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Do Uterine Fibroids Affect Outcomes After Ovarian Stimulation And IUI?

Whether uterine fibroids affect pregnancy outcomes has long been debated. Styer et al from Massachusetts General Hospital/ Harvard Medical School investigated the association of non–cavity-distorting fibroids and pregnancy outcomes following ovarian stimulation with intrauterine insemination (OS-IUI) in 900 couples with unexplained infertility. All were participants in the Reproductive Medicine Network's Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation randomized clinical trial.

The women, aged 18 to 40 years, were randomized to receive clomiphene citrate, letrozole or gonadotropin until 4 cycles were completed or pregnancy occurred. All had a normal uterine cavity and at least 1 patent fallopian tube; 102 of the women (11.3%) had fibroids. Compared with the women without fibroids, the women with fibroids were older, were more likely to be African American and had a greater body mass index, higher mean serum follicle-stimulating hormone (FSH) levels, lower anti-Müllerian hormone levels and fewer antral follicles. There were no differences between the 2 groups in previous reproductive history, ovarian response, IUI mean total motile sperm count or endometrial lining thickness on the day of gonadotropin stimulation.

Overall conception rates between the women with and without fibroids did not differ, but clinical pregnancy rates were lower for those with fibroids in treatment cycles during which conception occurred (Table 1). African American women with uterine fibroids were more likely to have a clinical pregnancy loss at <12 weeks. This was not related to fibroid size, which did not differ significantly among racial/ethnic groups and ranged from 0.090 cm^3 to 504.0 cm^3. After adjustments for demographic, reproductive and treatment cycle factors, no differences were found between the groups for conception, clinical pregnancy, pregnancy loss or live-birth outcomes.

Conclusions and Clinical Implications

The findings of this study provided assurance that the presence of non–cavity-distorting fibroids does not affect live-birth outcomes. However, the clinical pregnancy rates following conception were lower than for those without fibroids, and the increased rate of pregnancy loss among African American women with fibroids needs further investigation.

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Table 1. Pregnancy outcomes after OS-IUI

Variable	Fibroids	No fibroids	*p* value
n	102	798	
Conception	37/102 (36.3)	296/798 (37.1)	.872
Clinical pregnancy among cycle with conception	22/37 (59.5)	237/296 (80.1)	.005
Fetal plurality			
Singleton pregnancy	19/37 (51.4)	189/296 (63.9)	.139
Twin pregnancy	2/37 (5.4)	39/296 (13.2)	.285
Triplet pregnancy	1/37 (2.7)	9/296 (3.0)	>.999
Pregnancy loss	15/37 (40.5)	93/296 (31.4)	.264
<12 wk	15/15 (100.0)	80/91 (87.9)	.357
≥12 and <24 wk	0/15 (0.0)	11/91 (12.1)	
Extrauterine pregnancy			
Ectopic	4/37 (10.8)	17/296 (5.7)	.271
Heterotopic	0/37 (0.0)	0/296 (0.0)	–
PUL	2/37 (5.4)	1/296 (0.3)	.034
Live birth	21/37 (56.8)	202/296 (68.2)	.161
<37 wk	2/21 (9.5)	39/201 (19.4)	.381
≥37 wk	19/21 (90.5)	162/201 (80.6)	

Combined treatment arms (clomiphene citrate, letrozole, gonadotropins). Data are presented as number of patients/total number (%). The χ^2 or Fisher exact test was used for categorical variables. PUL, *pregnancy of unknown location.*

Styer AK, Jin S, Liu D, et al; National Institute of Child Health and Human Development Reproductive Medicine Network. Association of uterine fibroids and pregnancy outcomes after ovarian stimulation–intrauterine insemination for unexplained infertility. Fertil Steril 2017;107:756-762.

Steroid and Antibiotic Use Before Embryo Transfer

Administering corticosteroids and/or antibiotics to women before embryo transfer (ET) has become routine at many in vitro fertilization (IVF) clinics. The practice stems from the hypothesis that the steroids would protect the embryo against a maternal immune response and the antibiotics would decrease the possibility of vaginal microbes being carried into the uterine cavity during transfer. Most studies that support use of the medications were performed when the standard protocol was to transfer a day-3 embryo at the cleavage stage. Now, however, transfer at day 5 at the blastocyst stage is preferred because of improved pregnancy rates.

To test the hypothesis that there would be no difference in outcomes of ET cycles with and without the medications, Kaye et al from the University of Connecticut reviewed cycles of women treated during the period of 2014 to 2015. Prior to July 2015, standard practice had been to give oral doses of methylprednisolone and doxycycline for 4 days beginning the day of oocyte retrieval or, if frozen embryos were used, for 4 days immediately preceding ET. This practice was then discontinued.

The majority of the 876 ETs had been at the blastocyst stage: 73.5% of the 442 medicated cycles and 88.5% of the 434 unmedicated cycles. The remaining ETs were at cleavage stage. Mean maternal ages at oocyte retrieval of the 2 groups were similar (34.8 years for the medicated group vs 34.1 years for the unmedicated group).

For the medicated group, the clinical pregnancy rate (CPR) was 56.1%; for the unmedicated group, 61.5% (unadjusted odds ratio [OR] 1.25; $p = .10$). Age, number of embryos transferred and stage of ET (day 3 vs day 5) correlated with CPR, while intracytoplasmic insemination vs conventional insemination and use of fresh vs frozen embryos did not. After adjusting for these variables, there was still no difference in CPR between the groups (adjusted OR 1.09; $p = .56$). Also similar were rates of ongoing pregnancy, clinical miscarriage and live birth.

Conclusions and Clinical Implications

This review found no significant difference in IVF outcomes when routine administration of corticosteroids and oral antibiotics before ET was discontinued. Continued use of the medications may be the result of habit rather than evidence-based medicine, and justification for their use needs updating.

Kaye L, Bartels C, Bartolucci A, et al. Old habits die hard: retrospective analysis of outcomes with use of corticosteroids and antibiotics before embryo transfer. Fertil Steril 2017;107:1336-1340.

Impact of Endometriosis On Male Partners

The negative effect endometriosis has on a woman's quality of life has been the subject of considerable research; however, much less attention has been given to the impact on the male partner. Culley et al from De Montfort University, United Kingdom, explored this issue in face-to-face, in-depth, semistructured interviews with 22 couples. All the women (mean age, 34.8 years) had laparoscopically diagnosed endometriosis and symptoms for ≥1 year. Their partners ranged in age from 25 to >50 years (mean age, 36.3 years); 9 couples had been in their relationship ≤5 years, the others for ≥6 years.

The interviews showed that endometriosis had a profound effect on sex and intimacy. Eleven couples reported sex to be rare or nonexistent; another 7 reported reduced frequency. This was related not only to dyspareunia but also to the woman's general fatigue, reduced sexual desire as a result of medication, low mood, stress from trying to get pregnant, bleeding during or after sex, and feeling generally unattractive and unfeminine.

Men were hesitant about approaching their partners to initiate sex. However, only 5 men regarded the lack of sex as a very significant problem for them; 12 stated they had accepted the situation, but 3 couples said the lack of sex had led to tensions and arguments. Eighteen couples reported that endometriosis had affected their plans about having children; 9 experienced fertility problems and sought investigation and/or treatment.

When asked about other areas of life, several men reported that endometriosis affected their employment in some way. Both men and women mentioned an impact on household income from the loss or reduction of the woman's earnings and the additional costs associated with hospital treatment and/or in vitro fertilization.

The couples also reported that the men provided emotional support. Men described their roles as involving caring, listening, understanding and "being there." Despite the negative ways in which endometriosis affected them, some men described how living alongside the condition had enabled them to become more sympathetic people and better partners. Others felt it had strengthened their relationship. Most of the men mentioned that the interview was the first time they had been asked about endometriosis and given the chance to articulate their experience.

Conclusions and Clinical Implications

The authors concluded that endometriosis can have a significant impact on the women's male partners, affecting several areas of life in various ways. There appeared to be a lack of support to help the men deal with the effects, which indicates that health care services, as well as support and information resources, should be offered to affected partners and couples.

Culley L, *Law* C, *Hudson* N, *et al*. A *qualitative study of the impact of endometriosis on male partners*. Hum Reprod 2017;32:1667-1673.

Frozen Vs Fresh Embryo Transfer

Although frozen embryo transfer has become increasingly common, few studies have compared the outcomes of freeze-only protocols with those of fresh embryo transfer. Wang et al from Stanford University School of Medicine, California, conducted a retrospective matched cohort study of patients from 12 fertility treatment centers across the United States.

Each cohort comprised 1455 cycles matched for similar distributions of clinical and treatment characteristics. The women's average age was 34.1 years. All had undergone controlled ovar-

Table 2. Pregnancy outcomes in matched data

Outcome	Fresh (%)	Freeze-only (%)	*p* value
Ongoing pregnancy rate	45.3 (42.7–47.9)	52.0 (49.4–54.6)	<.001
Implantation rate	42.0 (39.5–44.5)	46.8 (44.2–49.4)	<.01

Values in parentheses are 95% confidence interval.

Table 3. Ongoing pregnancy rates comparison between freeze-only and fresh cycles by progesterone (P) concentration and age

P at trigger	Age (y)	Fresh		Freeze-only		*p* value
		n	OPR (%)	*n*	OPR (%)	
≤1.0 ng/mL	≤35	302	56.4 (51.6–61.2)	284	54.6 (49.7–59.5)	.61
	>35	203	45.1 (39.8–50.5)	198	48.9 (43.5–54.3)	.33
>1.0 ng/mL	≤35	576	46.1 (42.3–49.9)	578	54.1 (50.3–57.9)	<.01
	>35	374	35.2 (31.0–39.5)	395	48.4 (44.0–52.8)	<.0001

Values in parentheses are 95% confidence intervals. OPR, *ongoing pregnancy rates.*

ian stimulation using various standard protocols according to established practice at the particular clinic. Oocytes retrieved transvaginally 35 to 36 hours after human chorionic gonadotropin or leuprolide acetate trigger administration were fertilized by either conventional in vitro fertilization or intracytoplasmic sperm injection.

The embryos were cultured to the blastocyst stage, then either transferred into the uterus or cryopreserved and transferred at a subsequent natural cycle or one induced by estrogen and progesterone supplementation. Among the indications for freeze-only cycles were premature progesterone elevation, patient preference and ovarian hyperstimulation syndrome.

The main outcome measures were the rates of implantation and ongoing pregnancy. Statistical analysis found the overall implantation and ongoing pregnancy rates to be significantly higher in the freeze-only cohort compared with the fresh-transfer cohort; the ongoing pregnancy rates differed by 6.7% (Table 2).

When analysis was stratified by age and progesterone concentration on the day of trigger, it showed that the difference in ongoing pregnancy rate depended on progesterone concentration at trigger (Table 3), but maternal age did not play a significant role. At concentrations of ≤1.0 ng/mL, the odds of ongoing pregnancy were not significantly different between the 2 cohorts:

- ≤35 years; odds ratio (OR) 0.93; 95% confidence interval (CI), 0.70–1.23; $p = .61$
- >35 years; OR 1.17; 95% CI, 0.86–1.58; $p = .33$

When the concentration of progesterone was >1.0 ng/mL, the odds of ongoing pregnancy were significantly higher for the freeze-only cohort:

- ≤35 years; OR 1.38; 95% CI, 1.11–1.71; $p < .01$
- >35 years; OR 1.73; 95% CI, 1.34–2.24; $p < .0001$

A sensitivity analysis suggested a trend in women with higher concentrations of progesterone toward more successful outcomes for freeze-only protocols in older women.

Conclusions and Clinical Implications

This retrospective multicenter study of matched cohorts showed significantly higher rates of implantation and ongoing pregnancy with the transfer of freeze-only embryos than of fresh embryos. It further suggested that freeze-only protocols may be particularly beneficial for women >35 years old who have a premature rise in progesterone. However, as the authors pointed out, other elements have to be considered when deciding on the best protocol for a particular patient. Prospective randomized clinical trials would provide more information.

Wang A, Santistevan A, Hunter Cohn K, et al. Freeze-only versus fresh embryo transfer in a multicenter matched cohort study: contribution of progesterone and maternal age to success rates. Fertil Steril 2017;108: 254-261.