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ORIGINAL ARTICLE

The impact of small and asymptomatic intramural and subserosal fibroids on female fertility: a case–control study

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STUDY QUESTION: Do small and asymptomatic intramural and subserosal uterine fibroids affect female fertility?

SUMMARY ANSWER: Small and asymptomatic fibroids that do not encroach the endometrial cavity appear to not markedly affect female fertility.

WHAT IS KNOWN ALREADY: The available evidence on uterine fibroids and fertility is limited. Most information has been obtained in IVF settings by comparing the success in women affected and not affected by fibroids. These studies have shown a detrimental effect of submucosal and possibly intramural fibroids. However, this study design provides information only on embryo implantation, not on female fertility in general.

STUDY DESIGN, SIZE, DURATION: A retrospective observational case–control study on 200 women whose partner was diagnosed with severe male infertility and 200 women with unexplained infertility was conducted. If the null hypothesis (that fibroids do not affect fertility) is valid, one would expect a similar prevalence of fibroids in the two study groups. Conversely, if fibroids do impact fertility, one would expect a higher prevalence among women with unexplained infertility. The study was carried out at the Infertility Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico covering a 5-year period between January 2014 and June 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We retrospectively recruited women seeking pregnancy whose partner was repeatedly documented to have a sperm concentration below 1 million/ml and matched them by age and study period to a group of women with unexplained infertility. The latter group of women was considered as a case group (infertile subjects), while the former group of women was considered as a control group (reflecting the general female population). Women with fibroids could be included in both study groups; only those with submucosal lesions were excluded.

MAIN RESULTS AND THE ROLE OF CHANCE: Fibroids were diagnosed in 31 women (16%) with unexplained infertility and in 32 women (16%) with severe male factor infertility. The adjusted odds ratio of carrying fibroids in women with unexplained infertility was 0.91 (95% CI: 0.52–1.58). Subgroup analyses according to number, dimension and location of fibroids failed to highlight an increased risk of infertility in any group.

LIMITATIONS, REASONS FOR CAUTION: This is a retrospective study and some inaccuracies in fibroids detection cannot be ruled out. Moreover, the relatively small sample size hampers robust subgroup analyses. Even though we excluded women with patent causes of infertility, some women with specific causes of infertility could have been included among controls (yet are expected to account for <10% of the group).

WIDER IMPLICATIONS OF THE FINDINGS: This study suggests that small fibroids that do not encroach the endometrial cavity do not markedly affect female fertility. This information is clinically relevant when counseling infertile women with small fibroids and an otherwise unremarkable diagnostic work-up. Surgery may still be considered but only in selected cases.

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Key words: fibroid / myoma / infertility / leiomyoma / fertility

WHAT DOES THIS MEAN FOR PATIENTS?

Currently available evidence indicates that the establishment of pregnancy is adversely affected by the presence of larger fibroids growing either within the uterine wall or into the uterine space. This notion is supported by several studies performed in IVF settings, i.e. by comparing the success of the procedure in patients with and without such fibroids. However, this study design does not provide information on the complex relation between fibroids and female fertility in general. Designing studies to obtain information on female fertility in general is challenging because of confounding factors such as age of the women and any previous pregnancy, both of which affect the development of fibroids. Overall, obtaining unbiased and informative evidence is difficult.

To address this intricate issue, we designed a study using women as controls whose partner had male infertility. These women reflect the general population and we assumed that they were fertile. They were matched by age to a second group of subjects with unexplained infertility, i.e. whose infertility diagnostic work-up was unremarkable. The women with unexplained infertility were considered as cases (infertile subjects), while those with infertile partners were considered controls (reflecting the general female population). Women with small fibroids on the outside of, or within, the uterine wall could be included in both study groups; we only excluded those with larger fibroids growing into the uterine space. If the null hypothesis (that smaller fibroids do not affect fertility) is valid, one would expect a similar prevalence of the fibroids in the two study groups. Conversely, if the fibroids do impact fertility, one had to expect a higher prevalence among women with unexplained infertility.

We selected 200 women per group. The prevalence of fibroids was identical, being 16%, in both groups. This result supports the idea that these lesions do not affect fertility. However, it must be underlined that only women with smaller, noninvasive fibroids were included and those with fibroids extending into the uterine space were excluded. Larger studies are now warranted to investigate the effects of larger lesions and to disentangle whether there are some particular type of fibroids that could be detrimental to fertility.

Introduction

The relation between fibroids and infertility remains controversial. There is a long-lasting consensus that submucosal lesions are detrimental but, for intramural and subserosal lesions, their impact is yet unclear (Somigliana *et al.*, 2007; Hur *et al.*, 2019; Metwally *et al.*, 2020).

Evidence from IVF studies suggests a detrimental effect of submucosal and intramural but not subserosal lesions. According to the most recent meta-analyses on this subject, the corresponding odds ratios (ORs) of live birth were 0.3 (95% CI: 0.1–0.8), 0.6 (95% CI: 0.5–0.7) and 1.0 (95% CI: 0.7–1.5), respectively (Somigliana *et al.*, 2007; Pritts *et al.*, 2009; Rikhraj *et al.*, 2020). On the other hand, evidence from IVF cannot be considered exhaustive. Only detrimental effects on embryo implantation can be identified with this model. The possible deleterious effects of fibroids on sperm transport and tubal function cannot be captured. In addition, one may also argue that the lower OR of successful pregnancy for submucosal and intramural lesions observed in IVF settings may reflect only a lower fecundity rather than an increased infertility. In other words, this type of evidence does not allow to rule out that women with fibroids may just require a longer time to achieve a pregnancy rather than being infertile (Somigliana *et al.*, 2021).

Unfortunately, the available studies on fibroids and female fertility are few and inconclusive (Parazzini *et al.*, 1996; Marshall *et al.*, 1998; Bulletti *et al.*, 1999; Faerstein *et al.*, 2001; Wise *et al.*, 2004; Wellons *et al.*, 2008; Templeman *et al.*, 2009; Johnson *et al.*, 2012; Yasui *et al.*, 2018; Karlsen *et al.*, 2020; Somigliana *et al.*, 2021). The findings are indeed exposed to important confounders due to selection biases, including the diagnostic methods used, an unclear temporal relation between fibroids and infertility, the definition of infertility, failure to adjust for fibroids characteristics (size, location, number), or the association of fibroids with other causes of infertility such as endometriosis and older age (Stewart *et al.*, 2016, 2017; Capezzuoli *et al.*, 2020). The use of fertile women as controls in such studies is also inaccurate due to the relevant protective effects of pregnancy on fibroids development (Laughlin *et al.*, 2011; Somigliana *et al.*, 2021). Only a large prospective longitudinal observational cohort study that recruits women prior to initiating pregnancy seeking could provide a robust conclusion. Unfortunately, this study design requires important

organizational efforts and huge financial resources and, not surprisingly, evidence of this type is not yet available.

In this study, we aimed at providing information on the possible impact of fibroids on female fertility using an alternative, but possibly efficient, study design. Specifically, we retrospectively included infertile women whose infertility diagnostic work up was unremarkable (unexplained infertility) and matched them by age and study period to a control group of women whose partner was diagnosed with a severe male factor cause of infertility. The women with unexplained infertility were considered as cases (infertile women), while those with infertile partners were considered as controls (reflecting the general female population). Women with intramural or subserosal fibroids could be included in both study groups. If the null hypothesis (that the fibroids do not affect fertility) is valid, one had to expect a similar prevalence of fibroids between the two study groups. Conversely, if fibroids do impact fertility, one had to expect a higher prevalence among women with unexplained infertility.

Materials and methods

The records of women who were referred to the Infertility Unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico between January 2014 and June 2020 were retrospectively reviewed. Only those with a completed diagnostic work-up and who were younger than 40 years were considered. This latter criterion was decided to exclude women with age-related infertility since, in older women, these cases become undistinguishable from those with unexplained infertility (Somigliana *et al.*, 2016; ESHRE Capri Workshop Group, 2017). In addition, women were not included if they reported previous gynecological surgery or if they were diagnosed with irregular menstrual cycles, uterine malformations, endometrial polyps, endometriosis, adenomyosis, pelvic inflammatory disease or hydrosalpinx. This choice was taken to limit confounding. Women with fibroids with a mean diameter $\geq$5 cm were excluded since this was an indication to surgery. We were exclusively interested in women with pure severe male infertility and in those with unexplained infertility. Therefore, we excluded women with other known factors of infertility. In line with this intent, we also excluded women with submucosal fibroids types 0–3 because a causal relation with infertility is deemed ascertained (Somigliana *et al.*, 2007; Hur *et al.*, 2019). We first selected the group of those whose partner was cryptozoospermic (semen analyses repeatedly showing a sperm concentration below 1 million/ml). Subsequently, these women were matched in a ratio 1:1 by age ($\pm$1 year) and study period (with the following women fulfilling the selection criteria within 6 months) to a group of women with unexplained infertility. In both study groups, women were recruited based on the ultrasound assessment made at the time of the diagnostic work-up for infertility regardless of the achievement of subsequent pregnancies. According to the null hypothesis, the presence of intramural or subserosal fibroids was not considered a cause of infertility and therefore women with these lesions could be similarly included in both study groups. The primary aim of the study was verifying this hypothesis, thus comparing the frequency of fibroids in these two groups. The study was approved by the local ethical committee (*Comitato Etico Milano Area 2, N. 501/2020*). Women did not sign an informed consent since the study was retrospective. However, all women who were referred to our unit provided an informed consent for their data to be used for research purposes and those denying this consent were excluded.

The policy of our unit for fibroids management is generally conservative. We recommend surgery only for submucosal fibroids type 0, 1 and 2, for intramural or subserosal fibroids larger than 5 cm and for those associated with symptoms such as metrorrhagia, pelvic pain or abdominal discomfort. For type 3 fibroids, a shared decision with the woman was taken. We exclusively recruited women who underwent a complete diagnostic work-up. This assessment included a serum evaluation (FSH and estradiol in early follicular phase, progesterone in 2–3 independent assessments around the window of implantation, anti-Mullerian hormone and antibodies against *Chlamydia trachomatis*), two semen analyses and, in the absence of a severe male factor cause of infertility, a hystero-salpingo contrast sonography (HyCoSy) to assess tubal patency. Semen analyses were performed and interpreted based on WHO recommendations (WHO (World Health Organisation), 2010). In addition, the women systematically underwent an in-depth transvaginal ultrasonography in a dedicated setting. The ultrasound assessments were exclusively performed by five expert physicians with at least 5 years of experience in transvaginal ultrasonography. A standardized and meticulous evaluation of the pelvis was performed (Groszmann and Benacerraf, 2016). If present, all fibroids were recorded (location and size). Their location was described according to the revised FIGO classification (Munro *et al.*, 2011, 2018). In cases of unclear location (possible distortion of the endometrial cavity), women could undergo hysterosonography or hysteroscopy to rule out the presence of submucosal lesions. Information that could be obtained from hystero-contrast sonography was not deemed sufficient. The mean dimension of the lesions was calculated as the mean of the three perpendicular diameters. Images were not systematically stored in our Unit, and they were therefore not available for review. Magnetic resonance imaging was not performed because the accuracy of sonography is high and the costs are lower (Shwayder and Sakhel, 2014; Lumsden *et al.*, 2015; Stewart, 2015). The information used in the study was obtained from medical records. Databases were exclusively used for the initial screening of eligible subjects.

Data analyses were performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 23.0. The study was conceived as a case–control study. Cases were women with unexplained infertility and controls were those with infertile partners. For continuous variables, normality was assessed using Shapiro–Wilk test. Data were reported as mean $\pm$ SD, median [interquartile range] or number (percentage) and compared using Student's *t*-test, non-parametric Mann–Whitney test or Fisher's exact test, as appropriate. The association of fibroids with infertility was explored using the OR. A logistic regression model was used to adjust for baseline characteristics found to significantly differ between the two groups. To better ascertain the possible confounding effect of age (due to the risk of inclusion of some cases of age-related infertility among those with unexplained infertility), the analysis was repeated including only women younger than 35 years. Finally, subgroup analyses were pre-planned for the number of lesions (one versus two or more), location (at least one lesion type 3–5 versus all lesions classified as type 6–7) and dimension (mean diameter of the larger fibroid $<$2 versus $\geq$2 cm).

We aimed at including 400 women (200 with severe male infertility and 200 with unexplained infertility). This sample size was calculated based on a 10% expected proportion of women with fibroids among

women with a male cause of infertility, claiming, as clinically relevant, a 2-fold higher proportion among women with unexplained infertility and setting type I and 2 errors at 0.05 and 0.20, respectively. Based on the characteristics of our population of infertile couples, we deemed that extending our retrospective investigation over a 5-year period (up to 2014) could allow this target to be reached.

Results

The flow diagram of the study is shown in Fig. 1. There were 205 women with severe male factor infertility identified. Matching was not possible in five cases, leaving 200 women with male infertility and 200 women with unexplained infertility for data analyses. Azoospermia was diagnosed in 52 cases of male infertility (26%). The remaining 148 cases of male infertility had cryptozoospermia (74%). Baseline characteristics of the studied subjects are shown in Table I. A statistically significant difference emerged for duration of infertility, parity and BMI.

Fibroids were diagnosed in 31 women with unexplained infertility and in 32 women with male factor infertility. The OR of carrying fibroids in women with unexplained infertility was 0.96 (95% CI: 0.56–1.65). The paired analysis (McNemar test) also failed to highlight any significant association ($P = 1.00$). The OR adjusted for BMI, parity, length of the menstrual cycle and duration of infertility was 0.91 (95% CI: 0.52–1.58). Parity was entered in the multivariate logistic model as a dichotomic variable, while BMI, length of the menstrual cycle and duration of infertility were entered as simplified ordinal variables as shown in Table I (as they were not normally distributed and could not be easily transformed into normal variables). The analysis was repeated in women younger than 35 years (N = 102 + 102). In this subgroup, fibroids were diagnosed in 10 women with unexplained infertility and in 18 women with male factor infertility. The OR of carrying fibroids in women with unexplained infertility was 0.51 (95% CI: 0.22–1.16). The paired analysis (McNemar test) also failed to highlight any significant association ($P = 0.15$). The OR adjusted for BMI, parity, length of the menstrual cycle and duration of infertility was 0.47 (95% CI: 0.20–1.11).

The subgroup analyses according to number, dimension and location of the fibroids are illustrated in Table II. ORs refer to the risk of being infertile (i.e. belonging to the group of women with unexplained infertility) when carrying fibroids. No significant associations emerged in the different subgroups.

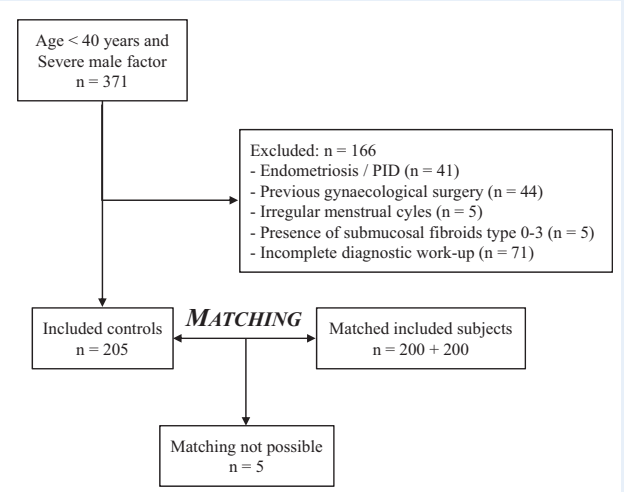

Figure 1. Flow diagram of the study. Initial criteria allowed us to identify 371 women aged <40 who were diagnosed with severe male infertility. Once we excluded those with patent causes of infertility, 205 remained. These latter women were matched by age and study period to a group of women with unexplained infertility. Matching was not possible in five cases. Overall, 200 women with severe male infertility and 200 with unexplained infertility were selected. PID, pelvic inflammatory disease.

Discussion

In this study, we failed to highlight any association between infertility and the presence of fibroids not encroaching the endometrial cavity. Restricting the analyses to women younger than 35 years and

Table I Baseline characteristics of the two groups.

Characteristics	Male infertility n = 200	Unexplained n = 200	P-value
Age (years)	34 [32–36]	34 [32–36]	0.92
BMI (kg/m^2)			0.005
<18	11 (5%)	12 (6%)	
18–25	130 (65%)	156 (78%)	
>25	59 (30%)	32 (16%)	
Smoking	40 (20%)	47 (24%)	0.47
Previous pregnancy	52 (26%)	50 (25%)	0.91
Previous deliveries	33 (17%)	16 (8%)	0.01
Duration of infertility (years)			0.002
≤2	82 (41%)	49 (24%)	
2–5	71 (36%)	94 (47%)	
≥5	47 (23%)	57 (29%)	
AFC	14 [9–20]	13 [8–18]	0.36
Day 3 serum FSH (IU/ml)	6.8 [5.9–8.3]	6.8 [5.7–8.4]	0.86
AMH (ng/ml)	2.1 [1.2–4.1]	2.1 [1.4–3.4]	0.76
Menstrual cycle duration (days)			0.08
<26	15 (7%)	17 (9%)	
26–30	156 (78%)	168 (84%)	
>30	29 (15%)	15 (7%)	
Race			0.78
Caucasian	170 (85%)	167 (84%)	
Others	30 (15%)	33 (16%)	

Data are presented as median [interquartile range] or number (%).
AFC, antral follicle count; AMH, anti-Mullerian hormone.

Table II Subgroup analyses according to number, dimension and location of fibroids.

Variable	Crude		Adjusted	
	Odds ratio [95% CI]	*P*-value	Odds ratio [95% CI]	*P*-value
Number of fibroids				
1	0.70 [0.37–1.36]	0.30	0.66 [0.34–1.29]	0.23
≥ 2	1.74 [0.71–4.26]	0.23	1.67 [0.66–4.21]	0.28
Dimension (mean diameter) (mm)				
<20	1.13 [0.61–2.08]	0.70	1.06 [0.57–1.99]	0.85
≥20	0.60 [0.21–1.68]	0.33	0.57 [0.20–1.64]	0.30
Location				
Intramural	0.86 [0.45–1.64]	0.65	0.81 [0.42–1.59]	0.54
Subserosal	1.19 [0.50–2.84]	0.69	1.11 [0.46–2.68]	0.82

Odds ratios refer to the risk of being infertile (i.e. belonging to the category of unexplained infertility).
Women were classified as carrying intramural fibroids if they had at least one lesion type 4–5. Those with only lesions type 6–7 were classified in the subserosal category.

performing subgroup analyses according to number of lesions, dimension and location failed to detect any subgroup at increased risk.

To the best of our knowledge, our study design has not been previously employed. In this regard, we must recognize that our methodological approach may appear, at first view, convoluted and unsettling. On the other hand, this study design has several strengths. Some typical confounders associated with both fibroids and infertility (such as parity, lifestyle habits and use of contraceptive methods) are overcome. In addition, the retrospective design that facilitated recruitment was not a major weakness. Indeed, the data were obtained within the context of a systematic and standardized ultrasound assessment. Major diagnostic inaccuracies were therefore unlikely. For those who may be interested in replicating our approach in other settings, the essential points of our study design are the following: (i) excluding older women to avoid inclusion of cases of age-related infertility among subjects with unexplained infertility; (ii) using as controls women whose infertility is certainly due to a male factor (though only including cases with severe impairment of semen); and (iii) excluding from both cases and controls women with known causes of infertility. On the other hand, despite the matching design, the two groups differed for some baseline variables, and we had to perform a multivariate analysis. Some of them, such as the difference in the duration of infertility, were expected (couples with severe male infertility are referred for IVF earlier) but we opted for an adjusting analysis rather than an additional criterion of matching. Of note, study design may also be considered to investigate the impact of type 3 fibroids, as well as other debated causes of infertility in the future.

Some limitations obviously remain. Firstly, misdiagnoses may have occurred. We may have erroneously included, among women with unexplained infertility, some cases with undetected causes of infertility such as mild/minimal endometriosis. Even if the performance of an in-depth sonography allowed us to exclude advanced forms of the disease, some cases of early endometriosis with only superficial peritoneal lesions could have been missed (Guerriero *et al.*, 2016). On the other hand, the relation between this form of the disease and infertility remains controversial and, if present, the magnitude of the effect is certainly modest (Guzick *et al.*, 1994; Balasch *et al.*, 1996; Somigliana *et al.*, 2017). To note, given the association between fibroids and endometriosis, this bias is expected to inflate rather than dilute the association with fibroids. The negative findings emerging from our analysis tend, therefore, to exclude a critical role of this bias. In this context, one may also consider the possibility to have erroneously included infertile women also among the controls (the male factor cases). In particular, we could have included women with female factor unexplained infertility. This may inevitably occur but, given the unremarkable findings of the female assessment, this group was expected to affect <10% of women (Evers, 2002). Finally, it must be acknowledged that we may have included some women with specific causes of infertility in the control group (e.g. those with tubal factor infertility). Of note, women with an infertile partner did not undergo hystero-salpingo contrast sonography to assess tubal patency. The impact of such a misdiagnosis is however expected to be minimal given the expected prevalence of tubal factor or other specific causes of infertility in the general population well below 10% (Somigliana *et al.*, 2016).

Secondly, a fibroid-related selection bias in the whole population studied is likely. Even if our inclusion criteria did not select women based on the dimension and number of fibroids, women with more advanced conditions could have been excluded because they previously underwent operations in other settings. Indeed, our own policy is also to recommend surgery for submucosal fibroids type 0, 1 and 2, for intramural and subserosal fibroids larger than 5 cm and for those nodes associated with symptoms. As a matter of fact, most included cases had few and small fibroids. This aspect must be clearly taken into consideration when drawing inferences from our findings. Larger multicenter studies using a similar study design are warranted to include a reasonable number of cases with more advanced conditions and to identify those fibroids that could be harmful (taking into consideration dimension, number and location). Even if our study fulfilled the planned sample size, it was insufficient to perform robust subgroup analyses.

Finally, the matching design could be an additional source of concern (Vandenbroucke *et al.*, 2007). The matching design in case–control studies is fraught with difficulties, especially as matching is attempted on several risk factors, some of which may be linked to the exposure of prime interest (as in age in our study). On the other hand, the detrimental effects of age on natural fertility and fibroids development are fundamental, but complex and certainly not linear. For this reason, we opted for matching rather multivariate analyses. We also decided to exclude women older than 40 to reduce confounders.

The optimal study design to disentangle the relation between fibroids and infertility is a prospective longitudinal observational cohort study that recruits women prior to initiating pregnancy seeking. More specifically, all recruited women would have to undergo a preliminary clinical and instrumental assessment (ultrasound or MRI) to record the presence of fibroids and to rule out other causes of infertility (including submucosal fibroids and male factor infertility). Moreover, women would have to be monitored over time to identify modifications in the number and dimension of the fibroids. Finally, the sample size should

be sufficiently large to include a consistent group of women with fibroids and to allow reliable subgroup analyses based on location and size of the lesions. Overall, this would be a very complex study that requires important organizational efforts and huge financial resources. In fact, such a study is not available.

However, despite some limitations, some studies have provided valuable insights and deserve to be briefly considered here. Bulletti *et al.* (1999) recruited women with unexplained infertility with and without fibroids (106 + 106) and evaluated the chances of natural pregnancy over the next 6 months. They exclusively included women with advanced conditions (at least one fibroid larger than 4 cm) and did not exclude submucosal lesions. They showed an OR of pregnancy in women without lesions of 2.2 (95% CI: 1.1–4.7). Johnson *et al.* (2012) and Karlsen *et al.* (2020) tried to draw some information using time to pregnancy rather than frequency of infertility. The main idea was that, if fibroids interfere with natural conception, affected women may need a longer time to conceive. However, both studies failed to show any significant association. Johnson *et al.* (2012) showed an adjusted OR of subfertility in women carrying fibroids of 1.0 (95% CI: 0.8–1.1). In the study from Karlsen *et al.* (2020) the adjusted OR was 1.3 (95% CI: 0.7–2.6). Of note, also in these studies, women with submucosal fibroids were not excluded.

Discerning clear clinical messages from the available conflicting literature is an arduous task (Somigliana *et al.*, 2021). There is the need to combine conflicting evidence. Firstly, there is biological experimental evidence suggesting a detrimental effect on the capacity of the endometrium to receive the embryos and on the motility of the uterus (Somigliana *et al.*, 2007; Stewart *et al.*, 2017). Secondly, IVF studies suggest a detrimental effect of intramural but not subserosal lesions (Pritts *et al.*, 2009; Rikhraj *et al.*, 2020). Thirdly, except for the study by Bulletti *et al.* (1999), the other two previously published informative studies on natural conception, and our findings, tend to rule out a harmful effect of fibroids (Johnson *et al.*, 2012; Karlsen *et al.*, 2020). The extreme heterogeneity of fibroids in terms of number, size and location further complicates the interpretation of the findings (Stewart *et al.*, 2016). In addition, from a clinical perspective, one has also to keep in mind that the benefits of surgery remain to be ascertained. Overall, it is tempting to speculate that small (<5 cm) non-submucosal fibroids should be considered unremarkable and should not be operated. Conversely, women carrying large fibroids may benefit from surgery, in particular if the lesions cause symptoms. However, a clear threshold cannot be extrapolated from the literature. Moreover, the clinical scenario may be more complicated to interpret when there are multiple small lesions and nuanced symptoms. A shared decision-making approach should be pursued in these cases. The counseling should take into consideration the history of previous interventions, symptoms, age, ovarian reserve, the potential delay in conception due to the need to wait for uterus healing, and possible obstetric complications associated to both the presence of fibroids or to previous surgery for fibroids.

In conclusion, small asymptomatic fibroids not encroaching the endometrial cavity do not appear to significantly affect fertility. However, this evidence does not exclude the possibility that, in some circumstances, fibroids can be deleterious. Further evidence is warranted to disentangle the precise characteristics of women who may be infertile because of fibroids and who may thus benefit from surgery.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

V.B.: implemented the study, collected the data and corrected the draft. M.R.: collaborated in the data collection and statistical analyses. I.L.V.: collaborated in data collection and corrected the draft. M.C.: collaborated in data collection and corrected the draft. L.M.: designed the study, discussed and corrected the draft. P.V.: implemented the study, provided supervision, corrected the draft. E.S.: designed the study, wrote the first draft and collaborated in the statistical analyses.

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Conflict of interest

E.S. reports grants from Ferring, grants and personal fees from Merck, and grants and personal fees from Theramex outside the submitted work. All the other authors do not have any competing interests to declare.

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