ORIGINAL ARTICLE: EARLY PREGNANCY

Luteal start vaginal micronized progesterone improves pregnancy success in women with recurrent pregnancy loss

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Objective: To assess the effectiveness of luteal start vaginal micronized P in a recurrent pregnancy loss (RPL) cohort.
Design: Observational cohort study using prospectively collected data.
Setting: Not applicable.
Patient(s): Women seen between 2004 and 2012 with a history of two or more unexplained pregnancy losses <10 weeks in size; endometrial biopsy (EB) performed 9–11 days after LH surge; and one or more subsequent pregnancy(ies). Women were excluded if concomitant findings, such as endometritis, maturation delay, or glandular-stromal dyssynchrony, were identified on EB.
Intervention(s): Vaginal micronized P was prescribed at a dose of 100–200 mg every 12 hours starting 3 days after LH surge (luteal start) if glandular epithelial nuclear cyclin E (nCyclinE) expression was elevated (>20%) in endometrial glands or empirically despite normal nCyclinE (≤20%). Women with normal nCyclinE (≤20%) who did not receive P were used as controls.
Main Outcome Measure(s): Pregnancy success was an ongoing pregnancy >10 weeks in size.
Result(s): One hundred sixteen women met the inclusion criteria, of whom 51% (n = 59) had elevated nCyclinE and 49% (n = 57) had normal nCyclinE. Pregnancy success in the 59 women with elevated nCyclinE significantly improved after intervention: 6% (16/255) in prior pregnancies versus 69% (57/83) in subsequent pregnancies. Pregnancy success in subsequent pregnancies was higher in women prescribed vaginal micronized P compared with controls: 68% (86/126) versus 51% (19/37); odds ratio = 2.1 (95% confidence interval, 1.0–4.4).
Conclusion(s): In this study, we found that the use of luteal start vaginal micronized P was associated with improved pregnancy success in a strictly defined cohort of women with RPL. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Recurrent pregnancy loss, recurrent miscarriage, progesterone, endometrium, cyclin E

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Recurrent pregnancy loss (RPL), defined as two or more pregnancy losses at less than 10 weeks in size (1), is a challenging clinical problem with few evidence-based treatment options. Factors associated with RPL are numerous, including genetic, endocrine, anatomic, immunologic, infectious, and autoimmune. Evaluation and management of RPL patients involves comprehensive testing and close monitoring of subsequent pregnancies.

The role of endometrial factors in early gestation and pregnancy loss is an area of increasing interest. Studies of uterine secretions by Burton et al. have revealed that the endometrial glands may play a larger role in early pregnancy than previously thought. Burton et al. demonstrated that endometrial glands remain active until at least 10 weeks of pregnancy. Glycoproteins MUC-1 and glycodelin A secreted by the endometrial glands are phagocytized by the placental syncytiotrophoblast, indicating a nutritive role in early embryonic development (2, 3). Additionally, multiple studies have demonstrated a decreased concentration of MUC-1 in endometrial biopsies (EBs)

Received June 29, 2016; revised October 26, 2016; accepted November 29, 2016.
M.D.S. has nothing to disclose. D.M. has nothing to disclose. M.W. has nothing to disclose. H.J.K. is the inventor of a patent related to the monitoring of endometrial glandular development.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.11.029

obtained from women with RPL compared with fertile controls, indicating an association between RPL and deficiencies in endometrial glandular activity (4, 5).

Glandular development and endometrial maturation can be assessed based on the appearance of hematoxylin and eosin– (H&E-) stained endometrial tissue using the eight morphologic markers proposed by Noyes et al. in 1950 (6). Unfortunately, this morphologic classification has been shown to have high interobserver and intraobserver variation (7). Coutifaris et al. demonstrated that the ability of histologic evaluation to discriminate between fertile and infertile couples is poor (8). The investigators suggested that continued research focusing on molecular markers of endometrial development should be pursued.

This study uses the endometrial molecular marker, nuclear cyclin E (nCyclinE), a cell cycle regulator that changes in intensity and subcellular localization throughout the menstrual cycle. Dubowy et al. reported that abnormal nCyclinE expression in endometrial glands, defined as greater than 20% after day 20 of the menstrual cycle, correlates with a history of infertility and may be a useful molecular marker of endometrial development (9).

P induces a secretory transformation of the endometrium; it is essential to achieve and maintain pregnancy. Therefore, vaginal micronized P is commonly used empirically in women with RPL of <10 weeks in size. Several studies have examined the clinical utility of vaginal, oral, and/or IM P in improving the live-birth rate in women with either first trimester spotting or a history of RPL (10–12). A Cochrane review and meta-analysis suggested that P supplementation could improve the live-birth rate in women with three or more pregnancy losses (10). However, these studies had heterogeneous cohorts, variable routes of P administration, and the use of P after women were already symptomatic with vaginal bleeding.

In 2015, Coomarasamy et al. performed a randomized trial of vaginal P in women with recurrent miscarriage, defined as three more pregnancy losses in the first trimester (13). Women were randomized to 400 mg of vaginal micronized P twice daily or matched placebo, starting after a positive pregnancy test but no later than 6 weeks of gestation. The live-birth rate was similar between groups, 66% versus 63%. Although the trial was well conducted, we question the late start and high daily dose of P administered.

It is well known that the midcycle LH surge promotes luteinization of the granulosa cells with consequent increased P production. P supplementation is routinely prescribed in assisted reproduction to improve endometrial development, starting shortly after the LH trigger. Therefore, if nCyclinE, a marker of endometrial development, is abnormally elevated in the luteal phase in a cohort of women with a history of RPL of <10 weeks in size, we hypothesize that vaginal micronized P starting 3 days after the LH surge may be effective in improving their subsequent pregnancy outcomes.

MATERIALS AND METHODS

Patients

Approval was obtained from the University of Chicago Institutional Review Board (IRB) to prospectively collect data and tissue from women and their partners seen in the University of Chicago Recurrent Pregnancy Loss Program for future research in RPL. All of the subjects gave written informed consent. Approval was obtained from the University of Illinois IRB for this specific study.

Subjects were identified using the University of Chicago Recurrent Pregnancy Loss Database (Microsoft Access 2007), created by one of the authors (M.D.S.). The database was queried for all women seen between July 2004 and April 2012 who had a history of RPL, defined as two or more "unexplained" (miscarriages with chromosome errors excluded) pregnancy losses of less than 10 weeks in size, an RPL evaluation including an EB 9–11 days after LH surge, and at least one subsequent pregnancy, conceived without the use of fertility drugs, closely monitored in the University of Chicago Recurrent Pregnancy Loss Program. Women with histologic findings on EB, including maturation delay, glandular-stromal dyssynchrony, and intraglandular neutrophils and macrophages were excluded (n = 32). Any discrepancies or omissions in the data set were corrected by chart review.

The RPL diagnostic screening protocol was previously described with definitions of positive and negative results (14). In brief, a laboratory evaluation for RPL included TSH, PRL, cytogenetic analysis of both partners, and antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and beta-2-glycoprotein IgG, IgM). An office hysteroscopy was also performed to evaluate the uterine cavity.

Criteria for Abnormal nCyclinE Expression

The EB was performed 9–11 days after the LH surge, documented by self-administered urinary LH testing; patients were advised to use condoms or abstain from intercourse in this cycle.

The LH surge was defined as day 13 of the menstrual cycle. The endometrium was evaluated histologically after H&E staining, according to the Noyes et al. criteria (6). In addition, immunohistochemical staining for nCyclinE expression in endometrial glands was performed and interpreted by one of the authors (H.J.K.), as described elsewhere (9). Reliability was assessed in a cohort of 100 patients whose samples underwent repeated immunohistochemical staining (mean of six per patient). Excellent reliability was established with an intraclass correlation of 0.76 (95% confidence interval [CI], 0.70–0.82). An abnormal result was defined as greater than 20% nCyclinE by maximizing the odds ratio (OR) for pregnancy rates above and below different cutoffs. To determine the appropriate cutoff value, testing was performed in a group of 118 women seeking infertility evaluation at Yale University. There was a 42% pregnancy rate among women with nCyclinE ≤20% and an 8% pregnancy rate for women with nCyclinE >20% (OR = 0.12, 95% CI, 0.02–0.99; P=.027).

Management Strategy

Commercially available vaginal micronized P (Endometrin or Prometrium) was prescribed at a dose of 100–200 mg every 12 hours starting 3 days after the LH surge (luteal start) and continued until 10 weeks of gestation in women with elevated nCyclinE (>20%). Some women with normal nCyclinE (≤20%) insisted on using empiric vaginal micronized P,