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ORIGINAL ARTICLE *Infertility*

Decreased pregnancy rate is linked to abnormal uterine peristalsis caused by intramural fibroids

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BACKGROUND: The relationship between fibroids and infertility remains an unsolved question, and management of intramural fibroids is controversial. During the implantation phase, uterine peristalsis is dramatically reduced, which is thought to facilitate embryo implantation. Our aims were to evaluate (i) the occurrence and frequency of uterine peristalsis in infertile women with intramural fibroids and (ii) whether the presence of uterine peristalsis decreases the pregnancy rate.

METHODS: Ninety-five infertile patients with uterine fibroids were examined using magnetic resonance imaging (MRI). Inclusion criteria were as follows: (i) presence of intramural fibroids, excluding submucosal type; (ii) no other significant infertility factors (excluding endometriosis); and (iii) regular menstrual cycles, and MRI performed at the time of implantation (luteal phase day 5–9). The frequency of junctional zone movement was evaluated using cine-mode-display MRI. After MRI, patients underwent infertility treatment for up to 4 months, and the pregnancy rate was evaluated prospectively.

RESULTS: Fifty-one patients fulfilled the inclusion criteria, and 29 (57%) and 22 (43%) patients were assigned to the low (0 or 1 time/3 min) or high frequency ($\geq$2 times/3 min) uterine peristalsis group, respectively. Endometriosis incidence was the same in both groups. Ten out of the 29 patients (34%) in the low-frequency group achieved pregnancy, compared with none of the 22 patients (0%) in the high-frequency group ($P < 0.005$). Comparing pregnant and non-pregnant cases, 4 of 10 patients (40%) and 9 of 41 patients (22%), respectively, had endometriosis (not significant).

CONCLUSIONS: A higher frequency of uterine peristalsis during the mid-luteal phase might be one of the causes of infertility associated with intramural-type fibroids.

Key words: uterine fibroma / cine magnetic resonance imaging / uterine peristalsis / infertility / intramural fibroids

Introduction

Uterine fibroids are the most common solid pelvic tumors found in women, and are estimated to occur in 20–50% of women, with increased frequency during the late reproductive years (Verkauf, 1992). Despite this impressive epidemiological burden, the majority of fibroids are asymptomatic and do not require treatment (Somigliana *et al.*, 2007).

In fertility treatment, it is generally accepted that the anatomical location of a uterine fibroid (submucosal, intramural or subserosal), is an important factor in determining the treatment plan (Donnez and Jadoul, 2002). If the fibroids are of the submucosal type, they can be effectively resected with a hysteroscope, which is a less invasive surgical technique. On the contrary, intramural or subserosal lesions should be treated by laparotomy or laparoscopy (Donnez and Jadoul, 2002). However, in some cases myomectomy leads to surgical complications and adhesion formation. In the case of intramural fibroids, patients are required to cease fertility treatment for several months following surgery to allow the uterine scars to heal. However, even with these precautions, scarring has been known to

cause uterine rupture during labor or pregnancy (Somigliana et al., 2007). Moreover, whereas meta-analyses consistently showed a detrimental effect of submucosal but not subserosal fibroids on treatment outcomes, conclusions regarding intramural lesions have been conflicting (Donnez and Jadoul, 2002; Somigliana et al., 2007). Therefore, management of intramural fibroids continues to be difficult and discordant. To address this problem, we decided to examine the mechanisms through which fibroids may influence fertility.

Although the mechanism by which fibroids may reduce fertility is uncertain, it is believed that fibroids might interfere with embryo implantation (Richards et al., 1998). This detrimental effect on implantation may be mediated by the occurrence of abnormal uterine contractility (Fujiwara et al., 2004; Somigliana et al., 2007), but as far as we know there have been no comprehensive studies regarding intramural fibroids, infertility and uterine contractility.

During the implantation phase, it is well known that uterine peristalsis is dramatically reduced, which is thought to aid in implantation of the embryo in the endometrium (Fanchin et al., 1998; Togashi, 2007; Fanchin and Ayoubi, 2009). Recent major changes in ultrafast magnetic resonance imaging (MRI) techniques have enabled acquisition of serial images, at intervals of only a few seconds. The cine mode display (cine MRI) of these sequential images enables direct visualization of uterine contractility (Togashi, 2007). Using a cine MRI display, we have confirmed that no uterine corporal peristalsis was noted in the healthy volunteers during the mid- and late-luteal phases (Orisaka et al., 2007). However, in the pilot study, we have also revealed that three out of five patients who have intramural fibroids showed uterine peristalsis during the time period of the implantation window (luteal phase day 5–9) (Orisaka et al., 2007). The aims of this study are to evaluate the following: (i) the occurrence and frequency of uterine peristalsis in infertile women with intramural uterine fibroids; and (ii) whether the presence of uterine peristalsis decreases the pregnancy rate.

Materials and Methods

A total of 95 patients with uterine fibroids who desire pregnancy were examined by MRI between September 2008 and October 2009 at four hospitals (Teikyo University Mizonokuchi hospital, Keio University, Fukui University and Takinogawa clinic) after obtaining approvals from the ethics committee at each institute. Among 95 subjects, 51 fulfilled the following inclusion criteria: (i) they had intramural fibroids without submucosal type; (ii) in advance of the MRI test, all patients underwent screening for infertility factors at each hospital; (iii) MRI was performed during the time of the implantation window (luteal phase day 5–9).

Patients had no other significant infertility factors (excluding endometriosis) in the screening test, i.e. anovulation, corpus luteum insufficiency, tubal disease or abnormal semen analysis of the partner. In detail, patients had regular menstrual cycles of about 28 days and basal levels of serum FSH, LH and prolactin on menstrual cycle day 3–5 were within the normal range (criteria: FSH 3.5–12.5 mIU/ml, LH 2.4–12.6 mIU/ml and prolactin 4.9–29.3 ng/ml). Serum estradiol and progesterone concentrations in the mid-luteal phase were above 100 pg/ml and 10 ng/ml, respectively. Patients showed no tubal obstruction in the hysterosalpingography test. Sperm concentration of the partner was above 20×10^6/ml (World Health Organization, 1992). After the screening tests, the functional status of the ovaries was monitored using a basal body temperature (BBT) chart. An analysis of BBT graphs was carried out, where a rise in temperature of at least 0.2°C above the preceding 6 days (and occurring in <48 h) which is sustained for at least 11 days would indicate that ovulation had occurred (Ayres-de-Campos et al., 1995). All patients included in this study showed unequivocal biphasic cycles in their BBT chart. We designated the day showing an elevated temperature at least 0.2°C as luteal phase day 1. The implantation window (luteal phase day 5–9) was judged retrospectively using the BBT chart (judged by gynecologists O.Y., M.O., H.O., H.A.).

By routine MRI study, the information retrieved included the location, number and size of fibroids. Also the presence of endometriosis and a distorted uterine cavity was examined. The conditions for cine MRI have been described elsewhere (Orisaka et al., 2007). MRI studies were performed using a 1.5-T magnet unit (MRI machine from Siemens Medical Systems at Takinogawa clinic or from GE Healthcare at Teikyo University, Keio University and Fukui University) with a six channel array coil. Under quiet respiration, a total of 30 serial images were obtained by single-shot fast spin-echo sequence [repetition time (TR)/echo time (TE) = 6000/78 ms, field of view = 240 mm, slice thickness = 10 mm, matrix = 256 × 256], every 6 s for 3 min in the mid-sagittal plane of the uterus. All images in one study were summated into one image and displayed sequentially on the cine mode display at 250 ms intervals. Subsequently, conventional axial and sagittal T2 weighted images (T2WIs, TR/TE = 4000–4720/90–111 ms) and axial T1WIs (TR/TE = 400–550/7.0–8.5 ms) were obtained using fast spin-echo techniques to detect endometriosis and uterine fibroids. One radiologist (T.H.) interpreted the images, without knowledge of the patients' menstrual cycle. Evaluated points included (i) perception of movement of the junctional zone on the cine mode display, (ii) frequency of that movement, if perceivable, (iii) the presence or absence of endometriosis and (iv) the location and number of uterine fibroids. Patients were divided into two groups based on the frequency of uterine peristalsis; <2 times/3 min (low-frequency group) and ≥2 times/3 min (high-frequency group), as described (Togashi, 2007). After receiving MRI, the patients underwent treatment for infertility at each hospital for up to 4 months. Briefly, ovulation induction was performed without use of drugs (natural cycle), or with clomiphene citrate or hMG for 2–3 courses, respectively. Clomiphene citrate (50–100 mg) was started on cycle day 5 for 5 days. HMG (75–150 mIU) was administered on cycle day 3 and continued according to the ovarian response. Depending on the previous ovarian response or the treatment history at a previous hospital, an appropriate treatment was chosen. The size of follicles was checked frequently using transvaginal ultrasound until the diameter of the leading follicle reached 18 mm or greater, and the timing of ovulation was estimated. In some cases, hCG at a dose of 5000 IU was administered. Intrauterine insemination (IUI) was performed when motile sperm concentration was $<20 \times 10^6$/ml. Luteal phase support was not provided.

Data for age, period of infertility, number of fibroids and maximum diameter of fibroids in different groups were expressed as median with minimum–maximum range and compared using the Mann–Whitney *U*-test (Statcel software). Additional patient information and results were analyzed by 2 × 2 contingency table analysis. Statistical significance was set at $P < 0.05$.

Results

The distribution of patients, as categorized by peristalsis frequency, is shown in Table I. Among 51 infertility patients harboring intramural fibroids, 29 (57%) and 22 (43%) patients were assigned to the low- and high-frequency group of uterine peristalsis, respectively. Clinical characteristics of patients in both groups are presented in

Table I The distribution of women with infertility categorized by frequency of uterine peristalsis (per 3 min).

Peristalsis frequency (/3 min)	Number of Patients (total 51)
0	19
1	10
2	1
3	6
4	10
5	3
6	2

Table II Patients with intramural-type fibroids were divided into two groups, based on the frequency of uterine peristalsis; <2 times/3 min (low-frequency group) and ≥2 times/3 min (high-frequency group).

	Low-frequency peristalsis	High-frequency peristalsis	
Patients (number)	29	22	
Age (years)	36 (29–41)	37 (29–41)	Median (min–max range) N.S.
Infertility period (month)	24 (3–84)	24 (4–108)	Median (min–max range) N.S.
Infertility (number of patients)			
Primary	20	17	
Secondary	9	5	N.S.
History of IVF (number of patients)			
No	24	18	
Yes	5	4	N.S.

Clinical characteristics of both groups are shown.
N.S., not significant.

Table II: the data are comparable for age, gravida, infertility period and the ratio of patients undergoing IVF treatment.

The MRI study showed that the endometriosis morbidity, the number of fibroids, the maximum diameter of fibroids and ratio of patients having a distorted uterine cavity were the same in both groups (Table III). Uterine fibroids were located only in the corpus uteri and fundus uteri. There was no case of isthmic and cervical fibroma.

After receiving MRI, 6 out of 29 patients in the low peristalsis group and 6 out of 22 in the high peristalsis group underwent hMG treatment, while others had natural cycles (timed intercourse or IUI) or clomiphene citrate treatment (Table IV). IUI was performed in 9 out of 29 patients and 4 out of 22 patients in the low and high peristalsis groups, respectively.

Table III Patients with intramural-type fibroids were divided into two groups, based on the frequency of uterine peristalsis; <2 times/3 min (low-frequency group) and ≥2 times/3 min (high-frequency group).

	Low-frequency peristalsis	High-frequency peristalsis	
Patients (number)	29	22	
Endometriosis (number of patients)			
No	22	16	
Yes	7	6	N.S.
Number of fibroid	2.8 ± 2.8	3.5 ± 3.0	N.S.
Maximum diameter (mm)	53 ± 17	58 ± 21	N.S.
Deformed uterine cavity (number of patients)			
No	14	12	
Yes	15	10	N.S.
Pregnancy			
number of patients (%)	10 (34%)	0 (0%)	$P < 0.005$

Magnetic resonance imaging (MRI) findings and pregnancy rates within 4 months after MRI study are shown.
N.S., not significant.

Ten out of 29 patients (34%) achieved pregnancy in the low-frequency group within 4 months, while none of the 22 patients (0%) in the high-frequency group achieved pregnancy ($P < 0.005$) during the same 4-month period. All conceptions were achieved with non-IVF techniques. As shown in Table IV, seven and three patients achieved pregnancy with natural cycle and clomiphene citrate treatment, respectively. One out of 10 pregnant cases utilized IUI, and others became pregnant with timed natural intercourse.

Discussion

It is well described that the direction and frequency of uterine peristalsis significantly varies during the cycle phases (Fanchin and Ayoubi, 2009). Uterine peristalsis is active during the periovulatory and menstrual phase, and the direction is cervix to fundus during the periovulatory phase and fundus to cervix during the menstrual phase. However, during the luteal phase, uterine peristalsis is barely observed (Togashi 2007, Orisaka *et al.*, 2007; Togashi, 2007). These results support the concept that uterine peristalsis is related to uterine function, namely such activities as sperm transport, embryo implantation and discharge of menstrual blood (Zervomanolakis *et al.*, 2007). With ultrasonography, Fanchin *et al.* examined the uterine peristalsis of infertile patients who do not have uterine abnormalities (Fanchin *et al.*, 1998; Fanchin and Ayoubi, 2009) and demonstrated a negative correlation between the frequency of uterine peristalsis on the day of embryo transfer and pregnancy outcome. Although they recorded uterine peristalsis on luteal phase day 2, not the implantation window (luteal phase day 5–9), they did show that high-frequency

Table IV The distribution of fertility treatment and pregnancy outcome in 51 patients: ovulation induction was performed without drugs (natural cycle), and with clomiphene citrate or hMG.

Ovulation induction	Patients (number)	Pregnancy (number)
Low-frequency group		
Natural		
Timed intercourse	14	7
IUI	5	0
Clomiphene citrate		
Timed intercourse	2	2
IUI	2	1
HMG		
Timed intercourse	4	0
IUI	2	0
High-frequency group		
Natural		
Timed intercourse	11	0
IUI	3	0
Clomiphene citrate		
Timed intercourse	2	0
IUI	0	0
HMG		
Timed intercourse	5	0
IUI	1	0

When motile sperm concentration was $<20 \times 10^6$/ml, intrauterine insemination (IUI) was performed. Data are shown as the number of patients in the low (<2 times/3 min) and high (≥2 times/3 min) frequency uterine peristalsis groups.

endometrial waves on the day of embryo transfer appear to affect the IVF-embryo transfer outcome in a negative manner, perhaps by expelling embryos from the uterine cavity (Fanchin *et al.*, 1998). In a previous study using cine MRI, we found that during the time of the implantation window, although no corporal contractions were noted in healthy volunteers, some patients with intramural-type fibroids exhibited uterine peristalsis (Orisaka *et al.*, 2007).

A critical and still unsolved question is the relationship between fibroids and infertility. Management of the intramural-type fibroid is very controversial in the field of reproductive medicine (Donnez and Jadoul, 2002; Somigliana *et al.*, 2007). Here, we focused on the occurrence of abnormal uterine contractility caused by intramural fibroids, and examined whether this has a detrimental effect on the pregnancy rate in infertility patients. We found that less than half of the patients with intramural fibroids exhibited abnormal uterine peristalsis during the mid-luteal phase. Interestingly, in the high-frequency peristalsis group, no patients achieved pregnancy, while one-third of the patients in the low peristalsis group achieved pregnancy. Comparing the low- and high-frequency peristalsis groups, there is no difference in the number of fibroids, the maximum diameter of the fibroids and the incidence of a deformed uterine cavity (Table III). Also, when comparing pregnant ($n = 10$) and non-pregnant cases ($n = 41$), no difference was found in the number of fibroids, the maximum diameter of the fibroids and the incidence of a deformed uterine cavity (data not shown).

The relationship between abnormal peristalsis and fibroids (i.e. deformation of uterine cavity, number and size) has been unclear. As estrogen induces peristalsis (Mueller *et al.*, 2006), aromatase expression in fibroids (Bulun *et al.*, 2005), which might result in elevated tissue estrogen concentration, could be a contributory factor. Further study is needed to examine this hypothesis.

Endometriosis is one of the most important factors of infertility (Maruyama *et al.*, 2000). In the present study, when comparing pregnant ($n = 10$) and non-pregnant cases ($n = 41$), 4 out of 10 patients (40%) and 9 out of 41 patients (22%) had endometriosis, respectively, and the difference was not significant. Meanwhile, the endometriosis morbidity was comparable between low and high peristalsis groups (Table III). This finding implies that endometriosis has little or no impact on uterine peristalsis at the time of the implantation window, whereas others have found that uterine peristalsis was suppressed during the periovulatory phase in patients with endometriosis (Kido *et al.*, 2007).

We utilized MRI technology to detect uterine peristalsis. With ultrasonography, it is difficult to clearly detect the endometrium because of deformation caused by fibroids. Furthermore, pressing the uterus with a transvaginal transducer may induce uterine contraction (Lesny *et al.*, 1998). Thus, the cine MRI method is favorable for evaluating patients with fibroids.

In the present study, we demonstrate that abnormal uterine peristalsis in the presence of intramural fibroids could be one of the reasons for a decreased pregnancy rate in these patients. Studies are warranted to investigate if myomectomy for patients in the high peristalsis group is a constructive method to normalize uterine peristalsis.

Authors' roles

O.Y., T.H., M.O., H.A., S.O., M.H., H.H., T.F. contributed to the study design, O.Y., T.H., M.O., H.A., S.O., M.F., H.O., Y.S., O.N. executed the study, O.Y., Y.O. performed the analysis, O.Y., Y.O., M.O., S.O. contributed toward drafting the manuscript and H.A., M.H., F.K., Y.Y., Y.T. involved in critical discussion.

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Conflict of interest statement: none declared.

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