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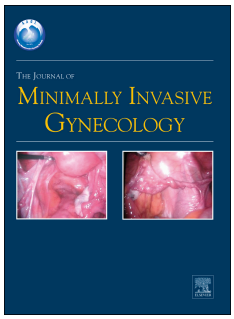

The impact of laparoscopic surgical management of deep endometriosis on pregnancy rate

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The impact of laparoscopic surgical management of deep endometriosis on pregnancy rate

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Capsule: Laparoscopic treatment of lesions is an effective treatment for deep endometriosis-related infertility. The treatment of multiple lesions is associated with higher chance of conception.

Running title: Laparoscopic treatment of deep endometriosis and pregnancy-rate

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Objectives: To evaluate the impact of laparoscopic excision of lesions on deep endometriosis related infertility.

Design: Retrospective study

Setting: Endometriosis tertiary referral centre

Population: A group of 115 patients who had undergone laparoscopic surgery for infertility with histological confirmation of deep endometriosis.

Methods: Patients medical records and operative reports were reviewed. Telephone interviews were conducted for long-term follow up of fertility outcomes.

Main outcome and measures: Evaluation of fertility outcome following laparoscopic treatment of deep endometriosis by spontaneous conception and by assisted reproductive technology (ART) correlated with lesion number, size and localization (anterior, posterolateral, douglas and multiple localization).

Results: After a mean follow up of 22 months the overall pregnancy rate was 54.78 % (n=63) with a live-birth rate of 42.6% (n=49).

Amongst those patients given the chance to conceive spontaneously (n=70) the overall pregnancy rate was 60% (n=42), 38.5% (n=27) conceived spontaneously and 21.4% (n=15) by ART.

The removal of multiple localization of the disease was associated with a higher pregnancy rate after surgery. When comparing isolated lesion size and disease localization there was no difference in pregnancy rate. Furthermore those patients who underwent surgical eradication of the disease for the first time had a higher pregnancy rate (OR 4.18).

Conclusions: This study demonstrates that laparoscopic excision of deep endometriosis enhances pregnancy rate, both by means of spontaneous conception or following use of assisted reproductive techniques. First surgical treatment of multiple lesions was associated with higher pregnancy rates while isolated lesions influenced the pregnancy-rate irrespective of their location and size.

Key Words: infertility, deep endometriosis, laparoscopic treatment, lesion localization, pregnancy-rate

Introduction

Endometriosis is a chronic gynaecological disease characterized by ectopic implants of endometrial tissue outside the uterine cavity. Although the prevalence of endometriosis is difficult to determine, it is estimated to affect 5-15% of women mainly of reproductive age [1].

Endometriosis significantly affects women's quality of life causing symptoms of pelvic pain, dysmenorrhoea, dyspareunia, dyschezia and infertility. The effect of endometriosis on fertility remains controversial with several proposed mechanisms contributing to a negative impact on fecundity. Although the precise mechanism has yet to be determined, the prevalence of endometriosis among infertile women has been reported in up to 50% of women, and 30-50% of patients with endometriosis are infertile [2]. The two most reliable hypothesis explaining endometriosis related infertility are increased intraperitoneal inflammation and distorted anatomy secondary to dense pelvic adhesions [3]. Reduced embryo and oocyte quality may also be implicated, in addition to impaired utero-tubal transport, which has also been described [4,5].

Laparoscopic surgical treatment of mild endometriosis whether by means of ablation or excision has proven effective in improving fertility when compared to diagnostic laparoscopy alone. These findings were confirmed by a recent Cochrane review demonstrating that laparoscopic surgery for treatment of endometriosis reduces overall pain and increases live birth or on going pregnancy rates [6].

Deep infiltrating endometriosis (DIE) is defined as invasion of greater than 5 mm of the peritoneal surface by endometriotic lesions most commonly located at the recto-vaginal septum, uterosacral ligaments, pararectal fossa and vesicouterine fold.

A lack of available data regarding surgical treatment of DIE and subsequent pregnancy rate exists.

The published guidelines regarding surgical management of infertility associated with DIE is varied with inconclusive data regarding optimal management of stage III and IV disease. Despite recommendations from a number of international bodies, controversy and uncertainty remains with no agreed consensus. Both ESHRE and ASRM advocate operative laparoscopy as a means of enhancing spontaneous pregnancy rates for women with AFS/ASRM stage 1-2 endometriosis, however, due to a paucity of evidence no firm

recommendations exist regarding optimal surgical management for stage 3-4 endometriosis [7,8].

The main aim of this study was to evaluate the impact of surgical treatment of DIE on pregnancy rate in patients with unexplained infertility. Our secondary objective was to analyse the effect of nodule number, size and disease localisation on DIE associated infertility.

Materials and Methods

This study included all patients of childbearing age (under 38 years of age) presenting with a minimum one-year history of unexplained infertility with imaging and/or symptoms suggestive of DIE. The study population comprised of 138 women who underwent laparoscopic treatment of DIE at the Department of Gynaecology, at Strasbourg University Hospital between March 2009 and September 2012. Institutional review board (IRB) approval was obtained.

Patients were retrospectively selected, based on the following criteria: histological confirmation of diagnosis of DIE, primary infertility, regular menstrual cycles (24 to 35 days), no menses abnormalities, no ultrasonographic or radiological features suggestive of endometriomas in order to focus specifically on the relationship between infertility and DIE alone, no previous surgery for infertility or endometrioma, no history of pelvic inflammatory disease. Data regarding semen analysis of the women's partner was also collected and a count < 15 million/ml was considered an exclusion criteria. Concomitant diagnosis of an associated endometrioma was also considered an exclusion criterion.

A subgroup of 37 patients were included, despite being previously operated for DIE related pain, as they had not wished to conceive at the time of their initial surgery and were operated in the same hospital by other surgeons making it possible to retrieve operative details. Amongst these patients, 17 were operated because of a symptomatic rectovaginal nodule (3 required rectosigmoid resection), 3 bladder nodules, 8 peritoneal implants, 2 cases of endometriosis were diagnosed in the specimens retrieved following appendectomy and in 7 the localization was not specified.

Patient characteristics including age, BMI, duration of unexplained infertility, previous ART treatment, previous surgery and preoperative symptom profile were recorded and are summarized in Table 1.

Review of all patients' medical records with documentation of endometriosis location, operative treatment, intra-operative and post-operative complications were recorded. Long-term follow up information was retrieved by telephone interview.

Preoperative findings including symptom profile and additional investigations (MRI, hormonal profile, transvaginal ultrasound evaluations, hysterosalpingography and diagnostic hysteroscopy) were collected.

Patients were divided according to disease localization into four subgroups: anterior, postero-lateral, pouch of Douglas and multiple localization.

The anterior group comprised of all patients with a nodule involving the bladder localized at the level of the vesico-vaginal septum or bladder dome.

The posterolateral group included all patients with isolated unilateral uterosacral ligament involvement.

The Douglas group included all patients with nodules confined to the recto-vaginal septum, sigmoid, rectum or torus uterinus.

The multiple localization group consisted of patients with 2 or more nodules at different sites i.e. nodule of both rectovaginal septum and uterosacral ligament or bilateral uterosacral disease. In cases of a large posterior nodule involving the pouch of Douglas and the uterosacral ligaments, the patients were considered as affected by a single nodule and the site defined according to the main area affected.

Finally, histological analysis of endometriotic nodule size was recorded and the dimensions compared between patients who did or did not conceive in a bid to understand the relevance of nodule size on fertility. Patients with multiple disease localization were excluded from analysis

All women were followed up by telephone interview between 12 and 24 months after surgery. Information regarding symptoms of pain (dysmenorrhoea, dyspareunia, chronic pelvic pain, dyschezia and dysuria), fertility and modality of conception (spontaneous/ART), newborn weight, time and mode of delivery were also recorded. No patients were prescribed postoperative medical therapy.

Successful conception was defined as a clinical pregnancy where a gestational sac was visualised on ultrasound.

All surgical procedures were performed by a single surgeon (AW) experienced in minimally invasive treatment of endometriosis. In all cases careful evaluation of the entire abdominal

cavity was performed and all visible endometriotic implants were removed and adhesions divided. Surgical technique included dissection, coagulation and excision using bipolar forceps and scissors or a monopolar hook. Bowel lesions were carefully evaluated and either a shaving, discoid or segmental resection performed depending on extent of infiltration. Ureterolysis was also performed and in some cases ureteric resection and re-anastomosis. In all cases a tubal patency dye test was performed at the end of the procedure (Table 2).

Statistical Analysis

The data was analysed using a computed based software Prism version 6.00, GraphPad Software, La Jolla California USA. The continuous data were assessed for distribution with D'Agostino - Pirson normality test. The parametric and non-parametric data was analysed using t-test and the Mann-Witney test. The categorical data was analysed with the Fisher exact test through a contingency table. Statistically significant differences were defined as those with a P-value <0.05.

Results

Amongst the 138 patients included in this study 23 (15.9%) were excluded due to missing long term follow up data, leaving a total of 115.

During the 2-year follow up 54.78 % (n=63) of patients conceived, with an overall birth rate of 42.6 % (n=49), the spontaneous pregnancy-rate was 26% (n=30) whilst 28,7% (n=33) conceived with ART.

The mean interval between surgery and confirmed pregnancy was 10.6 months (median 8), with a mean conception time of 11.72 when conceiving by means of ART and 10.19 for those conceiving spontaneously. Furthermore 2 patients were pregnant at the time of follow up, with 6 patients reporting more than one pregnancy: 3 patients reported 2 live births, 1 patient 2 live births and 1 voluntary termination of pregnancy and a further 2 patients reported 1 live birth and 1 miscarriage.

In order to determine if the removal of DIE lesion enhances the spontaneous pregnancy rate we divided the patients into two groups; those given the chance to conceive spontaneously for at least 12 months and those referred directly to ART because of prior history of failed ART attempt, according to our intern protocol.

Amongst those patients given the chance to conceive spontaneously (n=70) the overall pregnancy rate was 60 %, (n = 42) amongst which 38.5% (n=27) conceived spontaneously and a further 21.4% (n=15) with ART, with a live-birth rate of 54.4%.

Regarding the group referred to ART (n = 45) the pregnancy rate was 40% (n=18), with patients conceiving following ART after a mean of 1.6 induction cycles (rage 1-3).

A further 3 patients (6.6%) became pregnant spontaneously whilst awaiting medical assisted reproduction, the live-birth rate was 28.8% (Figure 1 and 2).

The disease localization analysis showed no significant differences in pregnancy-rate comparing single site lesions involving either the posterior or anterior compartment. There was, however, a significant higher pregnancy rate in those patients undergoing surgical excision of multiple localization of disease ($p < 0.05$) (OR 2.74; 95% CI 1.27 to 5.89) (Table 3).

The analysis of nodule dimension did not show any significant difference.

When patients were divided according to the occurrence of previous surgery for endometriosis, those who underwent at least one surgical intervention for endometriosis

prior to being enrolled in this study had a significantly lower pregnancy rate than those operated for the first time ($p < 0.001$). Indeed in patients previously operated, the pregnancy rate was 24.3% while in the other group it was 69.2% (OR 4.18; 95% CI 1.98 to 8.83) (Table 3).

In 13 cases it was not possible to completely excise the endometriotic lesions because of the potential risk of complications: 9 of them conceived (69.3%) whilst 7 delivered successfully (53.8%). There was no significant difference in pregnancy rates between patients with complete and incomplete surgery was not significant ($p=0.37$).

Discussion:

This study demonstrates that surgical treatment of endometriosis in young patients with severe disease is beneficial in enhancing both pregnancy and live-birth rates. The effect of surgery is greatest when being performed for the first time in patients with multiple site disease, irrespective of nodule size and disease localization. Excision of diseased tissue restores normal anatomy, significantly increasing the chance of spontaneous conception.

Laparoscopy remains the gold standard for the treatment of DIE by improving women's chances of conceiving spontaneously, enabling patients to avoid ART treatment and minimizing healthcare costs [9,10].

Previous studies have demonstrated that surgery for DIE improves both symptom relief and quality of life outcomes, however, the debate on subsequent fertility remains largely unanswered. This study, in keeping with previous randomized observational studies, advocates surgical therapy as a means for increasing fertility in women with endometriosis, revealing pregnancy rates up to 59% [10,11]. More than one study also showed significant benefits of laparoscopic surgery on pregnancy rates and live birth rates in cases of mild endometriosis, with earlier resumption of intercourse and shorter time to conception when compared to laparotomy (AFS stage 1-2) [12-16].

The pathogenesis of DIE-associated infertility includes increases in inflammatory mediators, pre-ovulatory changes in the follicle content and changes in the intra-peritoneal environment which adversely affect fertilisation and implantation [17,18].

The combination of surgery followed by ART has previously been reported as a more effective strategy in treating infertility. Surgical treatment may avoid pre-ovulatory impairment of the oocyte, whilst ART can evade the effect of anatomical distortion [19].

The distribution of lesions in our study confirmed predominance for the posterior pelvic compartment (retrocervix, rectovaginal septum, rectosigmoid, uterosacral ligaments and posterior vaginal fornix) followed by involvement of the anterior pelvic compartment (round ligaments, uterovesical fold, bladder) and lastly multiple disease localization.

To our knowledge this is the first study to analyse pregnancy rates according to different disease localization, with no significant difference found when comparing single site disease involvement.

Despite a slightly increased impact of posterior compartment disease, this study confirmed a much lower reported association between anterior compartment disease involvement and infertility, with a pregnancy rate of 37% after surgical treatment [20,21].

The surgical treatment of multiple localization DIE significantly improved pregnancy rates when compared with isolated lesions suggesting a more pronounced effect on the pelvic environment and subsequent chance of conception, with greater anatomical distortion as a possible explanation. There is however a distinct lack of data in the literature regarding the effect of single site or multiple DIE lesions on fertility outcomes.

The present study also showed no significant influence of nodule size on fertility outcomes. As our unit is a tertiary referral centre for the treatment of DIE, the smallest nodule size in our cohort was 1.9 cm, representing a potential source of bias when evaluating this parameter.

The dilemma regarding radicality of treatment is still on-going [22]. Whilst simply removing peritoneal implants restores the peritoneal environment and enhances fertility, others feel that an aggressive resection of all residual disease is necessary [15,23-25]. Stepniewska et al reported higher pregnancy rate in patients undergoing complete excision of disease involving the posterior compartment, including bowel resection when required, in comparison to those patients in whom residual disease remained (35 % vs 21%)[23].

Extensive surgery in women with infertility related DIE is often discouraged due to the perceived risk of severe intra and post-operative complications even when performed by an experienced surgeon in a tertiary referral centre [26,27]. Nevertheless in our series the intraoperative complication rate remained low (2.6%) consisting largely of minor complications while the overall postoperative complication rate was 7.8% of which 5 cases were attributed to major complications according to the Dindo Clavien classification [28].

Complications related to endometriosis surgery are an in evitable part of any surgical practice. Awareness of the perceived benefits of a procedure and its related morbidity is of paramount importance and a balance between radicality of disease excision and preservation of organ function should be struck. In this series small subcentimetric nodules were not excised in 13 cases because of potential risk of compromising nerve supply or

bowel function, whilst having little perceived impact on pregnancy outcomes. Although it is not possible to refute that, some active lesions may have been left in place, it is unlikely they would have significantly impacted on fertility outcomes due to the effect of peritonization of the area and subsequent exclusion from the peritoneal cavity, a theory postulated in previous studies and supported by our data [29].

Due to the retrospective nature of this study it was not possible to differentiate the presence of concomitant adenomyosis amongst patients, a factor that may itself have a negative impact on pregnancy rates and coexists with DIE in 48.7% of cases [30,31].

Another important outcome of our study was the negative influence of repeated surgery on fertility outcomes with significantly higher pregnancy rates in those patient undergoing endometriosis surgery for the first time (24.3% vs 69.2).

In this study the mean time to conception was 10.6 months, a finding slightly longer when compared with similar data in the literature. This small discrepancy could be attributed to inconsistencies with the definition of terms. Notably, the time elapsed between surgery and conception is often described using interchangeable terms such as median time, mean time, days to reach half of pregnancy, or monthly fecundity rates making accurate data interpretation difficult. In case of severe endometriosis that may require bowel resection, Daraï et al reported a median time to conception of 11 in 2011, reduced to 6 months in those patients who conceived spontaneously, with a rise to 20 months in those undergoing IVF. Stepniewska reported time to reach half the pregnancy as varying between 696 days to 1417 according to the completeness of the surgery[12,23,24].

The pivotal role of first surgery for the treatment of DIE and the advantages of referring patients to specialized centres has been well documented, with our data further reinforcing this concept. Timely surgical treatment in patients wishing to conceive is equally important with the life-table analysis confirming higher chance of conception within two years of surgery [23,24,32,33].

In conclusion, these results demonstrate that laparoscopic surgery for infertility related DIE significantly improves pregnancy rates. Patients with multiple localization of the disease represent a cohort most likely to benefit in terms of positive fertility outcome as well those undergoing DIE surgery for the first time.

These findings can be incorporated into everyday practice, and used to counsel patients appropriately, providing an individualised, patient-centred approach and therapeutic

304 strategy in women with severe DIE wishing to conceive. Laparoscopic excision alleviates
305 painful symptoms, improves sexual function, strengthens couple's relationships and
306 positively impacts on women's quality of life, further illustrating the benefits of surgical
307 treatment for endometriosis related infertility [34].

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Legend of figures

Figure 1: The graph shows the rate of spontaneous conception or following ART in the group of patients who got the chance to conceive spontaneously (n=70) and in those referred directly to ART (n=45).

Figure 2: (A) cumulative percentage regardless postoperative fertility treatment; (B) cumulative percentage of conception according to the chance to conceive spontaneously. ART: patients referred directly to assisted reproduction; Spontaneous: Patients who got the chance to conceive spontaneously for 12 months and than referred to ART.

Table 1: Characteristics of the patients included in the study.

Characteristic	Patients (n =115)
Age *(mean; SD)*	30.3 ± 5.78
BMI *(mean; SD)*	26.3 ± 3.02
Duration of infertility (mo) *(mean; SD)*	22.6 ± 8.52
Preoperative ART (*n; %*)	45 (39.1)
Preoperative medical treatment [1] (*n, percentage*)	19 (16.5)
Previous Surgery[2] (*n; %*)	49 (41.6)
Previous surgery for Endometriosis (*n; %*)	37 (32.1)
Previous surgery for other indication [3] (*n; %*)	25 (21.7)
Preoperative Pain Symptoms (*n; %*)	101 (87.8)

[1] *5 patients were treating at moment of surgery with oral contraceptives and 14 with GnRH analogue*
[2] *13 patients underwent more then one procedure*
[3] *Indication: 15 appendectomy, 5 cholecystectomy, 1 rectosigmoid resection, 1 umbilical hernia and 3 non-endometriotic ovarian cyst*

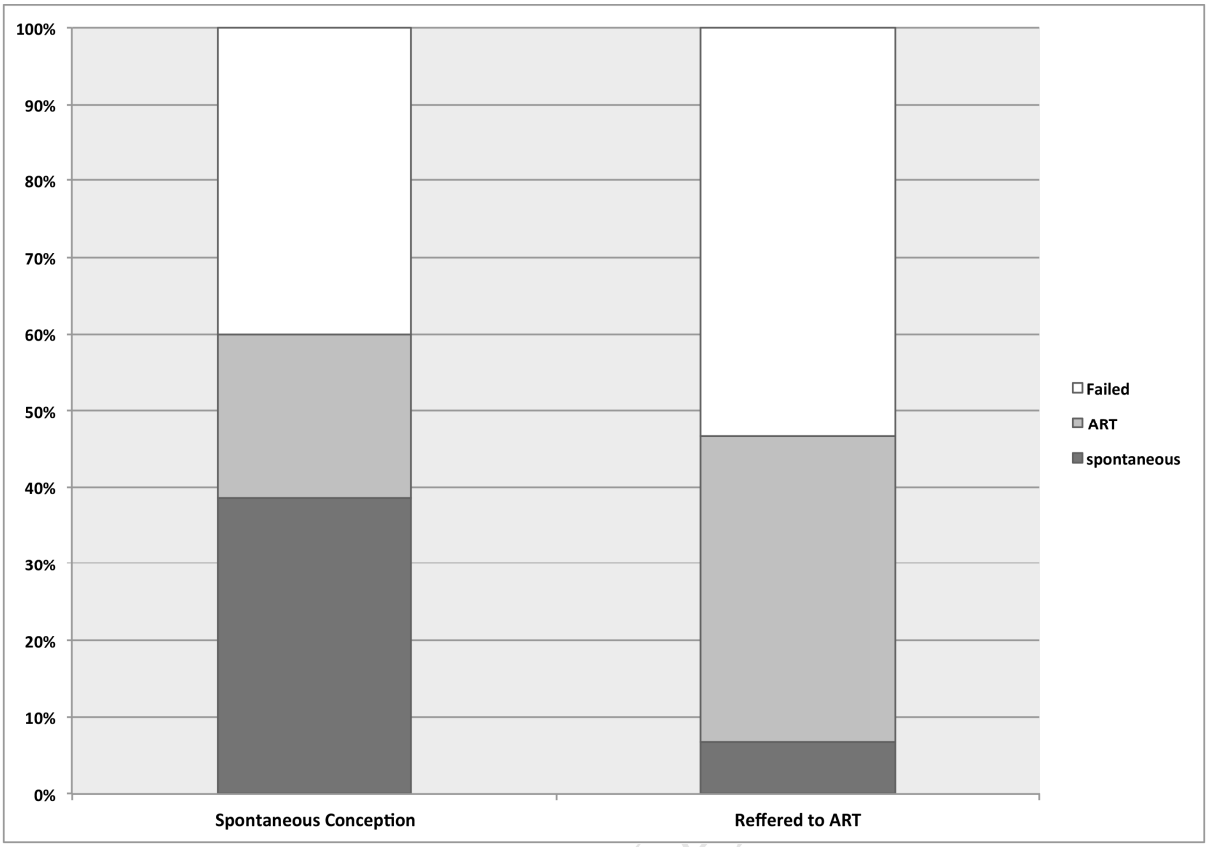
Table 2: Details of the procedure and of the follow up.

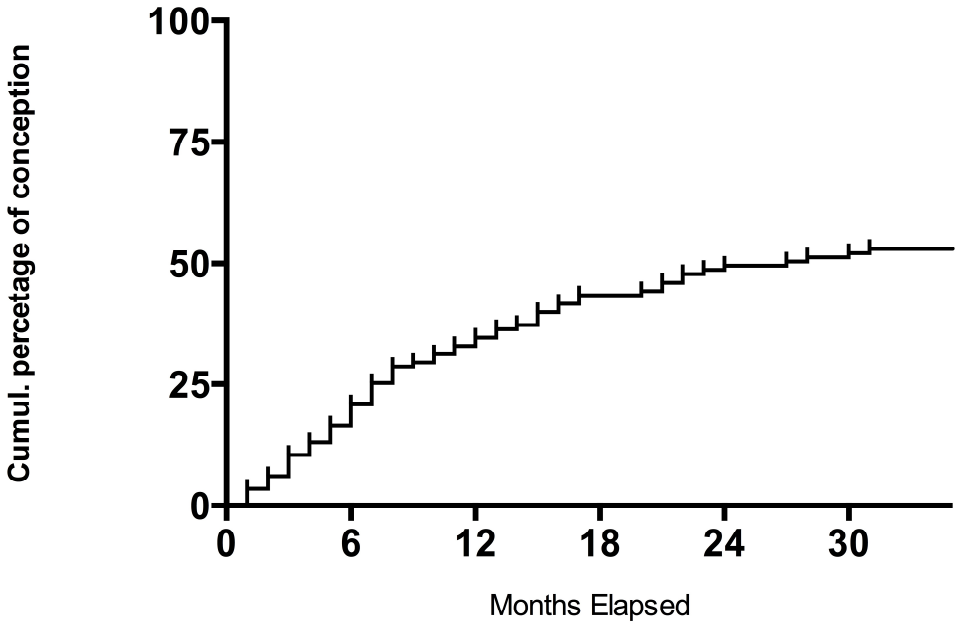
Characteristic	Patients (n =115)
Duration of Surgery *(min) (mean; SD)*	144 ± 57.3
Hospitalization *(days)(mean; SD)*	4.5 ± 1.93
Partial Cystectomy (*n; %*)	23 (20)
Bladder Shaving (*n; %*)	11 (9.5)
Bowel Resection (*n; %*)	19 (16.5)
Bowel Shaving (*n; %*)	39 (33.9)
Douglas/Torus resection with vaginal opening (*n; %*)	24 (20.8)
Douglas/Torus resection without vaginal opening (*n; %*)	11 (9.5)
Ureteral Resection (*n; %*)	4 (3.4)
Incomplete Surgery [1] (*n; %*)	13 (11.3)
Intra-operative Complications (*n; %*)	3 (2.6)
Post-operative Complications (*n; %*)	9 (7.8)
Bladder [2] (*n; %*)	3 (6.0)
Bowel [3] (*n; %*)	2 (2.6)
Haematoma [4] (*n; %*)	5 (4.3)
Additional procedure [5](*n; %*)	13 (11.3)
Follow Up *(months)*	22.5 ± 8.6
Recurrence (*n; %*)	19 (16.5)
Reintervention (*n; %*)	11 (9.5)

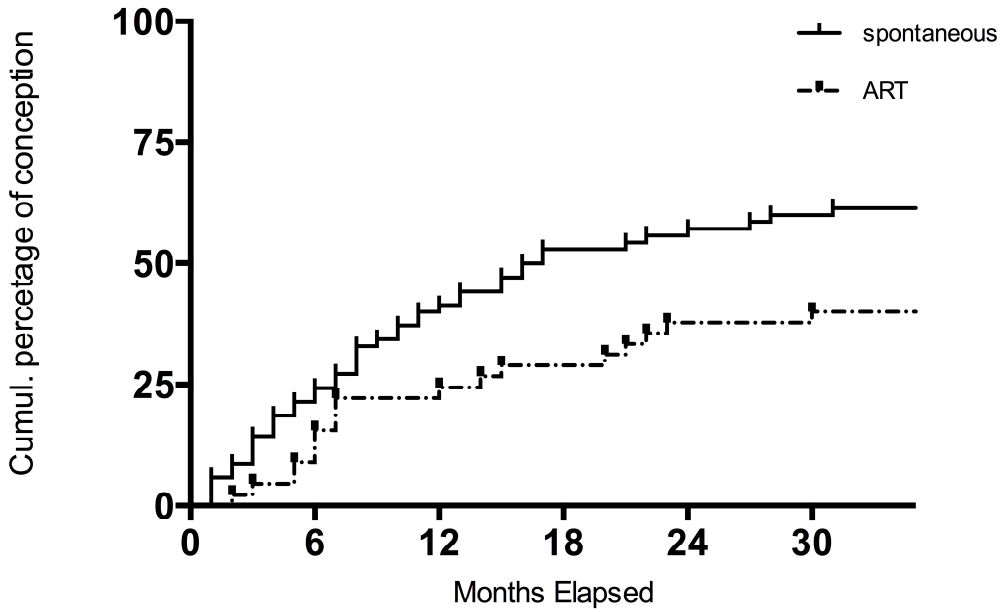
[1] The surgery was considered incomplete because of risk of further complication: 8 low rectal localization (<5cm) and 5 for risk of damaging pelvic innervation; [2] 2 vesico-vaginal fistulas and 1 urinoma; [3] 1 recto-vaginal fistula and 1 persisting postoperative pain;[4] 1 patient required a second look laparoscopy due to an infected haematoma resulting in a recto-vaginal fistula; [5] 4 appendectomy, 5 unilateral salpingectomy, 1 bilateral salpingectomy, 2 omentoplasty and 1 ileostomy.

Table 3: Comparison of determinant factor for infertility between the two groups.

	Pregnant (n=63)	**Not Pregnant (n=52)**	**P**
Age (yrs)*(mean; SD)*	30,52 ± 4.35	31.1 ± 4.03	0.54
< 35 (*n; %*)	48 (76.1)	40 (76.9)	0.65
> 35 (*n; %*)	15 (23.8)	12 (23)	0.65
BMI (kg/m^2)*(mean; SD)*	25.4 ± 2.83	26.3 ± 2.62	0.07
Preoperative medical treatment (*n; %*)	8 (12.6)	11 (21.1)	0.3
Duration of infertility (years)(*mean; SD)*	22.87 ± 8.3	23.39 ± 8.2	0.6
Previous surgery for endometriosis (*n; %*)	9 (24.3)	24 (64.8)	**<0.001**
Complete Removal of the disease (*n; %*)	54 (85.7)	48 (92.3)	0.26
Nodule dimension *(cm)(mean; SD)*	3.1 ± 0.97	3.5 ± 1.45	0.42
Additional Procedure (*n; %*)	8 (12.6)	5 (9.6)	0.76
Salpingectomy (*n, %*)	3 (4.7)	2 (3.8)	1.0
Localization			
Single (*n; %*)	27 (42.8)	35 (67.3)	**0.01**
Anterior (*n; %*)	6 (9.5)	10 (19.2)	0.17
Uterosacral (*n; %*)	4 (6.3)	2 (3.2)	0.68
Posterior midline (*n; %*)	17 (26.9)	23 (44.2)	0.07
Multiple Localization (*n; %*)	36 (57.1)	17 (32.6)	**0.01**
Posterior midline and USL (*n; %*)	23 (36.5)	12 (23.0)	0.15
Anterior and posterior (*n; %*)	13 (20.6)	5 (9.6)	0.12
Follow Up *(months)(mean; SD)*	21.8 ± 9.8	23.4 ± 9.6	0.51







http://www.AAGL.org/jmig-23-1-JMIG-D-15-00445

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Précis: Laparoscopic treatment of lesions is an effective treatment for deep endometriosis-related infertility. The treatment of multiple lesions is associated with higher chance of conception.