Endometrial causes of recurrent pregnancy losses: endometriosis, adenomyosis, and chronic endometritis

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Chronic inflammatory processes affecting the endometrium, as encountered in endometriosis, adenomyosis, and chronic endometritis, alter endometrial receptivity. These disorders are associated with early pregnancy losses and possibly recurrent pregnancy losses (RPL). In the cases of endometriosis, other factors associated with the disease also are susceptible of causing miscarriages and possibly RPL, such as an impact of intrapelvic inflammatory processes affecting the oocyte and embryo in case of natural conception. Conversely these latter effects obviously are bypassed in case of assisted reproductive technology. Chronic inflammation of the endometrium in the condition known as chronic endometritis also causes early pregnancy losses and RPL with beneficial effects achieved when specific treatment is undertaken. (Fertil Steril® 2021;115:546–60. ©2020 by American Society for Reproductive Medicine.)
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Implantation and pregnancy development require a functional and optimal interplay between a good quality embryo – euploid – and a receptive endometrium. It is admitted commonly that approximately 15% of all pregnancies end early, before completion of the first trimester, with fewer than 5% of women experiencing two early pregnancy losses and 1% experiencing three pregnancy losses. The latter, those with ≥ 3 early pregnancy losses, is the most commonly admitted definition of recurrent pregnancy losses (RPL). However, today investigations for RPL are often already initiated in couples who experienced 2 successive pregnancy losses. Because the majority of all early pregnancy losses are due to genetically abnormal embryos, one easily understands that these numbers sharply increase with age, following the steep age-related increase in the incidence of aneuploidy.

Genetic-related RPL as well as occurrences linked to immunologic, endocrinologic, coagulation, and uterine anatomical disorders are addressed in other articles of this series (Scott, Alecsandru, and Carbonnel). The present article addresses the endometrial causes of RPL and notably those related to inflammation, as encountered in endometriosis and chronic endometritis (CE). We will address the practical measures to be deployed in case of assisted reproductive technology (ART) conducted in women with endometriosis and treatments recommended for CE, as well as reviewing the practical measures for adequately diagnosing these two conditions.

This review will address the current literature on RPL and impaired endometrium due to endometriosis/adenomyosis and/or CE. The article will be divided into two major parts: the first section addresses endometrial factors due to endometriosis/adenomyosis, whereas the second part addresses the role CE in RPL.

ENDOMETRIOSIS, ADENOMYOSIS, AND RPL

Endometriosis

Background and rationale. Endometriosis is an estrogen-dependent chronic condition defined as the presence of ectopic endometrial-like tissue (stroma, glands, and fibrosis), causing local inflammatory responses (1) and producing pain and infertility. The endometriosis-dependent factors that interfere with fertility are multiple and

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all are relative rather than absolute causes of infertility. Indeed, severe endometriosis has been encountered occasionally in women who had conceived seemingly without difficulty but also sometimes experienced miscarriages or RPL. Endometriosis affects up to 40% of patients with infertility and has been often, but not always, associated with poorer ART outcomes, including decreased yield of mature oocytes (2), lower implantation rates (3, 4), and decreased pregnancy rates (3–5).

A 2002 meta-analysis of IVF success rates in patients with endometriosis found that pregnancy rates were decreased compared with control patients, with lower fertilization, implantation rates, and number of oocytes retrieved (6). However, more recent results on the impact of endometriosis on ART outcome often draw contradictory conclusions on these topics (7). Indeed, some reports show equal outcome in case of endometriosis in terms of embryo euploidy (8) and implantation rates (9), as compared with disease-free controls. As discussed later in this article, the differences on the impact of endometriosis on fertility mainly depend on whether pregnancies occur naturally (in vivo) or through ART, with recent reports showing little impact in the latter case.

In this section of the review, we summarize the available literature on the impact of endometriosis on RPL. Given the extreme heterogeneity of the available studies in terms of methodology, no meta-analysis was attempted.

Endometriosis and early pregnancy losses: what is the evidence? We have sorted the factors causing infertility according to the presumed pathophysiology of the process involved (10). For example, we looked at the effects of endometriosis on endometrial proliferation, immune modulation, angiogenesis, and other mechanisms linked to the disease that are susceptible to alter the capacity to receive the embryo and permit the proper development (10–13).

Generally, the impact of endometriosis on RPL risk can result from different mechanisms. First, there is an effect of toxic pelvic factors altering oocyte quality through direct and persistent effects exerted on gametes/embryos during temporary exposure while passing through the distant segment of the Fallopian tube. This phenomenon, although transitory, possibly increases the risk of embryo aneuploidy. This mechanism only occurs in cases of natural conception because exposure to tubal and pelvic environments is bypassed in cases of ART. Second, there are inflammation-dependent alterations of the eutopic endometrium. This results in altered endometrial changes during the window of implantation (WOI), impaired predecidual transformation, and ultimately defective placentation. These alterations can have several obstetric consequences, including early pregnancy losses and possibly RPL. In cases of ART, only the impact of endometriosis on the eutopic endometrium, including altered placentation, is involved, possibly leading to early pregnancy losses and RPL (14). Chronic eutopic endometrium inflammation appears to be linked closely to CE, as discussed later in this review.

Oocyte and embryo quality. It has long been advocated that oocyte quality and the follicular environment are impaired in cases of endometriosis, leading to an altered maturation process (3). Some authors suggested that a possible alteration in the meiotic spindle could increase the rate of aneuploidy in patients with endometriosis and reduce pregnancy chances in this population (15, 16). In endometriosis, alterations of the meiotic spindle apparatus have been described (17–19). This raises questions as to whether oocytes in patients with endometriosis could be more susceptible to meiotic errors and chromosomal instability (17, 19). This in turn could lead to an increase in aneuploidy and, thus, higher rates of miscarriage and pregnancy losses.

In an elegant and simply designed study, Juneau et al. (8) provided convincing data that challenge the possible role of this hypothesis in ART. Indeed, these authors reported equal euploidy rates in women affected by endometriosis and age-matched controls (8). The latter findings are supported by further data reporting equal pregnancy and live birth rates in patients with endometriosis, provided (17, 18), as discussed later in this article, that dispositions are taken to avoid the endometrial effects of the disease (9).

Endometrial effects. One fundamental phenomenon that could explain the relationship between endometriosis and RPL was noted by Wilcox et al. (20). These authors reported that women who implant outside the normal WOI had an increasing risk of miscarriage and RPL (20). Biochemical mechanisms have been described that support the concept that delayed WOI with retarded progesterone-induced histologic transformations, such as a disrupted balance between glycodelin, integrins, Mucin-1, pinopods, leukemia inhibitory factor, and many others (21–25), may cause miscarriages. Further descriptions of essential biomarkers of endometrial receptivity also have been described in cases of endometriosis (25, 26).

It appears that the most important component of endometrial alterations encountered in endometriosis is linked to inflammation-mediated histologic changes (27, 28). This is believed to be the primary mechanism responsible for the progesterone resistance observed in endometriosis using DNA microarray analysis (29, 30). This condition also is accompanied by an increase in estrogen receptor dominance observed during the secretory phase (31, 32). Today, the inflammatory component of endometrial changes is considered to be the root cause of impaired implantation (33, 34). Progesterone also limits estrogen action by an induction of 17b-hydroxysteroid dehydrogenase-type 2 (HSD17bII) in the endometrium, which converts E2 to the less-active estrone (E1) (35). These complex mechanisms of induction and inhibition of gene expression lead to a shift of expression during the WOI, ranging from direct actions of progesterone to mechanisms involving paracrine and autocrine factors (27, 36–38).

One of the better-described endometrial biomarkers associated with the WOI is the b-3 integrin (23, 39, 40). Studies have documented how integrin expression is aberrant in many inflammatory conditions associated with implantation failure, including endometriosis, (41–44) and CE (see section that follows). Lessey et al. (41) also reported excessive endometrial expression of BCL6 leading to altered endometrial receptivity.

Aromatase (p450arom) is overexpressed in all inflammatory conditions and in cases involving the endometrium, including endometriosis (45, 46). Aromatase overexpression may be a predictor of implantation failure in fresh ART cycles (46, 47). Overexpression of this enzyme, coupled with decreased expression of the E2 metabolizing enzyme 17-b hydroxysteroid dehydrogenase II (45, 48, 49), increases bioavailable E2 in the endometrium, potentially accounting for aberrantly high estrogen receptor and proliferation (31, 35, 50, 51). Estrogen is a potent inhibitor of endometrial b-3 integrin (52), and is involved in embryo attachment and invasion (53–56). Alterations in eutopic endometrial metabolism of E2 in endometriosis is regulated by complex changes in autocrine and paracrine signaling associated with inflammation (27, 50, 57–59), driven in part by prostaglandin E2 (59, 60) produced in response to E2-regulated cycylo-oyxgenase 2 (61, 62) and hypoxia-induced factor-1 (62). Hypoxia-induced factor-1a is stabilized by activation of signal transducer and activator of transcription-3 recently shown to be overexpressed in women with endometriosis and infertility. Cycylo-oyxgenase 2 and signal transducer and activator of transcription-3 expression have been linked to inflammatory cytokines such as interleukin (IL)-17 and IL-6 (63–65), which also are elevated in women with endometriosis (66) Conversely, despite reports of increased uterine natural killer (uNK) cells in infertility, Freitag et al. (67) could not find any evidence that patients with endometriosis are more prone to elevated uterine uNK cell.

Endometrial alterations encountered in endometriosis appear to be corrected in cases of blockage of ovarian function, including in E2 and progesterone cycles prescribed for timing frozen embryo transfers (FET). In support of the latter, Bishop et al. (9) observed no differences in pregnancy outcomes in case of FET of euploid blastocysts in patients with endometriosis as compared with their counterparts undergoing ART for male factor infertility. Based on these findings, one currently recommends to offer a freeze all and deferred embryo transfer strategy in case of endometriosis (68), an approach not increasing the risk of endometriosis flare (69).

Endometriosis and obstetric outcomes alterations. Historically, pregnancy was seen as having a positive, treatment-like, impact on endometriosis and its symptoms (70, 71). This was seen to result from anovulation and amenorrhea preventing bleeding of endometriotic tissue but also from different metabolic, hormonal, immune, and angiogenesis changes related to pregnancy (72, 73). However, recent evidence supports the hypothesis that endometriosis also could affect pregnancy development through different mechanisms, including endocrine/inflammatory inbalance, molecular and functional abnormalities of the eutopic endometrium, defective deep placentation, and decidualization of endometriotic tissue (74–77).

Actual obstetric complications encountered in cases of endometriosis. The risk of obstetric complications in cases of endometriosis was reported widely recently (78–81), although some studies fail to find such links (9, 82–85). Also, the incidence of endometriosis may be associated with genetic or lifestyle factors, which are likewise associated with a higher pregnancy loss (e.g., smoking) (12, 13, 86, 87). A recent meta-analysis concluded that women with endometriosis have a statistically significant higher risk of preterm birth, miscarriage, placenta previa, small for gestational age infants, and cesarean delivery (79). Also, in endometriosis, activated macrophages can secrete pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and tumour necrosis factor α in the peritoneal cavity (88) and proinflammatory cytokines that might trigger venous thromboembolism during pregnancy (81)

For example, a large Scottish cohort study compared pregnancy outcomes in 5,375 women having surgically confirmed endometriosis with that of 8,710 pregnant women without endometriosis during the same time period. The authors concluded that endometriosis predisposes women to an increased risk of early pregnancy loss and later pregnancy complications (89). Furthermore, a recent retrospective cohort study of 588 fresh ART cycles and 150 FET cycles showed an increased rate of miscarriages following fresh embryo transfers in cases of endometriosis (14).

In contrast with the studies already mentioned, Maggiore et al. (84) concluded in a recent systematic review that endometriosis complications during pregnancy are rare and that there is no evidence that the disease has major detrimental effects on pregnancy outcome. Furthermore, a recent publication reported that the risk of miscarriage is not increased in women with endometriosis achieving pregnancy through ART, regardless of the use of fresh embryo transfer or FET (82).

In conclusion, although oocyte and embryo alteration is encountered likely in cases of natural conception, these alterations, resulting from pelvic toxicity, are bypassed with ART. Indeed, there is good evidence of normal euploidy rates in women with endometriosis (8, 9). Moreover, the alterations of the eutopic endometrium likewise are avoided in cases of ovarian suppression such as those existing in cases of E2 and progesterone treatment for FET. Indeed, implantation rates are unaltered in endometriosis in cases of frozen euploid blastocyst transfers (9, 90). Taken together, the findings of normal euploid rates in endometriosis (8) and unaltered implantation rates in case of euploid frozen blastocyst transfers (9) indicate that ART with differed embryo transfer is the treatment of choice in cases of endometriosis (7, 90). In support of the latter, we reported in a recent large cohort study (91) on nonselected frozen blastocyst transfers a low incidence of $<5\%$ of repeated implantation failure after three euploid blastocyst transfers.

Adenomyosis

Background and rationale. Adenomyosis is defined by the presence of ectopic endometrium, endometrial glands and stroma, developing in the myometrium. First described in 1860 by Carl von Rokitansky (92), even before the descriptions of endometriosis, adenomyosis was until recently a purely histopathologic diagnosis made after hysterectomy. New noninvasive methods, such as ultrasounds and magnetic resonance imaging (MRI), now allow in vivo diagnosis in the infertile population (93–95). This has led to a better understanding of the epidemiology, natural history, and

consequences of the disease on fertility and obstetric outcome.

The adenomyosis–infertility story is not a simple one. Originally, when the diagnosis of adenomyosis was made histologically on surgical pieces, the single most common factor associated with the disease was multiparity. And yet, we now see adenomyosis as a possible cause of infertility and altered obstetric outcome, including miscarriages and RPL (96–99). However, others see adenomyosis as an inert pathology, having no impact on reproductive function (98, 100, 101), including ART. A meta-analysis including nine studies of ART outcomes in women with and without adenomyosis diagnosed using MRI reported a reduction of up to 28% in pregnancy rates, whereas miscarriages were increased (31.9%) as compared with controls (14.1%) (97).

Pathophysiology of RPL risk in women with adenomyosis. Two main categories of mechanisms are implicated in the practical consequences of adenomyosis on reproduction and the risk of miscarriages and RPL.

The first category, inflammatory processes taking place within the eutopic endometrium induce cellular and biochemical alterations. Adenomyosis may alter the normal response to progesterone, just like that seen in cases of endometriosis, which is often associated (102, 103). These findings include progesterone resistance, decreased progesterone receptor (PR) isoform B (102), and methylation defect (104). Recent reports indicated that Hox-A10 gene expression is decreased in both mice models (105) and in the secretory-phase endometrium of women with adenomyosis (106). Dysregulation of endometrial leukemia inhibitory factor is seen also during the WOI (107, 108). NR4A receptors drive decidualization of human endometrial stromal cells by transcriptional activation of FOXO1A. Moreover, both NR4A and FOXO1A are down-regulated in adenomyotic tissue, which may partake in the impairment of decidualization (109). Some inflammatory markers are increased, such as IL-1b and corticotropin-releasing hormone (110), as well as natural killer cells, macrophages (111), and a spectrum of cytokines (112). Also, there is evidence that adenomyosis induces an epigenetic dysregulation of genes (104, 113, 114).

The second category, uterine contractility and endometrial peristalsis encountered in adenomyosis, may lead to implantation disorders and defective deep placentation and, in turn, miscarriages and RPL. It has been suggested that by altering the normal myometrial architecture and function of the uterus, adenomyosis disrupts the normal uterine peristalsis (115). The subendometrial myometrium (inner myometrium or junctional zone), which is embryologically distinct from the outer myometrial layers, is the primary contributor to uterine peristalsis. Thickening of the junctional zone, best evaluated with MRI, is found in most women with adenomyosis. The cellular modifications of this muscular layer with the invasion of glands and stroma impact the normal peristaltic activity and are seen as partaking in the proper positioning of the implanting embryo. The latter has been seen as possibly altering pregnancy chances and placentation quality, thereby increasing the risk of miscarriages and RPL (116–119). Local hyperestrogenism is thought to further amplify this phenomenon (120). The frequent coexistence of endometriosis and adenomyosis impairs our ability to understand precisely the specific role of adenomyosis itself (78).

In conclusion, together with decreased ART outcome, adenomyosis is associated with increased miscarriage rates and possibly RPL (78, 96). The management of adenomyosis when encountered in case of RPL is debated. Certain studies recommend the use of gonadotropin-releasing hormone analogues, which have been documented to reduce the thickness of the junctional layer on MRI evaluation, although the clinical value on future pregnancy outcome has not been validated yet (121, 122).

Chronic endometritis

Background and rationale. Chronic endometritis is a persistent slight inflammation of the endometrial lining (123, 124). Chronic endometritis is a puzzling pathology often ignored by many gynecologists because it is generally asymptomatic and difficult to diagnose. Clinically CE shows no specific signs, being commonly accompanied only by mild symptoms like abnormal uterine bleeding, vague pelvic discomfort, and leukorrhea (123, 124).

The cause of CE is believed to stem from an altered endometrial microbiota. The latter can be investigated through classical endometrial cultures (125) and, more recently, using molecular profiling using 16SRNA analysis specific for different bacteria (126, 127). Fluid hysteroscopy is also an effective technique for diagnosing CE based on the presence of subtle endometrial signs like focal or diffuse hyperemia, polypoid aspect, and presence of micro-polyps (126, 128). Yet, the diagnostic accuracy of hysteroscopy is strongly dependent on the skill and expertise of the operator (126–128).

For these reasons, histology is today considered the gold standard for diagnosing CE based on identifying and counting plasma cells within the endometrial stromal (129–132). For this, immunohistochemical (IHC) staining with CD138 permits simple and reliable identification of plasma cells in the endometrial tissue, thereby gaining popularity over classical histology analysis (133).

However, inconsistencies exist regarding the number of CD138-stained cells that is required in the endometrial stroma for carrying a definitive diagnosis of CE. In practice, several criteria have been used in different studies (134).

In recent years, in contrast with the previously mentioned description of mild symptoms in CE, several articles indicated that CE heavily may reduce reproductive capacity by impairing endometrial receptivity and interfering with conception. A higher incidence of CE has been observed in women with infertility, implantation failure, and RPL (135–141). Live birth rates in women with a history of RPL and untreated CE are very poor (7%) (141). On the other hand, data in the literature suggest that ongoing pregnancy rates are improved significantly after antibiotic therapy and resolution of the prevailing inflammatory condition.

Pathophysiology. Different mechanisms may explain the increased risk of RPL in women affected by CE. An inflammatory process within the endometrium may cause cellular and biochemical alterations. Endometrial inflammation alters the mechanisms securing the timely arrival of a viable blastocyst in a receptive endometrium during the WOI (142). In humans, the endometrium undergoes a series of changes leading to embryo receptivity during a limited period, normally occurring 5 to 7 days after ovulation and lasting for about 4 days (cycle days 20–24) during the WOI (143). In women with CE, several alterations in the cellular and biochemical processes leading to optimal endometrial receptivity have been described.

Cellular alterations. In cycling women, the endometrium undergoes a physiological process of inflammation. The number of leukocytes present in the endometrium of healthy women varies throughout the menstrual cycle. Leukocytes account for <10% of stromal cells in the proliferative and early secretory phase, but their number dramatically increases, starting from the midsecretory phase, further expanding during the late secretory phase and early pregnancy (144). However, in cases of CE, the quantity, organization, and distribution of endometrial leukocytes show drastic modifications. In particular, B lymphocytes, which are <1% of the entire leukocyte population in the normal human endometrium, increase in number and infiltrate both the endometrial functional layer (the portion shed with the onset of menstruation) and basal layer. There, B lymphocytes trespass the glandular epithelium and invade into the lumens of glands (132, 133, 136, 144–146).

Significant variations in the number of CD68+ macrophages, CD8+ T cells, and Foxp3+ Treg cells are seen in the endometrium of patients with CE compared with non-CE controls (147, 148). Contrasting results have been reported in the modifications of uNK cells that regulate trophoblast invasion and enhance vascular remodeling by extravillous trophoblast (16, 26).

Biochemical variations. As with other chronic inflammatory diseases, like rheumatoid arthritis and inflammatory bowel diseases, IL-1b, inteferon-g, and tumor necrosis factor (TNF)-alpha are overexpressed in cases of CE (149, 150). Exposure to TNF-a is known to increase local estrogen biosynthesis in endometrial glandular cells (151). This may be correlated with the occurrence of endometrial micropolyps and polypoid endometrium, the hysteroscopic findings characteristic of CE (152, 153).

Several adhesion molecules and chemokines involved in B-cell extravasation and migration (CD62E, CXCL1, and CXCL13) are expressed aberrantly in endometrial endothelial and epithelial cells in cases of CE (149, 150). This altered immune response provides an abnormal microenvironment for the recruitment of circulating B cells into the endometrial stromal compartment and gravitation of these lymphocytes to the glandular areas. Furthermore, a fraction of recruited endometrial B cells may differentiate in situ into endometrial stromal plasmacytes (ESPC). In women with CE, ESPC express a high level of multiple immunoglobulin (Ig) subclasses (IgM, IgA1, IgA2, IgG1, and IgG2) with a predominance of IgG2 (154). The excessive mucosal antibodies in CE potentially have a negative impact on the embryo implantation process. These local immune responses in CE rarely develop into systemic inflammation because the values of the peripheral levels of circulating leukocyte, serum C-reactive protein, and fever indexes of affected patients remain within the normal ranges (155).

By contrast, the expression of the genes potentially associated with embryo receptivity (IL11, CCL4, IGF1, and CASP8) and decidualization (RPL and IGFBP1) appears downregulated in the endometrium in cases of CE (150).

Recently, the role of microRNAs has been investigated. In lipopolysaccharide (LPS)-treated endometrial stroma, cell expression of the microRNAs miR-643 was decreased and TNF-alpha receptor-associated factor 6 (TRAF6) protein level, a regulator of NF-kB implicated in inflammatory diseases, was enhanced. The overexpression of miR-643 suppresses LPS-induced secretion of inflammatory cytokines (TNF -α, IL-1β, and IL-6) and activation of the NF-kB pathway. Also, TRAF6, a validated target of miR-643 and TRAF6 restoration, reversed the effects of miR-643 on inflammation response in LPS-treated human endometrial epithelial cells. Collectively, miR-643 attenuated LPS-induced inflammatory response by targeting TRAF6, indicating a novel avenue for treating CE (156).

These findings support the idea that, in the case of CE, the endometrium shows an abnormal response to ovarian steroids and is unable to modulate its component cells into a receptive phenotype (150, 157).

Abnormal uterine contractility. Women with CE show altered patterns of wave-like patterns of uterine contractions, both during the periovulatory and midluteal phases. Altered uterine contractility and "irritability" of the uterine wall at the moment of implantation may impair receptivity and explain the symptoms related to CE such as pain, abnormal uterine bleeding, infertility, increased miscarriage rates, and possibly endometriosis (158).

Looking at the prevalence of CE reported in literature, we see a wide interstudy variance ranging from 8%–72% (158). Different reasons can explain the different results, namely, that CE was investigated in a relatively small cohort (<100) of patients and conventional tissue staining was used for the detection of ESPC. Similarly, the effectiveness of antibiotic treatment also shows wide interstudies variability, and, more importantly, treatment paradigms and the molecules used are completely different.

The response of CE to antibiotic therapy has been examined in various cohort studies (127, 128, 130). The cure rate, as determined by the reduction of ESPC density in a repeat endometrial biopsy specimen after antibiotic therapy, was found to range from 57%–100% (136, 140, 147, 159, 160). The positive impact of antibiotic therapy on clinical outcomes among subjects with CE also had been examined in several cohort studies involving women with recurrent abortions, unexplained infertility, and recurrent implantation failure (126, 136, 140, 160, 161). Notwithstanding the encouraging clinical results

from cohort studies, there is still a lack of formal demonstration of a definitive cure rate of CE after antibiotic therapy compared with no treatment.

In the present review, we aimed at assessing the actual risk of RPL in women with CE and confirming the beneficial effects of antibiotic treatment.

Systematic Review on the Links Between RPL and CE

Search strategy. This was a systematic review and an aggregate data meta-analysis of published data on the prevalence of CE in women affected by RPL and on the cure rate after antibiotic therapy. The review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (9).

The literature search was conducted from August 11–21, 2020 via Google Scholar (https://scholar.google.it/), as the search database, and covered a time ranging from 2010 until August 2020. We used "endometritis" and "miscarriage" as key words to include all the research articles addressing possible relationships between CE and RPL. The research database scanned the headers, the abstract, and the main text for the key words. Moreover, a manual completion of the references, cited in the selected articles, was thoroughly conducted.

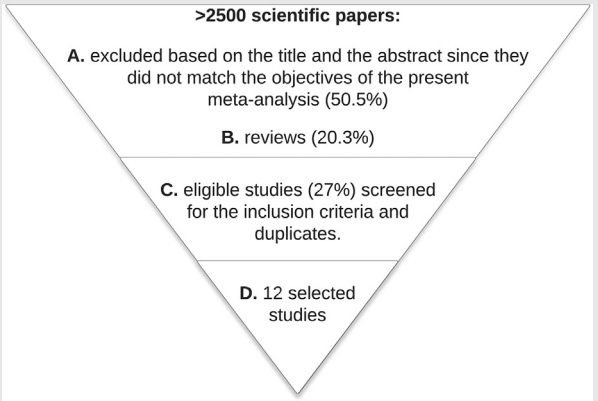
Study selection. The literature search and resulting data extraction was performed independently by two authors (E.C. and R.D.N.) and then cross-checked. Both authors read the full text of all relevant articles and produced a list of eligible articles, which was further reduced for the studies included in the present meta-analysis.

Eligibility criteria and final study inclusion criteria. More than 2,500 studies were identified with Google Scholar. Thereafter, most of the published reports were excluded based on the title and the abstract because they did not match the objectives of the present study (50,5%). The remaining part consisted of reviews (20.3%) and eligible studies (27.0%): the latter ones being screened for the inclusion criteria and duplicate publications. In the end, only 12 research studies (134, 137, 140, 141, 147, 154, 159, 161–165) were included in the final selection for our meta-analysis (Fig. 1) (134, 136, 137, 140, 141, 147, 159, 160, 162, 164–166).

Specific exclusion criteria were studies not written in English/Italian/French/Spanish or not focusing on the role of CE in RPL. Book chapters, case series, review articles, and abstracts were excluded. References were handled using the Endnote program (version X3 for Windows, Thomson Reuters).

To evaluate their comparability, the selected publications needed to meet participants, interventions, comparisons, outcomes, and study design (PICOS) method criteria according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (https://www.equator-network.org/reporting-guidelines/prisma/), as follows: case-control, cohort, and cross-sectional studies (Study design) published as original articles, which reported the prevalence of CE (Indicator) in the population of women with RPL (Population) and eventually the live pregnancy rate (Outcome 1) and CE cure rate (Outcome 2) after the antibiotic therapy evaluated with hysteroscopy and/or histology on endometrial biopsy. Interestingly, four studies (137, 147, 162, 164) evaluated a wider population simultaneously looking at both RPLs and recurrent implantation failure. However, the present aggregate-data meta-analysis included only the subpopulation of the aforementioned studies to focus on its main question: investigating the prevalence of CE in a RPL population and the fertility outcome expressed as live pregnancy rate after evaluation and therapy with antibiotics. In three case-control studies, the PICOS' Comparator is respectively identified with healthy and fertile patients with no clinical conditions (134, 164) and patients with abnormal vaginal bleeding or other indications for hysteroscopy except for RPL (165) (Table 1). In each study, the risk of biases emanated from the lack of standard diagnostic criteria for CE, different histological criteria, and whether pathologists were blinded for the histologic findings, present only in our previous study, Cicinelli et al. (161), and in the article by Zolghadri et al. (164). Moreover, other possible sources of biases included: the clinical experience and team number of gynecologists who performed the hysteroscopies, the timing of endometrial biopsies in the menstrual cycle, and the length of follow-up for assessing fertility outcome.

FIGURE 1



Flow diagram for meta-analysis of the chronic endometritis (CE) among women affected by recurrent miscarriage (RM; and the LBR at fertility follow-up).

Pirtea. Endometrial causes of recurrent pregnancy losses. Fertil Steril 2020.

Statistical Analysis

The present aggregate-data meta-analysis was conducted using the R statistical environment (The R Foundation for Statistical Computing), specifically the packages "meta" and "metapro" (167, 168). The prevalence and odds ratios are represented as frequencies (%) or numbers with 95% confidence interval (CI). The heterogeneity of data was evaluated using funnel plots and by calculating the I^2 value (>50% was judged as highly heterogeneous). Because it was extensive, we preferred using the random-effect model (REML). We

TABLE 1

Principal features of the 12 articles selected for aggregate-data meta-analysis.

Study, y	Study design	Timing of the hysteroscopy and diagnostic criteria	Pathological diagnostic criteria for CE	Antibiotic therapy	Evaluation of the CE eradication
Zargar, 2020	Monocentric cross-sectional study	Follicular phase Focal or diffuse endometrial hyperemia, stroma edema, and endometrial micro-polyps (<1 mm)	≥5 CD138+ plasma cells/20 HPSs by a target pathologist	Guided by the antibiogram results, doxycycline 100 mg orally twice a d for 21 d	Not mentioned
Barat, 2019	Bicentric case-control study (controls=vaginal bleeding or other hysteroscopy indication, except for RM)	Follicular phase Endometrial bleeding, endometrial micro-polyps (<1 mm)	>1 plasma cell at the highest visual power with morphological evaluation	Not mentioned	Not mentioned
Li, 2019	Monocentric retrospective study	Midluteal phase	≥5 CD138+ plasma cells/30 HPSs	Single course of 500 mg levofloxacin orally twice a d plus 400 mg metronidazole orally once a d for 14 d	≥5 CD138+ plasma cells/30 HPSs
Liu, 2018	Monocentric case-control study Controls=healthy women with ≥1 live birth within the previous 2 y	7 d after LH surge detection	CD138+ cell count per unit area (≥5.15 cells/0.1 mm^2)	Not mentioned	Not mentioned
Vomstein, 2018	Retrospective study Not mentioned are the centers' numbers.	Midluteal phase	>5 CD138+ cells/mm^2	Doxycycline (200 mg/d for the 1st d and 100 mg/d for the next 20 d)	CD138+ cells (>1 mm^2) All the persistent cases had CD138+ cells < mm^2
Song, 2017		Different phases 6 skilled gynecologists	≥1 CD138+ plasma cells/10 HPSs	Not mentioned	Not mentioned
Bouet, 2015	Prospective observational study	Follicular phase	≥5 CD138+ plasma cells/10 HPSs	Doxycycline 200 mg twice a d for 14 d	Not performed
McQueen, 2015	Monocentric, retrospective study	Not mentioned	1–5 plasma cells/HPS or discrete clusters of <20 plasma cells by CD138 staining (IHC staining score)	Doxycycline 100 mg twice a d for 14–21 d	1–5 plasma cells/HPS or discrete clusters of <20 plasma cells by CD138 staining (IHC staining score)

Pirtea. Endometrial causes of recurrent pregnancy losses. Fertil Steril 2020.

TABLE 1

Continued.

Study, y	Study design	Timing of the hysteroscopy and diagnostic criteria	Pathological diagnostic criteria for CE	Antibiotic therapy	Evaluation of the CE eradication
Cicinelli, 2014	Monocentric retrospective study	Follicular phase Micro-polyps (<1 mm) fluctuating in the cavity, stromal edema, and focal or diffuse hyperhemia All the hysteroscopies were performed by 2 of the authors	If positive hysteroscopy→ endometrial biopsy studied in blind by the pathologist after H&E staining→superficial stromal edema, increased stromal density, and pleomorphic stromal inflammatory infiltrate dominated by lymphocytes and plasma cells (> 1 plasma cell/ HPS)	Positive culture: therapy guided by antibiogram results: if gram-negative→ ciprofloxacin 500 mg twice a d for 10 d if gram-positive→ amoxicillin + clavulanate 1 g twice a d for 8 d If Mycoplasma or U urealyticum→ josamicine 1 g twice a d for 12 d Negative culture: single dose of ceftriaxone 250 mg i.m. plus doxycycline 100 mg orally twice a d for 14 d with metronidazole 500 mg orally twice a d for 14 d (CDC guidelines) Persistent CE: protocol repeated up to 3 times. If previous Mycoplasma and U. urealyticum → minocycline 100 mg twice a d for 12 d	If positive hysteroscopy→ endometrial biopsy studied in blind by the pathologist after H&E staining→superficial stromal edema, increased stromal density, and pleomorphic stromal inflammatory infiltrate dominated by lymphocytes and plasma cells (>1 plasma cell/HPS)
McQueen, 2014	Monocentric observational cohort study	Not mentioned	H&E >1 plasma cell in the whole section	Maximum 2 antibiotic courses Ofloxacin 400 mg and metronidazole 500 mg orally twice a d for 14 d (covered the 23% of cure failure) Or doxycycline alone or doxycycline and metronidazole ciprofloxacin and metronidazole	H&E >1 plasma cell in the whole section

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TABLE 1

Continued.

Study, y	Study design	Timing of the hysteroscopy and diagnostic criteria	Pathological diagnostic criteria for CE	Antibiotic therapy	Evaluation of the CE eradication
Kitaya, 2011	Monocentric retrospective study	6–8 d after LH surge detection Micro-polyps (<1 mm) fluctuating in the cavity, stromal edema, and focal or diffuse hyperemia	Puntuacte immunostaining for CD138+ cells under a light microscope at a magnification of 400x observed by 2 independent pathologists in 10 nonoverlapping stromal areas and 20 glandular lumina	Cefcapene pivoxil hydrochloride hydrate (Flomox) 100 mg orally 3 times per d for 14 d	Puntuacte immunostaining for CD138+ cells under a light microscope at a magnification of 400x observed by 2 independent pathologists in 10 nonoverlapping stromal areas and 20 glandular lumina
Zolghadri, 2010	Monocentric, case-control study Fertile women without known medical issues nor previous miscarriages who had >2 pregnancies	Follicular phase	≥ 1 plasma cell HPS studied in blind by the pathologist after H&E staining	Not mentioned	Not mentioned

Note: CDC = Centers for Disease Control; CE = chronic endometritis; H&E = hematoxylin and eosin; HPS = hematoxylin-phloxine-saffron; IHC = immunohistochemical; i.m. = intramuscular; LH = luteinizing hormone; RM = recurrent miscarriage.

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also performed a meta-regression of the live birth rate (LBR) in the presence of influencing factors (prevalence of CE alone or in combination with the cure rate) and a subsequent "analysis of variance test" for choosing the best predictive model. A two-sided *P* value < .05 was considered as an index of statistical significance.

Because this study was a systematic review and meta-analysis, formal ethical approval was not required.

RESULTS

The 12 studies selected and included in the present aggregate-data meta-analysis and review of the literature are listed, summarized, and compared in Table 1. Specifically, we reported the study design (numbers of centers involved, observational study subtype, and characterization of eventual controls), the timing of hysteroscopy, and (when specified) its diagnostic criteria, pathological diagnostic criteria, antibiotic regimens, and how the investigators evaluated the CE eradication.

Correlation Between CE and RPL

The present model of meta-analysis estimates the prevalence of CE among women affected by RPL either using hysteroscopy or histologic diagnosis when specified by the authors. The distinction was made between IHC criteria using CD128+ plasma cell count or simply traditional histologic identification of plasma cells using morphological features when available. The incidence of CE followed a normal distribution with a random effect model displaying high variability (I^2= 93.01%), as shown in the funnel plot. Hence, we performed a REML (Fig. 2). The estimate of CE incidence in women with RPL was 29.67 % (95% CI 20.81–38.53).

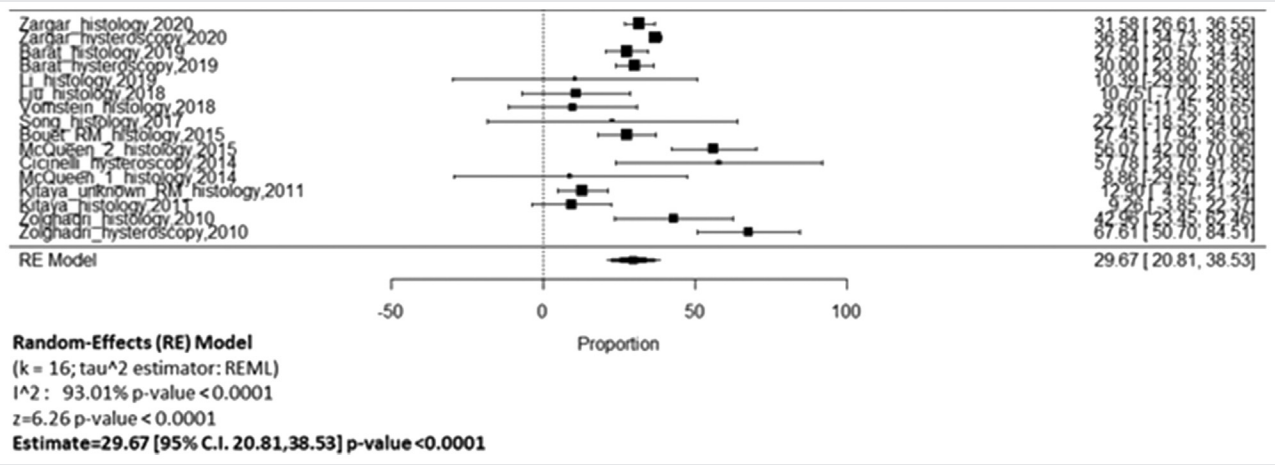
Clinical Outcome and Cure Rate After Antibiotics in Women With CE and RPL

Antibiotic treatment was significantly effective in 87.90% of cases for treating CE. In our previous study, we reported a lower percentage of success of 56.7%.

Effects of Antibiotic Therapy and Cure of CE on LBR

The present forest plot shows the different proportions of LBR among studies that looked at fertility follow-up. The estimated LBR was 62.41% (95% CI 54.83–69.99), with a highly significant *P* value (<.0001). Strikingly, after a meta-regression using three different REMLs (LBR, LBR and CE, and LBR+CE+cure rate) and the subsequent comparison using analysis of variance to choose the best predictive model of the population, we found a highly significant positive correlation (0.33; *P*<.0001) of CE on LBR and a positive but nonsignificant trend of cure rate on LBR. Therefore, we judged the REML model that regressed the outcome LBR with the measure of CE as the affecting variable being the best model for predicting the population with LBR.

FIGURE 2



Forest plot displaying the results of the meta-analysis with the binary outcome (chronic endometritis [CE], absent CE) in the individual group of patients with recurrent miscarriages (RMs).

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DISCUSSION

The present systematic review and aggregate data meta-analysis primarily aimed at evaluating the role of CE in RPL. For this purpose, we evaluated the prevalence of CE in women with RPL and the effect of antibiotic treatment on reproductive outcomes reported as LBR.

Prevalence of CE

Comparing all 12 studies, we found an estimated prevalence of CE among the population of women affected by RPL of 29.67 % (95% CI 20.81–38.53; $P>.0001$). These results indicate that it is crucial to define the cause etiology of RPL so that patients can receive the best treatment and experience higher LBR. However, the estimate of CE incidence may be altered by biases linked to the different diagnostic means (hysteroscopy, histological, IHC) and criteria (i.e., number of CD138+ or plasma cells/hematoxylin-phloxine-saffron ore section or mm^2).

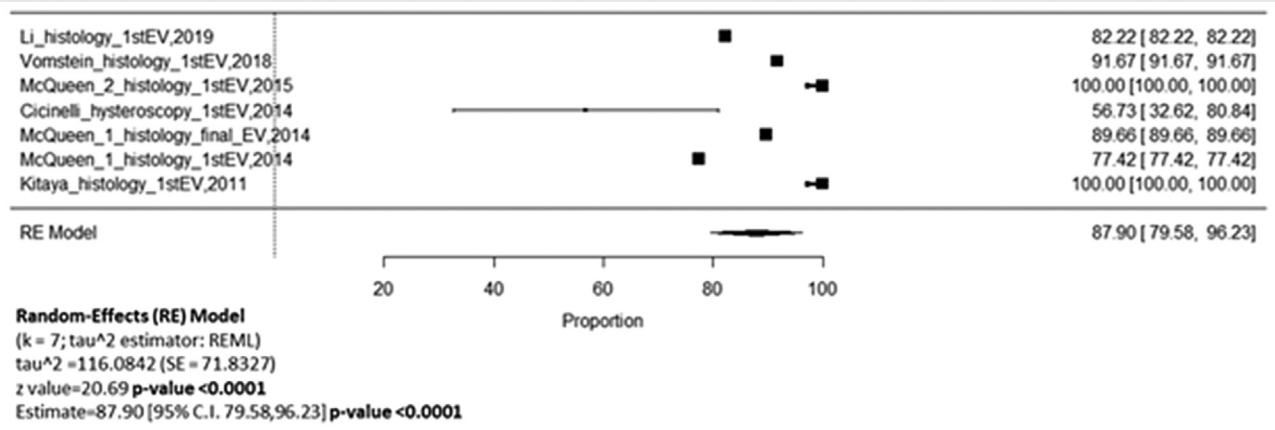
Treatment of CE

Accumulating evidence supports the effectiveness of the oral antibiotic for treating CE. The present meta-analysis evaluated and compared a subset of studies that treated CE with antibiotics and mentioned the subsequent cure rate at the follow-up with hysteroscopy and endometrial biopsy with or without IHC support. The incidence of cure rate after antibiotic treatment in women with RPL and CE was not homogeneous (Fig. 3) probably, because of the different techniques used for making the diagnosis. In our previous study, we based the diagnosis of CE eradication not only on histologic findings but also on hysteroscopy (160). This could have overestimated the actual persistence of CE after therapy together with a shorter duration of antibiotic treatments (<14 days). Notably, we also had a higher value of baseline detection of CE causing a possible bias when conducting the control hysteroscopy (160). The different methods of CE eradication are listed in Table 1.

Pregnancy outcome after antibiotic treatment for CE is debated. Some studies suggest that oral antibiotic treatment potentially improves pregnancy outcome in women with infertility with CE. In a before-and-after study, McQueen et al. (140) showed that antibiotic treatment increased LBR in women with CE who had a history of RPL (7% [7/98] before vs. 56% ([8/50] after treatment). The cumulative LBR in women with RPL in the CE cured group was 88% (21/24), whereas in the non-CE group LBR was 74% (180/244) (140). These findings support the idea that antibiotic treatment is a promising therapeutic option to improve pregnancy outcomes in women with infertility with CE. Prospective randomized controlled trials are required to verify these results. Interestingly, the presence of CE in higher proportions in the RPL population significantly improves LBR after treatment (Fig. 4). A possible explanation could emanate from the different criteria used for CE diagnosis when studying RPL. This should guide antibiotic therapy when trying to optimize the clinical follow-up of these patients.

In summary, the studies and data presently available point at a significant role of CE as a cause of RPL. Clinically, it is important to stress that CE can be treated successfully with antibiotic therapy with an estimated cure rate of 87.90% in the affected population. Strikingly, fertility outcome is improved in women who underwent antibiotic therapy. The significant inverse correlation between LBR and cured CE in women affected by RPL points at a possible standard for RPL.

FIGURE 3



Forest plot displaying the results of the meta-analysis with the outcome cure rate in the individual group of treated patients with recurrent miscarriage (RM) and chronic endometritis (CE).

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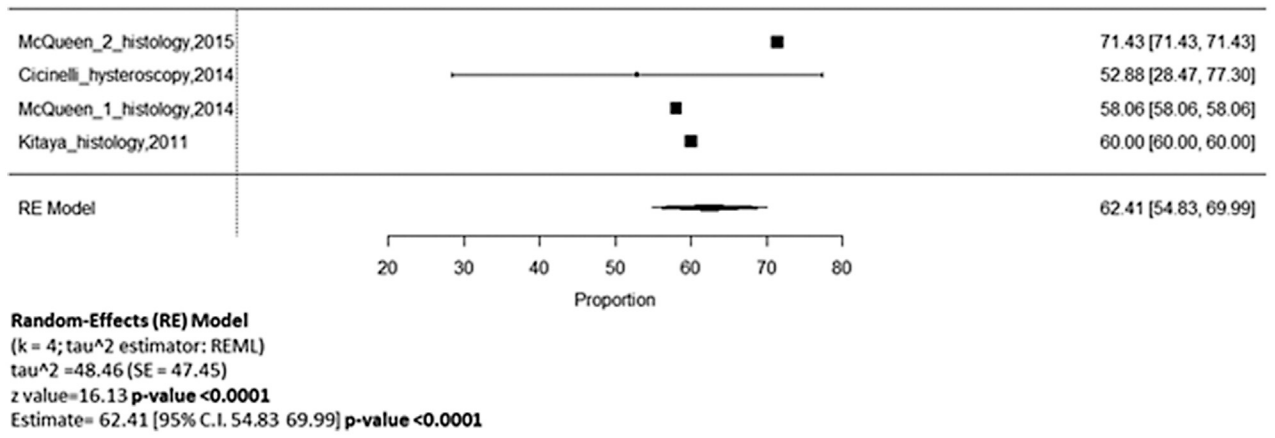
FIGURE 4



Forest plot displaying the results of the meta-analysis with the outcome live birth rate (LBR) in the individual group of treated patients with recurrent miscarriage (RM) and chronic endometritis (CE).

Pirtea. Endometrial causes of recurrent pregnancy losses. Fertil Steril 2020.

CONCLUSION

Recurrent pregnancy loss is an important clinical entity with no universally established definition. Classically defined after three miscarriages, investigations are started commonly now after two occurrences only. The true incidence of RPL is unknown, and the true relevance of numerous factors that have been implicated in its pathogenesis remains a matter of discussion. Pregnancy loss concerns arise frequently in couples with infertility, especially in the setting of ART cycles. Pathologies resulting in chronic endometrial inflammation in case of endometriosis-adenomyosis and CE have been associated with increased risk of RPL.

The primary messages concerning endometriosis, adenomyosis, and CE association with RPL are as follows: endometriosis has to be identified in patients with infertility particularly in cases of RPL because this finding calls for ART treatment with deferred embryo transfer, and CE must be sought for in women experiencing RPL because its treatment, antibiotic therapy, has been shown to improve the outcome of further pregnancies.

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