Preterm birth after recurrent pregnancy loss: a systematic review and meta-analysis

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Objective: To evaluate the impact of recurrent pregnancy loss (RPL) on the risk of preterm birth (PTB) in subsequent pregnancies.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Pregnant women with and without a history of RPL.
Intervention(s): PubMed, Embase, Google Scholar and Cochrane trial registry were used to identify relevant studies.
Main Outcome Measure(s): The odds ratios (ORs) for the association between RPL and PTB across included studies were evaluated. Effect estimates were pooled using a DerSimonian and Laird random-effects meta-analysis model.
Result(s): Eighteen studies met the inclusion criteria. A total of 58,766 women with a history of RPL and 2,949,222 women without a history of RPL were included. A pooled OR of 1.60 (95% confidence interval [CI], 1.45–1.78; 18 observational studies; $I^2 = 85.6\%$) was observed in our random-effects meta-analysis. A trend toward higher odds of PTB is observed with the increasing number of pregnancy losses: 2 RPLs (pooled OR, 1.31; 95% CI, 1.09–1.57; $I^2 = 88.9\%$); ≥ 2 RPLs (pooled OR, 1.58; 95% CI, 1.27–1.96; $I^2 = 71.7\%$); and ≥ 3 RPLs (pooled OR, 1.81; 95% CI, 1.58–2.07; $I^2 = 73.6\%$). The analysis of the risk of PTB for patients with unexplained RPL demonstrated a significantly heightened risk of PTB in this subgroup (pooled OR, 2.05; 95% CI, 1.46–2.89; $I^2 = 21.0\%$). Inconsistent adjustment for confounders and significant between-study heterogeneity were noted in this study.
Conclusion(s): Despite significant heterogeneity among studies, we found that women with a history of RPL had significantly higher odds of delivering preterm infants in subsequent pregnancies.
Clinical Trial Registration Number: CRD 224763. (Fertil Steril® 2022;117:811-9. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Recurrent pregnancy loss, recurrent miscarriage, spontaneous abortion, preterm birth, perinatal outcome

It is estimated that 15%–25% of all pregnancies end in miscarriage, and recurrent pregnancy loss (RPL) occurs in 5% of all women (1–3). The definitions of RPL have varied. Historically, RPL has been defined as ≥ 3 consecutive pregnancy losses (4, 5). However, more recently, the American Society for Reproductive Medicine and the joint International Committee for Monitoring Assisted Reproductive Technology and World Health Organization glossary established RPL as ≥ 2 consecutive clinical pregnancy losses (1, 6, 7). Clinical pregnancy losses are then defined as those occurring at <20 completed weeks of gestation where either a gestational sac was observed on ultrasound or tissue was visualized at uterine evacuation (1). Common etiologies for RPL include antiphospholipid syndrome, balanced reciprocal translocations, congenital or acquired uterine abnormalities, uncontrolled diabetes or thyroid disease, and chronic endometritis (8). Although RPL is rare, the emotional, physical, and financial burdens associated with RPL are unequivocal. Over the years, research into the management of RPL aimed mostly at establishing a live birth (9, 10). However, relatively little is known

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about the perinatal outcomes in a pregnancy after RPL.

Preterm birth (PTB) is an outcome of particular clinical interest. It occurs in 5%–18% of births worldwide, and its cause is often unknown (11). Complications of PTB are the leading cause of preventable death in children aged <5 years (12). Those who survive are often afflicted with short- to long-term morbidities, such as respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, sepsis, intraventricular hemorrhage, and cerebral palsy (13).

Recurrent pregnancy loss is not currently described as a risk factor for PTB. Prior literature on the subject reports conflicting data on the association between RPL and the risk of PTB in a subsequent pregnancy (14–17). Adequate identification of potential risk factors for PTB is critical to improving our understanding of PTB and will guide the establishment of potential interventions to mitigate the risk of PTB. As such, we performed a systematic review and meta-analysis to evaluate the risk of PTB among women with RPL.

MATERIALS AND METHODS

Systematic Search

We conducted a comprehensive search on Medline, Embase, Google Scholar, and Cochrane trial registry from inception until February 2021 for studies describing the association between RPL and the risk of PTB in a subsequent pregnancy. Retrospective and prospective observational studies, randomized control trials, and case series were deemed eligible for screening. Keywords including preterm birth, recurrent pregnancy loss, and spontaneous abortion were used. Our search strategy was developed with the assistance of a medical librarian at Conway Harvard Medical Library. Medical Subject Headings were used for the identification of synonyms, and we examined the reference list of our full-text articles to search for additional relevant studies (details on search strategy in Supplemental Appendices, available online). No language or date restrictions were applied to the search. The study protocol has been registered with the International Prospective Register of Systematic Reviews registry of systemic reviews (CRD 224763) and can be accessed through the International Prospective Register of Systematic Reviews website. Institutional Review Board approval was not required, given that the data presented in this study are publicly available.

Study Selection

We included studies where the population consisted of women with a history of RPL (defined as 2 or more pregnancy losses), where the comparator group consisted of women without a history of RPL, and where the outcomes assessed included PTB (defined as a live birth before 37 completed weeks of gestation). Studies were excluded if they were comparative interventional studies examining specific treatments for RPL or if they targeted prespecified causes for RPL. Review articles, case studies, conference proceedings (abstracts and presentations), and unpublished studies were also excluded. Articles published in languages other than English were translated by individuals with medical backgrounds and fluency in that specific language. Relevant citations were screened by two independent reviewers, and eligible studies were advanced to full-text review. The full-text review was again completed by two separate reviewers. Disagreements were resolved by consensus or by a third reviewer.

Data Extraction and Quality

Two reviewers independently extracted data in duplicate. Publication date, population, exposure, and outcome data were compiled. We contacted study investigators for clarification when study methods or results were either not reported or unclear. We assessed the risk of bias and methodological quality for each included study, in duplicate, using the Newcastle-Ottawa Scale (NOS) for observational cohort and case-control studies (18). Any disagreements were resolved by the consensus of all study investigators.

Statistical Analysis

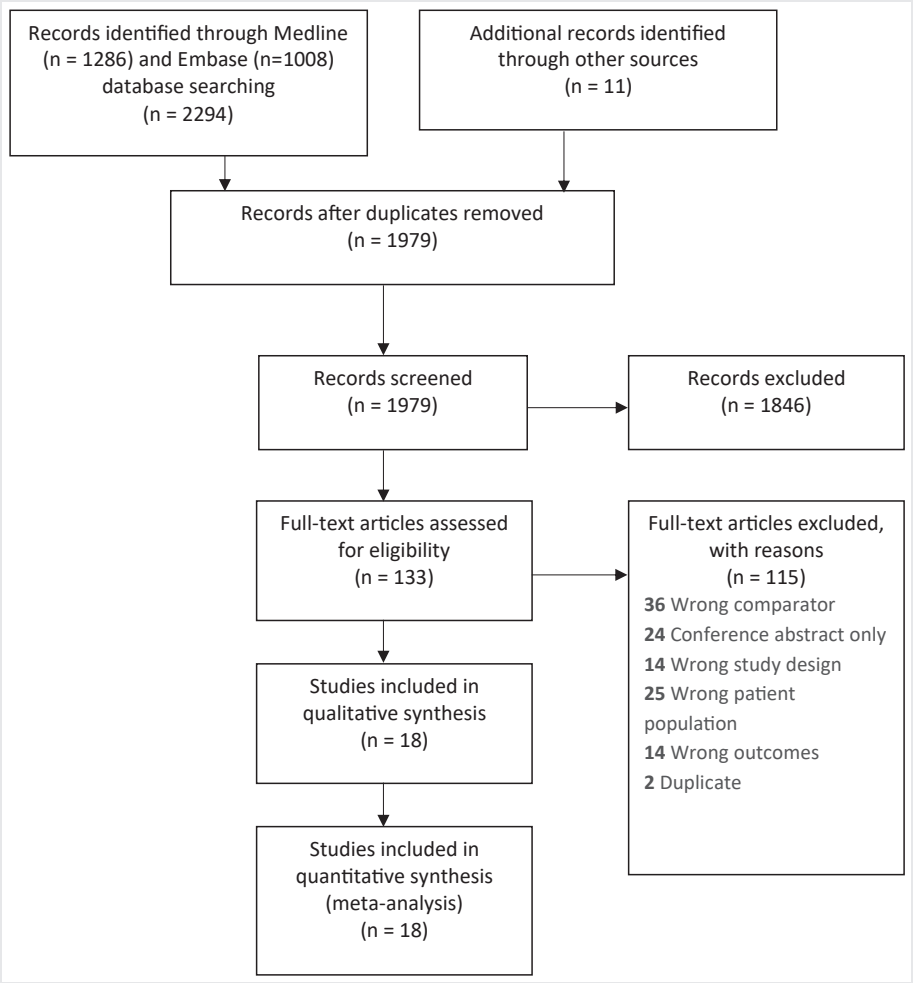
The DerSimonian and Laird random-effects models were used to conduct the meta-analysis with Stata/IC 16.1. A random-effects meta-analysis was selected because of the heterogeneity underlying the study designs and study population. Inverse variance study weights were used, and study results were presented as odds ratios (ORs) with their respective 95% confidence intervals (CIs). We used adjusted OR when available, otherwise unadjusted OR when no adjusted odds were reported in the study. Effect measures for studies that reported outcomes on more than one RPL groups were pooled separately based on the number of RPLs. Subgroup analyses based on the number of RPLs and for those with unexplained RPL were performed. Sensitivity analyses were then completed to evaluate the influence of individual studies on the primary analysis and for the detection of time trends. We assessed heterogeneity between studies using the χ^2 test for homogeneity and the I^2 statistic. An I^2 of $\geq$50% was considered to be reflective of significant study heterogeneity. Publication bias was evaluated through visual inspection of the funnel plot and Egger test.

RESULTS

Study Characteristics

The systematic search yielded 2,305 results. A total of 1,979 titles and abstracts were reviewed after the removal of duplicates, of which 1,846 studies were excluded for failure to meet the inclusion criteria (Fig. 1). Overall, 133 full-text articles were reviewed, of which 18 met the criteria for inclusion in our systematic review and meta-analysis. Figure 1 indicates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram depicting the study identification process (19). There were 17 cohort studies and 1 case-control study that met the inclusion criteria. Included studies were published between 1992 and 2021. A total of 3,007,988 patients were included in this study, of which 58,766 had a history of RPL. Studies originated from 12 countries across 4 continents. The mean age of the participants included in the RPL groups ranged from 26.3 to 35.2 years; the mean age in the non-RPL groups ranged from 23.9 to 35 years. The baseline characteristics of included studies are summarized in Table 1.

FIGURE 1



Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Wu. Recurrent miscarriage increases odds of preterm birth. Fertil Steril 2022.

Synthesis of Results

The incidence rates of PTB among the RPL groups ranged from 4.9% to 19.6% and from 1.5% to 14.0% in the non-RPL groups (Supplemental Table 1). The odds of PTB were found to be significantly increased in a subsequent pregnancy after RPL. The pooled OR from a random-effects meta-analysis for preterm delivery in patients with ≥ 2 or ≥ 3 miscarriages was 1.60 (95% CI, 1.45–1.78; 18 observational studies; $I^2 = 85.6\%$; $P < .0005$) (Fig. 2).

Subgroup analyses were completed by the number of pregnancy losses and for those with a diagnosis of unexplained RPL. A statistically significant trend toward higher odds of PTB was observed with the increasing number of pregnancy losses: 2 RPLs (pooled OR, 1.31; 95% CI, 1.09–1.57; 5 studies; $I^2 = 88.9\%$; $P < .0005$); ≥ 2 RPLs (pooled OR, 1.58; 95% CI, 1.27–1.96; 6 studies; $I^2 = 71.7\%$; $P = .003$); and ≥ 3 RPLs (pooled OR, 1.81; 95% CI, 1.58–2.07; 12 studies; $I^2 = 73.6\%$; $P < .0005$) (Fig. 2). The analysis of the risk of PTB for patients with unexplained RPL was also performed (Supplemental Table 2). It demonstrated a significantly heightened risk of PTB in this subgroup (pooled OR, 2.05; 95% CI, 1.46–2.89; 5 studies; $I^2 = 21.0\%$; $P = 0.28$) (Fig. 3). The results from these subgroup analyses were all in reasonable agreement with the primary meta-analysis and its pooled OR.

The risk of bias assessment was completed using the NOS. Case selection, comparability, and exposure were assessed for bias among case-control studies. Exposure selection, comparability, and outcome ascertainment were assessed for bias among the included cohort studies. A history of prior PTB was selected as the most important confounding factor when assessing comparability among studies. Each study was also assessed for adequate handling of confounding (Supplemental Table 3). Ten of the included studies were determined to be at low risk of bias (NOS score, ≥ 7); the remaining 8 studies were at moderate risk of bias. A sensitivity analysis was performed by only including articles deemed good quality by a NOS score of ≥ 7. It yielded comparable results to the main outcome (pooled OR, 1.53; 95% CI, 1.34–1.75; 10 observational studies; Supplemental Fig. 1). A cumulative effects meta-analysis by study year demonstrated stabilization of the effect estimates in the association between RPL and PTB

TABLE 1

Characteristics of included studies examining the effect of recurrent pregnancy loss on preterm birth.

Author, year[a]	Country	Design	Study period	RPL definition	Non-RPL definition	RPL n	Non-RPL n	RPL age (mean ± SD)	Non-RPL age (mean ± SD)
Thom, 1992 (35)	United States	Retrospective cohort	1984–1987	≥3 SA	First singleton live birth	638	3,099	26.3	23.9
Jivraj, 2001 (16)	United Kingdom	Retrospective cohort	1992–1998	≥3 SA	First singleton live birth	162	24,699	32 ± 5.4	28.3 ± 5.4
Buchmayer, 2004 (36)	Sweden	Retrospective cohort	1987–2000	≥2 SA	Singleton live birth with a history of ≤1 SA	1,742	600,141	NR	NR
Hammoud, 2007 (37)	Germany	Retrospective cohort	1991–1997	≥2 SA	No history of SA	1,133	58,253	NR	NR
Bhattacharya, 2010 (38)	Scotland	Retrospective cohort	1950–2000	2-3 SA	Singleton live birth without a history of SA	815	143,595	30.5	30.5
Nielsen, 2010 (39)	Denmark	Retrospective cohort	1986–2007	≥3 cSA	Singleton second-born live birth	213	510,264	NR	NR
Dempsey, 2014 (14)	Ireland	Prospective cohort	NR	Unexplained ≥3 cSA	Healthy pregnant women matched by age, ethnicity, body mass index, and smoking status	31	31	33.5	33.65
Gunnarsdottir, 2014 (40)	Sweden	Retrospective cohort	1995–2009	≥2 SA	Singleton live birth at ≥22 wk's gestation without a history of RPL	NR	NR	NR	NR
Field, 2015 (15)	Ireland	Retrospective cohort	2008–2011	≥3 SA	Singleton live birth without a history of RPL	2,030	28,023	NR	NR
Oliver-Williams, 2015 (41)	Scotland	Retrospective cohort	1980–2008	≥2 SA	Singleton live birth	14,677	646,382	NR	NR
Fawzy, 2016 (42)	United Kingdom	Retrospective cohort	2001–2007	≥3 cSA at <20 wks' GA	Singleton live birth	400	39,860	32.6 ± 5.7	29 ± 6.2
Yang, 2017 (43)	China	Retrospective case-control	2010–2013	≥2 cSA	Singleton live birth	164	328	33.97 ± 4.25	30.48 ± 3.65
Cozzolino, 2019 (44)	Italy	Retrospective cohort	2014–2015	≥2 cSA	Singleton live birth	53	65	35.2 ± 4.8	35 ± 3.1
Paz Levy, 2019 (45)	Israel	Retrospective cohort	1991–2014	2 cSA or any 3 SA	History of ≤1 SA	12,182	230,005	31.6 ± 5.75	28 ± 5.6
Sugiura-Ogasawara, 2019 (17)	Japan	Retrospective cohort	2011–2014	≥2 SA	Singleton live birth, 0 SA	4,557	71,356	NR	NR
Ausbeck, 2020 (46)	United States	Retrospective cohort	2008–2017	≥2 cSA at <12 wks' GA	Singleton live birth at ≥20 wk's gestation with a history of ≤1 SA	235	17,435	29.9 ± 5.5	25.6 ± 6.3
Ali, 2020 (47)	United Arab Emirates	Prospective cohort	2017–2019	≥2 SA	Women without a history of RPL	234	1,503	33.7 ± 5.6	32.6 ± 5.2
Rasmark Roepke, 2021 (48)	Sweden	Retrospective cohort	2003–2012	≥3 SA	Women without a history of RPL	4,971	57,410	NR	NR

Note: cSA = consecutive spontaneous abortion; GA = gestational age; N = population size; NR = not reported; PTB = preterm birth; RPL = recurrent pregnancy loss; SA = spontaneous abortion.

[a] Studies ranked by publication year, from the earliest to the most recent.

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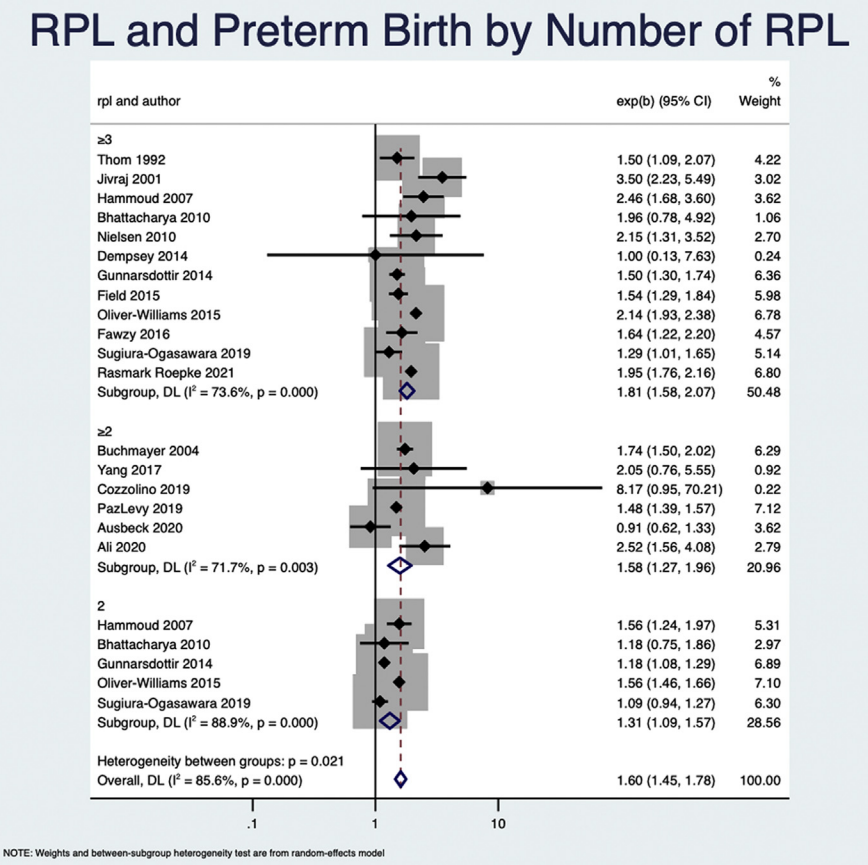
FIGURE 2



Forest plot for subgroup analysis demonstrating the odds of preterm birth in association with varying definitions of recurrent pregnancy loss (RPL) (2, ≥2, and ≥3). CI = confidence interval; DL = DerSimonian and Laird.

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after 2014 (Supplemental Fig. 2), but the overall effect has consistently illustrated the negative impact of RPL on PTB. The influence analysis did not suggest that any one study had a disproportionate impact on the results (Supplemental Fig. 3). Finally, there was no significant evidence of publication bias. Relative symmetry was observed on visual inspection of the funnel plot (Supplemental Fig. 4), and the Egger test did not show evidence of a small-study effect (P=.48; Supplemental Fig. 5) (20).

DISCUSSION

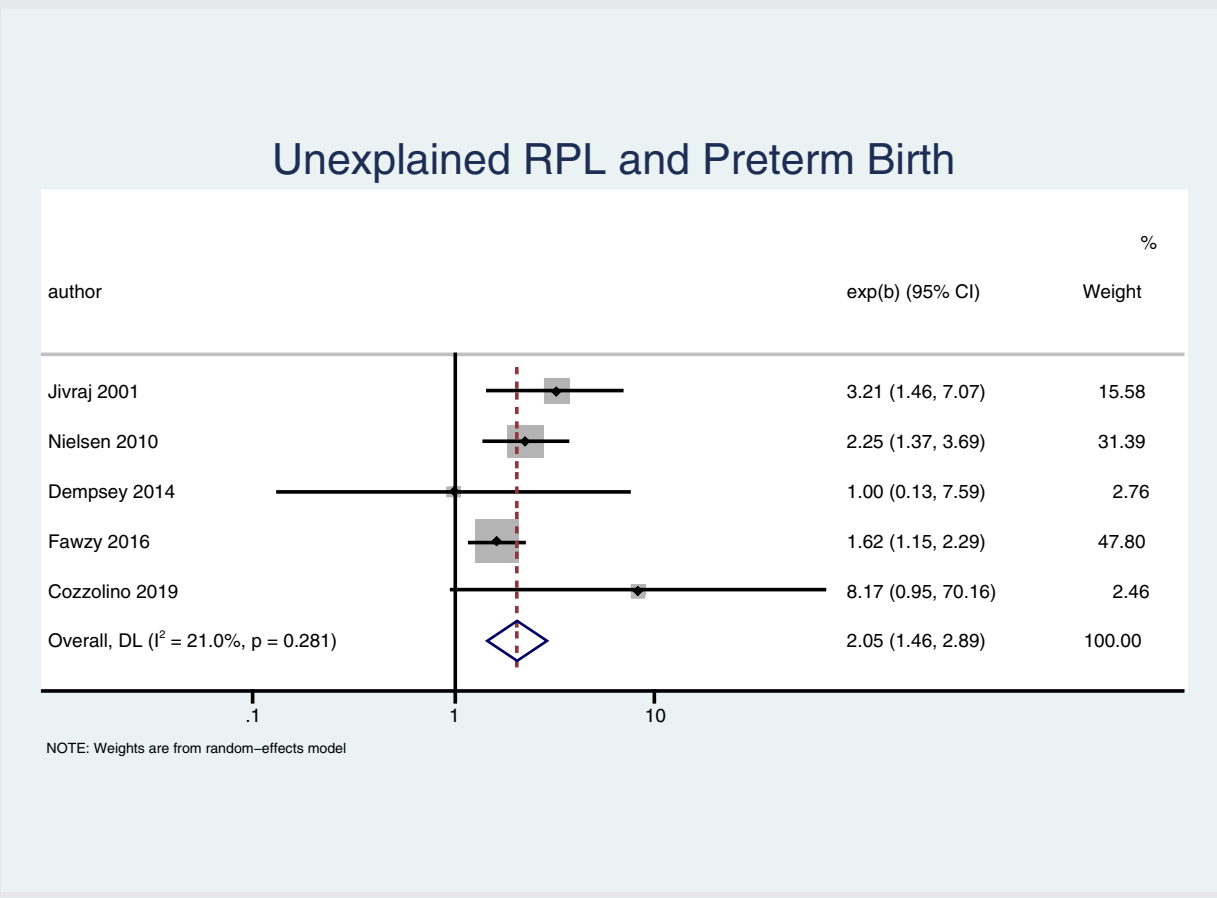
Summary of the Main Findings

The results of our systematic review and meta-analysis demonstrate that women with a history of RPL have a significantly increased risk of PTB in a subsequent pregnancy compared with those without an RPL history. This association is consistent across subgroup analyses of women with 2, ≥2, and ≥3 miscarriages, of women with a diagnosis of unexplained RPL, as well as in sensitivity analyses where only data from good-quality studies were tabulated. There was evidence of effect modification by the number of pregnancy losses: the odds of delivering a preterm infant were almost 1.3, 1.6, and 1.8 times as likely among women with a history of 2, ≥2, and ≥3 pregnancy losses, respectively, when compared with the women without a history of RPL. The mean incidence of PTB among the RPL groups ranged from 7.2% to 11.9%, whereas the mean PTB incidence in the non-RPL group was 5.8%. Unexplained RPL is another surprising but significant risk factor for PTB. Our results demonstrate that women with unexplained RPL have twice the odds of having PTB in a subsequent pregnancy compared with women without RPL.

Pathophysiology of RPL and PTB

By definition, "recurrent pregnancy loss" does not denote a specific defect or functional impairment. It remains unlikely that there is a causal association between RPL and PTB, but rather, both conditions are reflective of an underlying placental dysfunction. It is known that the development and delivery of

FIGURE 3



Forest plot for subgroup analysis demonstrating the odds of preterm birth in association with unexplained recurrent pregnancy loss (RPL). CI = confidence interval; DL = DerSimonian and Laird.

Wu. Recurrent miscarriage increases odds of preterm birth. Fertil Steril 2022.

a term infant requires implantation, placentation, and growth. Failure of any of these processes may result in first-trimester loss or, occasionally, RPL. It is thought that inadequate implantation leads to impaired placental function and, consequently, puts pregnancies at risk for poor fetal growth, placental abruption, preeclampsia, stillbirth, and preterm delivery (21, 22). It would be reasonable to surmise that this mechanism may, therefore, link RPL and PTB. Additionally, genetic association studies found that polymorphism in angiogenesis- and vasoconstriction-related vascular endothelial growth factor genes may be correlated with both RPL and PTB (23, 24). Their pathogenesis could also stem from genetic variation in the endometrial control of implantation or maternal adaptations to pregnancy (21, 25). A past review published in 2009 also examined the association between abortions and the risk of subsequent PTB (26). It examined both induced and spontaneous abortions but did not specifically investigate RPL. A similar dose-response of increasing PTB with the increasing number of miscarriages was observed. Indeed, of the 7 studies that included multiple spontaneous abortions, the investigators reported an odds of PTB of 2.27 (95% CI, 1.98–2.81) among women who had $\geq$2 abortions and 1.43 (95% CI, 1.05–1.66) among women with 1 abortion.

Management of RPL and Prevention of PTB

The high rate of spontaneous isolated losses in the general population, lack of a consistent definition for RPL, and relatively good prognosis for live birth among patients with RPL have made efforts to understand the obstetric management of these patients challenging. Few evidence-based treatments exist for the management of RPL, making it a frustrating diagnosis for patients and health care providers alike. Existing therapies mostly aim to address prespecified underlying etiologies of RPL, like antiphospholipid antibody syndrome or endocrinopathies. However, unless a treatable cause is identified, the overwhelming majority of patients with RPL are managed with supportive care (27–29). The role of progesterone supplementation in women with a history of RPL has garnered increasing attention. A 2019

Cochrane review found a reduction in the number of miscarriages for women given progesterone supplementation compared with controls (relative risk, 0.73; 95% CI, 0.54–1.00) (30), leading the way for the prevention of miscarriage through progesterone support. Progesterone has a role in preventing preterm delivery as well. It has effects on the myometrium, chorioamniotic membranes, and cervix, and a withdrawal of progesterone appears to be a key mechanism for cervical ripening. Over the last decade, weekly injections of 17-alpha-hydroxyprogesterone caproate have also been proposed to reduce the risk of PTB in women with a history of prior PTB (31). Additionally, assuming that vascular placental disease may be an underlying mechanism in RPL and PTB, antenatal aspirin could be considered for this population (32). In 2020, the ASPIRIN trial found that low-dose aspirin therapy initiated in early gestation resulted in a reduced incidence of preterm delivery (relative risk, 0.89; 95% CI, 0.81–0.98) (33). Certainly, the increased risk of PTB in patients with RPL warrants their designation as "high-risk pregnancies," and more intensive prenatal monitoring should be offered to pregnant women with a history of RPL.

Future Directions

Despite the lack of clarity on a possible common etiology or contributing factor, data remain convincing for an association between RPL and PTB. Our systematic review and meta-analysis demonstrate that women with a history of RPL are at statistically significant increased odds of delivering preterm infants. These findings are relevant to women who are trying to conceive, and to physicians that work in obstetrics and fertility. There is a clear need for well-designed, prospective studies to examine the association and causation of RPL and PTB. Additionally, there is a need to investigate the efficacy of available therapies, such as aspirin and progesterone supplementation, that may be used to prolong pregnancy in these women. Finally, the rates of other adverse perinatal outcomes related to placental dysfunction, including gestational hypertension, preeclampsia, intrauterine growth restriction, placental abruption, and perinatal deaths should also be evaluated in the setting of a pregnancy after RPL.

Strengths and Limitations

To our knowledge, this is the first systematic review and meta-analysis describing the association between RPL and the risk of PTB. The large sample size of 3,007,9878 women, of which 58,766 have a history of RPL, provides excellent precision to our estimates. Our rigorous methodology ensured that we interrogated all potential sources of heterogeneity by performing influence, subgroup, and sensitivity analyses. Most included studies were of good quality, where adequate population selection and ascertainment of exposure and of perinatal outcomes of interest were consistently performed. In addition, our study was not biased by language or geographic exclusions. Overall, there was little evidence of publication bias or small-study effects. This study also has several limitations. First, there was significant between-study heterogeneity ($I^2 > 50\%$ in the primary analysis of RPL and PTB). Namely, the studies used different definitions for RPL (2, ≥ 2, and ≥ 3; whether consecutive or with the same partner; primary or secondary RPL; and unexplained or not) and varying comparison groups (with no or <2 miscarriages), and data came from populations of diverse background and clinical settings. Therefore, despite our efforts with the aforementioned statistical analyses, between-study heterogeneity remained elevated. That said, in a stratified analysis by RPL definition and in the subgroup analysis of the association between unexplained RPL and PTB in a subsequent pregnancy, the pooled OR remained statistically significant, with a lower I^2. Second, the included studies were not consistent in their adjustment of confounders. Few studies adjusted for important risk factors for PTB, such as a history of prior PTB and preeclampsia. Those studies that did control for confounders adjusted for different covariates, thereby increasing between-study heterogeneity. Third, the underlying etiologies of RPL were not uniformly reported and adjusted for in the included studies. For instance, antiphospholipid syndrome is a known risk factor for PTB in the setting of RPL (34). The lack of adjustment for known RPL etiologies likely accounts for some unmeasured confounding. Fourth, all included studies were observational in design, and thus, there remains the possibility of residual confounding. Lastly, given that this was a meta-analysis of observational studies, we are unable to draw any conclusions about causality, albeit this was never the intention of this review. It is possible that RPL may be a downstream effect of underlying pathologies that predispose to preterm delivery.

CONCLUSION

In conclusion, this is the first systematic review and meta-analysis on the relationship between RPL and PTB, and it demonstrates a significant increase in the odds of PTB among women with a history of RPL. Consequently, women with a history of RPL may benefit from additional counseling and more intensive monitoring during subsequent pregnancies. Additional prospective observational studies are required to further elucidate the relationship between RPL and PTB.

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/33777

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril 2012;98:1103–11.
2. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Haberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ 2019;364:l869.
3. Linnakaari R, Helle N, Mentula M, Bloigu A, Gissler M, Heikinheimo O, et al. Trends in the incidence, rate and treatment of miscarriage-nationwide register-study in Finland, 1998-2016. Hum Reprod 2019;34:2120–8.

4. Jauniaux E, Farquharson RG, Christiansen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod 2006;21:2216–22.
5. Kolte AM, Bernardi LA, Christiansen OB, Quenby S, Farquharson RG, Goddijn M, et al. Terminology for pregnancy loss prior to viability: a consensus statement from the ESHRE early pregnancy special interest group. Hum Reprod 2015;30:495–8.
6. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril 2020;113:533–5.
7. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril 2017;108:393–406.
8. Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. Rev Obstet Gynecol 2009;2:76–83.
9. Kolte AM, Olsen LR, Mikkelsen EM, Christiansen OB, Nielsen HS. Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss. Hum Reprod 2015;30:777–82.
10. Serrano F, Lima ML. Recurrent miscarriage: psychological and relational consequences for couples. Psychol Psychother 2006;79:585–94.
11. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet Glob Health 2019;7:e37–46.
12. United Nations Inter-agency Group for Child Mortality Estimation (UN IGME). Level & Trends in Child Mortality: Report 2021, Estimates Developed by the UN Inter-agency Group for Child Mortality Estimation. New York: United Nations Children's Fund; 2021.
13. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008;371:261–9.
14. Dempsey MA, Flood K, Burke N, Fletcher P, Kirkham C, Geary MP, et al. Perinatal outcomes of women with a prior history of unexplained recurrent miscarriage. J Matern Fetal Neonatal Med 2015;28:522–5.
15. Field K, Murphy DJ. Perinatal outcomes in a subsequent pregnancy among women who have experienced recurrent miscarriage: a retrospective cohort study. Hum Reprod 2015;30:1239–45.
16. Jivraj S, Anstie B, Cheong YC, Fairlie FM, Laird SM, Li TC. Obstetric and neonatal outcome in women with a history of recurrent miscarriage: a cohort study. Hum Reprod 2001;16:102–6.
17. Sugiura-Ogasawara M, Ebara T, Yamada Y, Shoji N, Matsuki T, Kano H, et al. Adverse pregnancy and perinatal outcome in patients with recurrent pregnancy loss: multiple imputation analyses with propensity score adjustment applied to a large-scale birth cohort of the Japan Environment and Children's Study. Am J Reprod Immunol 2019;81:e13072.
18. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses; 2000.
19. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9, W64.
20. Sterne JAC, Egger M. Regression methods to detect publication and other bias in meta-analysis. In: Rothstein HR, Sutton AJ, Borenstein M, editors. Publication bias in meta-analysis: prevention, assessment, and adjustments. Chichester: Wiley; 2005.
21. Cartwright JE, Fraser R, Leslie K, Wallace AE, James JL. Remodelling at the maternal-fetal interface: relevance to human pregnancy disorders. Reproduction 2010;140:803–13.
22. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "Great Obstetrical Syndromes" are associated with disorders of deep placentation. Am J Obstet Gynecol 2011;204:193–201.
23. Galazios G, Papazoglou D, Tsikouras P, Kolios G. Vascular endothelial growth factor gene polymorphisms and pregnancy. J Matern Fetal Neonatal Med 2009;22:371–8.
24. Su MT, Lin SH, Chen YC. Genetic association studies of angiogenesis- and vasoconstriction-related genes in women with recurrent pregnancy loss: a systematic review and meta-analysis. Hum Reprod Update 2011;17:803–12.
25. Teklenburg G, Salker M, Heijnen C, Macklon NS, Brosens JJ. The molecular basis of recurrent pregnancy loss: impaired natural embryo selection. Mol Hum Reprod 2010;16:886–95.
26. Swingle HM, Colaizy TT, Zimmerman MB, Morriss FH Jr. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. J Reprod Med 2009;54:95–108.
27. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage. Hum Reprod 1999;14:2868–71.
28. Clifford K, Rai R, Regan L. Future pregnancy outcome in unexplained recurrent first trimester miscarriage. Hum Reprod 1997;12:387–9.
29. Stray-Pedersen B, Stray-Pedersen S. Etiologic factors and subsequent reproductive performance in 195 couples with a prior history of habitual abortion. Am J Obstet Gynecol 1984;148:140–6.
30. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database Syst Rev 2019;2019:CD003511.
31. Petrini JR, Callaghan WM, Klebanoff M, Green NS, Lackritz EM, Howse JL, et al. Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. Obstet Gynecol 2005;105:267–72.
32. Belhomme N, Doudnikoff C, Polard E, Henriot B, Isly H, Jego P. [Aspirin: indications and use during pregnancy]. Rev Med Interne 2017;38:825–32.
33. Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy (ASPIRIN): a randomised, double-blind, placebo-controlled trial. Lancet 2020;395:285–93.
34. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002;346:752–63.
35. Thom DH, Nelson LM, Vaughan TL. Spontaneous abortion and subsequent adverse birth outcomes. Am J Obstet Gynecol 1992;166:111–6.
36. Buchmayer SM, Sparen P, Cnattingius S. Previous pregnancy loss: risks related to severity of preterm delivery. Am J Obstet Gynecol 2004;191:1225–31.
37. Hammoud AO, Merhi ZO, Diamond M, Baumann P. Recurrent pregnancy loss and obstetric outcome. Int J Gynaecol Obstet 2007;96:28–9.
38. Bhattacharya S, Townend J, Bhattacharya S. Recurrent miscarriage: are three miscarriages one too many? Analysis of a Scottish population-based database of 151,021 pregnancies. Eur J Obstet Gynecol Reprod Biol 2010;150:24–7.
39. Nielsen HS, Steffensen R, Lund M, Egestad L, Mortensen LH, Andersen AM, et al. Frequency and impact of obstetric complications prior and subsequent to unexplained secondary recurrent miscarriage. Hum Reprod 2010;25:1543–52.
40. Gunnarsdottir J, Stephansson O, Cnattingius S, Akerud H, Wikstrom AK. Risk of placental dysfunction disorders after prior miscarriages: a population-based study. Am J Obstet Gynecol 2014;211:34.e1–8.
41. Oliver-Williams C, Fleming M, Wood AM, Smith G. Previous miscarriage and the subsequent risk of preterm birth in Scotland, 1980-2008: a historical cohort study. BJOG 2015;122:1525–34.
42. Fawzy M, Saravelos S, Li TC, Metwally M. Do women with recurrent miscarriage constitute a high-risk obstetric population? Hum Fertil (Camb) 2016;19:9–15.
43. Yang J, Wang Y, Wang XY, Zhao YY, Wang J, Zhao YY. Adverse pregnancy outcomes of patients with history of first-trimester recurrent spontaneous abortion. Biomed Res Int 2017;2017:4359424.
44. Cozzolino M, Rizzello F, Riviello C, Romanelli C, Coccia Elisabetta M. Ongoing pregnancies in patients with unexplained recurrent pregnancy loss: adverse obstetric outcomes. Hum Fertil (Camb) 2019;22:219–25.
45. Paz Levy D, Wainstock T, Sheiner E, Sergienko R, Landau D, Walfisch A. Maternal recurrent pregnancy loss is associated with an increased risk for long-term neurological morbidity in offspring. Dev Med Child Neurol 2019;61:91–7.
46. Ausbeck EB, Blanchard C, Tita AT, Szychowski JM, Harper L. Perinatal outcomes in women with a history of recurrent pregnancy loss. Am J Perinatol 2021;38:10–5.
47. Ali N, Elbarazi I, Ghazal-Aswad S, Al-Maskari F, H Al-Rifai R, Oulhaj A, et al. Impact of recurrent miscarriage on maternal outcomes in subsequent pregnancy: the Mutaba'ah Study. Int J Womens Health 2020;12:1171–9.
48. Rasmark Roepke E, Christiansen OB, Kallen K, Hansson SR. Women with a history of recurrent pregnancy loss are a high-risk population for adverse obstetrical outcome: a retrospective cohort study. J Clin Med 2021;10:179.

Parto prematuro después de pérdida recurrente del embarazo: una revisión sistemática y meta-análisis.

Objetivo: Evaluar el impacto de la pérdida recurrente del embarazo (PRE) en el riesgo de parto prematuro (PP) en embarazos subsecuentes.

Diseño: Revisión sistemática y meta-análisis.

Lugar: No aplicable.

Paciente(s): Mujeres embarazadas con y sin antecedente de PRE.

Intervenciones: Se utilizaron PubMed, Embase, Google Scholar y el registro de ensayos Cochrane para identificar estudios relevantes.

Medida(s) de resultado(s) principal(es): Se evaluó la relación de probabilidades (RP) para la asociación entre PRE y PP en los estudios incluidos. Las estimaciones del efecto se agruparon mediante un modelo de metaanálisis de efectos aleatorios de DerSimonian y Laird.

Resultado(s): Dieciocho estudios cumplieron los criterios de inclusión. Se incluyeron un total de 58,766 mujeres con antecedente de PRE y 2,949,222 mujeres sin antecedente de PRE. Una relación de probabilidades agrupadas de 1.60 (intervalo de confianza [IC] del 95%, 1.45–1.78; 18 estudios observacionales; I^2= 85.6%) fue observado en nuestro metaanálisis de efectos aleatorios. Se observa una tendencia hacia mayores probabilidades de PP con el creciente número de pérdidas gestacionales: 2 PRE (RP agrupadas, 1.31; IC del 95%, 1.09–1.57; I^2 = 88.9%); ≥2 RPL (RP agrupadas, 1.58; IC del 95%, 1.27–1.96; I^2 =71.7%); y ≥3 PRE (RP agrupadas, 1.81; IC del 95%, 1.58–2.07; I^2 = 73.6%). El análisis del riesgo de PP para pacientes con PRE inexplicable demostró un aumento significativo del riesgo de PP en este subgrupo (RP agrupadas, 2.05; IC del 95%, 1.46–2.89; I^2 = 21.0%). Se observaron ajustes inconsistentes para factores de confusión y heterogeneidad significativa entre los estudios.

Conclusión(es): A pesar de la heterogeneidad significativa entre los estudios, encontramos que mujeres con antecedente de PRE tuvieron significativamente mayor probabilidad de nacimiento de bebés prematuros en embarazos subsecuentes.