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PII: S1553-4650(19)30413-3
DOI: https://doi.org/10.1016/j.jmig.2019.08.032
Reference: JMIG 3934

To appear in: *The Journal of Minimally Invasive Gynecology*

Received date: 15 May 2019
Revised date: 29 August 2019
Accepted date: 31 August 2019

Please cite this article as: Pauline Breteau M.D. , Isabella Chanavaz-Lacheray M.D. , Chrystele Rubod M.D. Ph.D. , Mélusine Turck M.D. , Sophie Sanguin M.D. , Ionut Pop M.D. , Benoit Resch M.D. , Horace Roman M.D., Ph.D. , Pregnancy rates after surgical treatment of deep infiltrating endometriosis in infertile patients with at least 2 previous IVF/ICSI failures, *The Journal of Minimally Invasive Gynecology* (2019), doi: https://doi.org/10.1016/j.jmig.2019.08.032

Pregnancy rates after surgical treatment of deep infiltrating endometriosis in infertile patients with at least 2 previous IVF/ICSI failures

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Conflict of Interest/Disclosure Statement: No specific financial support was received for this study. Horace Roman received personal fees for participation in masterclasses organized by PlasmaSurgical Inc. The CIRENDO survey receives grant support from Rouen, Lille, Caen and Amiens University Hospital, France (the G4 Group), and the Association of Endometriosis Surgeons ROUENDOMETRIOSE, France.

Précis :

Surgical removal of deep infiltrating endometriosis by experienced surgical teams in women with a history of IVF-ICSI failures provides satisfactory pregnancy rates, be the pregnancy obtained naturally or after assisted reproductive techniques.

Abstract:

Study Objective: To assess the post-operative probabilities of pregnancy in patients with deep infiltrating endometriosis (DIE) and >= 2 previous IVF or ICSI failures.

Design: Retrospective study using data prospectively recorded in the CIRENDO database.

Setting: University tertiary referral center.

Patients: Infertile patients under the age of 43 years, having undergone >=2 previous IVF or ICSI failures, who were surgically managed for DIE.

Intervention: Complete excision of DIE.

Measurements and Main Results: Pregnancy rate after surgery was assessed. 104 infertile patients had surgery in 7 different centres participating in the database. 77 women intended to get pregnant post-operatively. Four patients who got pregnant by oocyte donation were excluded, resulting in a sample of 73 women. Patients' mean age was 31.9 years (SD 4.1), and the mean length of history of infertility was 48.4 months (26.5). Stage III and IV endometriosis were recorded in 83.6% of patients. Mean postoperative follow-up was 46.6 months (20.5). The postoperative pregnancy rate was 43.8% with a mean time from surgery to pregnancy of 11.1 months. 21.8% pregnancies were spontaneous, 31.2% were obtained by IVF, 21.8% by frozen embryo transfer, 18.7% by IVF-ICSI, and 3.1% by intrauterine insemination. Multivariate Cox analysis revealed that ovarian surgery, age ≥ 35 years old and stage 2 endometriosis were associated with the probability of conception.

Conclusion. Infertile women with 2 or more IVF-ICSI failures may be referred for surgery as it appears related to good postoperative pregnancy rates, particularly when endometriomas surgery is either not required or not performed. Surgery for DIE does not routinely delay conception, as it usually occurs during the year following surgery.

Key Words: Deep infiltrating endometriosis; IVF; ICSI; infertility; pregnancy.

Introduction

Endometriosis is a well-known cause of infertility. It has been estimated that 25 to 50% of patients with endometriosis are infertile (1). Several studies have shown that higher American Fertility Society (AFS)/American Society Reproductive Medicine (ASRM) stage is associated not only with lower fertility rate, but also with worse IVF results. Concerning stage III/IV endometriosis, authors showed a 21% relative reduction in implantation rate, and a 21% relative risk reduction in clinical pregnancies compared with controls (2).

Nowadays, one question remains debated: how should patients with a pregnancy desire and deep infiltrating endometriosis (DIE) be taken care of? Between primary surgery and assisted reproductive techniques (ART), which one provides the best management? Despite the absence of randomised trials, many physicians refer their patients to ART management before surgery. According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines published in 2014 (3), in infertile women with AFS/ASRM stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates. Considering the various results of studies in the literature, the French guidelines published in 2017 do not recommend primary surgery if the only aim is to

improve IVF results, but also advise a multidisciplinary approach in case of several failures of ART in order to discuss the possibility of surgery (4).

In 2012, Ballester et al demonstrated that in a population of 75 patients with colorectal endometriosis, the cumulative pregnancy rate after one, two and three ICSI-IVF cycles were 29.3, 52.9 and 68.6%, respectively (5). Thus, performing a third IVF procedure would allow for a 16% likelihood of pregnancy.

The objective of our study was to assess pregnancy rates after surgical treatment of deep infiltrating endometriosis in a group of patients with two or more previous IVF or ICSI failures.

Materials and methods

We performed a retrospective study using data prospectively recorded in the CIRENDO database. This is a prospective cohort enrolling patients who had surgery for endometriosis in one of the facilities participating to the cohort. The cohort is financed by the G4 Group (The University Hospitals of Rouen, Lille, Amiens and Caen, France) and coordinated by the corresponding author (H.R.) of the present study (NCT 02294825).

Patients

We identified patients under the age of 43 years, with a history of infertility, who had undergone two or more IVF or ICSI failures before the surgery for DIE. All patients enrolled in this study had complete excision of deep infiltrating endometriosis, that had been diagnosed by pelvic MRI examinations reviewed by experienced radiologists from our center, confirmed by positive histological result. Complementary exams such as transvaginal and rectal ultrasound, or computed tomography-based virtual colonoscopy were performed when required. Surgery was performed in one of the following centres

participating in the CIRENDO database: Rouen University Hospital, Lille University Hospital, Caen University Hospital, Amiens University Hospital, Clinique Mathilde in Rouen, Belvedere Maternity Hospital, or Dieppe General Hospital, France.

Technique

Deep endometriosis nodules were removed by excision. Procedures were performed by experienced surgeons with consistent background in endometriosis surgery. The completeness of the excision was affirmed intraoperatively, by surgeon feeling that no fibrous tissues with DIE appearance were left behind. Vaginal patches were removed each time the vagina was infiltrated. Procedures on the digestive tract were various: shaving, disc excision or colorectal resection with or without protective stoma, on the basis of several criteria, which have been previously discussed (6)(7). Colorectal resections and disc excisions were performed by multidisciplinary teams, including experienced general surgeons (6). To remove urinary tract nodules, several procedures were employed: bladder resection, ureterolysis, or resection of infiltrated ureters performed by multidisciplinary teams involving urologic surgeons. Procedures on ovarian endometriomas were performed depending on cyst size, past history of ovarian surgery, women's age and ovarian reserve. In patients with altered ovarian reserve, the cysts could only be drained. In patients managed in Rouen (University Hospital and Clinique Mathilde) endometriomas were managed by ablation using plasma energy (8). In facilities outside Rouen, endometrioma management was most of the time performed by cystectomy. Post-operatively, the surgeon advised patients on their capacity to conceive and recommended attempting spontaneous conception or planning ART, on the basis of criteria included in the Endometriosis Fertility Index (9).

Information was obtained from surgical and histological records and from self-questionnaires completed before surgery. Data recording, patient contact and follow-up were carried out by a clinical research technician. Women were included in the CIRENDO database only when endometriosis was confirmed by both surgical exploration and biopsy. Post-operative follow-up was based on data from the questionnaires completed at 1, 3 and 5 years. All patients enrolled in this study had at least 12 months of follow-up.

Before surgery, since their infertility had been explored, patients were usually on hormonal treatment to relieve pain symptoms (GnRH analogues, progestins or contraceptive pill). Post-operatively, women who wished to conceive and who had a chance of spontaneous pregnancy were allowed to try to conceive naturally for a limited period of 9 to 12 months. As increased post-operative time without hormonal treatment may increase risk of recurrence, beyond that period patients were advised to take hormonal treatment to suppress menstruation, and to schedule ART. Women with a formal recommendation of post-operative ART had continuous contraceptive pill intake, from the post-operative period to the first ART attempt and during two successive ARTs, to reduce risk of recurrence.

Post-operative pregnancies were assessed through the follow-up questionnaires in the CIRENDO database. If women had not yet filled the questionnaire, they were contacted by telephone or email. Pregnancies were defined by a positive Beta-HCG level >1,000 or an early ultrasound examination revealing an embryo with cardiac activity.

Statistical analysis

Statistical analysis was performed using Stata 11.0 software (Stat Corporation, Lakeway Drive, TX, USA). To compare patients who conceived with those who did not,

univariable analysis was performed using Chi-square test (qualitative variables), Student's t-test or Kruskall-Wallis test (continuous variables). Kaplan Meier's analysis was used to estimate the likelihood of pregnancy as a function of follow-up with 95% confidence intervals (CI), and the curves were compared using the log-rank test. The Cox model was used to assess independent predictive factors of pregnancy. $P < 0.05$ was considered statistically significant. The study was approved by the IRB of the Rouen University Hospital.

Results

From September 2009 to June 2016, 1,674 women undergoing surgery for endometriosis were recorded in the database. Among them, there were 104 patients under the age of 43 years, with a history of two or more IVF or ICSI failures (Fig 1). Of these 104 patients, 77 tried to conceive post-operatively**.** We excluded the 4 women who got pregnant by oocyte donation, thus our analysis was carried out in a population of 73 women.

Thirty two of the 73 women (43.8%) were pregnant after the surgery. Seven pregnancies (21.8%) were spontaneous, 10 (31.2%) were obtained by IVF, 7 (21.8%) by frozen embryo transfer, 6 (18.7%) by ICSI, and 1 (3.1%) by intra-uterine insemination. Data about conception mode were missing for one patient who was diagnosed with molar pregnancy (3.1%).

Patients' characteristics are presented in Table 1. Among the 73 women of our population, most of them had stage III or IV endometriosis: respectively 7 (9.6%) and 54 (74%), with a mean revised AFS (AFS-r) score of 73.1 (SD 46 .5). Women in the non-pregnant group had a statistically higher AFS-r score (83.3±49) than women in the

pregnant group (59.8±39.9) (p=0.03). Before surgery, the mean number of IVF/ICSI procedures was 3.7 (±2.1). Thirty-seven patients (50.7%) had a history of abdominal surgery and 52 (71.2%) of gynaecological surgery: 32 of them (43.8%) for pelvic pain, 27 (37%) for infertility and 36 (49.3%) for endometriosis. The first indication of the surgery was infertility in 63 patients (85%) and the pain in 10 patients (15%).

Among the patients who got pregnant twenty-seven pregnancies (84.4%) were obtained in patients with stage III/IV endometriosis; 22 pregnancies (68.7%) in patients with stage IV endometriosis and 5 (15.6%) with stage III endometriosis. The mean delay from surgery to the first postoperative pregnancy was 11.1 months (±11.1). Six women (18.7%) had an early miscarriage, 2 (6.3%) had an ectopic pregnancy. There was 1 molar pregnancy. Seventeen pregnancies (53.1%) ended by a delivery at term and 6 (18.7%) by a premature delivery. The live birth rate was 31.5% (23 women).

The intra-operative data of the pregnant group and the non-pregnant group are summarised in table 2. Non-pregnant women had significantly more lesions involving the sigmoid colon (44% vs 21.9%; p=0.05) and the rectum (65.8% vs 40.6%; p=0.03). Endometrioma surgery was recorded more frequently in the non-pregnant group (75.6% vs 53.1%; p=0.04).

The multivariate Cox analysis allowed us to identify 3 criteria associated with lower probability of conception: ovarian surgery (adjusted odds ratio OR 0.41, 95% CI [0.13-0.93]; p=0.03), age ≥ 35 years old (adjusted odds ratio OR 0.35, 95% CI [0.13-0.95]; p= 0.04; Table 3), and a minor endometriosis stage (adjusted odds ratio OR 0.09, 95% CI [0.01-0.63]; p= 0.02). The probability of conception was not significantly impacted by the management of deep colorectal endometriosis and associated male infertility (Fig 2).

Mean number of post-operative ART attempts was not significantly different between women who had or had not postoperative pregnancies: 1.1 (±1.1) vs. 1.4 (±1.6) (p=0.80). By the time the study ended, nineteen women (31.1%) were still trying to achieve spontaneous pregnancy, and had not yet planned either another ART, nor an oocyte donation.

Discussion

Our study shows that in a population of infertile women who had two or more IVF-ICSI failures, performing DIE complete surgery is associated to satisfactory postoperative pregnancy rate and live birth rate, either naturally or by ART. Postoperative pregnancy rate appears at least comparable to that reported in the literature in women without surgery, in whom ART management is prolonged over 2 IVF/ICSI procedures

The major limit of our study is related to the retrospective design and the lack of control group. We could not perform a comparative study between women who had surgery after >=2 IVF/ICSI cycles (enrolled in CIRENDO database) and women who had not surgery and continued the ART management with a 3rd or a 4th IVF/ICSI procedure (not enrolled in CIRENDO database). The inclusion in CIRENDO database only concerns patients having undergone surgery and depends on histological confirmation of endometriosis on specimen samples. Our results may be jeopardized by several confounding factors. Our sample is heterogeneous, baseline AFS-r score was different between women with and without pregnancy, several surgical procedures were carried out, surgeon's skill could vary, patients did not systematically have surgery with the unique goal of getting pregnant. However, this heterogeneity might reproduce the real life, and the Cox's model adjusted the results on baseline AFS-r score (endometriosis

stage), digestive tract surgery and ovarian procedures. Due to the small size of our population, generalizability of our study may be limited.

The strength of our study is rigorous prospective data recording by a dedicated clinical researcher who managed the follow-up of patients, with a very low rate of missing data.

We chose the cut-off of 2 IVF-ICSI because it represents a half of the 4 procedures which are reimbursed by the French Social Security. However, in our sample, the mean number of IVF-ICSI procedures performed before the surgery was 3.7±2.1. Thus, a majority of patients included in our sample actually had surgery after the 3rd IVF/ICSI cycle. The cut-off of two ART failures is also in relation to Ballester's 2012 study (5), which showed that pregnancy rate decreases after the third and the fourth IVF in patients with non-operated colorectal endometriosis. In daily practice in France, the question of colorectal surgery finally arises after two IVF failures and diagnosis of endometriosis, but this is not always the case for patients initially managed for infertility.

Several studies have shown an improvement in pregnancy rate in infertile women after surgery, however the level of evidence in not sufficient to support strong recommendations. Both ESHRE and French guidelines for the management of endometriosis concluded that in women presenting with DIE associated with infertility, available data do not allow any definitive conclusions regarding the interest of ART first or surgery first (3) (4).

Nevertheless, several publications of experienced surgical teams have shown the interest of removing DIE, not only to improve pain symptoms, but also to provide high postoperative pregnancy rate. In case of associated ovarian endometriomas, surgeon should take care to preserve the ovarian reserve, especially when a cystectomy is

considered (8). Stepniewska et al suggested that surgical removal of DIE enhanced both spontaneous pregnancy as well as fertility results in IVF. Thus, pregnancy rate was higher in patients who had colorectal resection compared with patients who had limited surgery leaving in situ colorectal endometriosis (10). Barri et al ultimately suggested that a combination of surgery and IVF was the best option for infertility associated with endometriosis (11). In our previous studies, pregnancy rate reached 65.8% when spontaneous pregnancies and those obtained after ART were taken together in women managed for endometriomas and colorectal endometriosis (8). Recently we reported fertility outcomes in a series of patients managed for rectal endometriosis, enrolled in a randomised trial and followed up over 4 years, where we recorded postoperative pregnancy rate as high as 81%, with a majority of spontaneous conceptions (12). These data show that DIE surgery is not harmful for postoperative conception, as overall pregnancy rate is at least as high as that observed after primary IVF (13).

Several studies have suggested that surgery even improved IVF results. In a prospective study comparing women managed by IVF respectively with and without first-line surgery, it was observed that pregnancy rate was significantly higher in the group of operated women (14). A recent retrospective study employing a propension score showed that the cumulative live birth rate was significantly higher for women who had first-line surgery followed by ART compared with first-line ART (15).

In studies assessing the impact of surgery on postoperative conception, surgical route may confound the outcomes. In 2006, a prospective study based on a shared-decision making approach suggested that the removal of rectovaginal DIE by laparotomy does not result in higher spontaneous pregnancy rate when compared to expectant management (16). However, these results were probably related to open surgery, which dramatically reduces the probability of spontaneous conception, as shown by Darai et al

(17). Conversely, when surgery is carried out laparoscopically, postoperative spontaneous conception is frequent (7).

The reasons for fertility improvement by DIE excision surgery are multiple. Firstly, it allows restoration of normal anatomy, combined with the suppression of dyspareunia, allowing more frequent and efficient sexual intercourse (18). Several studies have drawn similar conclusions regarding the improvement of ART results, though there is no clear explanation for these encouraging results (14)(17). Several of our patients had had up to 4 IVF procedures or were on the waiting list for oocyte donation and had finally turned to surgery to relieve their pain, after having given up any hope of pregnancy. For these reasons, our results may encourage surgeons to do their best to maintain the uterus even in women who « have no more hope of getting pregnant ».

When considering this pregnancy rate after DIE surgery in infertile patients, the question is why this management is not recommended to more symptomatic patients with deep endometriosis. The answer is probably related to the team to which the patients are first referred: either an ART or a surgical team (13).

Endometriosis is not always diagnosed and/or explored in case of infertility. The pain symptoms of the disease are often minimized either by the patient, or by the team, because they are not the priority in infertile women. Even in patients presenting with endometriomas, the evidence that endometriomas are frequently associated with DIE appears insufficient to push further for imaging assessment before IVF (19).

Physicians specialized in infertility care may be apprehensive about DIE surgery. First, there is a strong conviction that DIE surgery will delay ART, and therefore conception. However, our median time to pregnancy after surgery was short (10.1 ± 8.5 months), similar to the median time to pregnancy of 12 months following attempts to

conceive for all pregnancies (20). We recently reported a study showing that spontaneous conception may occur shortly after DIE surgery (6).

Second, there is a risk of ovarian reserve decrease after DIE surgery particularly when it is associated with ovarian endometrioma surgery (21). However, the presumed risk of ovarian reserve reduction is not necessarily related to pregnancy rate reduction, as shown by Bianchi (14), who observed a reduction in the number of oocytes retrieved in women with endometrioma cystectomy along with an overall significant increase in pregnancy rate. In our sample, 24% of endometriomas were either not treated or simply drained during the surgery. Although endometriomas drainage is systematically followed by recurrence of cyst in women with periods, this procedure facilitates follicles retrieval during postoperative IVF/ICSI procedures and is mandatory during the management of DIE in order to open the access on Douglas pouch. Furthermore, associated DIE lesions were systematically removed.

Third, the risk of surgical complications (22), which may be higher in less experienced teams (23), is such a worry to physicians that they are likely to discourage patients from having surgery. However, a recent study reported a satisfactory pregnancy rate in women with postoperative complications after DIE surgery (24).

Fourth, when the disease has not been thoroughly explored preoperatively, surgery may be incomplete, with only partial improvement of pain and fertility, giving the impression that surgery is ultimately useless.

It appears more reasonable to thoroughly explore infertile patients with symptoms suggesting pelvic endometriosis, even though their priority is conception. When DIE is suspected, patients should be informed of the good impact of surgery on fertility outcomes and pain symptoms and should be asked to choose between first line ART or surgery. After failure of the second IVF, it is our belief that the good option is not

to wait for further failure to advise surgery, which will not only improve spontaneous fertility, but also ART results. This discussion should take into consideration other factors as women's age, pelvic pain and associated infertility causes, such as dysovulation, low ovarian reserve, and sperm characteristics. However, women's age and increased number of ICSI–IVF cycles were associated with a decrease in clinical pregnancy rate (5). Conversely, a recent study including young patients managed for severe endometriosis showed that a low pre-operative AMH rate is not mandatorily related to bad PR, thus we suggest that low AMH level is not a good criterion to exclude surgery (25).

Conclusion

It is our opinion that DIE management should follow a global approach that not only provides a satisfactory likelihood of conception, but also improves pain symptoms and quality of life. Removing DIE by experienced surgical teams in infertile women may achieve both goals, particularly when endometriomas surgery is either not required or not performed. These encouraging results of experienced surgical teams, working hand in hand with ART teams in multidisciplinary expert centres, suggest that this is the way forward.

Acknowledgements: The authors are grateful to Amélie Bréant and Sophie Marinette for the management of data and Nikki Sabourin-Gibbs, Rouen University Hospital, for her help in editing the manuscript.

References

1. Collinet P, Decanter C, Lefebvre C, Leroy JL, Vinatier D. Endometriosis and infertility. *Gynecol Obstet Fertil* 2006;34:379-384.
2. Harb H, Gallos I, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. *BJOG* 2013;120:1308–1320.
3. Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W. ESHRE guideline: management of women with endometriosis. *Hum reprod* 2014;29:400-412.
4. Mathieu d'Argent E, Cohen J, Chauffour C, Pouly JL, Boujenah J, Poncelet C, Decanter C, Santulli P. Deeply infiltrating endometriosis and infertility : CNGOF-HAS Endometriosis Guidelines. *Gynecol Obstet Fertil Senol* 2018;46:357-367.
5. Ballester M, Mathieu d'Argent E, Morcel K, Belaisch-Allart J, Nisolle M, Daraï E. Cumulative pregnancy rate after ICSI– IVF in patients with colorectal endometriosis: results of a multicentre study. *Hum Reprod* 2012;27:1043-1049.
6. Roman H, Bubenheim M, Huet E, Bridoux V, Zacharopoulou C, Daraï E, Tuech JJ. Conservative surgery versus colorectal resection in deep infiltrating endometriosis infiltrating the rectum : a randomized trial. *Hum Reprod* 2018 Jan 1;33:47-57
7. Roman H, Moatassim-Drissa S, Marty N, Milles M, Vallée A, Desnyder E, Stochino-Loi E, Abo C. Rectal Shaving for deep endometriosis infiltrating the rectum : a 5 year-continuous retrospective series. *Fertil Steril* 2016;106:1438-1445.
8. Roman H, Quibel S, Auber M, Muszynski H, Huet E, Marpeau L, Tuech JJ. Recurrences and fertility after endometrioma ablation in women with and

without colorectal endometriosis: a prospective cohort study. *Hum Reprod* 2015;30:558–568.

9. Tomassetti C, Geysenbergh B, Meuleman C, Timmerman D, Fieuws S, D'Hooghe T. External validation of the endometriosis fertility index (EFI) staging system for predicting non-ART pregnancy after endometriosis surgery. *Hum Reprod* 2013;28:1280-1288.
10. Stepniewska A, Pomini P, Bruni F, Mereu L, Ruffo G, Ceccaroni M, Scioscia M, Guerriero M, Minelli L. Laparoscopic treatment of bowel endometriosis in infertile women. *Hum Reprod* 2009;24:1619–1625.
11. Barri PN, Coroleu B, Tur R, Barri-Soldevila PN, Rodriguez I. Endometriosis-associated infertility: surgery and IVF, a comprehensive therapeutic approach. *Reprod Biomed Online* 2010;21:179–185.
12. Roman H, Chanavaz-Lacheray I, Ballester M, Bendifallah S, Touleimat S, Tuech JJ, Farella M, Merlot B. High postoperative fertility rate following surgical management of colorectal endometriosis. *Hum Reprod* 2018;33:1669-1676.
13. Darwish B, Chanavaz-Lacheray I, Roman H. Swimming against the stream : is surgery worthwhile in women with deep infiltrating endometriosis and pregnancy intention? *JMIG* 2017;25:1-3.
14. Bianchi PH, Pereira RM, Zanatta A, Alegretti JR, Motta EL, Serafini PC. Extensive Excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. *J Minim Invasive Gynecol* 2009;16,174–180.
15. Bendifallah S, Roman H, Mathieu d'Argent E, Touleimat S, Cohen J, Daraï E, Ballester M. Colorectal endometriosis-associated infertility: should surgery precede ART? *Fertil Steril* 2017;108:525-531.

16. Vercellini P, Pietropaolo G, De Giorgi O, Daguati R, Pasin R, Crosignani PG. Reproductive performance in infertile women with rectovaginal endometriosis: is surgery worthwhile. *Am J Obstet Gynecol* 2006;195:1303-1310.

17. Daraï E, Lesieur B, Dubernard G, Rouzier R, Bazot M, Ballester M. Fertility after colorectal resection for endometriosis: results of a prospective study comparing laparoscopy with open surgery. *Fertil Steril* 2011;95:1903–1908.

18. Abbott J. Surgical treatment is an excellent option for women with endometriosis and infertility. *Aust N Z J Obstet Gynaecol* 2017; 1-3.

19. Chapron C, Santulli P, De Ziegler D, Noel JC, Anaf V, Streuli I, Foulot H, Souza C, Borghese B. Ovarian endometrioma : severe pelvic pain is associated with deeply infiltrating endometriosis. *Hum Reprod* 2012;27:702-711.

20. Nesbitt-Hawes EM, Campbell N, Maley PE, Won H, Hoosmand D, Henry A, Ledger W, Abbot JA. The surgical treatment of severe endometriosis positively affects the chance of natural or assisted pregnancy postoperatively. *Biomed Res Int* 2015,1-7.

21. Seyhan A, Ata B, Uncu G. The impact of endometriosis and its treatment on ovarian reserve. *Semin Reprod Med* 2015;33:422-428

22. Kondo W, Bourdel N, Tamburro S, Cavoli D, Jardon K, Rabischong B, Botchorishvili R, Pouly JL, Mage G, Canis M. Complications after surgery for deeply infiltrating pelvic endometriosis. *BJOG* 2010;118:292-298.

23. Bendifallah S, Roman H, Rubod C, Leguevaque P, Watrelot A, Bourdel N, Daraï E. Impact of hospital and surgeon case volume on morbidity in colorectal endometriosis management : a plea to define criteria for expert centers. *Surg Endosc* 2018;32:2003-2011.

24. Ballester M, Oppenheimer A, Mathieu d'Argent E, Touboul C, Antoine JM, Nisolle M, Daraï E. Deep infiltrating endometriosis is a determinant factor of cumulative

pregnancy rate after intracytoplasmic sperm injection/in vitro fertilization cycles in patients with endometriomas. Fertil Steril 2012;97:367-372.

25. Stochino-Loi E, Darwish B, Mircea O, Touleimat S, Millochau JC, Abo C, Angioni S, Roman H. Does preoperative antimullerian hormone level influence postoperative pregnancy rate in women undergoing surgery for severe endometriosis? *Fertil Steril* 2017 107:707-713.

Tables and figures:

Table 1. Characteristics of patients (n= 73) recorded in the CIRENDO database.

Tab
Data are n(%) or mean (±*SD*).

Parameter	Whole sample (n=73)	Pregnant women (n=32)	Non pregnant women (n=41)	p
Age	31.9 (±4.1)	31.7 (±4)	32.1 (±4.2)	0.67
BMI (kg/m2)	24.1 (±4.8)	23.2 (±3.9)	24.7 (±5.4)	0.21
Smoking	19 (26)	10 (31.2)	9 (22)	0.37
Duration of infertility (months)	48.4 (±26.5)	47.7 (±25.6)	49,1 (±27.7)	0.84
Number of previous ART	3.7 (±2.1)	3.9 (±2.3)	3.5 (±1.8)	0.39
- 2	28 (38.4)	12 (37.5)	16 (39)	
- 3	13 (17.8)	5 (15.6)	8 (19.5)	
- 4	15 (20.5)	6 (18.7)	9 (22)	
- 5	1 (1.4)	1 (3.1)	0	
- 6	7 (9.6)	3 (9.4)	4 (9.8)	
- 7	3 (4.1)	1 (3.1)	2 (4.9)	
- 8	4 (5.5)	2 (6.2)	2 (4.9)	
- 9	2 (2.7)	2 (6.2)	0	
Number of previous IVF	2.4 (±1.1)	2.5 (±1.2)	1.2 (±0.9)	0.30
- 1	10 (16.1)	3 (11.1)	7 (20)	
- 2	32 (51.6)	14 (51.8)	18 (51.4)	
- 3	12 (19.3)	6 (22.2)	6 (17.1)	
- 4	6 (9.7)	3 (11.1)	3 (8.7)	
- 5	1 (1.4)	0	1 (2.9)	
- 7	1 (1.4)	1(3.7)	0	
Number of previous ICSI	2.4 (±1.5)	3 (±1.7)	2.1 (±1.4)	0.10
- 1	12 (16.4)	2 (6.2)	10 (22)	
- 2	15 (20.5)	6 (18.7)	9 (19)	
- 3	9 (12.3)	4 (12.5)	5 (12.2)	
- 5	1 (1.4)	1 (3.1)	0	
- 6	3 (4.1)	1 (3.1)	2 (4.8)	
- 7	1 (1.4)	1 (3.1)	0	
Endometriosis Stage	3.5 (±0 .9)	3.4 (±1)	3.6 (±0.8)	0.22
- 1	4 (5.5)	3 (9.4)	1 (2.4)	
- 2	8 (11)	3 (9.4)	5 (12.2)	

- 3	7 (9.6)	5 (15.6)	2 (4.9)	
- 4	54 (74)	21 (65.6)	33 (80.5)	
Previous abdominal surgery	37 (50.7)	16 (50)	21 (51.2)	0.92
Previous gynecological surgery	52 (71.2)	22 (68.7)	30 (73.6)	0.68
Number of previous laparoscopies	0.91 (±0.8)	0.9 (±0.1)	0.9 (±0.1)	0.89
	35 (50)	14 (46.7)	21 (52.5)	
- 1	10 (14.3)	5 (16.7)	5 (12.5)	
- 2	3 (4.3)	1 (3.3)	2 (5)	
- 3				
Number of previous open surgeries	0.2 (±0.1)	0.1 (±0.1)	0.2 (±0.1)	0.35
	7 (11.1)	3 (9.4)	4 (9.8)	
- 1	1 (1.4)	0	1 (2.4)	
- 2	1 (1.4)	0	1(2.4)	
- 3				
Justification for previous surgeries	32 (44.4)	10 (32.3)	22 (53.6)	0.70
- Pelvic pain	27 (37.5)	13 (42)	14 (34.1)	0.50
- Infertility	36 (49.3)	11 (34.4)	25 (61)	0.02
- Endometriosis				
Cystectomy				
- Right ovary	19 (26)	4 (12.5)	15 (36.6)	0.02
- Left ovary	23 (31.5)	8 (25)	15 (36.6)	0.29
Unilateral oophorectomy	4 (5.5)	2 (6.2)	2 (4.8)	0.80
Adhesiolysis	15 (20.5)	1 (3.1)	14 (34.1)	0.001
Repair of fallopian tubes	4 (5.5)	1 (3.1)	3 (7.3)	0.43
Obstetrical antecedents				
- Number of previous pregnancies	0.3 (±0.6)	0.4 (±0.6)	0.2 (±0.5)	0.08
0	54 (76.1)	21 (65.6)	34 (85)	
1	13 (18.3)	9 (29)	4 (10)	
2	4 (5.6)	2 (64)	2 (5)	
- Living child				
0	58 (87.8)	24 (85.7)	34 (89.5)	
1	7 (10.6)	3 (10.7)	4 (10.5)	
2	1 (1.4)	1 (3.1)	0	
- Miscarriage	7 (10.6)	3 (10.7)	4 (10.5)	

- Ectopic pregnancies	4 (6.1)	3 (10.7)	1 (2.7)	
Psychological care	17 (10.6)	10 (31.2)	7 (17.1)	0.98

Table 2. Intraoperative findings and surgical procedures.

	Whole Sample (n=73)	Pregnant women (n=32)	Non pregnant women (n=41)	p
Operative route				
- Laparoscopy	71 (97.3)	32 (100)	39 (95.1)	
- Laparoscopy + laparotomy	2 (2.7)	0	2 (4.0)	
Operative time (min)	173.1 (±108.6)	155.7 (±99.1)	185.9 (±114.6)	0.25
AFS-r Score	73.1 (±46.5)	59.8 (±39.9)	83.2 (±49)	0.03
Douglas pouch complete obliteration	36 (40.3)	13 (40.6)	23 (56.1)	0.11
Associated localization				
- Rectal	42 (57.5)	16 (50)	26 (63.4)	0.25
- Sigmoid	25 (34.2)	7 (21.9)	18 (44)	0.05
- Ileal	7 (9.6)	2 (6.9)	5 (12.2)	0.39
- Appendix	7 (9.6)	1 (3.1)	6 (14.6)	0.09
- Diaphragm	11 (15.1)	3 (9.4)	8 (19.5)	0.23
- Deep endometriosis nodule	56 (76.7)	22 (68.7)	34 (83)	0.15
Rectum	40 (54.8)	13 (40.6)	27 (65.8)	0.03
Vagina	27 (37)	13 (40.6)	14 (34.1)	0.57
Bladder	6 (8.2)	4 (12.5)	2 (4.9)	0.24
Deep posterior endometriosis				0.90
- Left uterosacral ligament (USL)	8 (11)	4 (12.5)	4 (9.8)	
- Right USL	3 (4.1)	1 (3.1)	2 (4.9)	
- Left and Right USL	5 (6.8)	2 (6.2)	3 (7.3)	
- Rectovaginal septum	10 (13.7)	6 (18.7)	4 (9.8)	
- Left USL+right USL+ rectovaginal septum	38 (52)	15 (46.9)	23 (56.1)	
Surgical procedure on digestive tract	45 (61.6)	16 (50)	29 (70.7)	0.50
- Shaving	22 (30.1)	11 (34.4)	11 (26.8)	0.61
- Colorectal disc excision	4 (5.5)	1 (3.1)	3 (7.3)	0.40
- Colorectal resection	25 (34.2)	7 (21.9)	18 (44)	0.05
- Stoma	9 (12.3)	2 (6.2)	7 (17.1)	0.16
Surgical procedure on urinary tract	11 (15.3)	5 (15.6)	6 (15)	0.94
Right ovarian endometrioma				0.07

- No cyst	31 (44.3)	15 (46.9)	14 (73.2)	
- Non-treated cyst	3 (4.3)	3 (9.7)	0	
- Cyst drained and washed	8 (11.4)	1 (3.2)	7 (17.9)	
- Partial plasma energy ablation	15 (21.4)	6 (19.3)	9 (23.1)	
- Complete plasma energy ablation	12 (17.1)	4 (11.9)	8 (20.5)	
- Cystectomy	1 (1.4)	0	1 (2.6)	
Left ovarian endometrioma				0.03
- No lesion	27 (39.1)	16 (50)	11 (29.7)	
- Non-treated cyst	3 (4.3)	3 (9.4)	0	
- Cyst drained and washed	6 (8.7)	0	6 (16.2)	
- Partial plasma energy ablation	15 (21.7)	4 (12.5)	11 (29.7)	
- Complete plasma energy ablation	13 (18.8)	6 (18.7)	7 (18.9)	
- Cystectomy	3 (4.3)	2 (6.2)	1 (2.7)	
- Ovariectomy	1 (1.4)	1 (3.1)	0	

Table 3. Estimation of the probability of pregnancy (Cox multivariate model)

Table 3: Estimation of the probability of pregnancy beginning from the day of surgery depending on the risk factor (Cox multivariate model)					
Risk Factor	N(%)	Pregnancies (%)	HR	HR 95% CI	p
Digestive surgery					0.19
No	28 (61.6)	16 (50)	1		
Yes	45 (31.4)	16 (50)	0.51	0.19-1.4	
Ovarian procedure					0.07
No	26 (35.6)	15 (46.8)	1		
Yes	47 (64.4)	17 (53.1)	0.46	0.20-1.1	
Age ≥ 35 years					0.05
No	55 (75.3)	25 (78.1)	1		
Yes	18 (24.6)	7 (21.9)	0.36	0.13-1	
Male factor of infertility					0.29
No	33 (45.2)	17 (53.1)	1		
Yes	40 (54.8)	15 (46.8)	0.66	0.3-1.4	
Endometriosis Stage					
1	4 (5.5)	3 (9.4)	1		
2	7 (9.6)	2 (9.4)	0.1	0.01-0.71	0.02
3	8 (11)	6 (18.7)	0.54	0.11-2.6	0.44
4	54 (74)	21 (65.6)	0.32	0.06-1.6	0.16

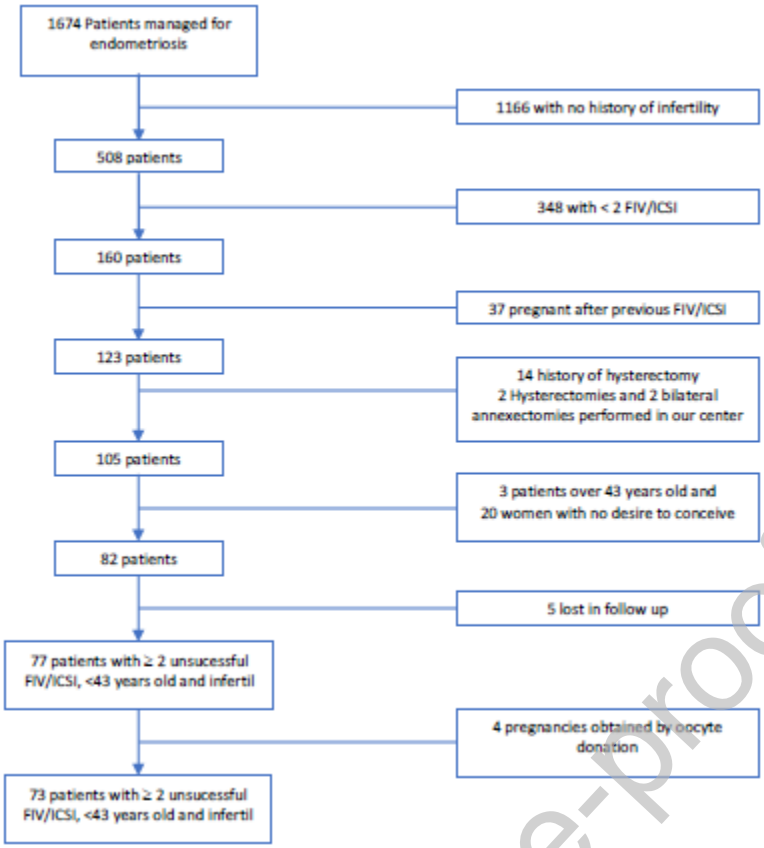

Figure 1. Flow diagram.

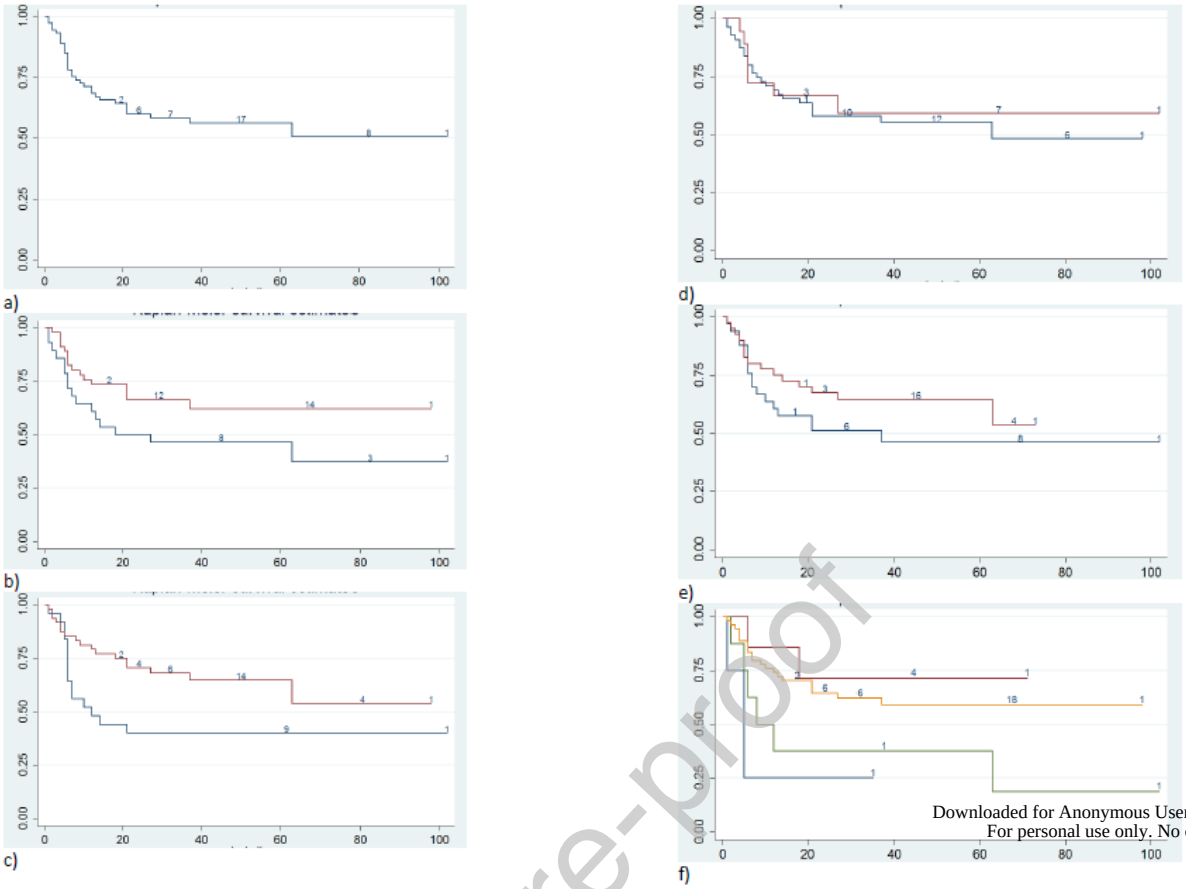

Figure 2. Kaplan-Meier curves presenting the probability of pregnancy (a), depending on associated digestive tract surgery (b), associated ovarian endometrioma surgery (c), women's age (d), associated male infertility (e) and endometriosis stage (f)