Chronic endometritis in women with recurrent early pregnancy loss and/or fetal demise

Dana B. McQueen, M.D.,[a] Lia A. Bernardi, M.D.,[a,b] and Mary D. Stephenson, M.D., M.Sc.[a,b]

[a] University of Chicago Recurrent Pregnancy Loss Program, Department of Obstetrics and Gynecology, University of Chicago; and [b] Department of Obstetrics and Gynecology, University of Illinois at Chicago, Chicago, Illinois

Objective: To assess the prevalence of chronic endometritis in women with a history of recurrent early pregnancy loss (REPL) and/or fetal demise (FD).
Design: Observational cohort study using prospectively collected data.
Setting: Recurrent pregnancy loss program in an academic medical center.
Patient(s): Three hundred ninety-five women with a history of two or more pregnancy losses of less than 10 weeks' size or a fetal demise of 10 or more weeks' size.
Intervention(s): All women had an endometrial biopsy. Chronic endometritis was treated with antibiotics, and a second endometrial biopsy was recommended as a "test of cure."
Main Outcome Measure(s): Subsequent live-birth rate (LBR).
Result(s): The overall prevalence of chronic endometritis was 9% (35/395) in this cohort; 7% (21/285) in the REPL group, 14% (8/57) in the FD group, and 11% (6/53) in the combined REPL/FD group. The cure rate was 100% after a course(s) of antibiotics. The subsequent cumulative LBR was 88% (21/24) for the treated chronic endometritis group versus 74% (180/244) for the group without chronic endometritis. The per-pregnancy LBR for the treated chronic endometritis group was 7% (7/98) before treatment versus 56% (28/50) after treatment.
Conclusion(s): There was a high prevalence of chronic endometritis in this cohort. The test of cure was 100% with antibiotics. Subsequent LBRs after treatment were encouraging. (Fertil Steril® 2014;101:1026–30. ©2014 by American Society for Reproductive Medicine.)
Key Words: Chronic endometritis, recurrent pregnancy loss, recurrent miscarriage, fetal demise, pregnancy

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Recurrent early pregnancy loss (REPL), which is defined as two or more pregnancy losses of less than 10 weeks' size, and fetal demise (FD), which is defined as a pregnancy loss of 10 or more weeks' size (1), are devastating to couples attempting to have a child. Despite extensive evaluation for maternal and paternal factors, such as a parental translocation, maternal thyroid disease, hyperprolactinemia, endometrial factor, uterine septum or adhesions, antiphospholipid syndrome, and inherited thrombophilia, nearly half of couples are left without an answer (2). It is controversial whether chronic endometritis is associated with REPL and/or FD.

Chronic endometritis is usually asymptomatic. It is defined histologically by the presence of plasma cells in an endometrial biopsy (3, 4). Chronic endometritis is associated with gonorrhea or chlamydia and nonsexually transmitted infections including escherichia coli, streptococcus, staphylococcus, enterococcus faecalis, and yeast. However, often a causal organism cannot be identified. Chronic endometritis can result from retained tissue, such as an incomplete pregnancy loss or retained placental tissue (5).

Limited publications exist regarding evaluation and treatment for chronic endometritis in pregnancy loss or infertility. In 2011, Kitaya reported on 54 women with recurrent pregnancy loss, which is defined as three or more consecutive losses of intrauterine pregnancies before 22 weeks of gestation. The prevalence of chronic endometritis in this study was

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Reprint requests: Mary D. Stephenson, M.D., M.Sc., University of Illinois at Chicago, 820 South Wood Street (MC 808), Chicago, Illinois 60612 (E-mail: msteph@uic.edu).

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9.3% (6). In 2011, Zolghadri et al. reported a case-control study of 142 women with unexplained recurrent miscarriage, which is defined as three or more pregnancy losses before 20 weeks of gestation or a fetus of less than 500 g, and 154 fertile controls. The unexplained recurrent miscarriage group had a significantly higher prevalence of chronic endometritis: 42.9% versus 18.2%, $P<.001$ (7). Neither study reported subsequent live-birth rates after antibiotic treatment.

In 2011, Kasius et al. reported a nested data analysis from a randomized controlled trial in which investigators performed hysteroscopy-guided endometrial biopsies in 606 asymptomatic patients with infertility (8); the prevalence of chronic endometritis was 2.8%. With diagnosis, patients and their partners were treated with 400 mg daily of ofloxacin. Despite a course of antibiotics, there was no significant difference in the subsequent cumulative live-birth rates between the infertility group treated for chronic endometritis and the infertility group without chronic endometritis.

Lastly, in a study by Johnston-MacAnanny et al., consisting of 33 women with recurrent implantation failure, the prevalence of chronic endometritis was 30.3% (9). The 10 affected women were treated with oral doxycycline 100 mg twice daily for 2 weeks; subsequent biopsy demonstrated a "test of cure" of 70% (7/10). The three women with persistent chronic endometritis were then prescribed ciprofloxacin 500 mg and metronidazole 500 mg twice daily for 2 weeks. Subsequently, the women treated for chronic endometritis had significantly lower implantation rates compared with the women who were not found to have chronic endometritis: 11.5% (3/26) versus 32.7% (18/55), $P = .0024$; however, the clinical and ongoing pregnancy rates were not significantly different. Although the cohort was limited in size, the high prevalence of chronic endometritis raises the question of causality.

The objective of this study was to determine the prevalence of chronic endometritis in strictly defined cohorts of REPL and FD women, to assess the test of cure after antibiotics and to report subsequent live-birth rates.

MATERIALS AND METHODS

Ethics approval was obtained from the Institutional Review Board at the University of Chicago. Written consent had been previously obtained from all subjects. To determine the cohort, a query was performed using Current Procedural Terminology codes 58100 (endometrial biopsy) and 58555 (diagnostic hysteroscopy) for all patients seen by one of the authors (M.D.S). Then the University of Chicago Recurrent Pregnancy Loss (RPL) Database (Microsoft ACCESS 2010) was queried for these patients, who were seen between July 2004 and February 2012, with either a history of REPL, which is defined as two or more documented unexplained (excluding miscarriages with chromosome errors) pregnancy losses of less than 10 weeks' size, or a history of FD, which is defined as at least one pregnancy loss of 10 or more weeks' size.

The University of Chicago RPL Program protocol was to defer the initial evaluation for at least 6 weeks after pregnancy loss and after at least one normal menstrual cycle. The evaluation consisted of cytogenetic analysis of both partners, serum TSH, serum PRL, office hysteroscopy, lupus anticoagulant, anticardiolipin IgG and IgM, and beta-2 glycoprotein-1 IgG and IgM. Although investigational, an endometrial biopsy (10, 11) and antiphosphatidylserine IgG and IgM were also included. With a concomitant history of FD, inherited thrombophilia testing, including factor V Leiden, prothrombin gene mutation, protein C, protein S, antithrombin, and homocysteine, was performed.

A chart review was performed on the subjects with REPL and/or FD to confirm that an endometrial biopsy was performed; if not, the subject was excluded. In subjects diagnosed with chronic endometritis, the antibiotic regimen and subsequent endometrial biopsy results were extracted.

Abnormal Test Results and Management Strategies

In this study, chronic endometritis was defined by the presence of plasma cells on endometrial biopsy. All women with chronic endometritis were treated with antibiotics and offered a second endometrial biopsy for test of cure. A second course of antibiotics was offered for persistent chronic endometritis. Partners did not receive treatment.

Definitions of abnormal evaluations and management of concomitant factors or diagnoses have been previously published (12). Briefly, a serum level of TSH <0.3 mU/L was considered hyperthyroidism, 2.5–4.0 mU/L was considered subclinical hypothyroidism, and more than 4.0 mU/L was considered hypothyroidism (13). Significant intrauterine adhesions in the upper two-thirds of the uterine cavity were classified as intrauterine adhesions. A septum extending more than 1.0 cm into the uterine cavity, with a smooth external uterine fundus evaluated with saline infusion ultrasound or three-dimensional ultrasound, was considered abnormal (12). Antiphospholipid syndrome was defined according to the international criteria by Miyakis et al. (14). Diabetes mellitus was diagnosed in women with a fasting glucose ≥ 126 mg/dL or a 2-hour glucose >200 mg/dL after a 75-g load (12). DNA testing was performed for Factor V Leiden G1691 mutation and prothrombin G20210 gene mutation. Serum levels of functional protein C activity of less than 63%, functional protein S activity less than 63%, antithrombin activity of less than 80%, or a fasting homocysteine of ≥ 14 mmol/L were considered abnormal (12).

Definitions

The primary outcome was subsequent live-birth rate (LBR). The cumulative subsequent LBR was defined as the number of women with at least one subsequent live birth divided by the number of women with at least one subsequent pregnancy after the endometrial biopsy(ies). The per-pregnancy LBR was defined as the number of pregnancies resulting in a live birth divided by all pregnancies. Only subjects who had at least one subsequent pregnancy were included in the LBR analyses.

Live births included all viable term and preterm births and ongoing pregnancies ($n = 18$) of at least 14 weeks of gestation that were lost to follow-up. Ectopics and terminations of pregnancy were excluded.