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Title

Long-term reproductive performance after surgery for ovarian endometrioma

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CONDENSATION

Ovarian endometrioma surgery *per se* does not appear to affect a woman's long-term reproductive performance or age of menopause.

ABSTRACT

Title

Long-term reproductive performance after surgery for ovarian endometrioma

Authors

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Objective

The aim of this study was to determine the long-term impact of different types of endometrioma surgery on reproductive performance and on age of menopause

Study Design

This was a longitudinal observational cohort study of 68 women with previous endometrioma surgery and 68 age- and weight-matched healthy controls. All participants' hospital records were reviewed and each woman completed a questionnaire and attended an interview. Pregnancy rates were compared between the study and control group. In the study group, pregnancy rates were compared before and after surgery.

Results

Amongst the 38 women desiring pregnancy after endometrioma surgery, 19 (50%) achieved a spontaneous pregnancy during the follow-up period. This was not significantly different from a pre-operative pregnancy rate of 48% (22/46).

Of these 19 patients, four achieved another pregnancy with fertility treatment. An additional eight patients conceived only with the help of fertility treatment, giving an overall long-term post-operative pregnancy rate of 71% (27/38). These results were significantly lower (p=0.0001) than the 98% (57/58) long-term natural pregnancy rate in the control group. Pregnancy rates in patients receiving fertility treatment significantly (p=0.001) increased from 7% (1/15) before surgery to 63% (12/19) post-operatively.

In post-menopausal women, the median (quartile) age at menopause was similar in the study (n=9) and control groups (n=6) [48 (45-52) *vs.* 49 (44-52) years, respectively]

Conclusion

Endometriomas *per se* appear to be the main cause of the reduced long-term reproductive performance of the affected patients, with little or no contribution from surgery. Furthermore, endometrioma surgery seems to improve the success rates of fertility treatment.

Key words

Reproductive performance

Ovarian endometrioma surgery

Fertility

Menopause age

BODY OF TEXT

Introduction

Surgery is the only effective treatment for symptomatic endometriomas [1, 2] but growing evidence suggests that excision of endometriomas causes significant damage to ovarian reserve [3]. The effect of this ovarian damage on reproductive performance remains largely uncertain.

There has only been one recent study investigating the long-term reproductive outcome after endometrioma surgery [4]. This retrospective ten-year follow-up study included 45 subfertile women who all underwent ablative surgery for ovarian endometrioma. The study reported a long-term pregnancy rate of 76%. However, the long-term impact of other types of surgery for ovarian endometriomas on reproductive performance remains to be investigated.

The influence of ovarian surgery for endometriomas on age of menopause has recently been investigated by Coccia and co-workers, who followed-up 239 women for up to 14 years after excision of endometrioma. They reported a 2.5% rate of premature ovarian failure and a trend towards earlier menopause in women undergoing bilateral endometrioma surgery [5].

The aim of the current study was to determine the long-term impact of different types of surgery for ovarian endometriomas on reproductive performance and age of menopause.

Material and Methods

Study Design and outcomes

This was a longitudinal observational cohort study of 68 women who had undergone surgery for ovarian endometrioma compared to a cohort of age- and body mass index (BMI)-matched healthy controls. The primary outcome was the long-term pregnancy rate after surgery for endometrioma. The secondary outcome was the age of menopause in women who were post-menopausal at the time of follow-up.

Ethical approval

This was given by the National Research Ethics Committee of the East Midlands (UK). Completion of the questionnaire by the participant was taken as consent to participate in the study.

Study Group

This included all patients who had undergone open or laparoscopic excision, ablation, drainage or unilateral oophorectomy for one or more ovarian endometrioma(s) between January 1999 and December 2009 at Royal Derby Hospital (RDH), UK.

Women who had undergone bilateral oophorectomy were excluded.

Potential participants were identified from the operative theatre database and their hospital records were screened to confirm their eligibility for the study. The hospital record of eligible patients were then reviewed and surgical data were collected including year of surgery, grade of surgeon, type of surgery, side

and size of the endometrioma and histological confirmation. Eligible patients were then sent an invitation letter, information sheet and study questionnaire covering the follow-up period. The questionnaire included questions about their fertility history before and after surgery and age of menopause. Non-responders were sent a reminder after 2-4 weeks.

Surgical procedures

Surgery was carried out by 18 consultant gynaecologists. In about half of the patients (53%) the procedure was carried out laparoscopically. In the majority of cases, the initial steps of surgery included mobilisation of the ovary followed by opening of the endometrioma with drainage of the contents and inspection of its interior. In cases treated by excision, the cyst capsule was stripped using two graspers and sent for histology. Any bleeding areas were diathermised with bipolar electro-coagulation. In cases of endometrioma ablation, the cyst's inner wall was ablated with either CO_2 laser or bipolar electro-coagulation. No suturing of the ovary was used. In some cases, an oophorectomy was carried out, removing the affected ovary. Similar procedures were followed in open cases.

Control Group

A control group of healthy women were recruited from RDH from April to July 2012. They were matched with the study group participants for age (± 2 years) and BMI (± 2 kg/m^2).

Women with any previous diagnosis of endometriosis, infertility, polycystic ovary syndrome, previous ovarian surgery or hysterectomy were excluded.

Statistical Analyses

All the data were entered into the Statistical Package for Social Sciences (SPSS), version 19, for analysis.

Numerical variables were compared using non-parametric tests, while categorical variables were compared using the Chi Square or Fisher's Exact tests. A p-value <0.05 was considered statistically significant.

Results

Study group

A total of 153 patients were identified from the theatre database to have had endometrioma surgery and fulfilled the inclusion criteria of the study. Of those, two patients were considered by their clinicians unsuitable to be contacted for the study due to special circumstances. Invitation letters and questionnaires were sent to the remaining 151 patients between July 2011 and March 2012. Four patients could not be reached due to change of address. Of the remaining 147 patients, one declined participation and 68 returned the completed questionnaire (46% response rate).

Of the 68 responders, 33 had undergone either excision (n=27) or ablation (n=6), 21 had had a unilateral oophorectomy and 14 had drainage of the endometrioma. The endometriomas had a median (quartile) diameter of 6.0 (4.8-8.0) cm.

Within the study group, 45 patients (66%) had unilateral endometrioma surgery and 52 (76%) had a single operation.

Comparison between study and control groups

The demographic characteristics of the study and control groups at the time of follow-up are given in Table 1.

Pregnancy rates

These were analysed only in women desiring fertility during the follow-up period, including 51 (75%) patients in the study group (38 after surgery) (Table 2) and 58 (85%) in the control group. In women who had undergone multiple surgeries, the analysis included pregnancies occurring since the first procedure.

Study versus control groups

Amongst the 38 women desiring pregnancy after surgery, 27 (71%) conceived at least once in the follow-up period, either naturally (n=19, 50%) or with the help of fertility treatment (n=8, 21%). Four of the 19 patients who conceived naturally, did so after conceiving with the help of fertility treatment (Table 2). The spontaneous pregnancy rate after surgery (50%) was significantly lower than the 98% (57/58) rate in the control group. A total of 19 endometrioma patients received fertility treatment during the post-operative follow-up period. Of those, 12 (63%) achieved a pregnancy. None of the control group women received fertility treatment.

Pre- versus post-operative pregnancies

In the study group, there was no statistically significant difference in spontaneous pregnancy rates before and after ovarian endometrioma surgery (Table 2).

The pregnancy rates in women receiving fertility treatment significantly (p=0.001) increased from 7% (1/15) before endometrioma surgery to 63% (12/19) post-operatively (Table 2). Before the endometrioma surgery, 15 patients received fertility treatment, including clomiphene citrate (CC, n=4), intra-uterine insemination (IUI, n=6) and in-vitro fertilisation (IVF, n=5). After the endometrioma surgery, 19 patients had fertility treatment, including CC (n=1), IUI (n=3) and IVF (n=15).

Total Number of children (including before and after surgery)

Women in the study group were significantly (p=0.001) more likely to remain childless during the follow-up period compared to women in the control group [11/51 (22%) *vs.* 1/58 (2%) respectively]. There was no statistically significant difference in the average number of children per woman between the two groups, although there was a trend towards a greater number of children in the control group (median, 2 *vs.* 1).

Age of menopause

Nine women in the study group and six in the control group were post-menopausal at the time of follow-up. The median (quartile) age of menopause

for the study group was 48 (45-52) years which was not different from that [49 (44-52)] of the control group.

Study group: analysis according to type of surgery

Women in the study group were divided into three subgroups according to the type of endometrioma surgery undertaken (excision/ablation, oophorectomy and drainage). Patients who had multiple procedures with more than one type of surgery were allocated to a subgroup according to the more radical procedure undertaken, i.e. in the following order: oophorectomy, excision/ablation, drainage. All the patients in the drainage group did not undergo any other additional type of surgery.

Table 3 describes the patient's characteristics across the groups and Table 4 shows the pregnancy rates according to type of endometrioma surgery. Table 5 presents the age of menopause in women undergoing endometrioma surgery in the different subgroups. There were more post-menopausal patients in the oophorectomy than in other subgroups (p=0.001), but the median age of menopause was similar in all subgroups.

Number and laterality of ovarian endometrioma surgeries

Figure 1 shows the long-term spontaneous and overall pregnancy rates according to the number and laterality of surgical procedures for endometrioma. There were no statistically significant differences between any of the results.

Comment

In this study, we have investigated the long-term reproductive performance in a cohort of patients with previous endometrioma surgery and compared the results with a matched group of healthy controls. To the best of our knowledge, this is the first study to address this important issue in women undergoing different types of endometrioma surgery. We found a significantly reduced long-term spontaneous pregnancy rate in the study group (50%) *versus* the control group (98%), suggesting a compromised reproductive performance in women with previous endometrioma surgery. We have also found similar natural pregnancy rates in the study group before and after endometrioma surgery, suggesting that surgery does not contribute to the adverse reproductive outcome.

Another finding of this study was the similar age of menopause in the two groups.

Study design

The ideal study design to investigate the long-term reproductive performance in women undergoing endometrioma surgery would be a prospective 10-year longitudinal cohort study or a randomised controlled trial with a control group of women with untreated endometriomas. Such a design would however not be feasible, as it would be unethical not to treat symptomatic endometriomas. We therefore think that the current cohort design including all surgically treated endometriomas is the best possible design for the objective of this study.

Response rate

Our response rate among the study group patients was 47% which is comparable to previous similar studies [6-8] .

Pregnancy rates

The *spontaneous* pregnancy rate for the study group (before and after surgery) was markedly lower than that of the control group. It is also lower than that expected in the general population (90% in the first year) [9, 10]. The overall combined pregnancy rate (including spontaneous and fertility treatment pregnancies) increased to 80% (Table 2), which was still significantly lower than for the controls. Our results are consistent with the study by Shimizu and co-workers who reported an overall long-term pregnancy rate of 76% (including spontaneous and IVF pregnancies) following ablation of endometrioma [4].

Women in the study group who sought fertility were more likely to remain childless compared to the control group.

Based on the above, it seems that women with endometriomas experience a significantly compromised reproductive performance. In order to investigate to what extent surgery could have contributed to the adverse reproductive performance in these women, pregnancy rates were compared before *versus* after surgery. In addition, pregnancy rates were compared between the excision/ablation *versus* drainage groups, the latter being used as a control due to the minimal or no ovarian damage expected with this treatment.

Our data showed similar spontaneous pregnancy rates before and after surgery as well as between different surgical modalities. These findings suggest that surgery does not contribute to the already compromised reproductive function in women with endometriomas. This may seem surprising given the fact that endometrioma surgery has been shown in our recent meta-analysis [3] to cause damage to ovarian reserve at least in the short- and medium-term. The possible explanation for this apparent discrepancy is that the post-operative reduction in ovarian reserve is not severe enough to compromise reproductive function. Another explanation is that the surgical damage is only temporary with recovery of the ovarian reserve in the long-term. This is further supported by the fact that age of menopause does not seem to be affected by surgery for endometrioma.

On the other hand, surgery for ovarian endometriomas seems to have markedly improved the success rates of fertility treatment. This is in disagreement with a recent Cochrane review which suggests that surgery for endometriomas does not seem to improve assisted reproductive treatment outcomes [11]. However, the authors of that review commented that there was not enough evidence for or against surgery at present and that further studies are required. The marked increase in fertility treatment success rate after surgery in our study may be explained by the fact that a much larger proportion of patients underwent IVF (rather than CC or IUI treatment) after endometrioma surgery.

Effect of number of surgeries (single/multiple) and laterality (unilateral/bilateral)

These subgroup analyses were carried out to try and account for possible confounding factors in our study group. There was no statistically significant difference in long-term pregnancy rates after single *versus* multiple endometrioma surgery. Similarly, pregnancy rates were similar after unilateral *versus* bilateral surgery. This is surprising, as bilateral ovarian surgery is expected to cause more damage to ovarian reserve [12, 13]. However, these results should be interpreted with caution given the small numbers in the subgroups analysed.

Age of menopause

The number of women who had their menopause during the follow-up period in our study group was small (n=9). It is therefore difficult to make firm conclusions about the findings. However, it would appear that the age of menopause is not affected by ovarian endometrioma or its surgical treatment. This may be because the magnitude of the damage caused by the surgery to the ovarian reserve is not enough to translate into early menopause.

There were more post-menopausal women in the oophorectomy compared to the other ovarian surgery subgroups (Table 5). However, this is most likely due to the age difference between the subgroups at the time of follow-up, as there was a trend for women in the oophorectomy group to be ten years older than women in the excision/ablation group (Table 3). Furthermore, the average age of menopause was similar across the subgroups.

Limitations

The main limitation of this study is its retrospective design which could have introduced potential bias. For example, the surgical technique may not have been identical in all cases, as surgery was carried out by a number of surgeons over an 11- year period. However, all surgeons were senior, with similar levels of experience and the procedures for ovarian surgery were fairly standard.

The other limitation is the study size (68 patients in each group). However, our study is larger than the only other study on the subject [4].

Implications of the results

Based on the results presented in this study, it appears that endometriomas *per se* are the main cause of the compromised reproductive function of these patients, with little or no contribution from surgery. Furthermore, surgery seems to enhance the success rate of fertility treatment. These findings are reassuring for patients with endometrioma who are seeking fertility and need surgery for their disease.

Conclusions

Women with ovarian endometriomas seem to have a significantly reduced reproductive performance compared to the general population. Surgery for this disease doesn't appear to further compromise reproductive function. On the contrary, surgery seems to improve success of fertility treatment. Further studies are required to validate and support these findings.

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Table 1

Demographic characteristics for the study & control groups at the time of follow-up

Table 2

Pregnancy rates before & after endometrioma surgery

Table 3

Study group: comparison of characteristics between women who have undergone different types of surgeries

Table 4

Comparison of pregnancy rates between subgroups of study patients undergoing different types of endometrioma surgery including Excision/Ablation (n=33), Oophorectomy (n=21) and Drainage (n=14)

Table 5

Comparison of age of menopause between subgroups of study patients undergoing different types of endometrioma surgery

Figure 1

Long-term pregnancy rates according to number and laterality of surgery

Table 1 *Demographic characteristics for the study & control groups at the time of follow-up*

Numerical data compared using Mann Whitney U test and proportions compared using χ^2

	STUDY GROUP (n=68)	**CONTROL GROUP (n=68)**	**p-value**
Characteristic	***median (quartiles)***	***median (quartiles)***	
Age (years)	40 (34-46)	41 (35-46)	NS
BMI (kg/m^2)	25 (22-29)	25 (22-28)	NS
	n (%)	***n (%)***	
Smoking	8 (12)	10 (15)	NS
Regular Menstruation	37 (56)	37 (55)	NS
Contraception			
IUS	5 (8)	17 (25)	0.009
Desiring Pregnancy	51 (75)	58 (85)	NS

NS=non-significant

Table 2 *Pregnancy rates before & after endometrioma surgery*

	Pregnancy rates		
	Before (1st) endometrioma surgery	After (1st) endometrioma surgery	Overall (before and after surgery)
Spontaneous	22/46 (48%)	19/38 (50%)	33/51 (65%)
Fertility treatment	1/15 (7%)	12/19 (63%) **	12/26 (46%)
Overall	23/46 (50%)	27/38 (71%)	41/51 (80%)

** p=0.001

NB: 4 of the 19 patients who conceived naturally also achieved a pregnancy with the help of fertility treatment and are included in the 12 pregnancies with fertility treatment

Table 3 *Study group: comparison of characteristics between women who have undergone different types of surgeries*

Numerical data compared using Mann Whitney U test and proportions compared using Chi Square

	EXCISION/ABLATION (n=33)	**OOPHORECTOMY (n=21)**	**DRAINAGE (n=14)**	**OVERALL (n=68)**	**p-value**
Characteristic	***Median (quartiles)***	***Median (quartiles)***	***Median (quartiles)***	***Median (quartiles)***	
Age (years)	36 (33-41)	46 (42-52)	42 (39-49)	40 (34-46)	NS
BMI (kg/m^2)	25 (23-31)	23 (22-27)	25 (22-27)	25 (22-29)	NS
Cyst diameter (cm)	6.5 (4.3-8)	5 (2-7)	6 (5-7)	5 (4-7)	NS
SURGERY	***n (%)***	***n (%)***	***n (%)***	***n (%)***	
Unilateral	15 (45)	17 (81)	13 (93)	45 (66)	0.008
Bilateral	18 (55)	4 (19)	1 (7)	23 (34)	
Single	22 (67)	16 (76)	14 (100)	52 (76)	NS
Multiple	11 (33)	5 (24)	0	16 (24)	

NS=non-significant

Table 4 *Comparison of pregnancy rates between subgroups of study patients undergoing different types of endometrioma surgery including Excision/Ablation (n=33), Oophorectomy (n=21) and Drainage (n=14).*

Data compared using Chi Square.

		Pregnancy rates				
		Excision/Ablation	**Oophorectomy**	**Drainage**	**Overall**	**P-value**
		n/n[1] (%)	***n/n[1] (%)***	***n/n[1] (%)***	***n/n[1] (%)***	
Before + After surgery	Overall	17/29 (59)	10/12 (83)	6/10 (60)	33/51 (65)	NS
After surgery	Overall	19/25 (76)	5/7 (71)	4/6 (67)	28/38 (74)	NS
	Spontaneous	13/25 (52)	4/7 (57)	2/6 (33)	19/38 (50)	NS
	Fertility treatment	9/13 (69)	1/3 (33)	2/3 (67)	12/19 (63)	NS

n= number of women achieving at least one pregnancy

n^1= total number of women seeking fertility

NS=non-significant

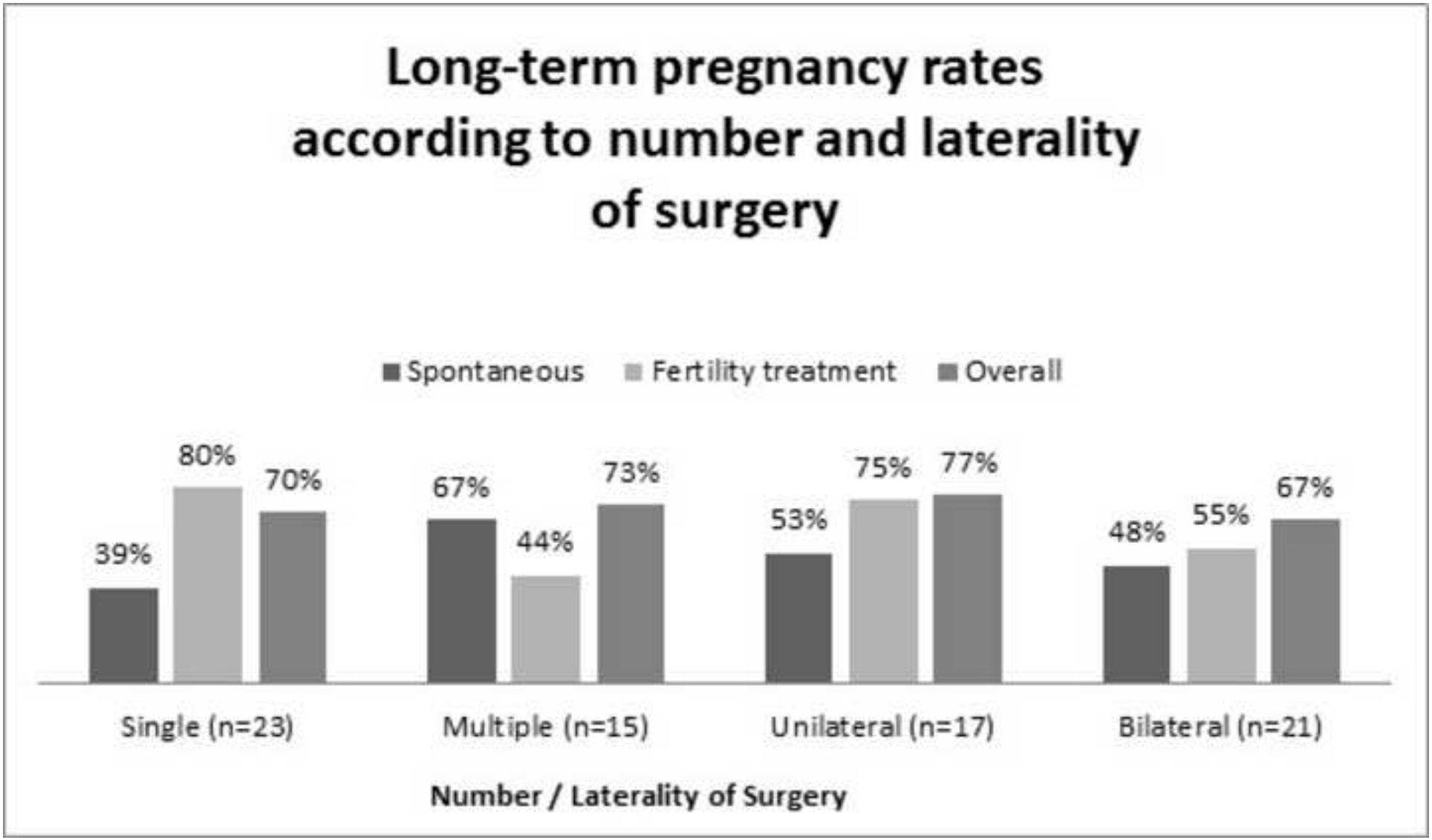
Table 5 *Comparison of* age of menopause *between subgroups of study patients undergoing different types of endometrioma surgery.*

Numerical data compared using Mann Whitney U test and proportions compared using Chi Square

	Post-menopausal n (%)	**Age of menopause (years) Median (quartile)**
Excision/ablation (n=33)	1 (<1)	47
Oophorectomy (n=21)	7 (33)*	48 (44-51)
Drainage (n=14)	1 (<1)	54
Overall (n=68)	9 (13)	48 (45-52)

* p=0.001

Fig1.jpg


Long-term pregnancy rates according to number and laterality of surgery
Spontaneous
Fertility treatment
Overall
39%
80%
70%
67%
44%
73%
53%
75%
77%
48%
55%
67%
Single (n=23)
Multiple (n=15)
Unilateral (n=17)
Bilateral (n=21)
Number / Laterality of Surgery