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Doppler ultrasound examination of uterine arteries on the day of oocyte retrieval in patients with uterine fibroids undergoing IVF

Ernest Hung Yu Ng[1] and Pak Chung Ho

Department of Obstetrics and Gynaecology, Queen Mary Hospital, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, People's Republic of China

[1]To whom correspondence should be addressed at: Department of Obstetrics and Gynaecology, 6/F, Professorial Block, Queen Mary Hospital, Pokfulam Road, Hong Kong. E-mail: nghye@hkucc.hku.hk

BACKGROUND: There is no consensus as to whether uterine fibroids have any adverse effects on the outcomes of assisted reproduction treatment. This prospective study compared implantation/pregnancy rates of women with and without fibroids undergoing IVF–embryo transfer and measured uterine blood flow indices of the fibroid group. METHODS: Patients who had fibroids that, during transvaginal scanning, were found to be not distorting the endometrial lining were placed in the fibroid group, while patients with normal uteri were controls. Those with previous myomectomy or pedunculated subserosal fibroids only were excluded. All received a standard ovarian stimulation regimen. Doppler ultrasound examinations of uterine arteries were carried out in the fibroid group prior to oocyte retrieval. RESULTS: Similar implantation/pregnancy rates, multiple pregnancy rates and pregnancy outcomes were noted in both groups. In the fibroid group, significantly lower pulsatility index (PI) and resistance index (RI) of the right uterine artery and the average of right and left uterine arteries were found in those failing to conceive than in those patients who subsequently conceived ($P < 0.001$). CONCLUSION: The presence of fibroids not distorting the endometrial lining does not adversely affect implantation and pregnancy rates during IVF–embryo transfer. Significantly lower uterine artery PI and RI were found in non-pregnant women with fibroids than in their pregnant counterparts.

Key words: assisted reproduction/Doppler ultrasound/IVF/uterine fibroids

Introduction

Uterine fibroids are the most common benign tumours found in women and they are present in 20–30% of women, with an increased frequency towards the end of reproductive life (Novak and Woodruff, 1979). Although the role of fibroids as a possible cause of infertility is still the subject of considerable debate (Buttram and Reiter, 1981; Vollenhoven *et al.*, 1990; Ubaldi *et al.*, 1995), myomectomy is often offered to infertile women with fibroids with an intention to improve the chance of spontaneous conception. A recent review (Vercellini *et al.*, 1998) of nine prospective studies on the effect of abdominal myomectomy on infertility suggests that about two-thirds of women with fibroids and otherwise unexplained infertility conceived after the surgery. However, definite conclusions regarding the effectiveness of myomectomy in the management of infertility could not be made because of the lack of comparison with expectant management in these studies.

There are only a few retrospective studies addressing the impact of fibroids on the outcomes of assisted reproduction treatment (ART; Table I). Implantation and pregnancy rates were not impaired in those patients with fibroids not distorting the uterine cavity (Seoud *et al.*, 1992; Farhi *et al.*, 1995; Ramzy *et al.*, 1998; Surrey *et al.*, 2001). In contrast, Eldar-Geva *et al.* and Stovall *et al.* found that patients with intramural fibroids had significantly reduced implantation and pregnancy rates when compared with those without fibroids or with subserosal fibroids only (Eldar-Geva *et al.,* 1998; Stovall *et al.,* 1998). A recent systematic review (Pritts, 2001) suggests that only those fibroids with a submucosal component are associated with adverse outcomes of ART. Therefore, there is still no consensus on whether fibroids have any adverse effects on the success of ART.

Various mechanisms have been put forward to explain the association between infertility and fibroids, including potential effects on sperm transport (Hunt and Wallach, 1974), uterine contractility (Iosif and Akerlund, 1983), endometrial changes (Delighdish and Loewenthal, 1970; Farrer-Brown *et al.*, 1971; Forssman, 1976) and implantation (Stevenson, 1964). Doppler ultrasound examination of uterine vessels is a non-invasive assessment of the uterine blood flow, which may affect uterine receptivity and implantation (Dickey, 1997). The use of Doppler ultrasound in patients with fibroids during ART

Table I. Summary of studies addressing the effect of fibroids on the pregnancy rate during assisted reproduction treatment

Authors	Inclusion criteria	Cycle characteristics	Fibroid position	Pregnancy rate/transfer (%)	
				Fibroid group	Control group
Seoud *et al.*, 1992	Fibroid diagnosed by laparoscopy, HSG or laparotomy	IVF cycles Details not given	Subserosal: 10 Intramural: 1 Submucosal: 0	41.6 (10/24)	29.0 (586/2018)
Farhi *et al.*, 1995	Fibroid diagnosed by P/E, HSG, TVS or hysteroscopy Uterus <12 weeks	IVF cycles Long protocol	Normal cavity: 28 Irregular cavity: 18	22.1 (31/140) Normal cavity: 30.2 Irregular cavity: 9.0	25.1 (32/127)
Eldar-Geva *et al.*, 1998	Fibroid diagnosed by TVS Submucosal: 9	IVF and GIFT cycles Long and short protocol	Subserosal: 33 Intramural: 46	22.6 Subserosal: 34.1 Intramural: 16.4 Submucosal: 10	30.1 (98/318)
Stovall *et al.*, 1998	Fibroid diagnosed by P/E First cycle only Normal cavity confirmed by HSG or TVS	IVF and ZIFT cycles Long protocol	Subserosal: 9 Intramural: 86 Submucosal: 0	37.4 (34/91)[a]	52.7 (48/91)[a]
Ramzy *et al.*, 1998	Fibroid diagnosed by HSG, laparoscopy or TVS Fibroid of <7 cm Normal cavity by TVS	IVF cycles Long protocol	Subserosal: 32 Intramural: 12 Submucosal: 0	45 (18/39)	42 (154/367)
Surrey *et al.*, 2001	Intramural fibroid diagnosed by TVS Normal cavity by hysteroscopy	IVF cycles Long and microdose flare up protocol Day 3 or day 5 transfer	Subserosal: 0 Intramural : 73 Submucosal: 0	50.7 (37/73)	59.2 (261/441)
Ng *et al.*[b]	Fibroid diagnosed by TVS Exclusion of pedunculated fibroids Normal cavity by TVS	IVF cycles Long protocol	Subserosal/intramural: 77 Submucosal: 0	26.0 (20/77)	23.7 (74/312)

[a]Statistically significant.
[b]The only prospective study.
GIFT = gamete intra-Fallopian transfer, HSG = hysterosalpingogram, P/E = physical examination, TVS = transvaginal scan, ZIFT = zygote intra-Fallopian transfer.

may therefore provide insight into the mechanisms leading to reduced implantation and pregnancy rates in these patients.

The objectives of this study were: (i) to compare the outcomes of women with and without fibroids undergoing IVF–embryo transfer treatment and (ii) to assess the significance of uterine blood flow indices measured by transvaginal Doppler ultrasound on the day of oocyte retrieval in those patients with fibroids.

Materials and methods

Patients attending the Assisted Reproduction Unit at the Department of Obstetrics and Gynaecology, The University of Hong Kong, Hong Kong for IVF–embryo transfer treatment were recruited when the following criteria were met: (i) presence of fibroids; (ii) long protocol of pituitary down-regulation used; and (iii) no distortion of the endometrial lining in both sagittal and coronal planes during transvaginal scanning both on day 2 of the treatment cycle and on the day of HCG injection. Exclusion criteria were: (i) history of myomectomy; (ii) presence of pedunculated subserosal fibroids only; (iii) short protocol of pituitary down-regulation; and (iv) cancellation of oocyte retrieval or embryo transfer. Patients with normal uteri and no history of myomectomy served as controls. Each patient was evaluated only once during the study period.

The details of the long protocol of ovarian stimulation regimen and gamete handling at our centre have been previously published (Ng *et al.*, 2000). All patients were pre-treated with buserelin (Suprecur; Hoechst, Frankfurt, Germany) nasal spray 150 μg four times a day from the mid-luteal phase of the cycle preceding the treatment cycle. On day 2 of the treatment cycle, transvaginal scanning was performed by E.H.Y.N. using a 6.5 MHz vaginal probe (Aloka Model SSD-5500; Aloka Co. Ltd., Tokyo, Japan). The uterus was visualized in both sagittal and coronal planes to determine the presence or absence of fibroids. The length, height and width of the largest fibroid was measured when multiple fibroids were seen. The diameter of the fibroid was the average of length, height and width and its volume was obtained using a formula for the volume of an ellipsoid ($\pi/6 \times \text{length} \times \text{height} \times \text{width}$). Oocyte retrieval was scheduled 36 h after the HCG injection, which was given i.m. when the leading follicle reached 18 mm in diameter and there were at least three follicles >15 mm in diameter. A maximum of three normally cleaving embryos were replaced into the uterine cavity 48 h after oocyte retrieval. Excess good quality embryos were frozen for subsequent transfer.

All Doppler ultrasound examinations of uterine arteries in those patients with fibroids were carried out by E.H.Y.N. at ~09.00 h, after the bladder was empty and prior to oocyte retrieval. Verbal consent was obtained from these patients prior to the Doppler ultrasound examination. Flow velocity waveforms were obtained from the ascending main branch of the uterine artery on the right and left side of the cervix in a longitudinal plane before it entered the uterus. The 'gate' of the Doppler was positioned when a vessel with good colour signals was identified on the screen. The pulsatility index (PI) and resistance index (RI) of the uterine arteries were calculated electronically when three similar, consecutive waveforms of good quality were obtained. Subsequent clinical management was not affected by the information on the blood flow indices, which were stored in the computer and retrieved for analysis only after completion

Table II. Comparison of demographic data between the fibroid group and the control group

Parameters *n* (%)	Fibroid group ($n = 77$)	Control group ($n = 312$)	*P*-value (χ^2-test)
Age[a] (years)	37.0 (30.9–43.1)	35.0 (25.8–40.0)	< 0.001[b]
Primary/secondary infertility	55/22	219/92	NS
Infertility duration[a] (years)	5.0 (2.0–13.0)	5.0 (1.0–13.0)	NS
Causes			< 0.001[b]
Tuboperitoneal	16 (20.8)	79 (25.3)	
Male	12 (15.6)	141 (45.2)	
Endometriosis	31 (40.3)	38 (12.2)	
Unexplained	13 (16.9)	39 (12.5)	
Mixed	5 (6.4)	15 (4.8)	

[a]Values given as median (2.5–97.5th centiles).
[b]Mann–Whitney *U*-test.
NS = not significant.

of the treatment cycle. The intra-observer coefficient of variation was 9.6% for PI and 4.1% for RI.

Statistical analysis

Only clinical pregnancies were considered and were defined by the presence of one or more gestation sacs or the histological confirmation of gestational product in miscarriages. Ongoing pregnancies were those pregnancies beyond 10–12 weeks gestation, at which stage the patients were referred out for antenatal care. Implantation rate was the proportion of embryos transferred resulting in an intrauterine gestational sac.

Patients were classified as those with fibroids (fibroid group) and without (control group). The primary outcome measures were implantation and pregnancy rates. Secondary outcome measures were Doppler indices of uterine arteries between pregnant and non-pregnant patients in the fibroid group. Continuous variables were not normally distributed and were given as median (2.5–97.5 centiles), unless indicated. Statistical comparison was carried out by Mann–Whitney *U*-test, χ^2 test and Fishers' Exact test, where appropriate. A *P*-value (two-tailed) of < 0.05 was taken as significant.

Results

Between February 2000 and April 2001, 389 consecutive patients were recruited: 77 (19.8%) in the fibroid group and 312 (80.2%) in the control group. A single fibroid was found in 57 (74.0%) patients and 20 (26.0%) had multiple fibroids, ranging from two to six in number. The median diameter of the largest fibroid was 2.1 cm (mean 2.4; 2.5–97.5 centiles: 1.0–6.1 cm) and the median volume of the largest fibroid was 5.0 ml (mean 13.7; 2.5–97.5 centiles: 0.5–120.9 ml). No cervical fibroids were seen during the study period.

The patients in the fibroid group were significantly older and had more cycles with endometriosis as the cause of infertility, when compared with the control group (Table II). There were no differences in the type and duration of infertility. Both groups had a similar distribution of cycle attempts and proportion of conventional IVF and ICSI cycles (data not shown).

Despite a significantly higher dosage of gonadotrophin being used in the fibroid than the control group (Table III), no significant differences were shown in the basal FSH level, duration of gonadotrophin administration, serum estradiol level, number of oocytes obtained/fertilized and number of embryos cleaving/frozen between the two groups. The endometrial lining was significantly thicker in the fibroid group than the control group (median 13.0 versus 12.0 mm; $P = 0.014$, Mann–Whitney *U*-test). Both groups had a comparable number of embryos transferred, and similar pregnancy and implantation rates, multiple pregnancy rates and pregnancy outcomes (Table IV). Pregnancy rates were similar for different causes of infertility (data not shown).

In the fibroid group, significantly lower PI and RI of the right uterine artery and the average of right and left uterine arteries were noted in patients who failed to conceive than those who subsequently conceived (Table V). There were again no significant differences in demographic data, ovarian response, endometrial thickness and number of embryos replaced between pregnant and non-pregnant patients in the fibroid group (data not shown). Uterine artery PI and RI were not correlated with the age of the women, duration of infertility, volume of the largest fibroid, serum estradiol level on the day of HCG injection and number of oocytes obtained. A significant difference ($P = 0.04$) between the right and left uterine artery PI and RI was also found in non-pregnant patients of the fibroid group and similar number of follicles were aspirated from each side in these non-pregnant patients.

Discussion

This is the first prospective study examining the impact of fibroids on the success of ART, as other relevant reports were retrospective in nature (Seoud *et al.*, 1992; Farhi *et al.*, 1995; Eldar-Geva *et al.*, 1998; Ramzy *et al.*, 1998; Stovall *et al.*, 1998; Surrey *et al.*, 2001). We could not demonstrate any adverse effect on implantation and pregnancy rates of the fibroid group when compared with the control group. The sample size of this study allowed detection of 9% actual difference in pregnancy rate with a power of 80% at the 5% significance level. Patients in the fibroid group were significantly older and this may have reduced their pregnancy rates. A high dosage of gonadotrophin used in the fibroid group was probably related to older average age in this group. The difference in endometrial thickness between the fibroid

Table III. Comparison of ovarian responses and endometrial thickness between the fibroid group and the control group

Parameters Median[a]	Fibroid group (n = 77)	Control group (n = 312)	P-value (Mann–Whitney U-test)
Basal FSH levels (IU/l)	6.9 (4.1–14.3)	6.4 (3.0–11.0)	NS
Days of gonadotrophin	10.0 (7.0–19.2)	10.0 (7.0–18.0)	NS
Dosage of gonadotrophin (IU)	2175 (1335–5933)	1950 (1200–4680)	0.014
Serum estradiol (pmol/l)	6040 (1408–16787)	6790 (1183–18593)	NS
Endometrial thickness (mm)	13.0 (8.0–21.1)	12.0 (7.0–18.0)	0.014
No. of oocytes aspirated	8.0 (2.0–29.0)	9.0 (2.0–23.4)	NS
No. of oocytes fertilized	5.0 (1.0–17.1)	6.0 (1.0–18.0)	NS
No. of cleaving embryos	5.0 (1.0–17.1)	5.5 (1.0–16.2)	NS
No. of embryos frozen	3.0 (0–12.0)	3.0 (0–13.0)	NS

[a]2.5–97.5th centiles.
NS = not significant.

Table IV. Comparison of treatment outcomes between the fibroid group and the control group

Parameters n (%)	Fibroid group (n = 77)	Control group (n = 312	P-value (χ^2-test)
No. of embryos replaced			NS
One	8 (10.4)	22 (7.1)	
Two	56 (72.7)	254 (81.4)	
Three	13 (16.9)	36 (11.5)	
Pregnancy rate/transfer	20/77 (26.0)	74/312 (23.7)	NS
Implantation rate	22/159 (13.8)	92/638 (14.4)	NS
Multiple pregnancy rate	3/20 (15.0)	19/74 (25.7)	NS
Pregnancy outcome			NS
First trimester abortion	4 (20.0)	6 (8.1)	
Ectopic pregnancy	1 (5.0)	1 (1.4)	
Ongoing pregnancy	15 (75.0)	67 (90.5)	

NS = not significant.

Table V. Comparison of Doppler indices of uterine arteries on the day of oocyte retrieval between pregnant and non-pregnant patients with intramural fibroids

Parameters Median[a]	Non-pregnant (n = 56)	Pregnant (n = 21)	P-value (Mann–Whitney U-test)
Right uterine artery			
PI	1.67 (1.04–3.72)	2.29 (1.44–3.73)	0.011
RI	0.80 (0.42–1.20)	1.00 (0.74–6.79)	0.001
Left uterine artery			
PI	2.01 (0.87–3.85)	2.11 (1.50–3.74)	NS
RI	0.83 (0.55–1.00)	0.85 (0.76–1.00)	NS
Averaged			
PI	1.91 (1.20–3.74)	2.30 (1.64–3.74)	0.046
RI	0.82 (0.59–1.10)	0.89 (0.80–3.90)	0.012

[a]2.5–97.5th centiles
PI = pulsatility index; RI = resistance index; NS = not significant.

group and the control group is unlikely to be clinically significant because the median values in both groups were within the normal range reported in the literature (Turnbull *et al.*, 1995). The presence of fibroids was also associated with increase in endometrial thickness in post-menopausal women (Gull *et al.*, 2001).

Fibroids can be classified according to their position in relation to the uterus as submucous, intramural or subserosal (Tindall, 1987). A submucous fibroid distorts the uterine cavity and surgical removal is usually advised because of adverse effects on implantation and associated menorrhagia (Vercellini *et al.*, 1998). Significantly lower pregnancy rates were noted during assisted reproduction cycles in those patients with fibroids distorting the uterine cavity (Farhi *et al.*, 1995) or with submucosal fibroids (Eldar-Geva *et al.*, 1998). A normal uterine cavity was confirmed in this study by transvaginal

scanning on both the second day of the treatment cycle and the day of HCG injection. Transvaginal ultrasound examination of the contour of the endometrium is an accurate tool in the identification of submucous fibroids and polyps when compared with hysterosalpingogram and hysteroscopy (Stadtmauer and Grunfeld, 1995).

A fibroid is considered to be intramural when <50% of the fibroid protrudes into the serosal surface of the uterus and normal uterine cavity, whereas a subserosal fibroid has >50% protruding out of the serosa (Tindall, 1987). Intramural and subserosal fibroids were not treated separately in this study and peduculated subserosal fibroids were excluded. The above classification may not be applicable to infertile patients attempting to become pregnant, as the mechanisms leading to infertility in case of fibroids are poorly investigated and understood. The degree of myometrial wall involvement and the extension of fibroids close to the mucsoal surface may be more relevant in infertile patients. These parameters have been poorly described in most imaging studies (Cohen and Valle, 2000). Moreover, there is a lack of consensus in the literature as to exactly how these categories are defined (Bajekal and Li, 2000).

Different methods have been used to document the size of fibroids, including the mean diameter of the largest fibroid (Seoud *et al.*, 1992; Ramzy *et al.*, 1998; Stovall *et al.*, 1998), mean of the sum of all fibroids' diameters (Eldar-Geva *et al.*, 1998; Surrey *et al.*, 2001) and total volume (Surrey *et al.*, 2001). There is a large range in the diameter and volume of the largest fibroid noted in the current study. The mean diameter of the largest fibroid in this study was 2.1 cm, while those reported by others (Seoud *et al.*, 1992; Ramzy *et al.*, 1998; Stovall *et al.*, 1998) were 3–4 cm. This may be related to the prospective nature of this study. Although Surrey *et al.* in a regression model did not find any correlation between the diameter/volume of fibroids and implantation rate, it would be too early to conclude that large fibroids have no adverse effect on the implantation rates (Surrey *et al.*, 2001). Large fibroids were usually excluded from studies (Farhi *et al.*, 1995; Ramzy *et al.*, 1998). Myomectomy is more often performed in patients with large fibroids as symptoms such as dysmenorrhoea, menorrhagia and pressure symptoms tend to be more frequent and severe in these patients (Buttram and Reiter, 1981).

Fibroids may lead to infertility because of obstruction of gamete transport and impaired implantation. IVF–embryo transfer treatment performed on patients with fibroids clearly provides a good model to study the implantation process. During IVF treatment, uterine blood flow measured by Doppler ultrasound is an important factor contributing to uterine receptivity. Patients who become pregnant usually show lower vascular impedance than those who do not. The implantation rate is decreased when uterine artery PI is ⩾3.3–3.5 at the time of HCG administration, oocyte retrieval or embryo transfer (Dickey, 1997). It has also been reported that the chance of pregnancy was maximal when uterine arterial PI was in the range 2.00–2.99 and that lower arterial impedance indices on the day of embryo transfer did not lead to higher pregnancy rates (Steer *et al.*, 1992).

Previous studies (Kurjak *et al.*, 1992; Sladkevicius *et al.*, 1996) indicated that significantly lower PI (range 1.36–2.17) and RI (range 0.74–0.8) were recorded in the uterine arteries of patients with fibroids than in those with normal uteri. Surrey *et al.* measured baseline uterine artery blood flow (PI) during the mid-follicular phase of natural cycles, but could not find any difference between those with and without fibroids (Surrey *et al.*, 2001). A significant difference in uterine artery blood flow exists between natural and stimulated cycles (Coulam *et al.*, 1994; Tekay *et al*., 1996). To the best of our knowledge, we are the first group to examine the uterine blood flow during stimulated cycles of patients with fibroids. In the fibroid group, non-pregnant patients had a significantly lower uterine PI and RI compared with pregnant patients, although a significant overlap existed between pregnant and non-pregnant women.

Our finding was in contrast to data published regarding general IVF patients (Dickey, 1997). We postulate that the presence of fibroids results in significantly reduced uterine PI and RI, but the blood flow towards the endometrium may be compromised because of drainage of blood towards fibroids. Vascularized fibroids showed significantly lower uterine PI and RI than avascularized fibroids (Kurjak *et al.*, 1992). Blood flow to the endometrium was not documented in this study, as the visualization of endometrial colour signals would be difficult in the case of anterior wall fibroids. We have recently demonstrated that excessive levels of serum estradiol (>20 000 pmol/l) may result in suboptimal blood flow to the endometrium, despite very low uterine PI and RI in these group (Basir *et al.*, 2001). There was an increase in the number of subjects demonstrating absent or minimal endometrial colour signals in these excessive responders. The increased blood flow shown by low uterine PI and RI might be directed through the utero–ovarian collaterals to the enlarged ovaries.

In conclusion, the presence of fibroids not seen to be distorting the endometrial lining on transvaginal ultrasound scanning would not adversely affect implantation and pregnancy rates during IVF–embryo transfer treatment. Doppler ultrasound examination prior to oocyte retrieval showed significantly lower uterine PI and RI in non-pregnant women with fibroids than in their pregnant counterparts.

References

Bajekal, N. and Li, T.C. (2000) Fibroids, infertility and pregnancy wastage. *Hum. Reprod. Update*, **6**, 614–620.

Basir, G.S., Lam, T.P.W., Chau, M.T., Ng, E.H.Y., O, W.S. and Ho, P.C. (2001) Colour Doppler analysis of peri-implantation utero–ovarian haemodynamics in women having excessively high estradiol concentrations after ovarian stimulation. *Hum. Reprod.*, **16**, 2114–2117.

Buttram, V.C. and Reiter, R.C. (1981) Uterine leiomyomata: etiology, symptomatology and management. *Fertil. Steril.*, **36**, 433–445.

Cohen, L.S. and Valle, R.F. (2000) Role of vaginal sonography and hysterosonography in the endoscopic treatment of uterine myomas. *Fertil. Steril.*, **73**, 197–204.

Coulam, C.B., Bustillo, M., Soenksen, D.M. and Britten, S. (1994) Ultrasonographic predictors of implantation after assisted reproduction. *Fertil. Steril.*, **62**, 1004–1010.

Delighdish, L. and Loewenthal, M. (1970) Endometrial changes associated with myomata of the uterus. *J. Clin. Pathol*., **23**, 676–680.

Dickey, R.P. (1997) Doppler ultrasound investigation of uterine and ovarian blood flow in infertility and early pregnancy. *Hum. Reprod. Update*, **3**, 467–503.

Eldar-Geva, T., Meagher, S., Healy, D.L., MacLachlan, V., Breheny, S. and Wood, C. (1998) Effect of intramural, subserosal, and submucosal uterine fibroids on the outcome of assisted reproductive technology treatment. *Fertil. Steril.*, **70**, 687–691.

Farhi, J., Ashkenazi, J.A., Feldberg, D., Dicker, D., Orvieto, R. and Rafael, Z.B. (1995) Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. *Hum. Reprod.*, **10**, 2576–2578.

Farrer-Brown, G., Beilby, J.O. and Tarbit, M.H. (1971) Venous changes in the endometrium of the myomatous uterus. *Obstet. Gynecol.*, **38**, 743–745.

Forssman, L. (1976) Distribution of blood flow in myomatous uteri as measured by locally injected 133-xenon. *Acta Obstet. Gynecol. Scand.*, **55**, 101–104.

Gull, B., Karlsson, B., Milsom, I. and Granberg, S. (2001) Factors associated with endometrial thickness and uterine size in a random sample of postmenopausal women. *Am. J. Obstet. Gynecol.*, **185**, 386–391.

Hunt, J.E. and Wallach, E.E. (1974) Uterine factors in infertility: an overview. *Clin. Obstet. Gynaecol*., **17**, 44–64.

Iosif, C.S. and Akerlund, M. (1983) Fibromyomas and uterine activity. *Acta Obstet. Gynecol. Scand*., **62**, 165–167.

Kurjak, A., Kupesic-Urek, S. and Miric, D. (1992) The assessment of benign uterine tumor vascularization by transvaginal color Doppler. *Ultrasound Med. Biol*., **18**, 645–649.

Ng, E.H.Y., Yeung, W.S.B., Lau, E.Y.L., So, W.W.K. and Ho, P.C. (2000) High serum oestradiol levels in fresh IVF cycles do not impair implantation and pregnancy rates in subsequent FET cycles. *Hum. Reprod.*, **15**, 250–255.

Novak, E.R. and Woodruff, J.D. (1979) Myoma and other benign tumors of the uterus. In *Gynecologic and Obstetric Pathology*, 8th edn. W.B.Saunders. Philadelphia, USA, pp. 260–278.

Pritts, E.A. (2001) Fibroids and infertility: a systematic review of the evidence. *Obstet. Gynecol. Surv*., **56**, 483–491.

Ramzy, A.M., Sattar, M., Amin, Y, Mansour, R.T., Serour, G.I. and Aboulghar, M.A. (1998) Uterine myomata and outcome of assisted reproduction. *Hum. Reprod.*, **13**, 198–202.

Seoud, M.A.F., Patterson, R., Muasher, S.J. and Coddington, C.C. (1992) Effects of myomas or prior myomectomy on in vitro fertilization (IVF) performance. *J. Assist. Reprod. Genet*., **9**, 217–221.

Sladkevicius, P., Valentin, L and Marsál, K. (1996) Transvaginal Doppler examination of uteri with myoma. *J. Clin. Ultrasound*, **24**, 135–140.

Stadtmauer, L. and Grunfeld, L. (1995) The significance of endometrial filling defects detected on routine transvaginal sonography. *J. Ultrasound Med*., **14**, 169–172.

Steer, C. V., Campbell, S., Tan, S. L., Crayford, T., Mills, C., Mason, B.A. and Collins, W.P. (1992) The use of transvaginal color flow imaging after in vitro fertilization to identify optimum uterine conditions before embryo transfer. *Fertil. Steril.*, **57**, 372–376.

Stevenson, C.S. (1964) Myomectomy for improvement of fertility. *Fertil. Steril.*, **15**, 367–384.

Stovall, D.W., Parrish, S.B., Van Voorhis, B.J., Hahn, S.J., Sparks, A.E.T. and Syrop, C.H. (1998) Uterine leiomyomas reduce the efficacy of assisted reproduction cycles: results of a matched follow-up study. *Hum. Reprod.*, **13**, 192–197.

Surrey, E.S., Lietz, A.K. and Schoolcraft, W.B. (2001) Impact of intramural leiomyoma in patients with a normal endometrial cavity on in vitro fertilization–embryo transfer cycle outcome. *Fertil. Steril.*, **75**, 405–410.

Tekay, A., Martikainen, H. and Jouppila, P. (1996) Comparison of uterine blood flow characteristics between spontaneous and stimulated cycles before embryo transfer. *Hum. Reprod.*, **11**, 364–368.

Tindall, V.R. (1987) Tumours of the corpus uteri. In *Jeffcoate's Principle of Gynaecology*, 5th edn. pp. 417–444. Butterworths & Co. (Publishers) Ltd., London.

Turnbull, L.W., Lesny, P. and Killick, S.R. (1995) Assessment of uterine receptivity prior to embryo transfer: a review of currently available imaging modalities. *Hum. Reprod. Update*, **1**, 505–514.

Ubaldi, F., Tournaye, H., Camus, M., Van der Pas, H., Gepts, E. and Devroey, P. (1995) Fertility after hysterosocpic myomectomy. *Hum. Reprod. Update*, **1**, 81–90.

Vercellini, P., Maddalena, S., De Giorgi, O., Aimi, G. and Crosignani, P.G. (1998) Abdominal myomectomy for infertility: a comprehensive review. *Hum. Reprod.*, **13**, 873–879.

Vollenhoven, B.J., Lawrence, A.S. and Healy, D.L. (1990) Uterine fibroids: A clinical review. *Br. J. Obstet. Gynecol.*, **97**, 285–298.

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