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Original Article

Pregnancy-related leiomyoma growth and pregnancy complications in pregnant women after IVF

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Abstract: Ovarian stimulation during in vitro fertilization (IVF) needs different medicaments. With this treatment, it may result in the growth of a leiomyoma however, the evidence is unclear. Further, the effect of a leiomyoma on pregnancy outcome is still vague. This study aims to provide accurate information on the possibility of intramural leiomyoma growth during pregnancy after IVF and identify adverse pregnancy outcomes related to the growth of leiomyomas. This prospective cohort study was set up with all single fetus pregnancies with at least one intramural leiomyoma at the Xiangya Hospital was from 1st May 2017 to 1st May 2019. The information was collected through questionnaires and hospital records. We compare the size of the leiomyoma and pregnancy complications between the two selected groups; group (A) consisted of women who got pregnant through IVF and group (B) consisted of women who had spontaneous pregnancies and thus acted as the control group. We observed that the growth of leiomyomas in group A was considerably higher, particularly during the first trimester of pregnancy (2.3 ± 1.267 vs. 3.06 ± 1.751; p 0.024). Also, higher occurrence of pregnancy complications such as preterm birth (47% vs. 20%), cesarean birth (80.5% vs. 69.4%) and postpartum hemorrhage (26% vs. 12%) were found in group A. The intramural leiomyomas were enlarged during initial pregnancy after IVF compared to spontaneous pregnancy, in particular before 14 weeks and this may be related to the IVF medicaments.

Keywords: Pregnancy, IVF, pregnancy outcome, leiomyoma size

Introduction

The expressions: ("leiomyoma", "Uterine fibroids", "myoma", "fibromyoma", "hysteromyoma", "fibroma") are all synonymous [1]. However, the term "leiomyoma" is used in the present classification system [2]. It is the most frequently occurring tumor in the uterus and female genital tract, with a very wide-range of incidence from 5.4% to 77% [3], and 0.1% to 11% during pregnancy [3]. Data on epidemiologic factors about leiomyoma risk are only partly elucidated [4, 5]. They include genetic and demographic characteristics [6], age, nulliparity, and body mass index (BMI) [1]. It is worthwhile to note that women experiencing IVF treatments may surpass 25% of leiomyoma cases [7].

Leiomyomas are asymptomatic in most patients (80%). On the other hand, when symptoms occur, leiomyomas can negatively affect quality-of-life [8, 9]. Although the previous study demonstrated that during pregnancy a leiomyoma may negatively impact pregnancy outcomes [4], further studies are required to clarify the effect. Besides, controversy exists regarding the impact of the leiomyoma on IVF outcomes and ongoing pregnancy [10-12].

Considering the increasing prevalence of leiomyomas in the pregnancy period, especially in cases of infertility that require IVF [1, 13], it is vital to acquire accurate knowledge on the possibility of such tumor growth after IVF cycles or during pregnancy, to make good decisions regarding IVF and prenatal counseling. Thus this study sought to provide accurate information on the possibility of intramural leiomyoma growth during pregnancy and after IVF cycles, and identify adverse pregnancy outcomes related to the growth of leiomyomas.

Materials and methods

Study design

The prospective cohort study of pregnant women with intramural leiomyomas was conducted at the Department of Obstetrics in Xiangya Hospital, China, from 1st May 2017 to 1st May 2019. To reach the objective of our study, all individual fetus pregnancies with at least one intramural leiomyoma were included. The presence of a leiomyoma was confirmed through an ultrasound examination. Data were collected using questionnaires and information was gathered on the expected obstetric and neonatal outcomes from the maternity database and chart reviews.

Inclusion criteria

Singleton pregnancies between 6 weeks gestational age and full term with at last one visible intramural leiomyoma, which didn't impair the endometrium were considered.

Exclusion criteria

Patients with leiomyoma encroaching on the cavity of the uterus, patients with difficulty with ultrasound to evaluate the characteristics of the leiomyoma, or if there was any suspected adenomyosis, patients who previously underwent myomectomy, or there wasn't any visible intramural leiomyoma during pregnancy, and multiple fetus pregnancies.

Procedures, variables assessment, and statistical analysis

The two groups of pregnant women (after IVF and spontaneous pregnancy) were recruited and compared. The case group (group A) had women with leiomyomas still reaching a viable pregnancy as affirmed by βHCG test positive and ultrasound examination after 5 weeks of embryo transfer (ET); and control group (group B) had natural intercourse related pregnant women with leiomyomas still achieving a viable pregnancy and being 6 weeks from the first day of the last period. Control women were matched to case women during the study period. The investigation during pregnancy was done by physicians with specific practice in obstetric sonography. The analysts received informed consent from all recruited patients.

Patients who were selected in group A underwent a serial ultrasound and hormonal test during the IVF cycle. Besides, these patients underwent suitable ovarian stimulation protocol, either a standard long protocol (18 women, 46.2%) or a short protocol (21 women, 53.8%). The mean ± SD duration of ovarian stimulation was 10.1 ± 2.3 days.

The change in the size of leiomyoma was analyzed at five different times as follows: (1) before pregnancy or IVF cycle, (2) 14 weeks (end of the first trimester), (3) 27 weeks (end of the second trimester), (4) before birth (end of the third trimester), and (5) 4 weeks after birth [14]. The sonographic appearance of the leiomyoma was characterized as symmetrical, well-characterized, hypoechoic and heterogeneous masses [15]. We classified leiomyomas which distorted the cavity line as submucosal and as mentioned earlier, any pregnancy with these lesions was excluded from the study. Also, the period of our study was divided into four subperiods: subperiod "a" (before pregnancy or IVF treatment to 14 weeks), subperiod "b" (from 14 weeks to 27 weeks), subperiod "c" (from 27 weeks to birth), and subperiod "d" (from birth to 4 weeks after birth). When an individual had more than one leiomyoma, the study focused on the dimensions of the largest leiomyoma during growth pattern analysis. A leiomyoma was considered unchanged if its size at the next scan was within ± 10% of the last measurement. Selected women did not experience surgery for their leiomyoma between the two examinations before birth. The mean ± SD time between the two echographic evaluations was 4.6 ± 3.4 months.

The main outcome measures were the size (cm) of the leiomyoma with obstetric and neonatal outcomes. The growth of the intramural leiomyoma, was calculated and the change in leiomyoma size (cm) and defined as follows: (1) increased leiomyoma, if it grew by ≥ 10% of its original size (cm) from the first scan; (2) stable leiomyoma, if the leiomyoma size stayed within ± 10% of its original size from the first scan; (3) decreased leiomyoma, if the leiomyoma size decreased by ≥ 10% of its original size from the first scan; and (4) disappeared leiomyoma, if at follow-up scans of the leiomyoma could not identified or distinguish it in the uterus anymore [16]. Univariate evaluation and multivariate logistic regression evaluation were per-

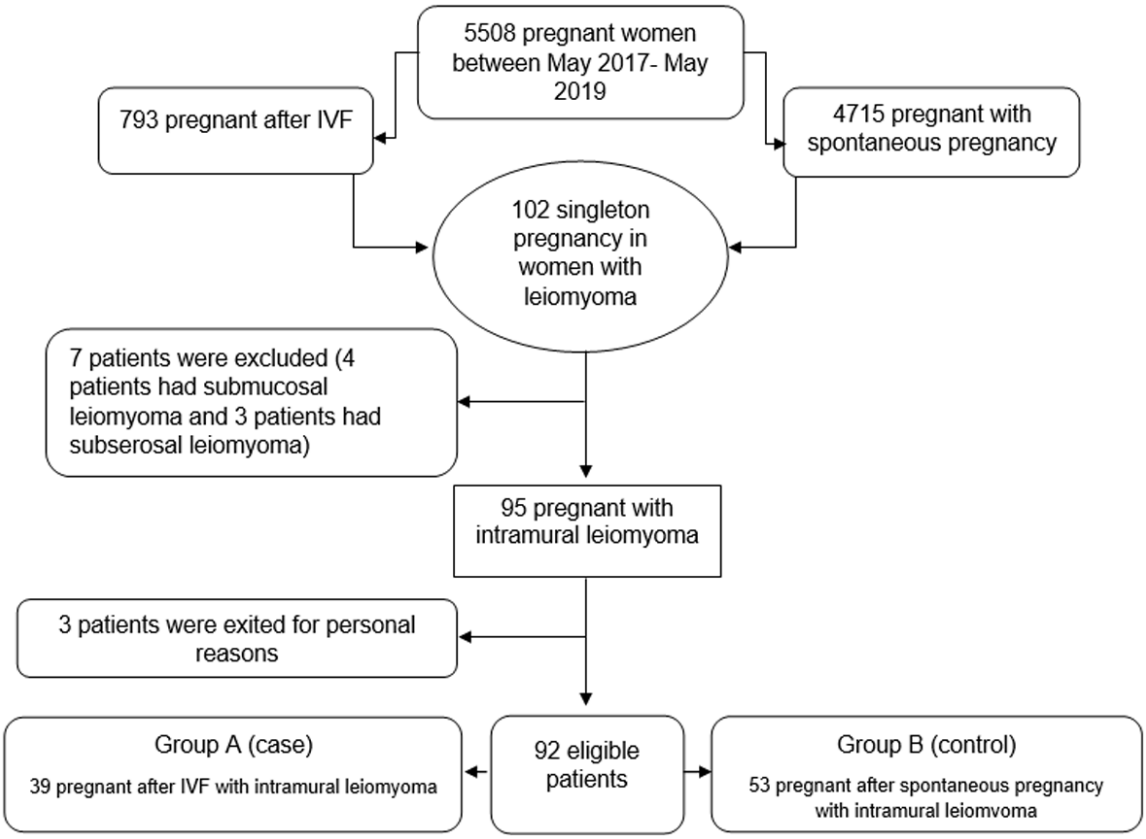

Figure 1. The flow diagram of the study.

formed. Obstetric and neonatal outcomes included mode of birth, miscarriage, preterm birth (PTB) (< 37 weeks), post-operative bleeding, premature rupture of membranes (PROM), and intrauterine growth restriction (IUGR). All procedures in this study followed the ethical standards of the hospital.

The collected data were analyzed using SPSS software, version 22. We used the chi-square (X^2) test for dichotomous data and Student t-test for continuous data. The results were expressed in mean ± standard deviation ($\bar{x}$ ± SD), a *p*-value < 0.05 was considered statistically significant. The chi-square test was used to compare the pregnancy complications between the two groups under 99% confidence level (C.L). All tests of hypothesis were two-tailed with a type 1 error rate fixed at 5%.

Ethical approval

The scientific research project approval was acquired from the Medical Ethics Committee of Xiangya Hospital of Central South University, with scientific research project approval number: 201612804, date: 31/12/2016.

Results

Demographic and morphological characteristics

The total number of pregnant women recruited for the study was (n=5508). Out of this, 4715 pregnant women naturally arising pregnancy while 793 were due to IVF. There were 102 individual pregnancies with leiomyomas that were initially considered, thus the prevalence of leiomyomas during pregnancy amounted to 1.9% of all patients in the study. Seven patients were later excluded (4 due to submucosal leiomyoma and 3 due to subserosal leiomyoma). Therefore, 95 patients were competent. Three patients were further removed from the study for personal reasons. Overall, leiomyomas were found in a cohort of 92 pregnant women. From the eligible 92 patients, 39 women with leiomyomas reaching a viable pregnancy as affirmed by ultrasound examination in 4 weeks after embryo transfer was considered as the case (group A), while 53 women with leiomyomas achieving a viable natural pregnancy were considered control (group B) (**Figure 1**).

Table 1. Obstetric history, demographic data, and morphological characteristics of groups A and B

Characteristic	Group A N=39 N (%)	Group B N=53 N (%)	*p*-value
Maternal age (years)			
< 35	18 (46.2%)	21 (39.6%)	< .01
≥ 35	21 (53.8%)	32 (60.4%)	
primiparous	10 (25.6%)	10 (18.8%)	< .01
Parity	29 (74.4%)	42 (80.2%)	< .01
BMI (kg/m^2)			
< 25	15 (38.5%)	18 (34%)	
25-30	91 (48.7%)	24 (45.3%)	< .01
> 30	5 (12.8%)	11 (20.8%)	
Preexisting of gestational diabetes	1 (2.5%)	2 (3.8%)	0.02
Previous pre-eclampsia	2 (5.0%)	2 (3.8%)	< .01
Previous PTB	2 (5.0%)	3 (5.7%)	0.05
Smoking	0 (0.0%)	0 (0.0%)	N/A
Drinking alcohol	0 (0.0%)	0 (0.0%)	N/A

Chi-square test. BMI: body mass index, N/A: Not applicable, PTB: preterm birth.

The participants were made up of the Han ethnic group. In total, 60.4% of the patients in group B were in advanced age (> 35 years) as compared to 53.8% in group A. This was without statistical significance as reported in the demographic data of the two groups, morphological characteristics, and obstetric history (**Table 1**).

Change in the size of leiomyoma

Considerable growth of leiomyomas was noticed (**Table 2**), particularly in the first trimester of pregnancies in the two groups (before 14 weeks), with the majority of the growth in group A compared with group B (*p*-value 0.024). For instance, in group A the mean diameter of leiomyoma increased from 2.3 to 3.2, the mean ± SD leiomyoma diameter was 2.3 ± 1.267 cm at the first scan; while in group B it rose from 3.06 to 3.9 (3.06 ± 1.751). On the other hand, the size of leiomyoma reduced after birth in group A (3.2 ± 1.6) and B (3.36 ± 1.841) without statistical significance (*p*-value 0.137). These results were found when the change of the leiomyoma size in subperiods between our two groups was compared (**Table 3**). We found a measurably significant distinction between subperiod (a) and subperiod (b), especially in group A, (-0.8872 ± 0.5961) and (-0.268 ± 0.33) respectively. This illustrated that the main increase in the size of leiomyomas occurred before 14 weeks of gestation. The results also, indicated that the size of leiomyoma in subperiod (d) was lower than (c) in both groups.

Pregnancy complications

Regarding the pregnancy complications (**Table 4**), our study compared the complications and risks between the groups with their respective diameters of the leiomyomas. The results confirmed that there was an increase in pregnancy complication especially PTB (*p*-value: 0.05), PROM (*p*-value: 0.01), miscarriage (*p*-value: 0.01), IUGR (*p*-value: 0.01), postoperative bleeding (*p*-value: 0.05), and cesarean birth in pregnancy after IVF compared to natural pregnancy. Also, the post-operative bleeding was significantly higher in pregnant women who underwent IVF than natural pregnancy (*p*-value: 0.05). This supports the hypothesis that women who underwent IVF with leiomyomas have a higher risk of gestation complications than pregnant women without IVF (OR 1.33 and *p*-value is 0.04).

The study employed subjects who experienced different modes of birth: normal birth mode, cesarean section, and cesarean birth with myomectomy. Only 7 pregnant women (19.4%) in group A and 15 (30.6%) in group B had normal birth modes. There was a significant increase in the caesarian mode of birth in both groups, especially in group A without reaching statistical significance between the two groups (*p*-value 0.3). There were 28 patients in the two groups (30.4%) who experienced myomectomy with cesarean birth (**Table 5**).

Discussion

The current study focused on pregnant women with intramural leiomyomas who achieved pregnancy by IVF and natural pregnancy. This was because these conditions offered us a good opportunity to prospectively obtain accurate information on the change in leiomyoma size and monitor their modifications at an early

Table 2. Compare the change of the size of leiomyoma between groups A and B

Time point	Group A (N=39)			Group B (N=53)			*p*-Value
	n	Mean (SD)	Min, max	n	Mean (SD)	Min, max	
Before pregnancy or IVF	39	2.3 (1.267)	0.3, 5.8	53	3.06 (1.751)	1.2, 9.1	0.024
14 weeks	39	3.19 (1.559)	0.3, 7.8	53	3.913 (2.1)	1.30, 11.60	0.073
27 weeks	36	3.4 (1.7)	0.3, 7.8	49	4.06 (2.213)	1.3, 11.6	0.139
Before birth	36	3.44 (1.69)	0.40, 7.6	49	4.09 (2.229)	1.3, 11.6	0.145
4 weeks after birth	36	3.2 (1.6)	0.40, 7.50	35	3.36 (1.841)	1.3, 8.3	0.137

Chi-square test. IVF: in vitro fertilization.

Table 3. Compare the change of the size of leiomyoma depending on subperiods between groups A and B

Sub-periods	Group A (N=39)			Group B (N=53)			*p*-value
	n	Mean (SD)	min, max	n	Mean (SD)	min, max	
A	39	-0.8872 (0.5961)	-1.08, -0.6939	53	-0.85 (0.84)	-1.08, -0.62	0.02
B	39	-0.268 (0.33)	-0.38, -0.16	50	-0.15 (0.3)	-0.24, -0.06	0.05
C	36	-0.036 (0.09)	-0.067, -0.0057	50	-0.028 (0.0858)	-0.0524, -0.0036	0.07
D	36	0.26 (0.45)	0.1, 0.4	49	0.2531 (0.31)	0.163, 0.3432	0.05

Paired t-test analysis. Subperiod "a" (before pregnancy or IVF to 14 weeks), subperiod "b" (from 14 weeks to 27 weeks), subperiod "c" (from 27 weeks to birth), and subperiod "d" (from birth to 4 weeks after birth).

Table 4. Pregnancy complications in groups A and B

	Miscarriage	IUGR	PTB	PROM	Post-operative bleeding	None
Group A N=39 N (%)	3 (7.6%)	1 (2.7%)	18 (48.6%)	1 (2.7%)	9 (24.3%)	8 (21.6%)
Group B N=53 N (%)	4 (7.5%)	2 (4%)	15 (29.4%)	1 (2%)	8 (15.5%)	25 (49%)
P-Value	0.07	0.01	0.05	0.01	0.05	0.07
Odds Ratio (C.L 99%)	0.05	0.06	0.06	0.05	0.04	0.05

Chi-square test. IUGR: intrauterine growth restriction, PTB: preterm birth, PROM: premature rupture of membrane.

Table 5. Mode of birth in groups A and B

Mode of birth	Group A N=39 N (%)	Group B N=53 N (%)	*p*-value
Normal	7 (19.4%)	15 (30.6%)	0.347
Cesarean	16 (44.4%)	19 (38.8%)	0.35
Cesarean + Myomectomy	13 (36.1%)	15 (30.6%)	0.347

Chi-square test.

stage during pregnancy. The prevalence of leiomyoma during pregnancy after IVF was 4.9% and 1.1% during natural pregnancy in this study. In a previous study, the rates ranged from 0.1% to 11% for natural pregnancy and exceed 25% in IVF treatment [4].

In our study, we noticed that the size of intramural leiomyoma increased in both women who got pregnant after IVF and natural pregnancy. It is of interest that the IVF pregnancy growth rate was stable, with growth typically in the first 14 weeks of pregnancy. Our data were consistent with previous reports on natural pregnancy [14, 17] (**Table 6**) and after IVF cycles [18, 19] (**Table 7**). In contrast, Benaglia [20] indicated that hyper ovulation during the process of assisted fertilization did not change the diameter of intramural and subserosal leiomyomas. Laughlin [21] also found that 36% of pregnant women had no identifiable leiomyoma in the postpartum scan, and 79% of the residual leiomyoma decreased in size. Further, Hammoud [22] noted a lack of size of the tumor during pregnancy. Some studies observed that leiomyomas experienced quickened development during pregnancy due to the impact of hormones but, the early rise in steroid hormones pending early pregnancy may not be enough to demonstrate the process of leiomyoma size change [23]. Other studies also showed that changes in leiomyomas size may

Table 6. Some studies which evaluated the size of leiomyoma during natural pregnancy

Study	N. women with leiomyoma	examination times	Results
Paolo Rosati, Italy-1992 [14]	12 patients	9 to 15 ultrasonographic examinations during pregnancy and 4 months before pregnancy.	Considerable increase in volume (+8%, $P < 0.001$).
Ahmad O Hammoud, USA-2006 [22]	107 patients	Three periods: the first study period (up until 19 weeks), the second (20-30 weeks), and the third (31-42 weeks).	Leiomyoma usually diminishes in volume during pregnancy.
Eze CU, Nigeria-2013 [17]	100 patients	3 scans during the prenatal ultrasound scan.	An expansion in leiomyoma means size from 60 mm to 63 mm between the first scan sequence and the second scan sequence and a decrease from 63 mm to 59 mm in the third survey sequence.

Table 7. Some studies which evaluated the size of leiomyoma before and during pregnancy after IVF cycle

Study	N. women	examination times	Results
B Zeyneloglu, Turkey-2002 [18]	23 patients underwent IVF	Not reported.	Growing leiomyoma during ovarian hyperstimulation may have expanded cellularity or mitosis. Leiomyoma related to fiery cytokines which may affect implantation.
Laura Benaglia, Italy-2010 [20]	72 patients underwent IVF	The sizes of the leiomyoma before and after treatment were compared.	Ovarian hyperstimulation in IVF does not change the size of subserosal/intramural leiomyomas.
Laura Benaglia, Italy-2013 [19]	50 patients underwent IVF	Scan performed the month preceding the stimulation and 4-5 weeks after the embryo transfer.	A statistically significant enlargement was observed just in the pregnant group.

occur as a result of hypertrophy and edema, stretching of the myometrium due to progressive expansion of the amniotic cavity [24]. Generally, during IVF treatment there is a considerable increase in serum E2 (Estradiol) concentration, and needs different medicines for ovarian stimulation. This treatment may take part in the progression of the leiomyoma, but no prof exists in literature regarding this [25]. Although the data suggested that IVF treatment may be a major factor in determining the change in the size of leiomyoma [14, 26], further studies are required to clarify this phenomenon.

Uterine leiomyomas are gradually gaining much attention due to their impact on pregnancy outcomes and female fertility [8, 16]. Bozdag [27] indicated that women with leiomyomas > 4 cm required more IVF cycles to have a continuing pregnancy, compared with women without leiomyomas. In this study, the rate of miscarriages, PTB, PROM, and post-operative bleeding observed in group A was higher than that of group B. These findings were compatible with a previous study [28]. In contrast, Bozdag [27] demonstrated no remarkable differences in pregnancy outcomes and live birth rates in uterine leiomyoma < 4 cm. Although pregnancy outcomes and IVF are most commonly seen with submucosal leiomyoma, whether intramural and subserosal leiomyomas can lead to negative pregnancy outcomes are controversial. Leiomyoma was also found to affect the mode of birth since most of the women with intramural leiomyoma had the cesarean mode of birth, especially in group A, unlike group B where normal delivery dominated. Interestingly, no differences were found between cesarean and cesarean with myomectomy in any size of leiomyoma between the two groups. Thus the presence and growth of intramural leiomyoma impacted pregnancy outcomes, and this effect was greater in IVF pregnancy patients [29]. It was not possible to infer the effects of smoking and drinking on leiomyoma or pregnancy outcomes since the patients assessed did not smoke or drink. Also, as the patients were from the Han ethnic group, it was not possible to infer the effects on other ethnic groups.

This study aimed to be clinically useful to physicians in pre-pregnancy and pre-birth advising of women with leiomyoma and women undergoing IVF process. In our study the patients were homogeneous to evade potential confounders, and only women with single pregnancy either from IVF or in natural pregnancy with visual leiomyomas were studied.

Despite the high-quality data gathered over the past 2 years, our study was challenged with the following limitations. First, among the variables analyzed, less than 1% had missing data. Second, the diagnosis of leiomyomas was only by ultrasound. Third, since leiomyomas may increase after birth, the period of following and evaluating pregnancy with a leiomyoma was not enough. It can be hypothesized that a one year period is not enough to exclude long-term detrimental effects of IVF medicaments on leiomyoma.

Future studies aiming to analyze the long-term effects of ovarian stimulation are recommended to evaluate the effects of IVF medicaments on leiomyoma. Although mechanisms underlying the relationship between leiomyoma and infertility, as well as adverse pregnancy outcomes are still poorly understood, further studies are needed to identify simple techniques to clarify this relationship such as measuring the uterine activity with leiomyoma by intravaginal ultrasound and/or hysterosonography, or even hysteroscopy in each case of leiomyoma before undergoing IVF cycle.

The intramural leiomyomas were enlarged during initial pregnancy after IVF in particular before 14 weeks. These findings suggest that the advisability of ultrasound monitoring pregnancy complications by leiomyoma, particularly during the first weeks of gestation is necessary.

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Disclosure of conflict of interest

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