Human Reproduction, Vol.26, No.4 pp. 834–839, 2011
Advanced Access publication on February 11, 2011 doi:10.1093/humrep/der015

Fibroids not encroaching the endometrial cavity and IVF success rate: a prospective study

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Submitted on August 17, 2010; resubmitted on December 28, 2010; accepted on January 13, 2011

BACKGROUND: The impact of fibroids, not encroaching the endometrial cavity, have on the rate of success of IVF is still controversial. Recent meta-analyses suggest a detrimental effect of intramural lesions but not subserosal lesions. However, they also emphasize the need for further evidence. In order to elucidate this, we designed a prospective cohort study to compare the rate of success of IVF in women with and without fibroids.

METHODS: Exposed women were those with asymptomatic intramural or subserosal fibroids with a diameter below 50 mm and who were selected for IVF. Unexposed women were those free of fibroids, who were matched to cases by age and number of previous IVF cycles. All recruited patients underwent hystero-sonography to rule out intra-cavitary lesions.

RESULTS: There were 119 cases and 119 controls recruited. The number of clinical pregnancies in women with and without fibroids was 28 (24%) and 22 (19%), respectively ($P = 0.43$). The adjusted odds ratio (OR) for pregnancy in affected women was 1.38 [95% confidence interval (CI): 0.73–2.60]. The number of deliveries was 22 (18%) and 16 (13%), respectively ($P = 0.38$). The adjusted OR was 1.45 (95% CI: 0.71–2.94). Similar results emerged when focusing exclusively on women carrying intramural lesions ($n = 80$ couples). There was no significant relationship between clinical outcome and either the number or size of the fibroids.

CONCLUSIONS: In asymptomatic patients selected for IVF, small fibroids not encroaching the endometrial cavity did not impact on the rate of success of the procedure.

Key words: uterine fibroid / myoma / IVF / infertility

Introduction

The relationship between uterine fibroids and infertility has been a critical and debated question for many years (Vercellini *et al*., 1998; Somigliana *et al*., 2007; Klatsky *et al*., 2008). Even if there is a biological plausibility supporting a causal relationship between fibroids and infertility, clinical data on this issue has been inconsistent and puzzling. Observational evidence from case–control and cohort studies generally failed to document an association, but this may be due to confounders (Somigliana *et al*., 2007). In this context, IVF in women with fibroids has been estimated to be a model of utmost interest to elucidate the relationship between these lesions and infertility. At least, it allows assessment of the impact of fibroids on the implantation of the embryo. A plethora of studies and six meta-analyses (Pritts, 2001; Donnez and Jadoul, 2002; Benecke *et al*., 2005; Somigliana *et al*., 2007; Pritts *et al*., 2009; Sunkara *et al*., 2010) have been published on this issue. There is an agreement that submucosal fibroids are detrimental, whereas subserosal lesions are not. The impact of intramural fibroids is more controversial. Whereas initial meta-analyses failed to document an harmful impact (Pritts, 2001; Donnez and Jadoul, 2002), the subsequent ones suggested a reduced pregnancy rate among women carrying intramural lesions (Benecke *et al*., 2005; Somigliana *et al*., 2007; Pritts *et al*., 2009; Sunkara *et al*., 2010). The most recent meta-analysis included 19 studies and reported a relative risk of pregnancy and live birth in women with fibroids of 0.85 [95% confidence interval (CI): 0.77–0.94, $P = 0.002$] and 0.79 (95% CI: 0.70–0.88, $P < 0.0001$), respectively (Sunkara *et al*., 2010).

Despite this growing body of evidence, the debate is still on-going. Of relevance here is the scientific quality of the available evidence (Pritts *et al*., 2009). Most studies are underpowered; only a minority of studies are prospective; proper investigations of the uterine cavity were not systematically performed and data have not been systematically controlled for age and number of cycles, which are two critical variables influencing the success of IVF (Pritts, 2001; Somigliana *et al*., 2007; Sunkara *et al*., 2010). Noticeably, meta-analyses cannot overcome most of these limitations and, in general, they should not be viewed as the referee of all controversial issues. The quality of the studies underlying these analyses is crucial. For this reason, it is deemed important to further explore this relevant aspect of reproductive medicine (Pritts *et al*., 2009). To this aim, we designed a prospective study recruiting women with fibroids selected for IVF. Women free of fibroids who also required IVF represented the unexposed group.

Materials and Methods

Patients who were selected for IVF between June 2007 and June 2009 at the Infertility Unit of the Fondazione Cà Granda Ospedale Maggiore Policlinico were considered for study entry. Women were eligible as cases if they were diagnosed with uterine intramural or subserosal fibroids with a mean diameter below 50 mm. This cut-off was decided based on previous comparative studies supporting a strong benefit of surgery in the advanced cases (Bulletti *et al*., 1999, 2004). The unexposed women were matched to cases for age and number of cycles. Specifically, controls corresponded to the subsequent woman with the same age ($\pm$1 year) and the same number of previous failed treatment cycles. Both patients who underwent classical IVF or IVF–ICSI were included. Exclusion criteria for both groups were the report of menstrual abnormalities and previous treatments for fibroid (i.e. myomectomy, uterine artery embolization and magnetic resonance imaging-focused ultrasound). Women previously achieving a pregnancy through IVF were also excluded. Since the oocyte donation program was not part of the treatments offered by our unit, the study did not thus include any women undergoing this kind of treatment. The local Institutional Review Board approved the study and all recruited patients signed an informed consent.

All patients underwent transvaginal ultrasound between Day 1 and Day 8 of the cycle during the month preceding the beginning of hyperstimulation. The precise location and dimension of the myomas were recorded at this time. Both affected and unaffected women also underwent a hysterosonography to rule out intra-endometrial lesions. This assessment was done by inserting an intrauterine device (sonde intrauterine standard, C.D.D., Paris, France) and injecting 20–40 ml of sterile saline. Scanning was done on two perpendicular planes (sagittal and coronary) during injection. Sonographic appearance of myomas was defined as symmetrical, well defined, hypoechoic and heterogeneous masses (Parker, 2007). When the ecographic appearance did not allow a reliable discernment between fibroid and adenomyosis, cases were excluded. Measurement of each myoma was carried out in three planes (sagittal, coronal and axial) at the level of maximum width. We included myomas with a minimum diameter of 10 mm. A myoma with $\geq$50% of its diameter bulging out of the uterine contour line was defined as subserosal. Intramural fibroids were those mostly within the uterine shape (Vercellini *et al*., 1999; Bajekal and Li, 2000). Myomas distorting the cavity line were defined as submucosal and patients with these lesions were not recruited. If more than one myoma was identified, the mean diameter of the largest was used as a reference. For location, women were considered to carry intramural fibroids if at least one of them was located intramurally, regardless of the number of lesions. All ultrasound scans were performed by only three physicians engaged for a long time in gynecological ecographies. Preliminary experiments showed an inter- and intra-observer variability for the measurement of the size of the myomas both consistently below 20%.

Patients were monitored and managed according to a standardized clinical protocol as reported elsewhere (Somigliana *et al*., 2008). Briefly, the dose of gonadotrophins was determined on an individual basis according to the characteristics of the patients as age, serum hormonal levels and antral follicle count. Patients underwent serial transvaginal ultrasound and hormonal monitoring during hyperstimulation. When three or more leading follicles with a mean diameter $>$18 mm were visualized, 5000 IU of hCG was administered s.c. Oocyte retrieval was performed transvaginally 36 h after the hCG injection. Embryo transfer was performed 48–72 h after the oocyte collection. Cycles were canceled if there was a poor or hyper-response of ovaries. We defined hyper-response as a serum estradiol level $>$4000 pg/ml and/or more than 20 follicles identified on ultrasound scan before hCG administration. Poor response was defined by the ecographic evidence of fewer than three follicles during ovarian hyperstimulation. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac 4 weeks after embryo transfer. Implantation rate was calculated as the ratio between the number of gestational sacks identified at this time and the number of embryos transferred. An active follow-up on pregnancy outcome was performed by checking data of the obstetrical department and by phone contact.

Data analysis was performed using the Statistics Package for Social Sciences (SPSS 15.0, Chicago, IL, USA). Data were compared using Student's *t* test, non-parametric unpaired Wilcoxon test, χ^2 test or Fisher's exact test, as appropriate. The main outcome chosen was clinical pregnancy rate. Baseline characteristics found to differ between the study groups ($P < 0.10$) were entered into a logistic regression model to control for confounders. The magnitude of the associations was quantified using odds ratios (ORs). Probability values $<$0.05 were considered statistically significant. The sample size was calculated setting the type I and type II errors at 0.05 and 0.20, respectively, and stating as clinically relevant demonstrating a 2-fold greater chance of pregnancy among women without fibroids. The rate of success used to calculate the sample size was the one observed in our unit in 2006, excluding women with fibroids (30%). On these bases, we estimated that the number of patients to be enrolled was about 120 women per group.

Results

There were 240 women initially included in the study, 120 with fibroids and 120 unexposed patients. After inclusion, one case subsequently declined to undergo treatment for personal reasons. The corresponding control was also excluded, leaving 119 couples for data analysis. A spontaneous pregnancy occurred in two women with fibroids before starting ovarian hyperstimulation. These patients were included in the analysis. Baseline characteristics of the two study groups are shown in Table I. The BMI was found to be significantly higher among women carrying fibroids. The mean difference was 1.5 kg/m^2 (95% CI: 0.6–2.4 kg/m^2). There was also a trend toward a difference in the indications for the procedure (Table I). Fibroids were isolated in 61 cases (51%). The numbers of women carrying 2, 3, 4 and 5 lesions were 21 (18%), 21 (18%), 11 (9%) and 5 (4%), respectively. In 80 cases (67%), there was at least one intramural fibroid. The mean $\pm$ SD and median (interquartile range) diameter of the larger lesion per patient was 22 $\pm$ 10 and 19 (15–27) mm, respectively.

Table I Baseline characteristics of women with and without fibroids (119 per group).

Characteristics	Women with fibroids	Unaffected women	P-value
Age (years)[a]	37.6 ± 3.0	37.6 ± 3.0	0.98
Previous IVF cycles[a]			1.00
0	80 (67%)	80 (67%)	
1	31 (26%)	31 (26%)	
≥2	8 (7%)	8 (7%)	
BMI (kg/m^2)	22.9 ± 3.9	21.3 ± 3.1	0.001
Duration of infertility (years)	3.2 ± 2.4	2.9 ± 1.8	0.25
Previous pregnancies	35 (29%)	28 (24%)	0.38
Previous gynecological surgery[b]	34 (29%)	27 (23%)	0.37
Day 3 serum FSH (IU/ml)	7.5 ± 3.2	7.9 ± 3.2	0.38
Indication to IVF			0.39
Male factor	64 (54%)	51 (43%)	
Tubo-peritoneal factor	20 (17%)	24 (20%)	
Unexplained/ reduced ovarian reserve	16 (13%)	18 (15%)	
Mixed	19 (16%)	26 (22%)	

Continuous variables were compared using the Student's t test. Categorical variables were compared using the χ^2 test.
[a]Exposed and unexposed women were matched for age and number of treatment cycles.
[b]Myomectomies were excluded as stated in the selection criteria.

Table II Ovarian stimulation outcome in women with and without fibroids.

Characteristics	Women with fibroids	Unaffected women	P-value
Protocol of stimulation[a]			0.37
Long protocol	64 (55%)	58 (49%)	
GnRH antagonist	53 (45%)	61 (51%)	
Canceled cycles[a]			0.006
Poor response	12 (10%)	7 (6%)	
Hyper-response	8 (7%)	0 (0%)	
Total dosage of rFSH (IU)[b]	2719 ± 1366	2696 ± 1407	0.90
Duration of stimulation (days)[b]	10.1 ± 2.4	9.9 ± 1.8	0.56
Serum estradiol at the time of hCG injection (pg/ml)[b]	1737 ± 847	1849 ± 950	0.44
Number of oocytes retrieved[b]	4.5 ± 3.1	4.5 ± 3.1	0.98
Number of embryos transferred[c]			0.07
1	13 (15%)	27 (27%)	
2	31 (36%)	40 (39%)	
3	42 (49%)	35 (34%)	

Continuous variables were compared using the Student's t test with the exception of the serum estradiol levels that were compared using the Wilcoxon test. Categorical variables were compared using the χ^2 test with the exception of the canceled cycle item that was compared using the Fisher exact test.
[a]Data refer to patients initiating the stimulation (117 cases and 119 controls). Two cases had a spontaneous pregnancy before initiating the stimulation.
[b]Data refer to patients undergoing oocyte retrieval (97 cases and 112 controls).
[c]Data refer to patients undergoing embryo transfer (86 cases and 102 controls).

IVF outcomes in the two study groups are shown in Tables II and III. The proportion of canceled cycles was significantly higher in women with fibroids. In this group, we also detected a trend toward a higher number of transferred embryos. The clinical pregnancy rate and delivery rate per started cycle did not differ between the two groups (Table III). The logistic regression model aimed at determining the adjusted ORs of pregnancy included the BMI, the indication, the item of canceled cycle and the number of embryos transferred. The resulting adjusted ORs per started cycle for pregnancy and delivery in affected women were 1.40 (95% CI: 0.72–2.75) and 1.53 (95% CI: 0.73–3.23), respectively. Among women with fibroids, we observed six twin pregnancies and two triplets, whereas among unexposed patients there were two twins and no triplets. A trend to a higher implantation rate was observed in women with fibroids ($P = 0.08$) (Table III). The logistic regression model used to calculate the adjusted OR for implantation in women carrying fibroids included the BMI and the indication. It resulted in an adjusted OR of 1.74 (95% CI: 0.98–3.08).

When including the two pregnancies occurring spontaneously, the numbers of clinical pregnancies in women with and without fibroids were 28 (24%) and 22 (19%), respectively ($P = 0.43$). The OR for pregnancy in women carrying fibroids adjusted for BMI and indication for IVF was 1.38 (95% CI: 0.73–2.60). The numbers of deliveries were 22 (18%) and 16 (13%), respectively ($P = 0.38$). The OR for delivery in affected women adjusted for BMI and indication to IVF was 1.45 (95% CI: 0.71–2.94). The spontaneous abortion rates in women with and without fibroids were 21% (6 out of 28) and 27% (6 out of 22), respectively ($P = 0.74$). All deliveries lead to viable infants.

The impact of the fibroids was also evaluated according to their location, number and dimension. These results are briefly summarized in Table IV. No clear associations between clinical outcomes and these factors emerged.

Discussion

In contrast to evidence from recent available meta-analyses, we failed to observe a detrimental effect of fibroids with a diameter <50 mm and not distorting the endometrial contour on the rate of success of IVF. For the entire cohort, the adjusted ORs of pregnancy, implantation and delivery in women with fibroids were 1.38 (95% CI: 0.73–2.60), 1.74 (95% CI: 0.98–3.08) and 1.45 (95% CI: 0.71–2.94), respectively. When specifically focusing on women carrying at least one intramural lesion ($n = 80$ couples), these ORs were 1.41 (95% CI: 0.67–2.98), 1.75 (95% CI: 0.90–3.39) and 1.36 (95% CI:

0.58–3.15), respectively. We also failed to document any significant relationship with the number and size of the lesions.

Some limits of the paper should be considered. First, one may argue that the inclusion of women with subserosal lesions was useless considering that the literature is more unanimous on the benignity of these lesions. In this regard, it is however noteworthy that there is a lack of consensus on the precise definition of submucosal, intramural and subserosal locations (Somigliana *et al.*, 2007). This inevitably renders comparisons among studies difficult. In our study, we referred to the most commonly used classification of Bajekal and Li (2000). These authors support the following definitions: submucous fibroids are those that distort the uterine cavity. Intramural fibroids are those which do not distort the cavity and with <50% of the tumor protruding into the serosal surface of the uterus. Fibroids protruding ≥50% out of the serosal surface are considered subserosal. In fact, many subserosal fibroids have an intramural component. Moreover, this classification does not take into consideration the dimensions of fibroids. Since the thickness of a normal uterine wall is 15–20 mm, all fibroids which do not distort the uterine cavity and with a mean diameter of more than 30–40 mm are classified as subserosal even if the lesion takes up the entire uterine wall. Indeed, their diameter is inevitably bulging out of the uterine contour line for more than 50%. Regardless of these anatomical considerations, it is noteworthy that our results were extremely similar even when considering exclusively women with intramural lesions. Our study power is, however, inevitably lower for this specific location and, consequently, conclusions are less definite. This is a main limitation of our investigation. Despite the scientific debate regarding the classification of fibroids, it has to be recognized that the concept of intramural lesions is strongly eradicated in clinical practice. There is thus the need to give clinicians clear and practical information for this location. Further evidence is required. In our institution, we are currently discussing the possibility of extending our study, focusing exclusively on intramural lesions. Given the necessity to provide evidence on the delivery rate and not merely on the pregnancy rate, a further 18–24 months will be needed from now to obtain definite data.

Secondly, some characteristics of the two groups slightly differed and we cannot thus exclude some confounding factors. The BMI was higher in women carrying fibroids. This may be a confounder since a higher BMI has been shown to negatively affect the rate of success of IVF (Lunenfeld *et al.*, 2004). We, however, estimate that this difference did not play an important role since the magnitude is mild (1.5 kg/m^2). Moreover, this confounder would be expected to act to increase the detrimental role of fibroids,

Table III **IVF outcome in women with and without fibroids.**

Characteristics	Women with fibroids	Unaffected women	*P*-value
Number of clinical pregnancies	26	22	
PR per started cycle[a]	22%	19%	0.52
PR per oocyte retrieval[b]	27%	20%	0.25
PR per embryo transfer[c]	30%	22%	0.18
Number of embryos implanted	35	24	
Implantation rate[c]	17%	11%	0.08
Number of deliveries	21	16	
DR per started cycle[a]	18%	13%	0.37
DR per oocyte retrieval[b]	22%	14%	0.20
DR per embryo transfer[c]	24%	16%	0.15

The χ^2 test was used for comparisons.
PR, pregnancy rate; DR, delivery rate.
[a]Data refer to patients initiating the stimulation (117 cases and 119 controls). Two women with fibroids had prior spontaneous pregnancies.
[b]Data refer to patients performing oocyte retrieval (97 cases and 112 controls).
[c]Data refer to patients performing embryo transfer (86 cases and 102 controls).

Table IV **The impact of fibroids on the clinical pregnancy rate according to location, number and size.**

Subgroup	No. of couples	Clinical pregnancy	Embryo implantation	Delivery
Location				
Intramural	80	1.41 (0.67–2.98)	1.75 (0.90–3.39)	1.36 (0.58–3.15)
Subserosal	39	1.22 (0.33–4.50)	1.22 (0.31–4.73)	1.60 (0.40–6.41)
Number				
1	61	1.40 (0.56–3.46)	1.87 (0.84–4.16)	2.16 (0.73–6.41)
≥2	58	1.24 (0.50–3.09)	1.54 (0.67–3.53)	1.01 (0.38–2.68)
Size				
<20 mm	60	1.31 (0.54–3.21)	2.09 (0.95–4.61)	1.55 (0.57–4.23)
≥20 mm	59	1.39 (0.55–3.50)	1.54 (0.64–3.66)	1.30 (0.47–3.61)

Data are reported as adjusted OR (95% CI) for pregnancy in women carrying fibroids.
The implantation data refer to women performing embryo transfer, whereas the clinical pregnancy rate and the delivery rate refer to the whole cohorts.
The logistic regression model used to calculate the adjusted ORs included the BMI and the indication to the procedure.

whereas, in contrast, we failed to show any effect. The ovarian stimulation outcome also partially differed. Despite matching for age, the proportion of canceled cycles and the number of transferred embryos were higher among women with fibroids. These two confounders are expected to influence the results in opposite ways. Their impact is, however, presumably low. In fact, the pregnancy rate per transfer and the delivery rate per transfer which are independent from the cancelation rate were similar in both groups. In addition, the implantation rate, which is supposed to be independent from both variables also, did not differ between groups. It even tended to be higher in women with fibroids ($P = 0.08$). Moreover, in order to definitely rule out a relevant impact on the results of the variables differing between the study groups, a logistic regression model including BMI, indication for treatment, the item of canceled cycle and the number of embryos transferred was built. No significant differences emerged from this analysis.

Finally, the grade of severity of the leiomyomatosis cases was generally low. In half of the affected women, there was only one lesion and the mean diameter of the fibroids was relatively small (22 mm). Our results cannot thus be inferred to the whole population of women with fibroids. Of relevance here is that a previous report showed that only fibroids larger than 40 mm would be detrimental (Oliveira *et al.*, 2004). This is, however, a common limitation of the vast majority of previous available studies on this point (Somigliana *et al.*, 2007; Pritts *et al.*, 2009; Sunkara *et al.*, 2010).

On the other hand, our study has some important strengths. It is prospective, the sample size is large, the uterine cavity was systematically investigated and unexposed women were matched for age and number of cycles, thus controlling for two factors known to markedly influence the rate of success of IVF. Matching also for ovarian responsiveness would have allowed us to better control also for this variable, but our study design did not allow for this since, in order to properly investigate the uterine cavity, the recruitment had to be done before starting the stimulation.

How can we explain the incongruence between our data and recent insights from meta-analyses? First of all, a type II error in our study cannot be excluded. Despite a large sample size, the 95% CI of the estimated OR remained relatively wide. Specifically considering intramural lesions, the 95% CI of the associations with pregnancy and delivery of the meta-analysis (0.77–0.94 and 0.70–0.88) overlap with our data (Sunkara *et al.*, 2010). A much larger sample size would have been required to definitely deny the results of these analyses. However, a type II error may not be the unique reason. Other factors may contribute to explain this contrasting result. Of relevance here are the characteristics of the selected patients. It has firstly to be pointed out that, in contrast to previous evidence, confounders are less likely in our study since we used an age- and cycle-matching design. Both variables are known to strongly affect the rate of success of the procedure. Secondly, affected cases selected in all the studies on this issue do not represent the entire population of infertile women with fibroids. In fact, a proportion of these women undergo surgery prior to referral. The main reasons are non-infertile complaints (menorrhagia or pelvic pain) and the severity of the disease. With regard of the latter, it is noteworthy that uterine leiomyomata is a heterogeneous condition varying from a small single subserosal fibroid to multiple large lesions that radically distort pelvic anatomy. Myomectomy has been shown to be effective in enhancing both natural fertility and IVF success rates in severe cases (Bulletti *et al.*, 1999, 2004; Casini *et al.*, 2006), but the question remains open for less advanced conditions. Due to uncertainties on this point, however, the policies leading women to surgery vary widely from one center to the next and among clinicians. This inevitably translates into differences in the characteristics of the fibroids of the affected women among studies.

In fact, the main problem now is delineating the limit between unremarkable and harmful fibroids. There is a need to go beyond the arbitrary geometrical classification and to reach a more in-depth knowledge of this neglected but complex disease (Pritts *et al*, 2009). Of further relevance here is the risk of pregnancy-related complications of fibroids. There is a need for a more comprehensive vision of this topic. Obstetrical complications arising after conception should also be considered. Although the present study tends to rule out a remarkable impact on the risk of abortion (the ORs of clinical pregnancy and delivery were similar), other possible complications should be taken into consideration. In particular, the most convincing evidence is in favor of an association with pelvic pain, placental abruption, placenta previa, intrauterine growth restriction and fetal malpresentation (Somigliana *et al.*, 2007). Not surprisingly, a higher rate of cesarean section has also been repeatedly reported (Somigliana *et al.*, 2007). On the other hand, one has also to consider the risk of pregnancy after a myomectomy. One of the major concerns here is the low, albeit clinically relevant, risk of uterine rupture during pregnancy or labor (Somigliana *et al.*, 2007). Although these points have to be kept in mind, their relative importance has yet to be clarified in the context of women selected for IVF. The above-mentioned risks have been documented in women with more advanced clinical conditions. Moreover, the recent improvement and diffusion of laparoscopic excision techniques (all women selected in our study are good candidates for this approach) may also modify the scenario.

From a clinical point of view, we believe that, at present, there is no indication to systematically remove fibroids not encroaching the endometrial cavity prior to initiating IVF. Our results did not indicate any deleterious effect on the pregnancy rate. At least, this is valid for asymptomatic patients with few small lesions as those observed in our cohort. Some detrimental effects cannot, however, be ruled out in some specific cases, but their identification is currently troublesome. Women should be informed about this possible harmful effect on conception as well as about pregnancy complications associated with fibroids or their removal, but they should also be reassured. In our view, surgery may be considered for advanced cases, after repeated IVF failures or if fibroid-related obstetrical complications (i.e. recurrent miscarriage) have been observed in the recent past.

In conclusion, our data suggests that, in asymptomatic patients selected for IVF, small fibroids with a diameter <50 mm and not encroaching the endometrial cavity do not impact on the rate of success of the procedure. This result should not, however, be used to conclude that all intramural or subserosal lesions are unremarkable. In fact, current available evidence indicates that at least some lesions may be deleterious. Future efforts should be aimed at identifying this subgroup of women.

Authors' roles

E.S., C.S. and G.R. conceived and designed the study. S.D.B., A.E.N. and L.B. acquired the data and participate to the analysis. P.V. and L.F. gave substantial contribution to the analysis and interpretation of the data. E.S. wrote the first draft and all the other authors revised it critically adding important intellectual content. All authors gave final approval to the final version of the manuscript.

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