lek. Anna Katarzyna Stępniewska

tytuł rozprawy

Role of laparoscopic treatment of bowel endometriosis in infertile patients: pain and fertility outcome

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu w dyscyplinie nauki medyczne

Promotor: prof. dr hab. Włodzimierz Baranowski

Klinika/ Zakład (miejsce wykonania pracy):
IRCCS Ospedale Sacro Cuore Don Calabria – Negrar (Verona) Italy, Department of Obstetrics and Gynecology, Gynecology Oncology and Minimally-Invasive Pelvic Surgery, International School of Surgical Anatomy-ISSA

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych Warszawskiego Uniwersytetu Medycznego

Warszawa 2023 r.

Słowa kluczowe:

endometrioza, niepłodność, ból podbrzusza, chirurgia laparoskopowa, jelito, esicaodbytnica

Key words:

Endometriosis, infertility, pelvic pain, laparoscopic surgery, bowel, rectosigmoid

Spis treści

Tytuł : Rola laparoskopowego leczenia endometriozy u kobiet z nieplodnoscia:

wplyw na objawy bolowe i plodnosc.

STRESZCZENIE

Endometrioza głęboka jelit może być przyczyną silnych dolegliwości bólowych (pelvic pain, dyschezja) Leczenie chirurgiczne, jeśli jest medycznie uzasadnione może zmniejszyć nasilenie objawów, , wymaga jednak wysoce specjalistycznych umiejętności chirurgicznych i powinno być wykonywane w ośrodkach referencyjnych. U kobiet niepłodnych decyzja o leczeniu jest szczególnie złożona, a rola operacji budzi kontrowersje ze względu na ryzyko powikłań mogących upośledzać płodność, z tego powodu w procesie decyzyjnym należy rozważyć zarówno możliwe powikłania operacji na jelicie grubym jak i potencjalne korzyści tego typu leczenia

Mimo wyników licznych badań dotyczących leczenia operacyjnego endometriozy, wciąż brakuje jednoznacznych danych, opartych na analizie statystycznej potwierdzających korzystnego wpływu resekcji ognisk jelitowych na płodność i ból. Jedyne dostępne dane pochodzą z badań obserwacyjnych przeprowadzonych w wysokospecjalistycznych ośrodkach. Celem niniejszej analizy była ocena nasilenia bólu i wpływu na płodność po laparoskopowym leczeniu endometriozy jelit u niepłodnych pacjentek, operowanych w ośrodku referencyjnym (Sacro Cuore Don Calabria, Negrar, Włochy).

Przedstawiono wyniki dwóch badań retrospektywnych (Stepniewska 2009, Stepniewska 2010) opublikowanych w Human Reproduction i Fertility and Sterility. Pierwsza publikacja skupia się na ocenie wpływu operacji usunięcia ognisk endometriozy jelit na płodność druga zaś obejmowała ocenę wpływu operacji na zmniejszenie nasilenia objawów bólowych i ryzyko nawrotu choroby.

Wszystkie pacjentki włączone do obu badań miały rozpoznaną niepłodność (starania o ciążę od co najmniej dwóch lat) z wykluczeniem innych przyczyn niepłodności. Dzięki temu wyniki badań odzwierciedlają rzeczywisty wpływ przeprowadzonego zabiegu na płodność kobiet. Decyzja o włączeniu do badania kobiet niepłodnych ma również tę zaletę, że wyklucza z grupy badanej pacjentki stosujące terapię hormonalną, która mogłoby wpłynąć na wyniki badania.

Do obu badań włączono trzy grupy pacjentek: kobiety, które przeszły operację usunięcia endometriozy z odcinkową resekcją jelita grubego, kobiety z endometriozą jelit, które przeszły jedynie częściowe (niekompletne) usunięcie innych ognisk endometriozy z pozostawieniem guza na esicy/odbytnicy oraz kobiety z umiarkowaną lub ciężką endometriozą z co najmniej jedną torbielą endometrialną wraz z głęboką endometriozą, ale bez nacieku jelit.

Porównanie wyników w tych trzech grupach pozwoliło na analizę zależności objawów i zaburzeń płodności spowodowanych endometriozą jelit i innymi postaciami choroby oraz obiektywną ocenę skuteczności leczenia chirurgicznego.

Na podstawie uzyskanych wyników stwierdzono pozytywny wpływ leczenia chirurgicznego w zakresie bólu i wskaźnika ciąż. Niecałkowite usunięcie endometriozy z pozostawieniem guza endometrialnego na jelicie grubym daje istotnie gorsze wyniki w zakresie poprawy płodności i redukcji bólu.

Innym ważnym aspektem, który należy wziąć pod uwagę w przypadku niepłodności związanej z endometriozą, jest współistnienie adenomiozy, dlatego też przedstawione są wyniki badania opisującego innowacyjną, małoinwazyjną metodę leczniczą z wykorzystaniem ablacji termicznej falami o częstotliwości radiowej (Stepniewska 2022). Leczenie to, wprowadzone początkowo w celu uniknięcia histerektomii, może stanowić przyszłość dla niepłodnych pacjentek z adenomiozą.

ABSTRACT

Bowel endometriosis may lead to severe pain symptoms. Surgical treatment, when indicated, improves symptomatology, however it requires highly specialized skills and should be performed in a referral center. In infertile women the decision about the treatment is particularly complex and the role of surgery is controversial because of complications which could impair fertility. Therefore, in the decision-making process, the possible complications of colorectal surgery should be balanced with the potential benefits of the treatment. Strong, evidence-based data about benefits on fertility and pain of bowel resection are lacking and the only data derive from observational studies performed in highly specialized centers.

Therefore, the aim of the present study was to evaluate pain and fertility outcome after laparoscopic treatment of bowel endometriosis in infertile patients performed in a referral center. The results of two studies are reported (Stepniewska et al. 2009, Stepniewska et al. 2010a), the first one focusing on the fertility outcome after surgery and the second one on symptoms and recurrence.

All patients included in these studies suffered from infertility for at least two years and performed evaluation of all infertility factors, so the results reflect a real result in endometriosisrelated infertility. The decision to include infertile women only has the advantage of avoiding estroprogestins use which could alter the outcome.

In both reported studies three groups of patients were included: women who underwent endometriosis surgery with colorectal segmental resection, women with surgical evidence of bowel endometriosis who underwent endometriosis partial removal without bowel resection, and women affected by moderate or severe endometriosis with at least one endometrioma and deep infiltrating endometriosis but without bowel involvement. Comparison of outcome in those three groups allowed the evaluation of symptoms and fertility related to bowel endometriosis and treatment

without possible influence of other endometriosis localizations, which often co-exist, taking part of a complex disease.

Good outcome in terms of pain and pregnancy rate are reported. The influence of bowel endometriosis was observed on both symptoms and fertility as the results differed between the groups with a worse outcome if bowel endometriosis was present, and particularly if in the group of patients with incomplete removal of endometriosis leaving the colorectal nodule. The results are discussed and comparison to other studies is performed.

An important element to consider in endometriosis-associated infertility is that of possible coexistence of adenomyosis, therefore the results of a study describing an innovative uterinesparing of adenomyosis with radio-frequency thermal ablation are reported (Stepniewska et al. 2022). This treatment, initially introduced for avoiding hysterectomy, may represent future perspective for infertile patients.

In the field of deep endometriosis and infertility, the presented results may represent an important milestone, describing the experience of a center with long-time expertise.

INTRODUCTION

Surgery of bowel endometriosis requires high capabilities and is related to possible risks. Currently, there are no guidelines based on strong evidence about indications for surgery. The only clear and widely shared indication is that of referral of patients to a center of expertise (Becker et al. 2022).

The role of surgery is particularly controversial in infertile women with bowel endometriosis. The possible complications of colorectal surgery may induce the propensity to perform a partial incomplete surgery removing the disease in more accessible sites leaving the colorectal nodule, as the one not directly related to conception. This kind of surgery may, however, result in persistence of symptoms and high risk of recurrence. Conversely, is a philosophy of always performing a radical surgery with the intention of avoiding any further surgery for the recurrence. This manner can be supported by the fact that repeated surgeries may enhance the risk of complications and also reduce fertility due to ovarian reserve damage leading in some cases to anticipated menopause.

Nevertheless the experience of a referral center is that of frequent management of patients who previously underwent multiple incomplete surgeries in small hospitals and still suffer from pain related to the persistence of the disease.

Therefore it becomes extremely important to study the real impact of bowel endometriosis on fertility and to understand the potential benefits and risks of colorectal surgery in terms of infertility as well as pain.

Surgery of endometriosis in infertile patients represents the object of scientific attention of extreme interest, as medically assisted techniques, even if effective in most cases for obtaining pregnancy, could not represent the only treatment for endometriosis, particularly in symptomatic patients and after repeated conception failure. The disease may lead, particularly in its deep form, to important pain symptoms. As it has a negative influence on personal quality of life, reproductive aspect and implies social and economic impact, it is crucial to identify the best treatment for each patient and reduce harm caused by the disease. While medically assisted procreation is widely diffused and accessible, surgery requires highly specialized experience.

Although the relationship between endometriosis and infertility may be noticed from the epidemiological data, as infertile women are more frequently affected by endometriosis than the general population and infertility presents more frequently in patients with endometriosis, the explanation of this connection from the pathophysiological point of view is not completely understood. In severe cases complete alterations of normal anatomical relationships necessary for a spontaneous conception may be observed. The tubal obstruction may be related to frequently to severe adnexal adhesions, while only in a small percentage of patients the tubal wall infiltration by endometriosis is present.

Other underlying mechanisms in which endometriosis may affect fertility are multiple and complex, and different possible immunological, hormonal and inflammatory alterations have been described. They include different molecular alterations involving not only ovaries but also peritoneal liquid and endometrium (De Ziegler et al. 2010) explaining the possible relationships between endometriosis and infertility even in cases without any ovarian cysts, without severe dyspareunia leading to difficulties in intercourses or fallopian tube occlusion. In fact, a reduced fertility has been described even in superficial endometriosis (Bafort et al. 2020, Becker et al.

2022).

In most cases endometriosis does not lead to a complete impossibility of conception but only to a reduction of spontaneous fertility, as longer time necessary for conception than in women of the same age, and a reduction of monthly fecundity rate in endometriosis have been observed (Akande et al. 2004). Tubal infiltration by endometriosis (Stepniewska et al. 2021) is a rare finding, while more frequently peritubal adhesions or local inflammation may induce infertility.

According to theories (Nisolle, Donnez 1997) about the pathogenesis of endometriotic lesions and their anatomical presentation, three types of endometriosis may be distinguished: superficial lesions, ovarian cysts called endometriomas and deep endometriosis (Vermeulen et al. 2021). The three types of endometriotic lesions usually co-exists making the clinical evaluation and correlation to symptoms more complicated. Deep endometriosis is characterized by oncomimetic extension and infiltration of different organs with multifocal localization (FIGURE 1), causing severe adhesions between infiltrated tissues and complete alteration of anatomy, with possible recurrences after surgery. The deep infiltration may result, in extreme cases, not only in severe symptomatology but also in organ damage like bowel occlusion or silent kidney function loss.

Deep endometriosis, defined as endometriotic tissue infiltrating organs for more than 5mm (Koninckx et al. 1991) or just under the peritoneal surface according to a recent definition (Vermeulen et al. 2021) represents a more aggressive and invalidating disease as it may cause organ damage. Its prevalence in the general population ranges between 0.2- 0.5%, and it increases among women with pain and infertility, to 3-10% (Koninckx et al. 2021).

Bowel infiltration is present in about 6-12% of women with endometriosis (Mereu et al. 2007, Ferrero et al. 2021, Barra et al. 2021, Ceccaroni et al. 2022). The infiltration of bowel wall occurs progressively from the outside, that is from the serosal layer, through the muscolaris related

to a possible stenosis of the bowel lumen, towards the inner layer – mucosa, affected in extreme cases. The surgical technique necessary for the removal of bowel endometriosis lesion depends on the extension and deepness of penetration of the disease, and the procedures include shaving, discoid resection and segmental bowel resection.

Endometriosis may cause different symptoms such as (Mereu et al. 2007, Ferrero et al. 2021, Barra et al. 2021, Ceccaroni et al. 2022) dysmenorrea, dyspareunia, dysuria, chronic pelvic pain, heavy menstrual bleeding and bowel symptoms like dyschezia, alternating constipation/diarrhea, tenesmus, abdominal bloating which may increase during the menstrual or periovulatory period. Asymptomatic deep endometriosis does not require treatment. In case of bowel infiltration other symptoms may include defecation urgency, feeling of incomplete evacuation and rectal bleeding, particularly in cases of mucosal infiltration. Large bowel nodules may cause sub-occlusive symptoms or complete occlusion requiring emergency surgery. Colorectal endometriosis may also induce rectal and bladder dysfunction related to hypertonia of the internal anal and urethral sphincter (Ferrero et al. 2021, Mabrouk et al. 2012).

Good results in terms of pain and fertility (Mereu et al. 2007, Ferrero et al. 2021, Barra et al. 2021, Ceccaroni et al. 2022) are reported after surgical treatment of bowel endometriosis. The decision to perform surgery is based on previous treatment failure and severity of symptoms and a first-line therapy for patients with pain who don't desire pregnancy is the medical hormonal treatment (Barra et al. 2021). In infertile women the decision about the treatment is particularly complex and should include careful evaluation of all possible infertility co-existing factors (Becker et al. 2022).

Reproductive results after bowel resection differ between studies with a variation of PR from 26% to 71% (Darai et al. 2010, Meuleman et al. 2014, Barra et al 2021) as often, to obtain a sufficiently numerous population, both fertile and infertile women are included.

AIM: Therefore the aim of the present study was to evaluate pain and fertility outcome after laparoscopic treatment of bowel endometriosis in infertile patients performed in a referral center.

METHODS:

We report the results of two studies (Stepniewska et al. 2009, Stepniewska et al. 2010a), the first one focusing on the fertility outcome after surgery and the second one on symptoms and recurrence.

The advantage of these studies is that both of them were performed in a Referral Center (Department of Obstetrics and Gynecology, Gynecology Oncology and Minimally-Invasive Pelvic Surgery, International School of Surgical Anatomy-ISSA, IRCCS Ospedale Sacro Cuore - Don Calabria) for all clinical and scientific steps such as preoperative evaluation, surgical treatment and follow-up evaluation. All patients included in these studies suffered from infertility for at least two years and performed evaluation on all infertility factors, so the results reflect a real result in endometriosis-related infertility. The decision to include infertile women only has the advantage of avoiding estroprogestins use which could alter the outcome.

In both reported studies three groups of patients were included: women who underwent endometriosis surgery with colorectal segmental resection, women with surgical evidence of bowel endometriosis who underwent endometriosis partial removal without bowel resection, and women affected by moderate or severe endometriosis with at least one endometrioma and deep infiltrating endometriosis but without bowel involvement. Comparison of outcome in those three groups allowed the evaluation of symptoms and fertility related to bowel endometriosis and its treatment

without possible influence of other endometriosis localizations, which often co-exist taking part of a complex disease.

The study on radio frequency treatment of uterine adenomyosis (Stepniewska et al. 2022) reports outcome on such a treatment in patients desiring to avoid hysterectomy even in presence of invalidating symptoms and allowing therefore not to exclude the possibility of pregnancy in these patients.

The aim of a surgical treatment is to obtain good results in terms of fertility and pain outcome with possibly rare complications and recurrences of the disease. Therefore these aspects are also reported in the studies, based on a short and on a long-term follow-up.

DISCUSSION

The presented studies report a good outcome in terms of both fertility and pain after surgery for deep endometriosis with colorectal involvement, related to a low complication rate. It is important to underline however, that these results may not be reproducible in another hospital as the surgery outcome is strictly related to the experience. In all cases the surgical procedures were performed in a referral center with a multidisciplinary team involved in all steps from the diagnosis, counseling and decision about the treatment and surgery. It is in line with actual recommendations, according to which the treatment of deep endometriosis should be performed exclusively in centers of expertise (Becker et al. 2022).

The role of a referral center is fundamental not only for the surgical treatment but also for the correct instrumental diagnosis and counseling, to avoid incomplete surgery related to underestimation of endometriosis extension and lack of the consent for bowel surgery. In fact, in the presented studies, the decision to perform or avoid bowel resection was made before surgery after adequate diagnosis and information given to the patient, and not because of intraoperative finding not suspected before. The correct instrumental diagnosis is also of extreme importance when surgery is not considered at all and the patient is a candidate for assisted procreation techniques.

In these cases, the parametrial infiltration with ureteral involvement not diagnosed before the ovarian hormonal stimulation may lead to silent hydronephrosis (Renier et al. 1995) and require renal function-saving procedures, which are particularly invasive in already ongoing pregnancy. Therefore, ultrasound plays an important role of diagnosis and staging of endometriosis (Leonardi et al. 2022, Ceccaroni et al. 2023, Barra et al. 2023). However, for the diagnosis of tubal endometriosis, ultrasonographic study is not insufficient if we consider the clear sign of hydrosalpinx as its marker, it is necessary to include other signs of adnexal involvement by endometriosis to increase the sensitivity of exam (Stepniewska et al. 2021). Tubal endometriosis may reduce the possibility of conception or increase risk of pelvic inflammatory disease (Clarizia et al. 2021) or extrauterine pregnancy (Ceccaroni et al. 2021).

The good results reported in the presented studies does not absolutely imply the indication to perform surgery in all cases of bowel endometriosis in infertile women. The decision to perform surgery in our studies was taken because of related pain symptoms, after careful analysis of other aspects of fertility and adequate counseling. Indications for bowel surgery in a benign condition like endometriosis, is still under debate. It will be probably impossible to obtain data from

randomized studies in this field for different reasons: first of all it is hardly acceptable to offer a surgical procedure to an asymptomatic woman, the second one is that most patients would not like to participate in a randomized trial. In fact, Vercellini performed a questionnaire about the possibility of being involved in a RCT and obtained results that only 2% of patients would agree to participate in it (Vercellini et al. 2015), which is understandable due to the invasiveness of this treatment. Usually surgery is performed in patients with severe pain while asymptomatic patients with endometriosis are referred for IVF.

While specific early complications of colorectal resection are anastomotic leakage (1.9%) and rectovaginal fistula, and additionally, one of a late surge is anastomosis stenosis (2.7-6.3%) (De Cicco et al. 2011, Barra et al. 2021, Bertocchi et al. 2019), those common to different surgical procedures for deep endometriosis in the posterior compartment are urine retention (820%) and bowel dysfunction (3.6%) (Barra et al. 2021). Other general risks possible for different laparoscopic surgical procedures include pelvic abscess (0.8-3.4%) (De Cicco et al. 2011, Barra et al. 2021), ureteral damage (0.5-3.7%), hemoperitoeum (2.5%), anastomotic bleeding (0.1-1%) and trocar access complications (<1:1000). The overall complication rate after segmental resection for endometriosis, according to a specific review (De Cicco et al. 2011) was of 22.2%.

In the field of fertility, despite good results in a majority of patients, postoperative complications could lead to fertility damage because of severe adhesions and make spontaneous conception difficult. Two patients of our study (Stepniewska et al. 2009) who experienced the bowel suture dehiscence did not conceive after surgery.

Ferrier (Ferrier et al. 2018) focused on the reproductive outcome in patients who had different postoperative complications including rectovaginal fistula, anastomotic leakage, deep pelvic abscess, ureter-hydronephrosis, urinary fistula and bowel obstruction, reporting a PR of

66.7% after grade IIIa complications, 40% after grade IIIb complications and no pregnancies after grade IV complications. However, when analyzed separately, pelvic abscess was related to a significantly lower PR (p=0.04). Also in patients who experienced an anastomotic dehiscence after colorectal surgery, a lower PR was reported (p=0.02), in line with our observations. Not all kinds of postoperative complications may lead, from the pathological point of view, to the damage of fertility. Those which are related to peritonitis like pelvic abscess, rectovaginal fistula or anastomotic dehiscence are at major risks, followed by uroperitoneum, and intraperitoneal bleeding which could cause adhesions. Other risks such as anastomotic stenosis, ureteral stenosis or urinary retention may hardly lead to a reduced postoperative fertility.

Another aspect important for postoperative fertility is that of the ovarian reserve damage, as in 49-60% (Scioscia et al. 2011) of severe endometriosis ovarian endometriomas are present. It has been reported that surgery of bilateral endometriomas is related to a risk of POI in 2.4% (Busacca et al. 2006) and to a risk of poor responder in 13% of cases (Benaglia et al. 2010). Therefore, when decision about the surgical treatment is under evaluation, these risk factors should be carefully considered and discussed with the patient (Becker et al. 2022, Mabrouk et al. 2015).

IMPROVEMENT OF PAIN SYMPTOMS

The pain in endometriosis may be caused by pelvic adhesions and deep lesions in the posterior compartment, while hyperalgesia may enhance the intensity of symptoms (Renner et al. 2012). Possible mechanisms in which endometriosis may induce pain include nociceptive, inflammatory and neuropathic pathways (Renner et al. 2012).

Similarly to other studies (Riiskjaer et al. 2018), a significant improvement of all pain components was observed after colorectal surgery. The percentage of patients with a complete regression of

pain after bowel resection was 81% for dyspareunia, 81% for dyschezia, 87% for non-menstrual pelvic pain and 76% for dysmenorrhea after a mean follow-up of 26.9 months. A systematic review including 1889 patients after colorectal resection for endometriosis reported that 54.9% were asymptomatic after one year follow-up for dysmenorrea, 62% for dyspareunia, 31% for nonmenstrual pelvic pain and 46% for dyschezia. (De Cicco et al. 2011).

It is interesting to notice that in our study even in cases of partial endometriosis removal, an improvement of all symptoms was observed. It may induce reflection about the influence of different endometriosis lesions on pain symptomatology, as the improvement was noticed for all components of pain studied in all groups. Moreover, the difference in percentage of patients completely asymptomatic and those without any pain improvement was different between the groups for all components such as dysmenorrhea, dyspareunia, dyschezia and non-menstrual pelvic pain, with the best outcome in patients without bowel endometriosis (group C), followed by colorectal resection (group A) towards non-radical endometriosis surgery (group B). Renner (Renner et al, 2012) suggested that it is possible to perform a pain mapping before surgery for endometriosis, however, in the present study, at least after surgery, the relationship between the pain and locations of the disease seem not be confirmed. Even if all other lesions were removed, the residual bowel endometriosis induced a partial persistence of all pain components and not only of dyschezia or dyspareunia which could be related to bowel nodule as the anatomical site.

RECURRENCE

Recurrence of symptoms after bowel resection was 10%, significantly lower than in the nonradical surgery group (Stepniewska et al, 2010a). It is in line with the results of a review on bowel resection for endometriosis (De Cicco et al. 2011) that reported the range of symptoms

recurrence of 4-54% for follow-up periods of 2-5 years.

The instrumental recurrence in our study after colorectal resection was 7%, while in the total population in our center it was 3.5% (Minelli et al. 2009). This could be explained by the use of estroprogestin treatment in other patients, while in infertile population it was not performed to allow conception.

Surgical recurrence occurred in 7% of patients after bowel resection. The surgical recurrence reported in a review of De Cicco was of 19.4% varying from 0 to 34% in a range of follow-up of 2-5 years (De Cicco et al. 2011). The time from surgery to recurrence in our study was 26 months confirming that a first period after surgery may be considered for a spontaneous conception, as actually indicated, in patients who have good probability of pregnancy (Boujenah et al. 2017).

BOWEL ENDOMETRIOSIS AND FERTILITY

The interesting aspect of our studies is the possible correlation between bowel endometriosis and its surgical treatment on fertility.

It was a completely new aspect, not noticed before, which became inspiration for other researchers. This correlation has been successively confirmed in another study, (Ferrero et al. 2014) including 35 women who underwent bowel resection and 18 with residual colorectal endometriosis. Similarly to our results, the PR for spontaneous pregnancy was significantly higher if colorectal resection was performed (40% vs 16.7%). For medically assisted conception the PR rate was not influenced by the radicality of surgery.

The results of meta-analysis of Cohen (Cohen et al. 2014) about fertility related to deep endometriosis confirm a potential influence of bowel endometriosis on fertility as a high spontaneous postoperative PR was observed among patients without bowel infiltration, of 50%. In

patients with bowel endometriosis the PR was 28.6% for spontaneous pregnancy after surgery and of 29% for IVF pregnancy rate, suggesting that in these patients a combined treatment may be beneficial, with an overall PR of 46.9%.

Successively (Darai et al. 2017), a review on fertility outcomes after bowel resection was published, reporting results on a total 854 women from 24 studies published between 1990 and 2015. The spontaneous PR after surgery was 31.4% while PR after IVF was 19.8 % (21.4% in infertile women and 15.5% in patients without previous infertility). Among women with residual bowel endometriosis the PR for spontaneous conception after surgery and for IVF was 26.5% and 27.4%, respectively. The overall PR in patients with residual bowel endometriosis was 37.9% and 51.1% in patients who underwent colorectal surgery, confirming a potential benefit of surgery on fertility in women with bowel endometriotic infiltration. The authors conclude that future studies are required to determine whether surgery should be offered to all or only selected patients after IVF failure.

Finally, a very recent study (Lapointe et al. 2022) confirmed that bowel resection significantly improves the possibility of spontaneous conception. The conclusion was, however, to perform multidisciplinary evaluation and adequate information to the patient when the decision about surgery is discussed.

Also Darai (Darai et al. 2011) confirmed a high PR after bowel resection, with the percentage of 43.6%, after a mean FU of 34 months. The population of study included not only infertile women, however a high percentage of spontaneous pregnancies was reported in both infertile and noninfertile women, with the PR around 31% in both cases.

Also the group of Meuleman (Meuleman et al. 2014) reported a good outcome in terms of fertility after colorectal surgery for endometriosis with a PR of 38% for spontaneous conception.

The study group included both infertile women and those without previous infertility.
Notably, most studies include women with and without infertility making the interpretation of the results more difficult, therefore the presented studies (Stepniewska et al. 2009, 2010a) remain still significant.

It is difficult to explain the pathogenetic mechanism in which bowel endometriosis could determine fertility, however it may be an expression of a more extensive and aggressive disease. We still don't know why in certain cases endometriosis grows and expands infiltrating the bowel and in other cases not. On the other hand, when an incomplete removal of endometriosis is performed, the residual bowel nodule is probably causing the inflammatory status leading to a reduced fertility.

While in preparation to IVF surgery is not indicated, unless there is organ important damage such as a subocclusive condition related to bowel endometriosis or hydronephrosis because of parametrial infiltration, surgical treatment enhances the chance of spontaneous conception, particularly in young patients. In our experience (Stepniewska et al. 2010b), good fertility results after surgery may be noticed in patients younger than 35, with a PR of 49% in patients under 30 and of 45% in population aged 30-34. No pregnancies occurred during the follow-up in patients over 34 after colorectal surgery. After surgery for endometriosis the first period of 12-18 months is particularly fertile (Pouly et al. 1996, Chapron et al. 1999), and half of pregnancies occur within the first 6 months.
These two concepts of postoperative fertile window and the influence of age on fertility, in addition to the anamnestic factors and adnexal status are the base for EFI, the score for endometriosisrelated fertility, developed successively, and actually recommended. (Becker et al. 2022)

According to actual recommendations (Becker et al. 2022), the decision on advising immediate assisted or spontaneous conception during a period of 3-6 or 12 months after surgery should be made with the use of EFI (Adamson and Pasta 2010), a score allowing to predict the probability of spontaneous PR after surgery. Moreover the ovarian reserve can also be integrated in the decision-making process, and a flowchart including the AFC after surgery have been suggested for this purpose. (Boujenah et al, 2017)

Moreover, the predicted EFI (Tomassetti et al. 2021), based on ultrasonographic staging, could also be useful when the decision about the treatment is made (Becker et al. 2022), based on instrumental evaluation. Before surgery, according to the actual recommendations, the predicted preoperative EFI score should be used when decision about surgery is made in infertile women – due to good ultrasonographic correlation with the intraoperative evaluation of the adnexal status the score may predict the possibility of spontaneous conception and enhance the indication for surgery or IVF in borderline cases.

Very interesting data came from a French retrospective study (Bendifallah et al. 2017), focusing on the dilemma of surgery versus IVF in colorectal endometriosis. The authors analyzed outcome in two different groups of patients: those who underwent first – line surgical treatment for bowel endometriosis and those who underwent first-line IVF. The better outcome was obtained after surgery, with a PR of 60% compared to 36% in first-line ART group. The results indicate good fertility outcome after colorectal surgery reflecting a possible indication of this treatment for infertility. The authors conclude, however, that in the decision about the treatment, the benefit expected after bowel resection should be weighed against the possible risks related to it.

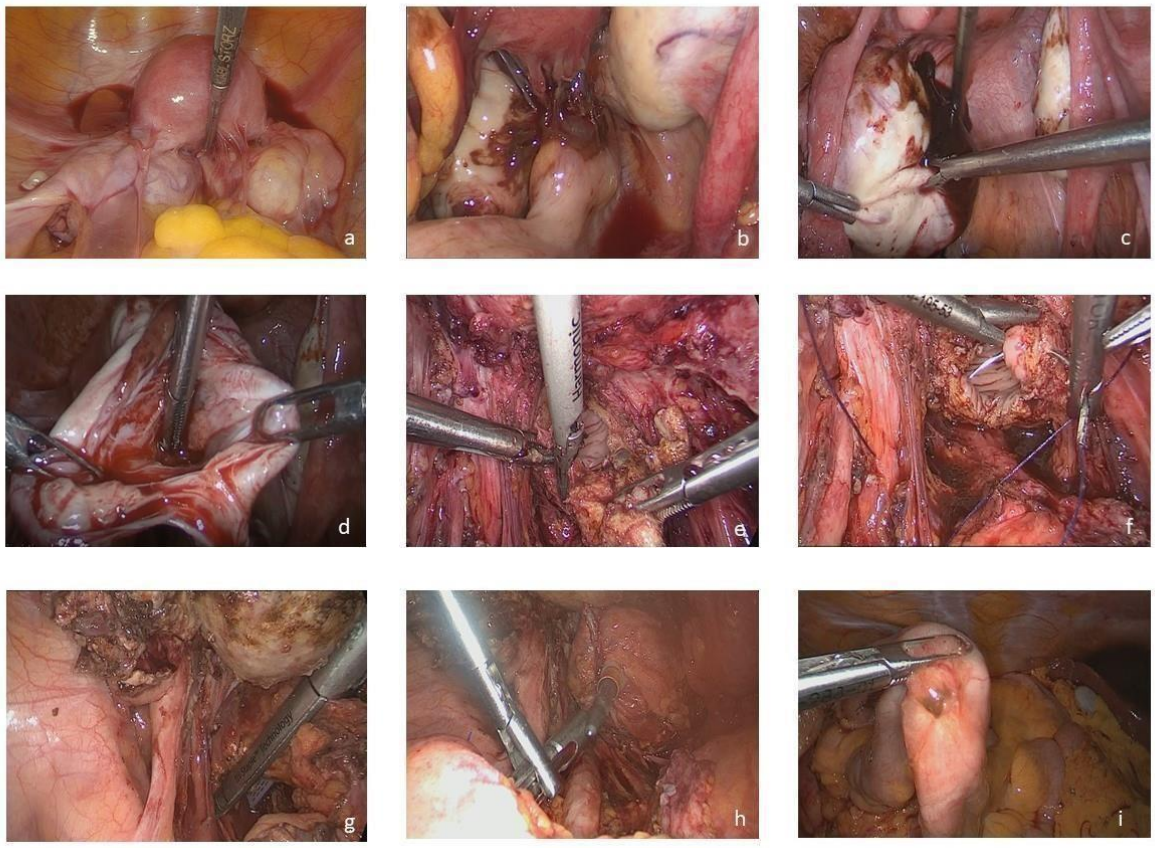
The challenge therefore, will be to obtain in the future a staging or flowchart to select patients who may benefit from the surgery and those candidates go directly to IVF, to avoid

unnecessary treatments and loss of time leading to psychological and economic impact. The future perspectives will for certain include in scores or flowcharts other aspects important for fertility such as preoperative ovarian reserve (evaluated by the AMH levels or AFC) or eventual association of uterine adenomyosis (and eventual type and staging of adenomyosis). In fact, a negative impact of adenomyosis on symptoms (Landi et al. 2008) and pregnancy outcome (Nirgianakis et al. 2021) has been observed. While the definitive treatment is represented by hysterectomy, new fertilitysparing treatments are researched for infertile women. Among them, radiofrequency allows a significant reduction of symptoms and avoids hysterectomy in a high percentage of cases, 87% (Stepniewska et al. 2022). Moreover, in the reported study, two term pregnancies occurred among patients who were already candidates for the demolitive treatment because of severe symptoms but avoided hysterectomy due to radiofrequency (Stepniewska et al. 2022).

CONCLUSIONS

The two presented articles indicate important aspects in the evaluation of infertile women with bowel deep endometriosis. The decision in these cases is complex and should be performed in centers of expertise. In different countries, including Poland, the current goal is to identify and develop a web of referral centers, giving first-, second- and tertiary- levels of care, focusing on administrative and organization aspects within the regional and national territory. A clear pathway for patients with suspected endometriosis should allow them to obtain correct diagnosis and treatment, with the optimization of resources and reducing psychological and medical impact. In the field of deep endometriosis and infertility, the presented results may represent an important milestone, describing the experience of a center with a long-time expertise.

FIGURE 1. Intraoperative findings in severe endometriosis: a-frozen pelvis, b-rectovaginal endometriosis infiltrating the bowel wall, c- ovarian endometrioma, d- enucleation of endometrioma, e- vaginal endometriosis, f- suture of vagina after resection of vaginal wall with endometriotic nodule, g- parametrial endometriosis, h – colorectal anastomosis after bowel segmental resection, i- ileal endometriosis



REFERENCES

- Adamson GD, Pasta DJ. Endometriosis fertility index: the new, validated endometriosis staging system. Fertil Steril. 2010 Oct;94(5):1609-15.

- Akande VA, Hunt LP, Cahill DJ, Jenkins JM. Differences in time to natural conception between women with unexplained infertility and infertile women with minor endometriosis. Hum Reprod. 2004 Jan;19(1):96-103.

- Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JM. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev. 2020 Oct 23;10(10):CD011031

- Barra F, Mikhail E, Villegas-Echeverri JD, Ferrero S. Infertility in patients with bowel endometriosis. Best Pract Res Clin Obstet Gynaecol. 2021 Mar;71:161-171.

- Barra F, Zorzi C, Albanese M, **Stepniewska A**, Deromemaj X, De Mitri P, Roviglione G, Clarizia R, Gustavino C, Ferrero S, Ceccaroni M. Ultrasonographic Findings Indirectly Predicting Parametrial Involvement in Patients with Deep Endometriosis: The ULTRA-PARAMETRENDO I Study. J Minim Invasive Gynecol. 2023 Jan;30(1):61-72.

- Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, King K, Kvaskoff M, Nap A, Petersen K, Saridogan E, Tomassetti C, Van Hanegem N, Vulliemoz N, Vermeulen N; ESHRE Endometriosis Guideline Group, ESHRE guideline: endometriosis, Hum Reprod Open 2022 Feb 26;2022(2).

- Benaglia L, Somigliana E, Vighi V, Ragni G, Vercellini P, Fedele L. Rate of severe ovarian damage following surgery for endometriomas. Hum Reprod. 2010 Mar;25(3):678-82.

- Bendifallah S, Roman H, Mathieu d'Argent E, Touleimat S, Cohen J, Darai E, et al. Colorectal endometriosis-associated infertility: should surgery precede ART? Fertil Steril. 2017;108(3):52531
- Bertocchi E, Barugola G, Benini M, Bocus P, Rossini R, Ceccaroni M, et al. Colorectal Anastomotic Stenosis: Lessons Learned after 1643 Colorectal Resections for Deep Infiltrating Endometriosis. J Minim Invasive Gynecol. 2019;26(1):100-4.

- Boujenah J, Cedrin-Durnerin I, Herbemont C, Bricou A, Sifer C, Poncelet C. Use of the endometriosis fertility index in daily practice: A prospective evaluation. Eur J Obstet Gynecol Reprod Biol. 2017 Dec;219:28-34.

- Busacca M, Riparini J, Somigliana E, Oggioni G, Izzo S, Vignali M, Candiani M. Postsurgical ovarian failure after laparoscopic excision of bilateral endometriomas. Am J Obstet Gynecol. 2006 Aug;195(2):421-5.

- Ceccaroni M, Finelli A, Manzone M, **Stepniewska A**, Clarizia R. Ectopic Pregnancy Caused by a Stenosing Tubal Localization of Deep Endometriosis. J Minim Invasive Gynecol. 2021 Jan;28(1):7-8.

- Ceccaroni M, Clarizia R, Mussi EA, **Stepniewska A**, De Mitri P, Ceccarello M, Ruffo G, Bruni F, Rettore L, Surico D. "The Sword in the Stone": radical excision of deep infiltrating endometriosis with bowel shaving-a single-centre experience on 703 consecutive patients. Surg Endosc. 2022 May;36(5):3418-3431.

- Ceccaroni M, Zorzi C, Albanese M, Clarizia R, **Stepniewska A**, Roviglione G, Ferrero S, Barra F.J Why to Use an Old Map to Explore a New World? The Time for Considering an Ultrasonographic Parametrial Topography Has Come. Minim Invasive Gynecol. 2023 Apr;30(4):271276.

- Chapron C, Fritel X, Dubuisson JB. Fertility after laparoscopic management of deep endometriosis infiltrating the uterosacral ligaments. Hum Reprod. 1999 Feb;14(2):329-32.

- Clarizia R, Capezzuoli T, Ceccarello M, Zorzi C, **Stepniewska A**, Roviglione G, Mautone D, Petraglia F, Ceccaroni M. Inflammation calls for more: Severe pelvic inflammatory disease with or without endometriosis. Outcomes on 311 laparoscopically treated women. J Gynecol Obstet Hum Reprod. 2021 Mar;50(3):101811.

-
-
- Cohen J, Thomin A, Mathieu D'Argent E, Laas E, Canlorbe G, Zilberman S, Belghiti J, ThomassinNaggara I, Bazot M, Ballester M, Daraï E. Fertility before and after surgery for deep infiltrating endometriosis with and without bowel involvement: a literature review. Minerva Ginecol.
  2014 Dec;66(6):575-87.

  Darai E, Carbonnel M, Dubernard G, Lavoue V, Coutant C, Bazot M, et al. Determinant factors of fertility outcomes after laparoscopic colorectal resection for endometriosis. Eur J Obstet Gynecol Reprod Biol. 2010;149(2):210-4.

- Daraï E, Cohen J, Ballester M. Colorectal endometriosis and fertility. Eur J Obstet Gynecol Reprod Biol. 2017 Feb;209:86-94.

- Darai 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(6):1903-8.

- De Cicco C, Corona R, Schonman R, Mailova K, Ussia A, Koninckx P. Bowel resection for deep endometriosis: a systematic review. BJOG. 2011;118(3):285-91.

- De Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. Lancet. 2010 Aug 28;376(9742):730-8.

- Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril. 1997 Oct;68(4):585-96

- Ferrero S, Leone Roberti Maggiore U, Scala C, Venturini PL, Remorgida V. Impact on fertility of colorectal endometriosis untreated during laparoscopy. J Minim Invasive Gynecol. 2014;21(6 (Suppl.)):S13-S4

-

- Ferrero S, Stabilini C, Barra F, Clarizia R, Roviglione G, Ceccaroni M. Bowel resection for intestinal endometriosis. Best Pract Res Clin Obstet Gynaecol. 2021 Mar;71:114-128.

Ferrier C, Roman H, Alzahrani Y, d'Argent EM, Bendifallah S, Marty N, Perez M, Rubod C, Collinet P, Daraï E, Ballester M. Fertility outcomes in women experiencing severe complications after surgery for colorectal endometriosis. Hum Reprod. 2018 Mar 1;33(3):411-415.

- Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 1991;55:759e65.

Koninckx PR, Ussia A, Adamyan L, Tahlak M, Keckstein J, Wattiez A, Martin DC. The epidemiology of endometriosis is poorly known as the pathophysiology and diagnosis are unclear. Best Pract Res Clin Obstet Gynaecol. 2021 Mar;71:14-26.

- Landi S, Mereu L, Pontrelli G, **Stepniewska A**, Romano L, Tateo S, Dorizzi C, Minelli L. The influence of adenomyosis in patients laparoscopically treated for deep endometriosis. J Minim Invasive Gynecol. 2008 Sep-Oct;15(5):566-70.

- Lapointe M, Pontvianne M, Faller E, Lodi M, Futcher F, Lecointre L, Wattiez A, Akladios C. Impact of surgery for colorectal endometriosis on postoperative fertility and pregnancy outcomes. Journal of Gynecology Obstetrics and Human Reproduction, 51 (4),2022

- Leonardi M, Uzuner C, Mestdagh W, Lu C, Guerriero S, Zajicek M, Dueckelmann A, Filippi F, Buonomo F, Pascual MA, **Stepniewska A**, Ceccaroni M, Van den Bosch T, Timmerman D, Hudelist G, Condous G. Diagnostic accuracy of transvaginal ultrasound for detection of endometriosis using International Deep Endometriosis Analysis (IDEA) approach: prospective international pilot study. Ultrasound Obstet Gynecol. 2022 Sep;60(3):404-413.

-
-

- Mabrouk M, Ferrini G, Montanari G, Di Donato N, Raimondo D, Stanghellini V, Corinaldesi R, Seracchioli R. Does colorectal endometriosis alter intestinal functions? A prospective manometric and questionnaire-based study. Fertil Steril. 2012 Mar;97(3):652-6

-
-

Mabrouk M, Pesci A, Zorzi C, Grassi T, Clarizia R, **Stepniewska A**, Scioscia M, Zamboni G, Ceccaroni M. Ovarian Reserve Reduction Due to Unintended Excision of Healthy Ovarian Tissue During Endometrioma Surgery: What is the Risk? Analysis of 170 Cases. J Minim Invasive Gynecol. 2015 Nov-Dec;22(6S):S173-S174.

- Mereu L, Ruffo G, Landi S, Barbieri F, Zaccoletti R, Fiaccavento A, **Stepniewska A,** Pontrelli G, Minelli L. Laparoscopic treatment of deep endometriosis with segmental colorectal resection: short-term morbidity. J Minim Invasive Gynecol. 2007 Jul-Aug;14(4):463-9.
- Meuleman C, Tomassetti C, Wolthuis A, Van Cleynenbreugel B, Laenen A, Penninckx F, et al. Clinical outcome after radical excision of moderate-severe endometriosis with or without bowel resection and reanastomosis: a prospective cohort study. Ann Surg. 2014;259(3):522-31.

Meuleman C, Tomassetti C, Wolthuis A, Van Cleynenbreugel B, Laenen A, Penninckx F, Vergote I, D'Hoore A, D'Hooghe T. Clinical outcome after radical excision of moderatesevere endometriosis with or without bowel resection and reanastomosis: a prospective cohort study. Ann Surg. 2014 Mar;259(3):522-31.

- Minelli L, Fanfani F, Fagotti A, Ruffo G, Ceccaroni M, Mereu L, Landi S, Pomini P, Scambia G Laparoscopic colorectal resection for bowel endometriosis: feasibility, complications, and clinical outcome. Arch Surg. 2009 Mar;144(3):234-9

- Nirgianakis K, Kalaitzopoulos DR, Schwartz ASK, Spaanderman M, Kramer BW, Mueller MD, Mueller M. Fertility, pregnancy and neonatal outcomes of patients with adenomyosis: a systematic review and meta-analysis. Reprod Biomed Online. 2021 Jan;42(1):185-206.

- Pouly JL, Drolet J, Canis M, Boughazine S, Mage G, Bruhat MA, Wattiez A. Laparoscopic treatment of symptomatic endometriosis. Hum Reprod. 1996 Nov;11 Suppl 3:67-88.

-
-
- Renier M, Verheyden B, Termote L. An unusual coincidence of endometriosis and ovarian stimulation. Eur J Obstet Gynecol Reprod Biol. 1995 Dec;63(2):187-9.

  Renner SP, Boosz AS, Burghaus S, Maihöfner C, Beckmann MW, Fasching PA, Jud SM.Arch Visual pain mapping in endometriosis. Gynecol Obstet. 2012 Sep;286(3):687-93.

- Riiskjaer M, Forman A, Kesmodel US, Andersen LM, Ljungmann K, Seyer-Hansen M. Pelvic Pain and Quality of Life Before and After Laparoscopic Bowel Resection for Rectosigmoid Endometriosis: A Prospective, Observational Study. Dis Colon Rectum. 2018;61(2):221-9.

- Scioscia M, Bruni F, Ceccaroni M, Steinkasserer M, **Stepniewska A,** Minelli L. Distribution of endometriotic lesions in endometriosis stage IV supports the menstrual reflux theory and requires specific preoperative assessment and therapy. Acta Obstet Gynecol Scand. 2011 Feb;90(2):136-9.
- **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 Jul;24(7):1619-25.

  Stepniewska A, Pomini P, Guerriero M, Scioscia M, Ruffo G, Minelli L. Colorectal endometriosis: benefits of long-term follow-up in patients who underwent laparoscopic surgery. Fertil Steril. 2010a May 1;93(7):2444-6

- **Stepniewska A**, Pomini P, Scioscia M, Mereu L, Ruffo G, Minelli L. Fertility and clinical outcome after bowel resection in infertile women with endometriosis. Reprod Biomed Online. 2010b May;20(5):602-9.

- **Stepniewska A,** Clarizia R, De Mitri P, Pesci A, Zorzi C, Albanese M, Trivella G, Guerriero M, Improda FP, Ceccaroni M**.** Role of ultrasonographic parameters for predicting tubal involvement in

- infertile patients affected by endometriosis: A retrospective cohort study. J Gynecol Obstet Hum Reprod. 2021 Dec;50(10):102208.

- **Stepniewska A,** Baggio S, Clarizia R, Bruni F, Roviglione G, Ceccarello M, Manzone M, Guerriero M, Ceccaroni M. Heat can treat: long-term follow-up results after uterine-sparing treatment of adenomyosis with radiofrequency thermal ablation in 60 hysterectomy candidate patients. Surg Endosc. 2022 Aug;36(8):5803-5811.

- Tomassetti C, Bafort C, Vanhie A, Meuleman C, Fieuws S, Welkenhuysen M, Timmerman D, Van Schoubroeck D, D'Hooghe T. Estimation of the Endometriosis Fertility Index prior to operative laparoscopy. Hum Reprod. 2021

- Vercellini P, Somigliana E, Cortinovis I, Bracco B, de Braud L, Dridi D, Milani S. "You can't always get what you want": from doctrine to practicability of study designs for clinical investigation in endometriosis. BMC Womens Health. 2015 Oct 22;15:89.

- Vermeulen N, Abrao MS, Einarsson JI, Horne AW, Johnson NP, Lee TTM, Missmer S, Petrozza J, Tomassetti C, Zondervan KT, Grimbizis G, De Wilde RL; International working group of AAGL, ESGE, ESHRE and WES. Endometriosis Classification, Staging and Reporting Systems: A Review on the Road to a Universally Accepted Endometriosis Classification. J Minim Invasive Gynecol. 2021 Nov;28(11):1822-1848.