review is to quantify the association between leiomyoma presence during pregnancy and the risk of spontaneous abortion with the hypothesis that uterine leiomyomas increase the risk of spontaneous abortion for general obstetric populations. Specifically, we aimed to review studies on which current knowledge is based, calculate a summary effect estimate, and evaluate how leiomyoma location, number, and size modify associated risk.

SOURCES

The plan and protocol for literature search, study selection, data extraction, and analysis were developed by one of the authors (A.C.S.) a priori and adhere to Meta-Analyses and Systematic Reviews of Observational Studies guidelines for reporting meta-analyses and systematic reviews of observational studies.⁸

All studies published in academic journals were identified through searches of electronic databases (MEDLINE, Web of Science, EMBASE, and Clinical-Trials.gov) using the terms “fibroid,” “leiomyoma,” “leiomyomata,” “myoma,” “miscarriage,” “abortion,” “fertility,” “fetal death,” and “pregnancy loss” (Appendix 1, available online at <http://links.lww.com/AOG/B3>, for full search strategies). All studies published in English between January 1, 1970, and December 20, 2016, were included in the search. Reference lists of included studies were hand-searched to ensure no eligi-

ble reports were missing. A list of all identified studies is available on request.

STUDY SELECTION

We included all studies that compared the risk of spontaneous abortion among pregnant women with leiomyomas with pregnant women without leiomyomas. Leiomyoma status had to be determined with imaging for all participants. Because we aim to assess the effect of leiomyomas on spontaneous abortion risk among women of typical reproductive potential, studies limited to women seeking care for recurrent miscarriage, infertility, or assisted reproductive technologies were excluded.

Inclusion screening and data extraction were performed using standardized forms implemented in Research Electronic Data Capture (Appendix 2, available online at <http://links.lww.com/AOG/B3>).⁹ The primary outcome was spontaneous abortion (definition varied across studies) among recognized pregnancies. Aspirational coding was completed for factors thought to be associated with both risk of spontaneous abortion among women without leiomyomas and with leiomyoma presence. Potential confounders included maternal age, race, alcohol, body mass index, parity, and prior terminations. Data were abstracted for leiomyoma characteristics (location, size, number) when available. Risk of bias was determined using the Newcastle-Ottawa Scale.¹⁰ Scores were converted to Agency for Healthcare Research and Quality classifications of good, fair, or poor quality.¹¹

Definition of Exposure	Confounders Adjusted	Definition of Outcome	Risk [†]	Quality [‡]
Leiomyoma(s) greater than 3 cm in diameter on ultrasonography before 20 wk of gestation	None	Loss before 20 wk of gestation	7.7% vs 6.8%	Good
Leiomyoma(s) on ultrasonography	None	—	13.6% vs 9.3%	Poor
Leiomyoma(s) on 1 st -trimester ultrasonography	None	Loss before 25 wk of gestation	14.0% vs 7.6%	Good
Leiomyoma(s) on ultrasonography	None	Loss before 24 wk of gestation	11% vs 5%	Poor
Leiomyoma(s) greater than 0.5 cm on research ultrasonography	Maternal age, race–ethnicity, alcohol use, prior terminations, parity	Loss before 20 wk of gestation	14.0% vs 10.9%	Good



Study eligibility, data extraction, and risk of bias were determined independently by two reviewers (ACS, SHJ). Percent agreement between authors for these steps was 99.5%, 98.0%, and 95.8%, respectively. Discrepancies between the two reviewers were resolved by a third party blinded to the other reviewers' decisions (SML). Study authors were contacted for missing information.

A random-effects meta-analysis was performed to calculate pooled risk ratios (RRs) and 95% CIs. We limited the meta-analysis to studies evaluating general obstetric populations (excluding studies limited to women undergoing amniocentesis) to arrive at an aggregate estimate most representative of the risk-relationship in women of typical reproductive potential. For the meta-analysis, adjusted point estimates were used when available. Q and I^2 statistics were used to test for heterogeneity between included stud-

ies. Begg's and Egger's tests were used to assess publication bias. We evaluated year of publication, study design, and study quality as potential sources of heterogeneity using metaregression. Meta-analyses by leiomyoma location, size, and number were performed if at least three studies presented a measure of association for the characteristic.

Only one study adjusted for confounders. Therefore, we performed a secondary analysis in which we used external estimates of confounding to account for bias attributable to unmeasured confounding in the studies that only reported crude estimates.^{12,13} This method compares the adjusted and unadjusted estimates from a study that presents both models to quantify U , the multiplicative bias produced from confounding.¹² This measure is used to estimate adjusted RRs in studies that do not measure and adjust for confounding factors using the equation: $RR_{\text{adjusted}} = RR_{\text{unadjusted}}/U$. We used

Table 2. Characteristics of Studies Restricted to Women Undergoing Amniocentesis*

Study	Study Years	No. of Participants [†]	Population	Definition of Exposure	Confounders Adjusted	Definition of Outcome	Estimate of Effect (95% CI)
Salvador et al, ²¹ 2002, U.S.	1994–2000	256 (128/128)	Women undergoing amniocentesis; exposed and unexposed matched by age and parity	Leiomyoma(s) greater than 1 cm in diameter on ultrasonography	None	Loss between 15 and 24 wk of gestation	Unadjusted RR 8.0 (1.02–63.04)
Cignini et al, ²⁰ 2011, Italy	1999–2005	21,219 (2,497/18,722)	Women undergoing 2nd-trimester amniocentesis	Leiomyoma(s) greater than 20 mm in diameter on pre-procedural ultrasonography	None	Loss within 4 wk of procedure	Unadjusted RR 3.0 (0.58–15.45)
Corrado et al, ²² 2012, Italy	2001–2009	2,990 (166/2,824)	Women undergoing amniocentesis, consecutive participants	Leiomyoma(s) greater than 2 cm in diameter on preprocedural ultrasonography at 15–19 wk of gestation	None	Loss before 24 wk of gestation	Unadjusted OR 3.4 (1.2–9.0)
Theodora et al, ²³ 2016, Greece	2004–2010	6,752 (165/6,587)	Women undergoing 2nd-trimester amniocentesis	Leiomyoma(s) greater than 20 mm in diameter on ultrasonography	Age, bleeding in pregnancy, prior terminations, prior 1st-trimester miscarriages, amniotic fluid staining	Loss before 24 wk of gestation	Unadjusted OR 2.71 (1.08–6.80), adjusted OR 2.52 (1.01–6.40)

RR, risk ratio; OR, odds ratio.

* All studies were retrospective cohorts.

[†] Reported as total (with leiomyomas/without leiomyomas).



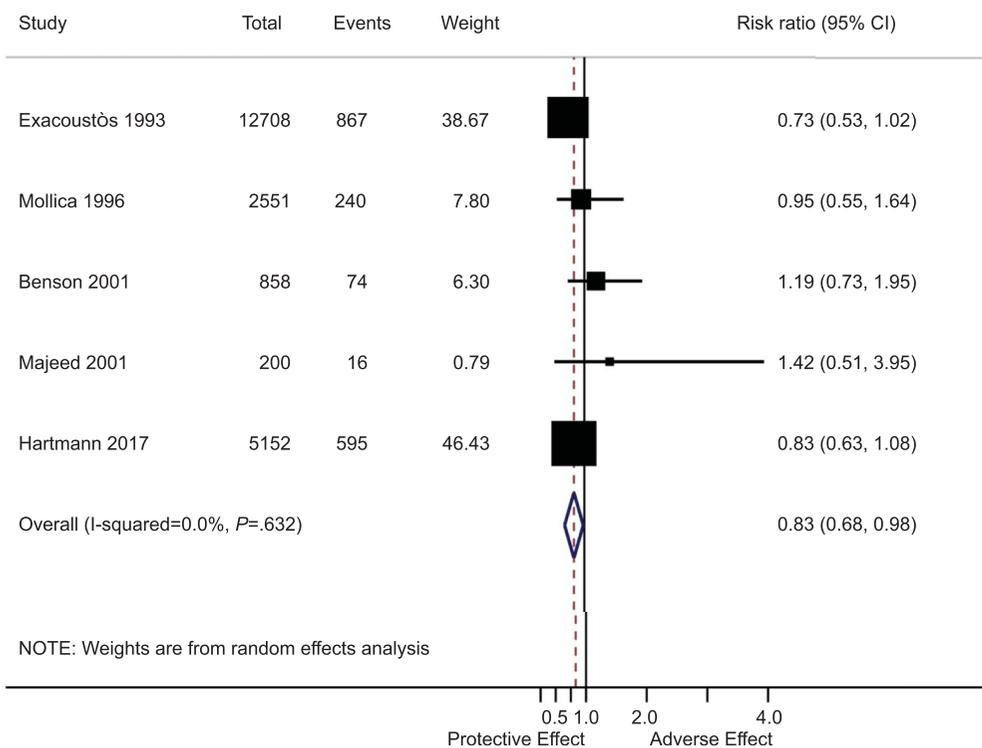
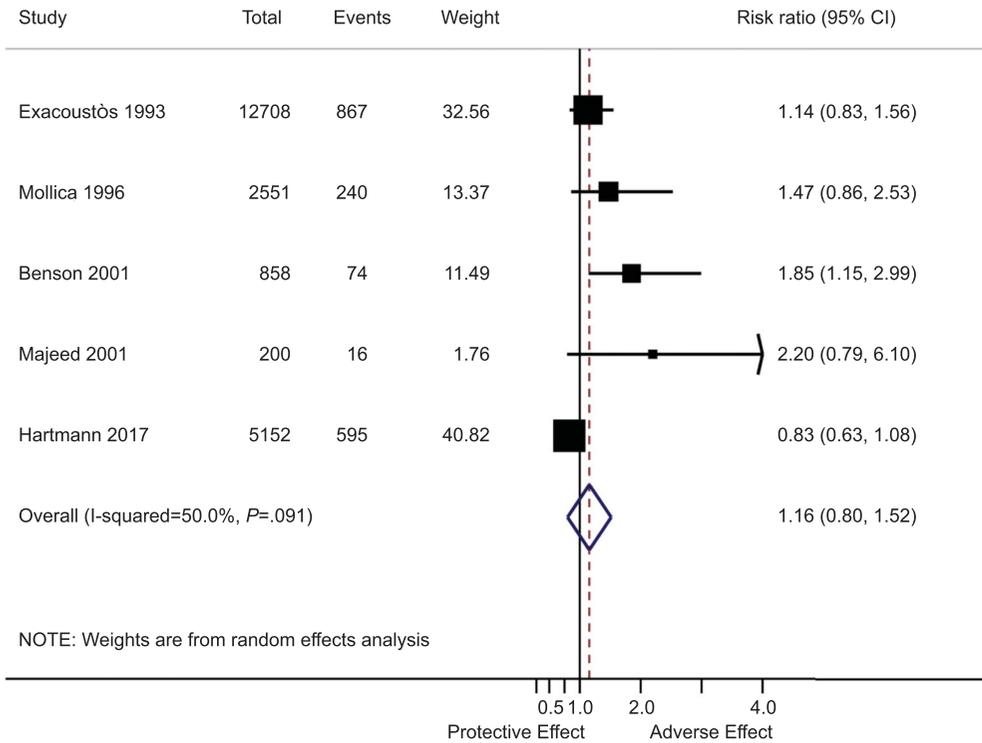


Fig. 2. A. Forest plot for the association between uterine leiomyomas and risk of spontaneous abortion. **B.** Forest plot for the association between uterine leiomyomas and risk of spontaneous abortion with crude point estimates adjusted using external estimate of confounding.

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estimates from the only study that presented adjusted models to estimate *U* (fully adjusted model included maternal age, race alcohol use, parity, and history of prior terminations). We then corrected the variance of the adjusted measures for the statistical error in the estimate of residual confounding.¹⁴ All analyses were performed in Stata 14.1 by one of the authors (A.C.S.).

RESULTS

Of 1,468 studies screened, nine were included in the systematic review and five studies were included in the meta-analysis (Fig. 1). Three of the studies were conducted in the United States, five in Europe, and one in the Middle East and study populations ranged from 200 to 21,219 participants. All publications included were observational cohorts; five enrolled a general obstetric population (Table 1),^{15–19} whereas four were restricted to women undergoing amniocentesis (Table 2).^{20–23} Three of the four studies among women undergoing amniocentesis reported leiomyoma presence that increased risk of loss after the procedure by an estimated factor between 2.5 and 8.0 (Table 2). Because these studies were limited to special high-risk populations and required the participant to have an ongoing pregnancy at the time of procedure, we describe these studies in the qualitative synthesis and exclude them in the quantitative analysis. Five studies were classified as good quality^{15,17,19,21,23} and four as poor quality^{16,18,20,22} based on Agency for Healthcare Research and Quality standards for quality grading (Appendix 3, available online at <http://links.lww.com/AOG/B3>).

Our meta-analysis included five studies with 21,829 participants from general obstetric populations (1,394 women with leiomyomas and 20,435 without).^{15–19} The meta-estimate does not suggest uterine leiomyomas are associated with an increased risk of spontaneous abortion (RR 1.16, 95% CI 0.80–1.52) (Fig. 2A). Heterogeneity of included studies was low (Q statistic 8.01, *P* value .09, τ^2 0.07) with some true between-study variation (*P* 50.0%). Year of publication, study design (retrospective cohort compared with prospective cohort), and study quality did not explain any additional between-study heterogeneity (analysis not shown). There were too few studies for the Begg's and Egger's tests to detect evidence of publication bias (*P* = .21 and *P* = .08). A trim-and-fill analysis predicted two missing studies pulling the corrected point estimate towards the null (RR 1.04, 95% CI 0.74–1.48).

Only one of the five studies in the meta-analysis adjusted for confounders of the relationship between leiomyomas and spontaneous abortion risk. We

Table 3. Leiomyoma Size and Number and Association With Spontaneous Abortion by Study

Study	n	Outcome Measure
Benson et al		Prevalence of SAB (%)
Leiomyoma size (cm)		
No leiomyomas	715	7.6
Less than 2	39	20.5
2–4	58	8.6
Greater than 4	46	15.2
Leiomyoma no.		
0	715	7.6
1	88	8.0
2	25	24.0
3	8	12.5
4 or more	22	27.3
Hartmann et al		Adjusted HR (95% CI)
Leiomyoma size*		
No leiomyomas	4,741	1.00 [referent]
Lowest quartile	143	1.12 (0.74–1.68)
2nd quartile	140	1.02 (0.65–1.59)
3rd quartile	141	0.52 (0.29–0.91)
Top quartile	140	0.62 (0.34–1.14)
Leiomyoma no.		
0	4,741	1.00 [referent]
1	398	0.84 (0.62–1.15)
2 or more	166	0.79 (0.51–1.23)

SAB, spontaneous abortion; HR, hazard ratio.

* Leiomyoma largest dimension: lowest quartile (0.51–1.36 cm), second quartile (1.36–2.35 cm), third quartile (2.35–3.62 cm), top quartile (3.62–13.20 cm).

approximated adjusted point estimates for the four studies that reported crude results using the data from Hartmann and colleagues as an external estimate of confounding.¹⁹ The meta-analysis with the adjusted estimates demonstrated leiomyoma status is not associated with increased spontaneous abortion risk (RR 0.83, 95% CI 0.68–0.98) (Fig. 2B). Two studies reported risk of spontaneous abortion by leiomyoma number or size: one presented crude results that suggest risk of loss increases with leiomyoma size and number¹⁵ and the other presented adjusted results that do not indicate a dose-dependent trend by either leiomyoma characteristic (Table 3).¹⁹

DISCUSSION

This meta-analysis, including 21,829 pregnancies from five cohort studies, indicates uterine leiomyoma presence is not associated with increased risk of spontaneous abortion among general obstetric populations. Strikingly few studies rigorously examine the association between uterine leiomyomas and spontaneous abortion risk. Many neglect common confounders such as maternal age and race, which are



known to be related to spontaneous abortion risk and leiomyoma presence.^{1,24} This is the first review on the association between leiomyoma presence and spontaneous abortion that specifically evaluates studies of general obstetric populations and the only review that quantitatively accounts for bias resulting from potential confounders. Our findings challenge common clinical belief and should cause us to reconsider understanding of uterine leiomyomas as a risk factor for spontaneous abortion in women of typical reproductive potential. The misconception that leiomyomas increase risk of spontaneous abortion in the general population may lead to undue anxiety for patients with leiomyomas, inappropriate risk counseling, or the recommendation of unnecessary surgeries.

Three past reviews on this association estimate uterine leiomyomas increase risk of spontaneous abortion by between 24% and 75%.⁵⁻⁷ These reviews are either intentionally⁷ or incidentally^{5,6} dominated by studies of special populations such as women seeking fertility treatment or with a history of recurrent miscarriage. None of these reviews quantitatively address possible bias resulting from maternal age or race in their main summary estimates.⁵⁻⁷

Women in this review were already pregnant or had to achieve pregnancy to be enrolled in the included cohorts and are a distinct population from women who are unable to conceive naturally. Submucosal or large intramural leiomyomas may decrease fertility by impeding implantation,⁵ and leiomyomas contributing to this phenotype may affect risk of loss differently from those characterized in this review. Therefore, the women in this review are different from those included in past reviews and the risk association described here more likely characterizes the relationship between leiomyomas and spontaneous abortion risk in a population of women of average reproductive potential.

The methods for the execution of this meta-analysis were rigorous and quantitatively strong. We are the first to present all relevant studies conducted in general obstetric populations on this association. Although several of the original studies do not present adjusted analyses, we use a method considered to be an effective tool for minimizing bias from unmeasured confounders.¹² Application of this method indicates crude estimates are biased and the fact that all studies describing a significant association between leiomyomas and spontaneous abortion risk are unadjusted should provide an impetus for reevaluating prior beliefs.

This meta-analysis should be interpreted in light of the following considerations. To optimally determine case status and capture spontaneous abortion events, participants should be enrolled before concep-

tion or in early pregnancy and undergo standardized imaging for leiomyoma assessment. This design is resource-intensive and difficult to implement on a large scale, and accordingly, four of the five studies included in the meta-analysis were retrospective analyses.¹⁵⁻¹⁸ These studies are subject to selection bias because they depend on care utilization, rely on availability of imaging data, and recruit participants solely from academic medical centers. Methods for defining exposure and outcome status varied between studies. One study only counted women as exposed if they had a leiomyoma with a dimension greater than 3 cm¹⁷ and three studies did not provide a minimum measurement threshold in their exposure definition.^{15,16,18} Variation in exposure definitions may introduce heterogeneity secondary to differential exposure classification. The gestational age cutoff for spontaneous abortion definitions ranged from 20 to 25 weeks of gestation.²⁵ Because losses are concentrated in early pregnancy with very few occurring beyond 20 weeks of gestation, we do not anticipate these differences to materially affect the summary estimate. Because four of the five studies fail to adjust for pertinent confounders, we attempted to account for bias using external estimates of unmeasured confounding.¹⁵⁻¹⁸ Our ability to estimate a bias-free summary measure using this method is dependent on how well the bias present in Hartmann et al reflects confounding present in other studies.^{12,13}

In conclusion, this systematic review and meta-analysis does not indicate that leiomyoma presence, location, number, or size is related to spontaneous abortion risk in general obstetric populations.

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