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## **Risk of bowel obstruction during IVF treatment of patients with deep infiltrating endometriosis**

Running Head: Bowel endometriosis and IVF

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### **Abstract**

*Introduction:* Women with endometriosis often experience pain and infertility. Medical treatment interferes with the possibility to attain pregnancy. For infertile women with endometriosis surgery is a possible treatment, but with advanced disease there is an

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increased risk of serious complications. With only limited pain, the women will often be referred for in vitro fertilization (IVF) treatment instead. The disease is estrogen dependant and during IVF treatment the women could theoretically experience worsening of their symptoms. *Material and methods:* The study is a retrospective cohort study of 76 women with bowel endometriosis treated conservatively and having IVF treatment. *Results:* Nine (11,8 %) of the women experienced severe worsening of their bowel related symptoms, including two patients presenting with colon ileus. One additional woman had no previous diagnosis of endometriosis before she presented with subocclusion of the bowel during IVF. In all cases the IVF treatment was stopped. *Conclusions:* Our study revealed that bowel endometriosis increases the risk of complications during IVF treatment. This is in contrast to several publications. However, our study population is different due to the fact that none of these women had previous operation for bowel endometriosis. In 88% of the cases the women completed fertility treatment without need for surgery.

#### **Keywords**

Endometriosis, in vitro fertilization, bowel endometriosis, deep infiltrating endometriosis, IVF, surgery, fertility

#### **Abbreviations**

DIE deep infiltrating endometriosis

IVF in vitro fertilization

GnRH gonadotropin analogue releasing hormone

MRI magnetic resonance imaging

## Key message

Women with bowel endometriosis risk aggravation of bowel symptoms during IVF treatment for infertility.

## Introduction

Endometriosis is defined by ectopic occurrence of endometrium-like tissue causing local inflammation with subsequent pain and infertility (1, 2). The disease is estrogen dependent and medical therapies include oral contraceptives, progestogen monotherapy, and gonadotropin analogue releasing hormone (GnRH) downregulation (3). These drugs can generally not be used when patients want to become pregnant, and surgery is the option when treatment is needed in this situation.

The predominant indication for surgery is pain. Radical removal of endometriotic tissue with preserved fertility is attempted and the approach depends on the phenotype of endometriosis. This includes peritoneal disease, where surgery improves the spontaneous pregnancy rate (4) and possibly also in vitro fertilization (IVF) outcome (5). Endometrioma surgery may reduce ovarian follicle reserve, indicating a conservative approach in infertility patients (6). However, there are also data showing increased fertility rate after surgery for endometrioma (7).

Deep infiltrating endometriosis (DIE) is the most severe form with invasive growth, typically in the rectovaginal septum with frequent involvement of the vagina and bowel wall (8). Surgery for bowel DIE is complex with risk of complications (9), and patients with sparse or no symptoms and those responding to medical treatment may therefore be treated conservatively (10). In a few of these women, stenosis of the bowel (11) or ureter (12) may develop, with compelling need for intervention.

IVF is often indicated when endometriosis patients want to become pregnant. This involves controlled ovarian stimulation, which might induce progression of DIE (13). In accordance, early reports indicated that IVF in DIE patients can result in bowel or ureter stenosis (14-16), although the precise mechanism is unknown. Subsequent prospective

studies have not provided evidence of symptomatic progression during IVF treatment (17-20), but this discrepancy could reflect less advanced disease in the study populations.

Some years ago, one of our conservatively treated women experienced a colon occlusion because of a large nodule of bowel endometriosis during IVF (in vitro fertility) treatment. Since this is a serious complication potentially leading to major and/or even acute surgery, we found that further evaluation of risk of bowel obstruction in women with conservative treatment of endometriosis during fertility treatment was important. The aim of this study was therefore to investigate the probability of bowel obstruction in women with bowel DIE during fertility treatment.

### **Material and methods**

Our department represents one of two Danish referral centers for endometriosis and receives patients with suspected or diagnosed DIE from the western part of Denmark (background population approximately 2.5 million).

The diagnosis is based on anamnestic history, clinical examination including transvaginal ultrasound and in the majority of cases also magnetic resonance imaging (MRI). Our department has a significant experience in transvaginal ultrasound in the diagnosis of bowel endometriosis, as described previously (21). The primary strategy is to treat the women conservatively, i.e. with medication including oral contraceptives, progestogens or levonorgestrel containing intra-uterine device in cases where the patient does not have a present fertility wish. The women are seen for clinical control every year for possible adjustment of the treatment. There is no systematic registration of visual analogy scale score regarding pain intensity, however, all clinical controls are performed by experienced specialists from the endometriosis team. In the case of worsening in symptoms, the women can contact the centre for additional control.

Surgery is performed when medical treatment has failed, in case of bowel or ureter stenosis and in infertility patients with unacceptable pain. In some cases the patients themselves want an operation despite our conservative approach.

We performed an audit of 179 consecutive women with bowel DIE treated conservatively from 2007-2013, representing 51% of cases referred to our centre with bowel involvement in the study period. The remaining 49% all had bowel resection performed (22). The diagnosis was based on clinical examination combined with transvaginal ultrasound and/or MRI. More than 85% had a MRI scan performed, the remaining transvaginal ultrasound only. Data collected included demographic information, date of birth, weight and height, previous operations for endometriosis (number), oophorectomy status, current medical treatment (at the time of audit), and results of MRI findings with respect to location(s) of endometriosis. This cohort has been described in details previously (22).

Among the women primarily treated conservatively, a subgroup had fertility treatment in the following years two years. We identified the women with IVF-related significant worsening of pain and/ or severe bowel stenosis leading to operation. For these women also patient files from other hospitals including fertility clinics were reviewed. Regarding fertility treatment all cycles were initiated with GnRH downregulation at day 21 in the previous cycle. Treatment was according to the danish guideline for IVF treatment.

#### *Ethical approval*

This study was registered and approved by the Danish Data Protection Agency, June 12. 2013. J.nr. 2013-41-2033. Written consent from the women was obtained.

#### **Results**

Out of 179 patients treated conservatively for DIE with bowel affection, 76 underwent IVF treatment during the study period. Nine of these women (11.8 %) experienced severe worsening of their bowel symptoms and were seen for additional control in our centre. In addition, one woman without previous diagnosis of DIE was referred to us with severe pain and had DIE with bowel involvement diagnosed. This woman was patient in our fertility clinic, but was not diagnosed with endometriosis before initiation of fertility treatment

despite the fact that she had dyschezia, dyspareunia and dysmenorrhea. MRI or transvaginal ultrasound for bowel involvement was not included at the examination at the fertility clinic.

The average age was 33 years and average body mass index was 24.2 (3.4). The protocol for fertility treatment was according to the Danish national guideline. This consists of 3 months of GnRH-agonist treatment with subsequent stimulation initiated two weeks after the last GnRH-agonist injection. The women received between 1087 and 5700 IE follicle stimulating hormone per IVF cycle and had in average 3 IVF attempts (range 2-7).

Table 1 shows details of all 10 women. Nine of the women had their bowel endometriosis diagnosed prior to IVF treatment. Seven of these had an MRI performed before IVF, the remaining three had the MRI performed prior to operation. The bowel nodules were all located in the rectum with only two located in the low rectum (below 5 cm from the anal verge). In four women we found two bowel nodules during surgery.

Two of the women presented with occlusion of the colon. One of these had ileostomy performed, while the other was treated with decompression through colonoscopy. Six women had sub occlusion and were treated conservatively including increased treatment with laxatives and GnRH downregulation (i.e. three months of GnRH downregulation with add-back therapy consisting of low dose estrogen/progestogen) until operation. In these cases the women's symptoms included severely increased pain, dyschezia, paradoxical diarrhoea and bloating. In some of the cases, the women had symptoms of stenosis of the bowel leading to toilet visits during the night. The last two women only had severe worsening of their pain symptoms without signs of severe stenosis.

All ten women had a successive bowel resection performed prior to continued fertility treatment. Following surgery, five women got pregnant after eventless IVF treatment, one got pregnant spontaneously, three did not get pregnant despite IVF treatment and one woman chose adoption instead of IVF.

## Discussion

Our results show that women treated medically for DIE with bowel involvement experience a significant risk of worsened symptoms when their treatment is replaced by controlled ovarian stimulation prior to IVF. This risk amounted to almost 12 percent in our population of 76 IVF patients with well-defined disease. Sub occlusion/occlusion of the bowel was the predominant problem at admission.

Interpretation of our results is impeded by the retrospective design, and a prospective study would have offered more specific data, e.g. concerning details of the IVF treatment that might predispose to pain recurrence and also registration of visual analogy scale scores. Strengths of the study include the large cohort with detailed diagnosis. With these considerations in mind, our data allow for comparison with existing data in the field.

Previous studies have shown diverging results on the risk of pain recurrence when DIE patients undergo IVF treatment. Santulli et al (18) reported detailed data on 102 endometriosis patients where 46% had DIE with bowel involvement. No worsening of symptoms was observed during or after IVF, but no information was given on the principles for conservative treatment. There was no data on how many of the women had an operation performed removing the bowel endometriosis. It is therefore possible that the endometriosis centres involved prior to IVF had a more active surgical approach compared to our principles, thereby having a larger proportion of patients undergoing primary surgery. This could reduce the potential for worsened symptoms during ovarian stimulation.

Benaglia et al also failed to detect any significant pain recurrence during IVF (17), but this series comprised only nine women with DIE, and the number of patients with bowel involvement and the criteria for conservative treatment were not specified. In addition, the nodules were quite small of size (average 10 mm).

Taken together, the divergence between these previous findings and our study might reflect differences in patient population. Thus, our conservative attitude toward bowel DIE may imply fewer overall major surgical complications, but a higher risk for significant pain development and need for surgery during IVF treatment.

Our series included only patients referred for specialized treatment, and we have no data on the remaining 66 patients who completed IVF treatment without being referred back to us due to worsening of symptoms. It is therefore possible that a larger number of patients have experienced significant pain. A prospective study is currently performed at our unit to evaluate this aspect.

Unfortunately, our data do not allow us to speculate regarding the mechanism leading to the growth of the bowel nodules. The influence of increased oestrogen level during stimulation is obvious; however, the majority of patients in our cohort did not experience severe worsening. In theory some of the women might have increased sensitivity to oestrogen due to more active endometriosis. Ovarian hyper stimulation syndrome is known as a cause of discomfort and pain. However, occlusion or sub occlusion of the rectum has to our knowledge not been described with ovarian hyperstimulation syndrome. None of the women in this study had large ovaries or increased intraperitoneal fluid when they were seen in our clinic – and therefore did not have ovarian hyper stimulation syndrome .

Seven of the women in this study have had a previous diagnostic laparoscopy showing frozen pelvis with severe adhesions between the bowel and the uterus. These women were all referred directly to a fertility clinic. In five of the women a MRI was performed by the IVF clinic after the referral. We suggest that the discovery of frozen pelvis requires a more thorough diagnostic evaluation, possibly at a referral centre for advanced endometriosis. One of the women had no diagnostic laparoscopy but was described with severe symptoms of advanced endometriosis. Also in such a case a referral for diagnosis could be justified.

In agreement with our findings, Roman et al reported data on 12 young women with conservatively treated bowel DIE and wish for pregnancy where bowel sub occlusion/occlusion developed - in three of these cases during IVF treatment (23). These 12 patients corresponded to 5% of 241 patients managed for bowel endometriosis in their centre. This indicates a significant risk of worsened symptoms when patients with untreated bowel DIE try to conceive.

Both medical and surgical preventive measures can be proposed to avoid problems when patients with bowel DIE undergo IVF treatment. GnRH pre-treatment improves IVF



outcomes (24) and would cause at least transient atrophy of DIE (25), but it is not known whether this is sufficient to prevent or dampen the worsening of symptoms in bowel DIE. The length of this potential effect in case of repeated IVF is also unclear. However, all women in this study had GnRH pre-treatment.

Primary surgery before start of IVF is another possibility to avoid worsened bowel symptoms. The presence of DIE is a determinant for poor IVF outcome (25) and some data (26-29) suggest that patients with bowel endometriosis benefit from surgical excision prior to IVF.

Further evidence is needed on this aspect and any anticipated positive effects should be weighed against the risk of complications to bowel surgery (30).

Everything considered, our data show that the risk of aggravated symptoms must be taken into account when patients with bowel DIE undergo IVF, and probably a significant number will present with need for intervention. Still 88% of the patients completed fertility treatment without compelling need for surgery. Suspicion of endometriosis by the anamnestic history or by finding of frozen pelvis at laparoscopy should lead to further diagnostic evaluation. or at least to thorough information to patients about the signs of bowel occlusion before IVF treatment.

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Table 1. Characteristics of patients experiencing worsening of symptoms during in vitro fertilization (IVF) treatment (N=10).

	<b>Diagnostic laparoscopy</b>	<b>Consequence of laparoscopy</b>	<b>MRI before IVF</b>	<b>Effect of fertility treatment</b>	<b>MRI after IVF</b>	<b>Bowel operation</b>	<b>Pregnancy after surgery</b>
1	no	-	Nodule 70x23 mm	2 IVF  colon ileus	no	Ileostoma  later resection  1 nodule	Yes  IVF
2	- 1year  Frozen pelvis	Fertility clinic	Nodule 23x9 mm	1 IVF  severe pain	no	Resection  1 nodule	Yes  IVF
3	- 10 years  normal	-	Nodule 70x11 mm	2 IVF  subileus	no	Resection  2 nodules	no
4	- 1 year  Frozen pelvis	Fertility clinic	no	3 IVF  subileus	Nodule 2 x10 mm	Resection  1 nodule	no
5	- 4 years  Frozen pelvis	Oral contraception	Nodule 20x10 mm	1 IVF  subileus	Nodule 55x16 mm	Resection  1 nodule	No wish
6	- 1 year  Frozen pelvis	Fertility clinic	Nodule 20x9mm	3 IVF  subileus	Nodule 30x9 mm	Resection  2 nodules	no
7	- 3 years  Frozen pelvis	Fertility clinic	Nodule 50x14 mm	2 IVF  Severe pain,	no	Resection  1 nodule	Yes  IVF
8	no	-	no	7 IUI	Nodule 40x23	Resection	Yes

				3 IVF subileus	mm	2 nodules	spontaneous
9	- 2 years  Frozen pelvis	Fertility clinic	Nodule  40x15mm	3 IVF  subileus	no	Resection  1 nodule	no
10	- 1 year  Frozen pelvis	Fertility clinic	no	5 IVF  subileus	no	Resection  2 nodules	Yes  IVF

- 1 year: means that the diagnostic laparoscopy was performed one year before the woman was seen at our clinic.

MRI, magnetic resonance imaging; IUI, intrauterine Insemination.