Altered uterine contractility in women with chronic endometritis

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Objective: To evaluate the alterations in endometrial waves (EW) originating from the contraction of the subendometrial myometrial layer in the periovulatory and midluteal phases in women diagnosed with chronic endometritis (CE).
Design: Case-control study.
Setting: University hospital.
Patient(s): Forty-five women referred for hysteroscopy and diagnosed with CE.
Intervention(s): Three-minute recording of transvaginal ultrasound scanning on sagittal uterine plane at periovulatory (cycle days 11–14) and midluteal phase (cycle days 19–22).
Main Outcome Measure(s): Direction and frequency of EW measured by transvaginal ultrasound scan.
Result(s): The direction and frequency of EW were analyzed offline as accelerated (four to eight times normal speed) image sequences using video editing software, and the results were compared with 45 cycling women without CE. The EW pattern was significantly different when comparing the women with CE and controls at both the periovulatory and midluteal phases. During the periovulatory phase, we observed retrograde contractions in 26.7% versus 88%, anterograde in 24% versus 0, opposing in 22.7% versus 12%, not propagated in 13.3% versus 0, and absent in 13.3% versus 0, respectively, in the CE cases versus the control group. During the midluteal phase, we observed not propagated (41.3% vs. 61.3%), opposing (24% vs. 25.4%), absent (16.1% vs. 13.3%), anterograde (13.3% vs. 0), and retrograde (5.3% vs. 0), respectively, in the CE cases versus the control group.
Conclusion(s): Women with CE show altered EW patterns in both the periovulatory and midluteal phases. Altered uterine contractility may aid in explaining the symptoms related to CE such as pain, abnormal uterine bleeding, infertility, and possibly endometriosis. (Fertil Steril® 2015;103:1049–52. ©2015 by American Society for Reproductive Medicine.)
Key Words: Chronic endometritis, endometrial waves, ultrasound, uterine contractility, uterine motility

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The nonpregnant uterus is not a quiescent organ but shows a contractility pattern that varies throughout the menstrual cycle. More in detail, uterine motility is characterized by endometrial waves (EW) (1) originating from the myometrium underneath the endometrium, called the subendometrial myometrium or junctional zone (JZ) (2).

During the menstrual cycle, EW vary in terms of amplitude, frequency, and direction. This is thought to be related to cycle-dependent changes in ovarian steroid levels; accordingly, at the JZ level, the expression of estrogen/progesterone (P) receptors shows a cyclic pattern that nearly completely parallels that of the endometrium (3). During the follicular phase, uterine contractility is stimulated by increasing estrogen serum levels, and the expression of estrogens, oxytocin, PGF2a, endothelin-1, and bradykinin receptors is known to increase. Conversely, in the luteal phase, due to the effects of progesterone, the expression of these receptors is down-regulated, with a consequent decrease in contractile activity (4).

In 2003, van Gestel et al. (5) demonstrated that transvaginal ultrasound (TVS) is a useful tool for studying EW, and they proposed the following classification on the basis of the direction and propagation of the contractions: fundus to cervix (anterograde), cervix to fundus (retrograde), opposing

Received September 23, 2014; revised and accepted January 5, 2015; published online February 11, 2015.
V.P. has nothing to disclose. M.M. has nothing to disclose. R.T. has nothing to disclose. P.C.M. has nothing to disclose. D.D. has nothing to disclose. E.C. has nothing to disclose.
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Fertility and Sterility® Vol. 103, No. 4, April 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.01.007

(conflicting waves starting simultaneously on the fundus and the cervix and meeting in the middle of the uterus), not propagating (myometrial activity starting chaotically from different sites), and absent.

The characteristics of EW patterns show cycle-dependent changes. In particular, anterograde EW predominate in the early follicular phase and are characterized by high amplitude and frequency. During the periovulatory phase, EW are mainly retrograde; during the secretory phase EW activity is nearly absent (6). From a physiologic and clinical point of view, it has been speculated that anterograde EW are finalized to empty the uterine cavity during the menstrual and early proliferative phases. Retrograde EW may be associated with the active transport of sperm from the vagina to the fallopian tubes whereas the quiescent status in the luteal phase may facilitate the process of embryo implantation (6–9).

In clinical terms, chronic inflammation may alter contractility patterns in hollow organs such as the bowel and bladder, inducing hypercontractility and dyskinetic conditions. This in turn alters the function of these organs, resulting in many pathologic states such as diarrhea, constipation, malabsorption, and dysuria (10, 11). Similarly, a chronic inflammation of the uterus could affect its motility.

Chronic endometritis (CE) is a poorly known entity consisting of a chronic inflammation of the endometrial lining (12). The most frequently involved agents are common bacteria and mycoplasma (13, 14). The gold standard for the diagnosis of CE is histology. Diagnosis is based on the presence of an inflammatory infiltration containing plasma cells in endometrial biopsy samples (15). We have demonstrated that fluid hysteroscopy provides a reliable diagnosis based on the presence of subtle signs like hyperemia, stromal edema, and presence of micropolyps (14, 16).

From a clinical standpoint, in most of cases, CE is a subtle pathology with aspecific symptoms such as abnormal uterine bleeding, pelvic pain, leukorrhea, or dyspareunia. Despite its mild symptomatology, CE is a frequent finding in women who experience repeated spontaneous abortions, and it may hamper reproductive capacity in spontaneous as well as in vitro fertilization (IVF) cycles. Moreover, CE was identified in 30.3% of patients who had repeated implantation failure at IVF, and a diagnosis of CE was associated with lower implantation rates (11.5%) after IVF cycles (17).

There is a lack of knowledge of pathogenetic mechanisms that link CE and infertility, recurrent miscarriage, repeated implantation failure at IVF. We have postulated that endometrial inflammation could be responsible for altered uterine motility, which justifies the association among these conditions. To shed light on these aspects, we evaluated the effect of CE on EW at the JZ in nonpregnant women. For this purpose, we compared the patterns of EW as assessed by TVS in different phases of the menstrual cycle in women who had received a diagnosis of CE and in women with no hysteroscopic/histologic evidence of CE.

MATERIALS AND METHODS

In the period of March 2012 to December 2013, we selected 45 women referred for hysteroscopy to the Obstetrics and Gynecology Department University of Bari in Italy who had received a diagnosis of CE. The indications for hysteroscopy were infertility (42.3%), recurrent miscarriage (35.5%), and abnormal uterine bleeding (22.2%). As the control group, 45 age-matched women with no evidence of CE at hysteroscopy and biopsy were enrolled. In the control group, the indications for hysteroscopy were infertility (56.3%), recurrent miscarriage (15.5%), and abnormal uterine bleeding (28.2%). Women of both groups had been hormone and drug-free for at least 2 previous months. They were nonsmokers, were not alcoholics, and showed no uterine or adnexal pathology at TVS. None had ever undergone previous pelvic surgery (Table 1).

The diagnosis of CE at fluid hysteroscopy was based on previously published criteria (14, 16). Briefly, the diagnosis relied on the presence of stromal edema, focal or diffuse hyperemia, and micropolyps. In all cases, histology confirmed the presence of CE assessed via eye-guided endometrial biopsies performed during hysteroscopy. The histologic diagnosis was performed upon the detection of stromal infiltrate dominated by plasma cells and of "spindle cell" changes in the endometrial stroma (15).

Before receiving any treatment and within 3 months after hysteroscopy, the women of both groups were referred for the TVS evaluation of the EW pattern during the periovulatory (days 11–14) and midluteal (days 19–22) phases of the same cycle. By using a 7.5-MHz transvaginal probe (Aloka Alfa-10), first we assessed the phase correspondence; in other words, the periovulatory period showed the presence of a Graafian follicle (>18 mm) with a trilaminar endometrial pattern of at least 7 mm thickness; the luteal phase showed a corpus luteum and a hyperechogenic endometrium. The uterus then was scanned on sagittal plane for 3 minutes, and the movies were recorded in digital format. All echographic studies were performed by one author (V.P.).

TABLE 1

Main clinical data of patients affected by chronic endometritis and controls.

Characteristic	CE (n = 45)	Controls (n = 45)	*P* value
Age (y)	30.4 ± 4.5	30.2 ± 3.5	.18[a]
Menstrual cycle length (d)	28.4 ± 0.9	28.2 ± 0.7	.23[a]
Parous	13	45	<.0001[b]
Smoking	No	No	–
BMI (kg/m^2)	21.06 ± 2.9	22.13 ± 3.4	.11[a]
Indication for hysteroscopy			
Infertility	42.3%	56.3%	
Recurrent miscarriages	35.5%	15.5%	
AUB	22.2%	28.2%	

Note: Values are expressed as mean ± standard deviation. AUB = abnormal uterine bleeding; CE = chronic endometritis; BMI = body mass index.
[a] Student's *t* test, *P*< .05.
[b] Chi-square test, *P*< .05.

Pinto. Uterine motility in chronic endometritis. Fertil Steril 2015.