Vaginal parturition decreases recurrence of endometriosis

Carlo Bulletti, M.D., Anna Montini, Ph.D., Paolo Levi Setti, M.D., Antonio Palagiano, M.D., Filippo Ubaldi, M.D., and Andrea Borini, M.D.

Unit of Physiopathology of Reproduction, Cattolica General Hospital and University of Bologna, Bologna; Department of Economics, University of Bologna, Bologna; Procreazione Medichemente Assistita Unit, Humanitas Hospital, Milan; Department of Obstetrics and Gynecology, University of Naples, Naples; Center for Reproductive Medicine, European Hospital, Rome; and Tecnobios Procreazione, Bologna, Italy

Objective: To evaluate the role of parturition in the recurrence of endometriosis.

Design: Retrospectively analyzed, prospectively obtained data.

Setting: Unit of Physiopathology of Reproduction, Health Care Unit of Rimini, and University of Bologna Cervesi General Hospital, Cattolica, Italy.

Patient(s): Three hundred forty-five patients with stage II–IV endometriosis, dysmenorrhea, and infertility were treated for endometriosis and divided into four groups according to parity and mode of parturition.

Intervention(s): The patients were laparoscopically treated for endometriosis upon the occurrence and recurrence of the disease. Ultrasound measurements of the uterine internal ostium (IOS) were performed at each study interval.

Main Outcome Measure(s): Degree of dysmenorrhea, occurrence and recurrence of endometriosis, and uterine IOS measurements were established and related to parity and mode of parturition.

Result(s): After parturition, dysmenorrhea recurrence was significantly higher in nulliparous women than in women with vaginal parturition. The endometriosis recurrence rate was higher in women who did not have vaginal parturition. The IOS significantly enlarged after vaginal delivery but not after cesarean delivery. There were significant negative correlations between IOS and the recurrence of endometriosis and dysmenorrhea. Odds ratios indicated that as the IOS enlarged, the risk of recurrence decreased.

Conclusion(s): Vaginal parturition plays a protective role in the recurrence of endometriosis. (Fertil Steril 2010;94:850–5. ©2010 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, parturition, cesarean section, dysmenorrhea, recurrence rate of endometriosis, retrograde bleeding, uterine contractions

Endometriosis is a debilitating, progressive disease that affects 1%–50% percent of premenopausal women (1–5), with a prevalence of 38.5% in infertile women and 5.2% in fertile women (6). Endometriosis may cause dyspareunia, dysmenorrhea, lower back pain, and infertility (7). In women with dysmenorrhea, the incidence of endometriosis is 40%–60%; in women with subfertility, it is 20%–30% (2, 8–10). A definitive diagnosis of endometriosis can be made only with laparoscopy. The recurrence of endometriosis is a clinical problem in terms of general health and reproductive potential.

Despite several hypotheses, the pathogenesis of endometriosis remains unclear. However, the notion that endometriosis results from the retrograde transport of endometrial debris through the uterine tubes and subsequent implantation in the pelvic peritoneum and visceral organs is compelling (11–15). The first clinical consequence of endometriosis is “infertility,” and pregnancy may reduce the recurrence of endometriosis (16) and dysmenorrhea through mechanisms that are not yet clear. The present study evaluated the role of parturition in reducing the recurrence rates of endometriosis and dysmenorrhea. We also investigated the role of uterine internal ostium (IOS) enlargement in the recurrence of endometriosis following vaginal parturition.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board at Rimini General Hospital, Rimini, Italy.

Patients

One thousand twenty-two infertile, nulliparous women with severe dysmenorrhea (aged 18–35 years) were evaluated between 1997 and 2003 in the Unit of Physiopathology of Reproduction at Rimini’s General Hospital. Inclusion and exclusion criteria used to select the study group were as follows. Nine hundred fifty-five of the women underwent laparoscopy, which was required to diagnose endometriosis; 760 did not have a partner with severe male factor, and women with
a partner with severe male factor were excluded; 655 had tubal patency, which was requested to establish the role of retrograde bleeding in the recurrence of the disease; and 460 were diagnosed with endometriosis stage II–IV according to the revised American Fertility Society (AFS) classification (17), and stage I cases were excluded. Four hundred thirty-three women had FSH serum levels of <13 mIU/mL before and after laparoscopic surgery; those with levels >13 mIU/mL were excluded. Eighty-eight patients were not followed-up owing to ectopic pregnancy, spontaneous abortion, nonelective cesarean section (cesarean for failure to progress), breastfeeding for more than 3 months, or relocation to a different geographic area and were excluded. Thus, the final sample consisted of 345 patients (mean age 26.8 ± 5.1 years). The patients did not use any adjuvant therapy in addition to salutary pain relief drugs for endometriosis after diagnosis. A second laparoscopy was performed for unacceptable increases in dysmenorrhea and/or the persistence of infertility.

**Study Groups**

Seventy-two (mean age 26.8 ± 5.2 years) of the 345 women were nulliparous (group 0), and 273 women (mean age 26.8 ± 5.1 years) delivered (group 3). In group 3, 175 women (mean age 27 ± 5.1 years) delivered spontaneously by the vaginal route (group 1) and 98 (mean age 26.5 ± 5.1 years) delivered by cesarean section (group 2). There were no significant age differences between the groups.

**Detection of Endometriosis**

Endometriosis was detected with laparoscopy and classified according to the AFS classification (17).

**Dysmenorrhea Rating**

The visual analog scale (VAS) was used to rate the pain associated with dysmenorrhea, rating from 1 (none) to 10 (worst ever) (18, 19).

**Design**

This cohort study of endometriosis recurrence was based on a sample of 345 patients (aged 18–35 years) with severe dysmenorrhea who underwent laparoscopy between 1997 and 2003 in the Unit of Physiopathology of Reproduction at Rimini General Hospital, Rimini, Italy. Patients who did not deliver were followed for 24 months after laparoscopy (72 nulliparous patients), the others until the first menstrual cycle after parturition (273 women). Dysmenorrhea was rated before the first laparoscopy (time 0), 6 months after laparoscopy or 6 menstrual cycles after delivery (time 1), 12 months after laparoscopy or 12 menstrual cycles after delivery (time 2), and 24 months after laparoscopy or 24 menstrual cycles after delivery (time 3). Endometriosis was diagnosed by laparoscopy and classified according to the revised AFS classification (17) by the two surgeons who performed the laparoscopies. Laparoscopies were performed at the outset of the study (time 0) and during follow-up (time 1, 2, or 3) at the time that endometriosis recurrence was diagnosed based on increasing dysmenorrhea and/or the persistence of infertility. These women underwent laparoscopy twice: at the time of recruitment, when endometriosis was both scored and treated, and at the time of recurrence between time 0 and time 3. Endometriosis scores (time 0) were not different between the groups.

**Internal Ostium Measurement**

The validity and reproducibility of ultrasound (US) internal ostium (IOS) measurements were established in a cohort of 80 women before the study. Two independent measurements of the IOS performed in each patient by two doctors varied insignificantly with each other and with three measurements in the same subject at different times by a unique doctor. Test comparisons were also made between the US measurement of IOS in candidates for hysterectomy and direct measurement in the specimens after hysterectomy, which did not significantly differ.

Uterine IOS corresponds to the last tract (approximately 1 cm) of the cervical channel between the vagina and uterine lumen cavity compartments. Measurement of the uterine IOS was performed by two independent experts in obstetrics and gynecologic ultrasound using an Elegra US (Siemens, Stuttgart, Germany) with the probe in the sagittal plane. The size of the IOS was established at times 0, 1, 2, and 3. There were no statistical interevaluator differences in the IOS measurements.

**Statistical Analysis**

Statistical analyses were performed by Stata 8 (Stata Corp, College Station, TX). Each variable was first analyzed descriptively as mean value and standard deviation. Group and time differences were analyzed with paired and unpaired Student *t* tests. Pairwise correlation coefficients were calculated to evaluate the relationship between quantitative and ordinal variables. Logistic regression was used to calculate odds ratios (OR). Risk ratios (RR) were also calculated. *P* values of <.05 were considered to be significant.

**RESULTS**

**Endometriosis Stage**

The mean stage of endometriosis for the 345 study patients, according to the revised AFS classification, was 3.1 ± 0.7. Individual group stages were 3.6 ± 0.5 (group 0; *n* = 72), 2.8 ± 0.7 (group 1; *n* = 175), 3.3 ± 0.7 (group 2; *n* = 98), and 3.0 ± 0.7 (group 3; *n* = 273). The mean stages of group 0 and group 3 were significantly different (*P* <.01), as were the mean stages of group 2 and group 1 (*P* <.01). The number of patients in each group with each stage is as follows.

Group 0: stage IV = 46 (64%); stage III = 20 (28%); stage II = 6 (8%).
Group 1: stage IV = 46 (26%); stage III = 54 (31%); stage II = 75 (43%).
Group 2: stage IV = 47(48%); stage III = 30 (31%); stage II = 21 (21%).
Group 3: stage IV = 93 (34%); stage III = 84 (31%); stage II = 96 (35%).

Dysmenorrhea
The mean dysmenorrhea scores were significantly different ($P<.01$) between nulliparous women 6 months after laparoscopy ($n=72; 3.66 \pm 2.0$) and those who had delivered and had a laparoscopy 6 months after the onset of menstruation (time 1; $n=273; 2.79 \pm 1.6$). Drop-outs in recording the VAS data decreased the number of samples analyzed. Corresponding scores at time 2 ($n=70; 5.2 \pm 1.9$ vs. $n=134; 4.2 \pm 1.6$) and time 3 ($n=69; 6.3 \pm 2.0$ vs. $n=58; 4.9 \pm 1.8$) were also significantly different (all $P<.01$).

IOS
The mean IOS size of the 345 patients at time 1 was $6.19 \pm 3.99$ mm. The IOS of women who delivered vaginally ($n=175; 9.24 \pm 3.22$ mm) was significantly larger than the IOS of women who delivered by cesarean section ($n=98; 3.3 \pm 1.67$ mm; $P<.001$) and those who were nulliparous ($n=72; 2.73 \pm 1.16$ mm; $P<.01$). The IOS at time 0 in women who had vaginal or cesarean deliveries ($n=273; 3.8 \pm 1.9$ mm) was significantly different than the IOS of the same women at time 1 ($7.1 \pm 3.2$ mm; $P<.001$). The mean IOS sizes of nulliparous women ($n=72$) at time 0 ($2.7 \pm 1.1$ mm) and time 1 ($2.7 \pm 1.6$ mm) were not significantly different. The mean IOS size of women who delivered vaginally ($n=175$) was significantly smaller at time 0 ($4.2 \pm 2.0$ mm) than at time 1 ($9.2 \pm 3.2$ mm; $P<.001$), whereas the IOS of women who delivered by cesarean ($n=98$) was not different between time 0 ($3.2 \pm 1.5$ mm) and time 1 ($3.3 \pm 1.7$ mm).

Dysmenorrhea and IOS
We did not observe an association between IOS at time 0 and the occurrence of dysmenorrhea at the 24-month follow-up ($r=0.3029; P=NS$). We observed a significant correlation between the mean IOS size of all patients at time 1 and dysmenorrhea scores at the 6-month ($r=-0.6763; P<.01$), 12-month ($r=-0.6882; P<.01$), and 24-month ($r=-0.6875; P<.01$) month follow-ups.

Endometriosis Recurrence and IOS
The mean uterine IOS size was significantly smaller in women with recurrent endometriosis than in women who did not have a recurrence $6 (n=22; 2.3 \pm 1.1$ mm vs. $n=323; 6.5 \pm 4.0$ mm; $P<.01$), $12 (n=39; 3.4 \pm 1.5$ mm vs. $n=306; 6.6 \pm 4.1$ mm; $P<.01$), and $24 (n=108; 4.6 \pm 3.1$ mm vs. $n=237; 6.9 \pm 4.2$ mm; $P<.01$) months after laparoscopy or the onset of menstruation after parturition.

When we analyzed women who had vaginal or cesarean deliveries, we observed a significantly smaller mean uterine IOS size in patients who experienced a recurrence of endometriosis than in those who did not experience recurrence after 6 ($n=5; 2.3 \pm 0.7$ mm vs. $n=268; 7.2 \pm 4.0$ mm; $P<.01$), 12 ($n=17; 3.7 \pm 1.6$ mm vs. $n=256; 7.3 \pm 4.0$ mm; $P<.01$), and 24 ($n=87; 5.0 \pm 3.2$ mm vs. $n=186; 8.1 \pm 3.9$ mm; $P<.01$) months.

When we analyzed women who had not given birth, we did not find significant differences in the mean uterine IOS size of those who had a recurrence of endometriosis ($n=17; 2.3 \pm 1.1$ mm) compared with those who did not ($n=55; 2.8 \pm 1.2$ mm) at the 6-month follow-up. For the same group, the differences in mean uterine IOS size between women who had recurrent endometriosis and those who did not was significant at the 12-month follow-up ($n=22; 3.1 \pm 1.4$ mm vs. $n=50; 2.5 \pm 1.0$ mm; $P<.05$) but not at the 24-month follow-up ($n=21; 2.7 \pm 1.0$ mm vs. $n=51; 2.7 \pm 1.3$ mm). There was a negative correlation between mean uterine IOS size at time 1 and the recurrence of endometriosis 6, 12, and 24 months after laparoscopy or the onset of menstruation after delivery (Table 1). The IOS size and recurrence of endometriosis were not associated in patients who had not delivered or those who delivered by cesarean section, but the association was significant in women who had delivered vaginally (Tables 1 and 2).

The significant ORs for endometriosis recurrence at 6 ($0.319813 \pm 0.06036; P<.005$) and 12 ($0.1509233 \pm 0.0540348; P<.005$) months for women who delivered compared with those who had not delivered suggest a protective role of parturition in endometriosis recurrence for up to 12 months. The ORs for the recurrence of dysmenorrhea in terms of uterine IOS size at 6 ($0.5645132 \pm 0.0331682; P<.005$), 12 ($0.537211 \pm 0.0342719; P<.005$), and 24 ($0.5446138 \pm 0.0339624; P<.005$) months demonstrate that a 1-mm enlargement of the IOS reduced the risk of dysmenorrhea recurrence by approximately 50%. The ORs for endometriosis recurrence in terms of uterine IOS size at 6 ($0.4255619 \pm 0.01005976; P<.005$), 12 ($0.7176887 \pm 0.0569736; P<.005$), and 24 ($0.84102 \pm 0.0300871; P<.005$) months indicate that a 1-mm enlargement of the uterine IOS reduced the risk of endometriosis recurrence by more than 50% at 6 months, 22% at 12 months, and 10% at 24 months.

**DISCUSSION**
A primary question regarding the medical management of endometriosis is how to control its recurrence. It is well known that after parturition, patients report amelioration of their symptoms and the recurrence of endometriosis is reduced. The present study demonstrates the positive role of vaginal delivery in reducing pain associated with dysmenorrhea and endometriosis recurrence. The study also suggests a mechanism by which vaginal delivery exerts this positive effect. Enlargement of the uterine IOS was related to pain relief and a reduction in the recurrence of endometriosis.
Assessing an individual’s level of pain is difficult. Standardized methods used in clinical studies, such as the VAS (19), the McGill questionnaire (22), a simple categoric scale (23), or quality of life scales, such as the SF-36 used to detect the impact of pain and the response to treatment (24), are not routinely used. The symptoms of endometriosis and its laparoscopic appearance do not always correlate (25). The severity of the endometriosis symptoms and the probability of diagnosis increases with age (2, 20), with the incidence peaking in the 40s (21). This fact further suggests a role for retrograde bleeding in endometriosis recurrence due to cumulative episodes of endometrial debris transport throughout the tubes. In the present study, women who were surgically treated for endometriosis and had vaginal parturition experienced a longer pain-free interval than women who underwent cesarean section. Medical treatment designed to interfere with ovulation generally provides effective pain relief, but the recurrence rate after the cessation of therapy is high, and this type of treatment will not resolve infertility or cure endometriosis (26).

The surgical treatment of endometriosis improves pregnancy rates and is the preferred initial treatment for infertility caused by the disease. In the present series of 345 women, 79.1% became pregnant within 2 years of surgery. Surgery also appeared to provide better long-term pain relief than medical treatment (7). However, the recurrence rate of endometriosis is reported to be 4.6%–31%, depending on the patient’s age and the anatomic site of implantation (16, 17, 27). Considering the evidence of pain relief in 50%–90% of patients 1 year after surgery and the high recurrence rate of endometriosis (28), treating endometriosis at the time of diagnostic laparoscopy seems to be logical. On the other hand, the 1-year pain-free interval that followed the first surgical treatment may allow patients and clinicians to opt for a second surgery once the pain reaches an unacceptable level and, for patients who desire to become pregnant, to avoid assisted reproductive technologies, as was the case in the present study. This strategy may be useful in the short-term to maintain fertility in women who wish to become pregnant, but long-term management should exclude multiple surgical procedures, and patients should be encouraged to pursue pregnancy at the earliest time that life circumstances allow (28).

For normal couples, the probability of achieving a live birth for any given month (i.e., fecundity) (29) ranges from 15% to 20% (30). In women with untreated endometriosis and infertility, monthly fecundity is 2%–10% (31). On the other hand, 25%–50% of infertile women have endometriosis, and 30%–50% of women with endometriosis are

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**TABLE 1**

Correlation of uterine IOS at time 1 and the recurrence of endometriosis.

<table>
<thead>
<tr>
<th>Interval (mo)</th>
<th>Entire study population (n = 345)</th>
<th>Nulliparous (n = 72)</th>
<th>Vaginal parturition (VP) (n = 175)</th>
<th>Cesarean section (CS) (n = 98)</th>
<th>VP + CS (n = 272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>n = 22</td>
<td>n = 16</td>
<td>n = 0</td>
<td>n = 3</td>
<td>n = 3</td>
</tr>
<tr>
<td></td>
<td>r = 0.2531</td>
<td>r = 0.1860</td>
<td>r = 0.1663</td>
<td>r = 0.1422</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .01</td>
<td>NS</td>
<td><em>P</em> &lt; .01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>n = 39</td>
<td>n = 22</td>
<td>n = 2</td>
<td>n = 12</td>
<td>n = 14</td>
</tr>
<tr>
<td></td>
<td>r = 0.2531</td>
<td>r = 0.2022</td>
<td>r = 0.2187</td>
<td>r = 0.0324</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .01</td>
<td>NS</td>
<td><em>P</em> &lt; .01</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>n = 108</td>
<td>n = 22</td>
<td>n = 19</td>
<td>n = 57</td>
<td>n = 76</td>
</tr>
<tr>
<td></td>
<td>r = 0.2718</td>
<td>r = 0.0094</td>
<td>r = 0.3562</td>
<td>r = 0.0746</td>
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</tr>
<tr>
<td></td>
<td><em>P</em> &lt; .01</td>
<td>NS</td>
<td><em>P</em> &lt; .01</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

*Note: NC = not calculated; NS = not significant.*

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**TABLE 2**

Rate of endometriosis recurrence according to study group.

<table>
<thead>
<tr>
<th>Interval</th>
<th>No. of recurrences</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo</td>
<td>22</td>
<td>39</td>
</tr>
<tr>
<td>12 mo</td>
<td>6.4</td>
<td>11.3</td>
</tr>
<tr>
<td>24 mo</td>
<td>.22.2</td>
<td>30.6</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>3.1</td>
<td>12.2</td>
</tr>
<tr>
<td>Vaginal parturition—group 1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vaginal and surgical deliveries—group 3</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>

*Note: NC = not calculated; NS = not significant.*
infertile (32). It has been established that there is a higher prevalence of endometriosis in infertile women (48%) than in fertile women (5%) (33), and infertile women are 6–8 times more likely to have endometriosis than fertile women (6).

In the present study, the recurrence rate of endometriosis was significantly lower in women who had vaginal parturition than in nulliparous women and those who delivered by cesarean section. Parity seemed to have a key role in establishing the recurrence rate of endometriosis. In fact, the incidence of endometriosis recurrence in women who had vaginal parturition was significantly lower than the recurrence rate detected in all of the remaining women in the study.

Considering the inefficiency of pharmacologic treatments intended to treat endometriosis (26), the primary concern for clinicians in managing endometriosis patients is to stop or limit recurrence. However, to overcome endometriosis recurrence, its pathogenesis must be clarified, and the cause of endometriosis is not known. Risk factors include early menarche and late menopause (8). The risks are consistent with the hypotheses that retrograde bleeding causes intrapelvic implantation of ectopic endometrium, which accumulates with each menstruation. Also supporting the retrograde bleeding hypothesis is the fact that oral contraceptives reduce the risk of endometriosis, and this protective effect persists up to 1 year after their discontinuation (8). Embryonic cells may give rise to deposits in the umbilicus, and retrograde menstruation may deposit endometrial cells in the diaphragm (8, 13, 34–36).

In the present study, we measured the uterine IOS and found that it enlarged after vaginal parturition but not after cesarean section. Enlargement of the IOS was inversely related to the recurrence of endometriosis, confirming the role of retrograde bleeding and providing a potential mechanism explaining how retrograde bleeding may determine the occurrence and recurrence of the disease. Pregnancy with parturition may also decrease dysmenorrhea by enlarging the uterine IOS, which, in turn, may facilitate endometrial discharge through the cervix rather than the uterine IOS tubes into the pelvis. A decrease of dysmenorrhea was not observed in women who underwent cesarean section; these data are related to the absence of IOS enlargement in women who delivered vaginally. Retrograde bleeding occurs in a large number of women, but the debris that flows through the tubes

FIGURE 1

(A) Pressure curve of a closed system. (B) Pressure curve determined by only one opening (cervical IOS). In this case, the rate of the internal pressure increase is counteracted by the size of the IOS and its discharge flow. (C) Pressure curves determined by the rapid pressure increase, which is faster than the IOS discharging time in the vagina. Only after the increase in pressure reaches the threshold for tubal opening are the contents of the internal uterine cavity discharged, first through both the cervical and tubal ostia and then by the cervical IOS only. Only Figure 1C represents retrograde bleeding.
implants in the pelvic organs and peritoneum in only some cases. Implantation may be due to an unexplained environmental or immunologic condition or to the continuous recurrence of retrograde bleeding itself.

Any attempts to describe the pathogenesis of endometriosis with algorithms used for other smooth muscle organs, such as the heart, bowels, and bladder, should include all of the parameters involved, such as wall elasticity, uterine contractions (UC), menstrual debris density, uterine cavity and tubal length, size of the tubal and cervical ostium, and cervix length. However, a simplified model uses the Bernoulli fluid dynamic principle and the physiology of UC. Assuming that the uterine cavity does not have ports (e.g., tubal and cervical ostia) that access the external compartment, UC would cause an increase in the intrauterine pressure, as described by the curve in Figure 1A. That curve is expressed by the elasticity of the smooth muscle organ. In vivo, the size of the tubal ostia is 1–2 mm, whereas the size of the cervical IOS is 2–9 mm depending on the patient and her history (i.e., nulliparous or delivered). If the cervical IOS is large, UC do not open the tube because the force is discharged through the kinetic displacement of endometrial debris through the cervix (Fig. 1B). However, if the IOS is small, UC may increase the internal pressure tone up to the opening of the tubes by discharging the debris throughout the tube (i.e., retrograde bleeding), reducing the internal pressure to the value for tubal closure (Fig. 1C). The dynamics of fluid displacement through the uterotubal compartment represents a possible mechanism for retrograde bleeding and the ectopic implantation of endometrial cells, as previously described (13). The proposed dynamic of debris displacement may explain the protective role of vaginal parturition–associated IOS enlargement in the reduction of endometriosis recurrence as described in the present study.

REFERENCES