

## UTERUS

# Effects of the position of fibroids on fertility

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### Abstract

This prospective, controlled study was performed in order to evaluate whether the location of uterine fibroids may influence reproductive function in women and whether removal of the fibroid prior to conception may improve pregnancy rate and pregnancy maintenance. We examined 181 women affected by uterine fibroids who had been trying to conceive for at least 1 year without success. The main outcome measures were the pregnancy rate and the miscarriage rate. Among the patients who underwent myomectomy, the pregnancy rates obtained were 43.3% in cases of submucosal, 56.5% in cases of intramural, 40.0% in cases of submucosal–intramural and 35.5% in cases of intramural–subserosal uterine fibroids, respectively. Among the patients who did not undergo surgical treatment, the pregnancy rates obtained were 27.2% in women with submucosal, 41.0% in women with intramural, 15.0% in women with submucosal–intramural and 21.43% in women with intramural–subserosal uterine fibroids, respectively. Although the results were not statistically significant in the group of women with intramural and intramural–subserosal fibroids, this study confirms the important role of the position of the uterine fibroid in infertility as well as the importance of fibroids removal before the achievement of a pregnancy, to improve both the chances of fertilization and pregnancy maintenance.

**Keywords:** Uterine fibroid, myoma, myomectomy, fertility, fecundability, pregnancy rate

### Introduction

Uterine fibroids are one of the most common benign tumors of the female genital tract [1,2], occurring in 20–50% of women of reproductive age [3]. In 95% of cases the fibroid is localized in the corpus uteri and only rarely in the cervix; usually it is characterized by multiple knots. The presence of uterine fibroids has been connected to fertility problems and many studies have been performed in order to define the correlation between fibroids and infertility. Unfortunately, we still cannot draw definitive conclusions on this matter [2].

Diverse theories have been proposed to explain how uterine fibroids may cause infertility [2,4]. One theory suggests that the hyperestrogenic environment may be responsible for the anovulatory cycles [5]. Pathological changes of the endometrium and myometrium, such as atrophy of the endometrium, elongation and distortion of the glands, cystic glandular hyperplasia, polyposis, endometrial venule ectasia and ulceration, may also determine implantation failure [5,6]. Others

have suggested that myomas may cause dysfunctional uterine contractility which may interfere with sperm migration, ovum transport or nidation [7].

Also, the anatomical location of the fibroid represents an important element in the generation of infertility in the following descending order: submucosal, intramural and subserosal [8]. Moreover, fibromyomata may be the cause of infertility especially if the knots develop close to the tubaric ostium; in such a case it may be obstructed and therefore passage of the spermatozoa or alternatively embryo transport may be precluded. Data concerning differences of the impact of submucosal, intramural and subserosal fibroids on fertility seem to be confusing and contrasting [8–18]. Submucosal and intramural fibroids are frequently associated with distortion of the uterine cavity which in turn would affect the establishment and maintenance of early pregnancy [9,10].

Finally, submucosal fibroids may cause infertility for another series of reasons. For example, Richards and collaborators sustain that the local inflammation caused

by mucus ulceration would alter the biochemical characteristics of intrauterine fluids, creating a hostile environment for the spermatozoa [7]. Moreover, submucosal fibroids may disrupt the endometrial blood supply, thus affecting nidation of the embryo [9,19].

The present prospective, controlled study was performed to evaluate whether the location of uterine fibroids may influence reproductive function in women and whether removal of the fibroid prior to fertilization may improve the pregnancy rate and pregnancy maintenance.

## Methods

### *Selection of patients*

Women referred to our centre from January 1998 until April 2005 for fertility problems were examined to be included in this study, which was approved by the local ethics committee. All women underwent routine examinations including the study of ovarian function (follicle-stimulating hormone, luteinizing hormone, estradiol and progesterone concentrations); prolactin, free triiodothyronine, free thyroxine and thyroid-stimulating hormone concentrations; post-coital test; transvaginal ultrasonography; hysterosalpingography; and analysis of the partner's semen. The transvaginal ultrasonography was performed also in order to diagnose the eventual presence of uterine fibroids.

After these examinations all patients who were found to be affected by uterine fibroids excluding all other causes of infertility were asked to participate in the study. Inclusion criteria were: age  $\leq 35$  years; infertility for at least 1 year; presence of one knot and/or fibroid of diameter  $\leq 40$  mm; and absence of other causes of infertility at the performed examinations. Exclusion criteria were: presence of two or more knots and/or fibroids of diameter  $> 40$  mm; body weight  $> 20\%$  of normal weight; and use of medication containing estrogens, progestins or androgens within 8 weeks prior to the study. Patients who met all these conditions were enrolled after giving written informed consent. Patients were also given information explaining that the presence of uterine fibroids has been correlated with infertility but final considerations are still not conclusive.

### *Study protocol*

After enrolment, patients were divided into groups according to the characteristics of their fibroids. Subsequently, women of each group were randomized into two subgroups, according to a randomization table. The first subgroup was treated with surgery (laparotomy or hysteroscopy) to remove fibroids, while the second subgroup was not treated. Patients were examined by transvaginal ultrasonography 3 months after surgery for control.

Patients who did not undergo surgery were asked to immediately start having regular fertility-oriented intercourse (intercourse during the 6-day fertile interval ending on the day of ovulation) [20,21]. Patients who underwent surgery were suggested to abstain from having sexual intercourse for 3 months and then to start having regular fertility-oriented intercourse. Patients were monitored for up to 12 months after study commencement. A clinical pregnancy was defined by the visualization of an embryo with cardiac activity at 6–7 weeks of pregnancy. Miscarriage was classified as clinical loss of an intrauterine pregnancy between the 7th and 12th weeks of gestation.

### *Statistical analysis*

Data were analyzed using the  $\chi^2$  test and a  $p$  value of 0.05 was considered to indicate a statistically significant difference.

## Results

One hundred and ninety-three patients were diagnosed as affected by uterine fibroid excluding all other causes of infertility and met the requirements of the inclusion and exclusion criteria. Of these, 181 decided to participate in the study. Among the 181 patients, 52 had submucosal fibroids (SM group) while 45 had intramural fibroids (IM group), 11 had subserosal fibroids (SS group), 42 had a mix of submucosal–intramural (SM–IM group) and 31 patients had a mix of intramural–subserosal fibroids (IM–SS group). All women had been suffering from infertility for at least 1 year (range: 1–5 years). Patients' characteristics are shown in Table I.

Ninety-two patients underwent surgical treatment: 30 patients with SM fibroids, 23 patients with IM fibroids, 17 patients with IM–SS fibroids and 22 with SM–IM fibroids. Consequently 89 patients were not subject to surgical treatment: 22 patients with SM fibroids, 22 with IM fibroids, 11 with SS fibroids, 14 with IM–SS fibroids and 20 with IM–SM fibroids. As shown in Table II, patients who underwent surgery demonstrated a higher pregnancy rate than women who were not treated surgically for fibroids elimination, even though the differences were statistically significant only in the case of SM and IM–SM fibroids. Women suffering from SS fibroids were not treated because there was little indication to surgery.

Out of 181 women, 68 become pregnant. Pregnancy rates according to the location of the fibroids and the different treatments are reported in Table II. Among the 68 women who became pregnant, 25 had a miscarriage. The percentage of miscarriages varied depending on both the location of the uterine fibroids and the treatment (Table III), being the highest in the groups of not-treated SM and IM–SS fibroids

Table I. Patients' characteristics.

	Group				
	SM ( <i>n</i> = 52)	IM ( <i>n</i> = 45)	SS ( <i>n</i> = 11)	IM-SS ( <i>n</i> = 31)	SM-IM ( <i>n</i> = 42)
Age (years)	31.4 ± 2.5	32.2 ± 1.9	32.4 ± 2.1	29.9 ± 1.6	32.2 ± 2.5
Years of infertility	1.9 ± 1.1	1.7 ± 0.6	1.6 ± 0.9	1.9 ± 0.7	1.5 ± 1.1
Body mass index (kg/m <sup>2</sup> )	24.3 ± 1.5	23.8 ± 2.4	23.1 ± 1.3	22.9 ± 1.7	23.7 ± 2.2

SM, submucosal; IM, intramural; SS, subserosal; IM-SS, mixed intramural-subserosal; SM-IM, mixed submucosal-intramural; data are presented as mean ± standard deviation; no significant differences among groups.

Table II. Effect of fibroid location and treatment on pregnancy rate.

Group	Treatment	No. of patients	No. of pregnancies	Pregnancy rate (%)	<i>p</i> Value
SM ( <i>n</i> = 52)	With surgery	30	13	43.3	<0.05
	Without surgery	22	6	27.2	
IM ( <i>n</i> = 45)	With surgery	23	13	56.5	NS
	Without surgery	22	9	40.9	
SS ( <i>n</i> = 11)	Without surgery	11	7	63.6	NS
IM-SS ( <i>n</i> = 31)	With surgery	17	6	35.3	
	Without surgery	14	3	21.4	
SM-IM ( <i>n</i> = 42)	With surgery	22	8	36.4	
	Without surgery	20	3	15.0	<0.05

SM, submucosal; IM, intramural; SS, subserosal; IM-SS, mixed intramural-subserosal; SM-IM, mixed submucosal-intramural; NS, not significant.

Table III. Effect of fibroid location and treatment on miscarriage rate.

Group	Treatment	No. of miscarriages/ no. of pregnancies	Miscarriage rate (%)
SM ( <i>n</i> = 52)	With surgery	5/13	38.5
	Without surgery	3/6	50.0
IM ( <i>n</i> = 45)	With surgery	4/13	30.8
	Without surgery	3/9	33.3
SS ( <i>n</i> = 11)	Without surgery	0/7	0
IM-SS ( <i>n</i> = 31)	With surgery	2/6	33.3
	Without surgery	2/3	66.6
SM-IM ( <i>n</i> = 42)	With surgery	4/8	50.0
	Without surgery	2/3	66.6

SM, submucosal; IM, intramural; SS, subserosal; IM-SS, mixed intramural-subserosal; SM-IM, mixed submucosal-intramural.

and treated/not-treated SM-IM fibroids. No cases of uterine rupture occurred.

## Discussion

SM, IM and mixed SM-IM fibroids have been claimed to be responsible for uterine cavity distortion and consequently they may affect the establishment and maintenance of early pregnancy [7]. Although the results of our study were not statistically significant in the IM and SM-IM groups of women, there was an overall tendency to have a higher pregnancy rate among the woman who underwent a

surgical treatment for fibroid removal compared with those who were not treated. Moreover, surgical treatment reduced the percentage of miscarriages in most of the groups of women considered. Consequently, our study seems to confirm that the anatomical location of the fibroid is highly relevant in terms of its influence on fertility status and pregnancy maintenance: submucosal, intramural and subserosal, in decreasing order of importance.

In fact, in the group of women with SM fibroids, when surgery was not performed the pregnancy rate was 27.2% with a miscarriage rate of 50.0%, whereas the corresponding rates were 43.3% and 38.5% in women who underwent surgery. The difference between the pregnancy rates was statistically significant ( $p < 0.05$ ). These data are in agreement with those of other authors [17], who showed that SM fibroids are an important determinant of infertility since the pregnancy rate increased after myomectomy.

Different results were obtained in the group of women with mixed SM-IM fibroids. In this case, in the subgroup of treated woman the pregnancy rate was 36.4% with a miscarriage rate of 50.0%, while in the not-treated subgroup these values were 15.0% and 66.6%, respectively. Again, the difference between the pregnancy rates was statistically significant ( $p < 0.05$ ). It is evident that, although there was a statistically significant difference in the pregnancy rates between the two groups, the miscarriage rates remained high in both cases.

In the IM and IM-SS subgroups the pregnancy rates were not statistically different, although there

was a slight tendency towards higher values in the treated subgroups. The pregnancy rate in the group with SS fibroids was evidently high (63.6%), notwithstanding the relative short duration of the follow-up period (12 months). In any case, we should emphasize that fibroids were also small ( $\leq 40$  mm) and not numerous ( $n \leq 2$ ).

Furthermore, our data suggest that SM fibroids are not a major cause of infertility. Indeed, a high percentage of women who achieved pregnancy with the sole prescription of regular fertility-oriented intercourse. The minor role of SM fibroids in determining a state of infertility found in this study is in agreement with the findings of Desolle and collaborators [18].

## Conclusion

Our study confirms that pregnancy rate and miscarriage rate may be affected by the presence of uterine fibroids. Although the results were not statistically significant in the groups of women with IM and IM-SS fibroids, there was a tendency toward a higher pregnancy rate and a lower miscarriage rate among all treated groups. Moreover, analyzing the results for the two groups in which a statistically significant difference was found (SM and SM-IM groups), we may emphasize the role of SM fibroids in infertility, even in comparison with the presence of different types of multiple fibroids (i.e. IM-SS). Thus our study acknowledges the important role that the position of the uterine fibroid plays in infertility as well as the importance of fibroids removal before the achievement of pregnancy, to improve both the chances of fertilization and pregnancy maintenance.

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