EndometriosiS
associated subfertility

Lisette van der Houwen

Surgical treatment

Assisted Reproduction Techniques

Endometriosis associated subfertility

Surgical treatment and assisted reproduction techniques

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Surgical treatment and assisted reproduction techniques

The studies presented in this thesis were performed at the department of Obstetrics and Gynaecology, Division of Reproductive Medicine, IVF Center and Endometriosis Center of the Amsterdam UMC, location VU medical center, Amsterdam, The Netherlands.

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Endometriosis associated subfertility

Surgical treatment and assisted reproduction techniques

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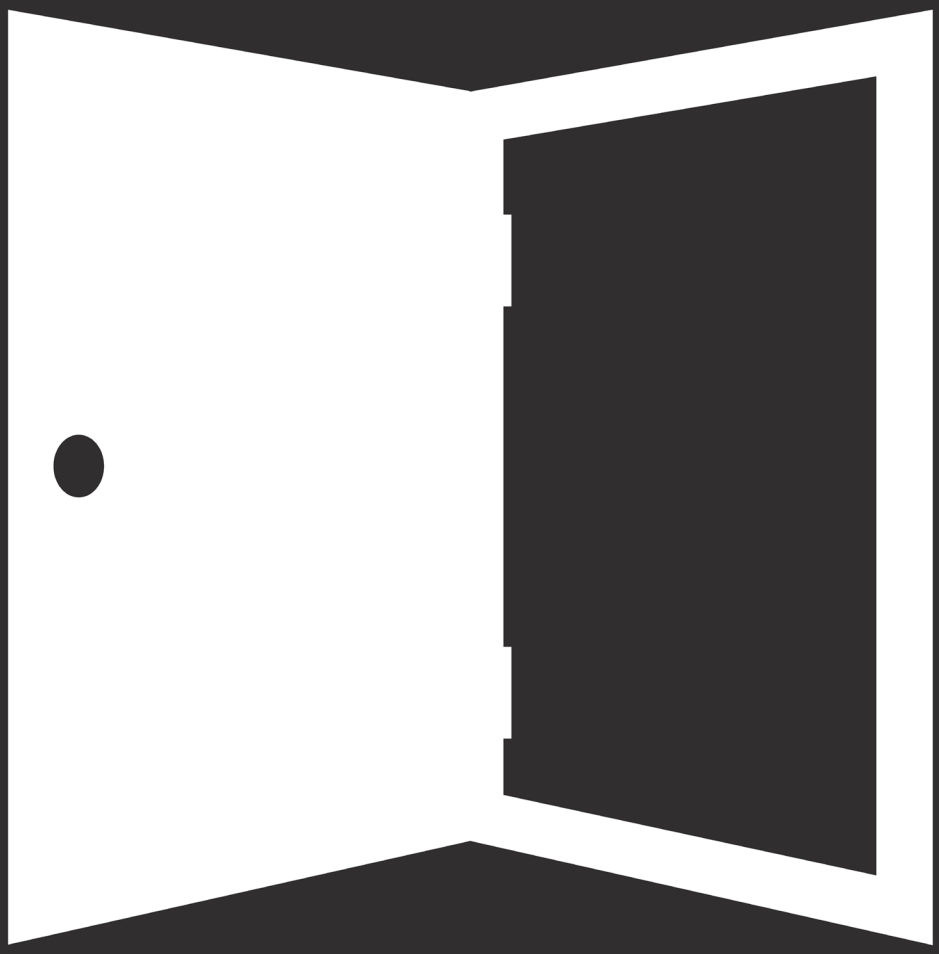
CONTENTS

Chapter 1	General introduction and outline of the thesis	**9**
Chapter 2	Long-term surgical outcomes after segmental colorectal resection in women with severe endometriosis. *Journal of Endometriosis. 2012;4:34-41*	**33**
Chapter 3	Efficacy and safety of intrauterine insemination in patients with moderate to severe endometriosis. *Reproductive BioMedicine Online. 2014;28:590-8*	**47**
Chapter 4	Pregnancy rates after intrauterine insemination in moderate to severe endometriosis: a systematic review and meta-analysis of observational studies. *Journal of Endometriosis and Pelvic Pain Disorders. 2017;9:158-167*	**63**
Chapter 5	Efficacy and safety of IVF/ICSI in patients with severe endometriosis after long-term pituitary down-regulation. *Reproductive BioMedicine Online. 2014;28:39-46*	**83**
Chapter 6	Patient satisfaction concerning assisted reproductive technology treatments in moderate to severe endometriosis. *Gynecological Endocrinology. 2014;30:798-803*	**99**
Chapter 7	Continuous oral contraceptives versus long-term pituitary desensitization prior to IVF/ICSI in moderate to severe endometriosis: study protocol of a non-inferiority randomized controlled trial. *Human Reproduction Open. 2019;1-8*	**115**
Chapter 8	Summary, general discussion and future perspectives	**133**
Appendices	Nederlandse samenvatting	**151**
	List of publications	**156**
	Dankwoord	**158**
	Curriculum Vitae	**165**



CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

BACKGROUND

Endometriosis is a benign gynecological disease in which endometrial cells grow outside the uterine cavity under the influence of estrogens. This disease affects around ten percent of women of reproductive age.[1] The etiology of endometriosis is still a matter of debate. Different theories have been proposed to explain its pathogenesis. The most prevalent one is the theory of Sampson which is based on observations of shed endometrial cells into the abdominal cavity via the fallopian tubes.[2]

The earliest clear descriptions of endometriosis are written by Diesterweg (1883)[3], Cullen (1896)[4] and Russel (1899)[5]. A quarter century later Sampson published a report on 'Perforating hemorrhagic (chocolate) cysts of the ovary' (1921)[6], followed by his well-known publication of his vision on the pathogenesis of endometriosis (1927)[2]. In the Netherlands in those days De Snoo completely disagreed with Sampson. He supported the theory of the development of endometriosis from more or less differentiated multipotent cells (i.e. 'genitoblasts'). His trainee J.C. Verhage concluded in 1937 that endometriosis is always located below the umbilicus, which pleads against the shed of endometrial cells and peritoneal implantation as postulated by Sampson.[7] In 1938, Torringa, who graduated at the Rijksuniversiteit van Groningen, stated that Sampsons theory must be rejected as long as implantation and proliferation of endometrial cells are not proven.[8] Almost 20 years later, the first experimental in vitro studies performed by Joosse demonstrated the growth of endometrial cells near the serosa.[9] It is assumed that those were the first steps in the assumption of Sampson's theory in the Netherlands.

Nowadays, the exact pathogenesis is still not yet fully clarified, but a complex multifactorial process of immunologic, inflammatory and hormonal factors is linked to the attachment of endometrial cells to the peritoneal lining, subsequent infiltration and proliferation of endometrial cells resulting in endometriosis lesions.[10] This dissemination, implantation and proliferation of endometrial cells is also observed as an iatrogenic phenomenon after surgery causing endometrial nodules in umbilical or caesarean scars.[11,12] Possibly dissemination of endometrial (stem) cells already occurs during embryogenesis[13], which might explain the development of thoracic endometriosis (i.e. coelomic metaplasia theory). It might even occur in early life during the neonatal endometrial bleeding shortly after birth leading to endometriosis in young adolescents.[14]

The presence of intra-abdominal endometrial lesions results in a variety of clinical symptoms like dysmenorrhea, dyschezia, haematochezia, dysuria, haematuria, dyspareunia and chronic pelvic pain, which are partially explained by the localization of endometrial tissue and the accompanied organ-dysfunction. Complaints relate to the menstrual cycle and can be progressive in nature.[15,16] On the other hand, patients can also be asymptomatic with endometriosis diagnosed during fertility work-up or as a co-incidental finding during other intra-abdominal surgery (e.g. sterilization).

Endometriosis can be divided in being peritoneal, ovarian or deep. To further classify severity different classification systems have been developed, based on surgical findings taking into account lesion appearance, anatomic location and presence of adhesions.[17] The revised

American Society for Reproductive Medicine (ASRM) staging score is most commonly used, taking into account the extension, and state the endometriosis as minimal (stage I), mild (stage II), moderate (stage III) or severe (stage IV) (Figure 1).[18] More severe deep endometriosis can be morphologically described by the Enzian score[a] in addition to the ASRM classification.[19,20] However, this scoring system is complex and only used in German speaking countries (Figure 2). Unfortunately, the extension of endometriosis disease classified by both systems are not correlated to severity of clinical symptoms.[17]

AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial		Complete
		4		40
OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Figure 1 Revised American Society for Reproductive Medicine Classification of Endometriosis. Reprinted with permission from Elsevier from Fertil Steril 1997;67:817-821.

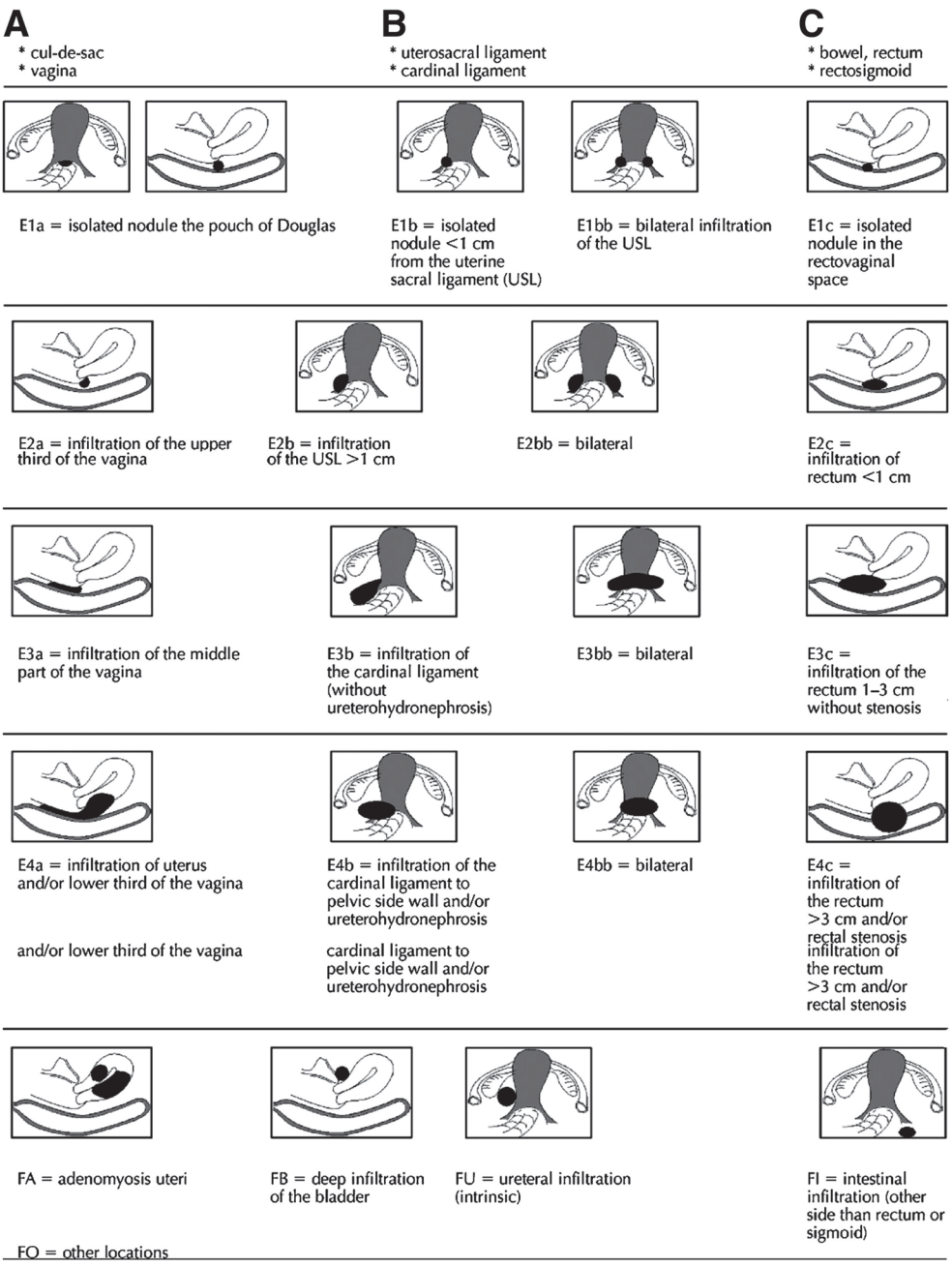


Figure 2 Enzian Classification of deep endometriosis. Reprinted with permission from Elsevier from *Fertil Steril* 2011;95:1574-1578.

To date the exact relation between endometriosis and infertility is not unraveled.[15,16] Mechanical distortions due to adhesions or hydro-/hematosalpinges may result in a disturbed ovum pick up and/or tubal transport function. However, in the absence of mechanical distortions conception can be disturbed, which is postulated to be the result of an immunological hostile intraperitoneal environment affecting oocyte quality and subsequent interaction between oocyte and sperm cell. Besides this, a diminished endometrial receptivity can result in decreased implantation rates. At last, ovarian endometriosis can diminish ovarian reserve due to the presence of endometrial cysts or due to (repeated) ovarian surgery (i.e. ovarian cystectomy).[21,22] (Figure 3)

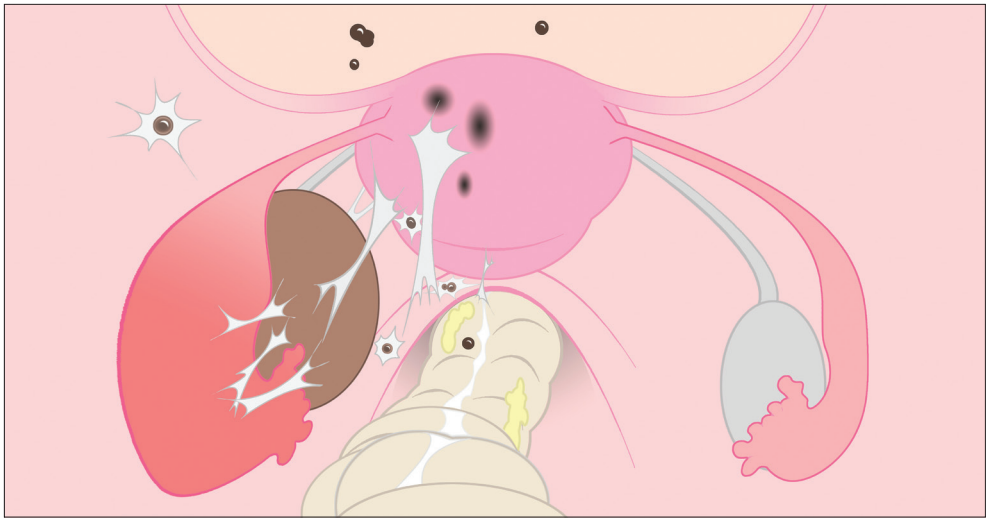


Figure 3 Illustration of intra-abdominal endometriosis with a normal anatomy presented at the right side and peritoneal endometriosis at the bladder and posterior uterine wall, with signs of (focal) adenomysosis, a large endometrial cyst at the left ovary, deep endometriosis located a the left sacrouterine ligament, rectal wall involvement, and adhaesions with a detrimental effect on the frimbriae and the ovum pick-up system with an abnormal functioning left fallopian tube due to a haematosalpinx. This illustrates the influence of endometriosis on fertility by anatomic distortions, a hostile intra-peritoneal environment due to an immunological reaction of those endometrial lesions, a diminished ovarian reserve due to the presence of an endometrial cyst and diminished implantation rates due to the presence of adenomyosis.

The extension of endometriosis classified by the revised ASRM classification and Enzian does not correlate to pregnancy rates as well.[23] To this extent, the endometriosis fertility index (EFI) score has been developed, predicting pregnancy in surgically diagnosed and treated patients with endometriosis (Figure 4).[24] This scoring system has been validated externally to predict naturally conceived pregnancies, and is a promising tool to be used in selecting patients with poor prognosis to start with assisted reproductive techniques (ART) and patients with good prognosis to try conceiving naturally.[25] In treatment decision making the results of the EFI score should be combined with information on patients sexual function, since this may be impaired in women with endometriosis related dyspareunia.[26]

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description		Left	Right		
4	=	Normal	Fallopian Tube				
3	=	Mild Dysfunction					
2	=	Moderate Dysfunction	Fimbria				
1	=	Severe Dysfunction					
0	=	Absent or Nonfunctional	Ovary				
			Lowest Score		+		=
				Left		Right	LF Score

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score		
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors			Total Surgical Factors		

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: Historical + Surgical = EFI Score

Figure 4 Endometriosis Fertility Index. Reprinted with permission from Elsevier from *Fertil Steril* 2010;94:1609-1615.

Currently, curative treatment options are unavailable. Symptomatic treatment of this chronic disease consists of analgesia, hormonal (suppression) therapy and/or surgical intervention. Uniform treatment strategies do not exist yet. Treatment is individually tailored by using the ASRM[15] and European Society of Human Reproduction and Embryology (ESHRE)[16] guidelines and should be focused on the reduction of endometriosis-related symptoms always taking into account an active or latent desire to become pregnant. In endometriosis related subfertility ART play an important role, including intrauterine insemination (IUI), in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), whether or not preceded by surgery and/or hormonal suppression.

TREATMENT FOR ENDOMETRIOSIS RELATED PAIN AND INFERTILITY

All recommendations concerning (surgical and assisted reproduction) treatment of endometriosis related pain and infertility are outlined in Table I with its corresponding level of evidence.[27] In the following paragraphs this will be discussed in more detail for peritoneal, ovarian and deep endometriosis with critical appraisal of effects of surgical treatment on pain and infertility and the (additional) value of ART.

Peritoneal endometriosis

Pain

The presence of peritoneal endometriosis is associated with abdominal pain and can surgically be treated by excision or ablation (by using coagulation, laser and/or plasma energy). Surgeons have a personal preference and differences in treatment efficacy on pain have not been demonstrated yet.[28,29] Surgical treatment of all visible endometriosis lesions can be combined with adhesiolysis. This restores pelvic anatomy, which possibly reduces abdominal pain. A systematic review of non-randomized, uncontrolled studies shows favorable effects of surgical treatment on reducing pain. However, recurrence of endometriosis related pain with or without the need for surgical re-intervention is seen in as many as 20-50% of patients.[30,31]

Five randomized controlled trials investigated the effect of surgery on pain compared to a diagnostic laparoscopy.[32] A beneficial effect of a therapeutic laparoscopy compared to a diagnostic procedure after six (OR 6.58 95%CI 3.31-13.10)[33-35] and twelve months (OR 10.0 95% CI 3.21-31.17)[35] was shown. Additionally, ablation followed by hormonal suppression therapy was more effective compared to a diagnostic procedure alone (OR 5.63 95%CI 1.18-26.83).[36] One randomized trial, investigating the effect of excision on pain measured on a visual analogue scale, was unable to show this beneficial effect.[37] However, this was an underpowered study (n = 16) and overall pain scores were very low. Currently, based on this Cochrane meta-analysis the ESHRE guideline recommends to treat all visible endometriosis lesions during laparoscopy for the treatment of pain complaints (level A evidence).[16]

Hormonal suppression therapy after surgery with oral contraceptives or gonadotrophin releasing hormone (GnRH) agonists is not recommended since there is no proven benefit on pain.[16,38] Although, it is shown in a randomized controlled trial that a combined approach of surgery followed by a GnRH agonist was most beneficial in reducing pain compared to surgery or GnRH agonist suppression therapy alone.[39] However, this study represents a casemix of patients with peritoneal as well as more severe disease. Nevertheless, the ESHRE guideline states that prescribing hormonal suppression therapy has no proven harm and might be prescribed as contraception or secondary prevention of endometriosis disease.[16]

Fertility

The effect of laparoscopic treatment (excision or ablation) on natural conception has been investigated in two randomized controlled trials.[40,41] Both trials were included in a Cochrane meta-analysis showing a beneficial effect on ongoing pregnancy after a therapeutic laparoscopy (OR 1.94, 95%CI 1.20-3.16).[32] From this meta-analysis it can be concluded that the number needed to treat is 8. This means that 8 women with peritoneal endometriosis treated by laparoscopy, resuls in one extra naturally conceived ongoing pregnancy. Based on this, it is advised to treat all visible endometriosis lesions including adhesiolysis rather than performing a diagnostic laparoscopy to increase pregnancy rates (level A evidence).[16]

The number needed to treat is calculated by using the data of the updated meta-analysis, including two studies of which one of those was published as abstract only.[41] The earlier published Cochrane meta-analysis included another trial[42], and reported a lower calculated odds ratio, which resulted in a higher number needed to treat of 12 patients to accomplish one extra naturally conceived pregnancy. Due to a potential publication bias, it can be discussed to assign the recommendation to surgically treat all peritoneal endometriosis to improve naturally conceived pregnancy to a lower level of evidence (i.e. level B evidence).

It has been reported in one study that in women with peritoneal endometriosis, visualized by laparoscopy, IUI with controlled ovarian hyperstimulation improves live birth rates compared to expectant management (OR 5.6, 95% CI 1.8-17.4).[43] This beneficial effect of IUI is probably an underestimation, since less women treated with IUI have had excision or ablation by laparoscopy compared to women in the expectant management group. Unfortunately, no randomized controlled confirmation studies comparing IUI (with controlled ovarian hyperstimulation) versus expectant management in women with peritoneal endometriosis have been published.

After surgery it is recommended to start IUI with controlled ovarian hyperstimulation within six months, since this results in similar pregnancy rates compared to women with unexplained infertility (indirect evidence, level C).[44] However, whether a combined approach of surgery and assisted reproduction treatment is superior to assisted reproduction treatment alone[45] or surgery alone[46,47] has only been investigated in several observational studies. Therefore no clear recommendations with regard to routinely surgically eradicate peritoneal endometriosis (in asymptomatic patients) prior to IUI or IVF/ICSI can be made. Besides, the question remains what treatment strategy should be advised (directly) after surgery.

Ovarian endometriosis

Pain

A straight relation between the presence of endometrial cysts and pain has not been demonstrated. It is thought that pain in women with endometrial cysts is associated with the presence of peritoneal endometriosis[48] and deep endometriosis[49]. So far, a randomized study investigating the effect on pain after performing cystectomy versus no (surgical) treatment has

not been performed. A randomized controlled trial comparing the effect of cystectomy and hormonal suppression therapy on pain is currently applied for financial support. Nevertheless, although this lack of evidence, cystectomies are worldwide commonly performed in both symptomatic and asymptomatic patients with the intention to reduce pain and improve fertility.

Fertility

No randomized controlled trials have been performed investigating the effect of cystectomy versus no treatment on natural pregnancy rates. Uncontrolled studies report naturally conceived pregnancy rates after cystectomy with a weighed mean pregnancy rate of 45%.[50,51] Most of the included studies were small and were unclear about the presence of uni- or bilateral endometrial cysts. Duration of follow up differed from 1 to 3 years.

Since the reported pregnancy rates after laparoscopy are higher than naturally conceived pregnancy rates after expectant management,[30] the ESHRE guideline recommends to consider laparoscopy to increase natural conception rates.[16] This recommendation is substantiated with evidence that the presence of endometrial cysts results in a diminished spontaneous ovulation rate in the affected ovary.[52] However, this is recently invalidated after publication of spontaneous ovulation rates in six subsequent cycles in women with unilateral endometrial cysts with no history of infertility or tubal dysfunction.[53] Since spontaneous ovulation rates were not affected by the presence of an endometrial cyst, it is concluded that the impact of endometrial cysts on fertility and its surgical removal must be further investigated.

Based on molecular, histological and morphological evidence, there is sufficient evidence that endometrial cysts have a detrimental effect on the surrounding ovarian tissue.[54] The content of endometrial cysts contains high amounts of free iron and increased levels of reactive oxygen species. This leads to an increased oxidative stress reaction, which is deleterious for the surrounding ovarian tissue. In combination with the presence of inflammatory molecules this leads to tissue fibrosis, resulting in a reduction of cortex-specific stromal cells and follicular loss. Due to progressive tissue damage and inflammation, changes in gene expression profiles have been observed. This results in smooth muscle cell metaplasia, which is also directly induced by reactive oxygen species. This causes decreased ovarian blood perfusion, reduced follicular maturation and decreased follicular density.[54] This is clinically expressed by decreased ovarian reserve, which is demonstrated in women with endometrial cysts. Lower anti Müllerian hormone (AMH) levels and lower antral follicle counts (AFC) were observed compared to women without endometrial cysts.[55] Besides, ovarian endometriosis is often accompanied with peritoneal[56] and/or deep endometriosis[57], with its intrinsic negative effect on fecundity regardless of ovarian response.

Although it is suggested that the presence of an endometrial cyst damages the affected ovary, it is not clear how this, and eventually performing a cystectomy, exactly affects fertility. Since (randomized) controlled trials are lacking, the recommendation by the ESHRE guideline to consider performing cystectomy to improve natural pregnancy rate must therefore be

questioned. However, in case a therapeutic laparoscopy is indicated, performing a cystectomy is recommended over drainage and coagulation of the endometrial cyst, since a cystectomy is superior in terms of reducing pain complaints, recurrence of endometrial cysts, and naturally conceived pregnancy rates (level A evidence).[16,32,58]

In women receiving IVF/ICSI with endometrial cysts present, similar pregnancy outcomes are reported compared to women without endometriosis. But, it is associated with higher cycle cancellation rates. Those conclusions are based on retrospective studies, included in a systematic review and meta-analysis concerning the impact of ovarian endometrial cysts on IVF/ICSI outcomes.[59] Unfortunately, none of the included studies reported surgical or IVF related adverse events. Furthermore, they concluded that surgically treated endometrial cysts have no detrimental effect at the outcome of IVF/ICSI.

Despite this lack of detrimental effect on IVF/ICSI outcomes, it is recommended not to perform cystectomy prior to ART, since it does not seem to improve pregnancy rates.[16] This recommendation is based on a Cochrane meta-analysis published in 2010.[60] This is in line with the results of two trials investigating the effect of transvaginal aspiration versus cystectomy[61] and versus no treatment[62] prior to ICSI in a randomized controlled setting. Comparable clinical pregnancy rates were observed, though, longer duration of stimulation and higher doses of follicle stimulation hormone after cystectomy were required. Unfortunately, so far no randomized controlled trials have been performed comparing cystectomy versus no treatment prior to IVF/ICSI. Thus, no firm conclusions on treatment benefits and risks can be made in this context.

Whereas pregnancy rates after IVF/ICSI do not seem to be negatively affected by presence of endometrial cysts, there are indications that cystectomy damages ovarian reserve. Initially in the past, performing a cystectomy was recommended for endometrial cysts ≥ 4 centimeter to histologically confirm the diagnosis endometriosis, and to reduce the risk of infection after follicle aspiration, and to improve the accessibility of follicles and possibly increase ovarian response.[63] Surgical excision of endometrial cysts results in loss of ovarian stroma and primordial follicles[64], which might lead to premature ovarian insufficiency, especially in repeatedly and/or bilateral ovarian surgery.[65] This is supported by a meta-analysis of eight prospective studies showing decreased AMH levels three months after cystectomy.[66] Subgroup analysis showed decreased levels nine months after surgery (n = 53). Recent studies concluded that this long-term effect of surgery on AMH levels could even be progressive.[55] Currently, it is unknown if the presence of an endometrial cysts per se has a progressive detrimental effect on AMH levels as well.

As an alternative to AMH levels, the antral follicle count measured by ultrasound might indicate the level of ovarian reserve. A systematic review and meta-analysis showed that the antral follicle count pre- and post-surgery were comparable, but compared to the contralateral ovary, the antral follicle count was lower three to six months after cystectomy.[67] The included studies of both systematic reviews[66,67] on ovarian damage are characterized by a high degree of clinical heterogeneity (i.e. different surgical techniques, surgical expertise, laboratory testing

methods and duration of follow up). Therefore, well established, extensive randomized trials are needed to determine the amount of ovarian damage of the presence of an endometrial cysts and its surgical removal. Since the amount of ovarian damage is related with the level of surgical expertise[68], this must be taken into account as well.

Fortunately, there is nowadays more international awareness to reduce iatrogenic damage to the ovary by avoiding repeated ovarian surgery. Besides this recommendation, novel surgical techniques are developed to minimize the detrimental effect on healthy ovarian tissue and therefore to improve fecundity. For instance, a combined approach of both stripping and ablation techniques is described by Donnez and colleagues. Excision of endometriomas (i.e. complete stripping of the cyst wall) might lead to destruction of normal ovarian tissue, due to an absence of a clear cleavage plane especially close to the hilus.[69] However, ablation is related to higher recurrence rates that further diminish ovarian function. Since most follicles are located near the hilus[70], iatrogenic damage might be limited by stripping of the cyst up to the hilus followed by vaporization of the remaining cyst wall at the hilus by using a CO2 laser. By using this technique, low recurrence rates and limited damage to the ovarian tissue were found.[69]

This was further investigated in a randomized controlled trial including women with bilateral endometrial cysts. After random allocation one ovary was treated by the stripping technique and the other ovary by the combined technique.[71] No differences were seen in the recurrence rate and pre- and postsurgical antral follicle counts. However, the study had a follow up of six months and was underpowered to detect a clinically relevant difference in cyst recurrences. Besides this, they used bipolar coagulation leading to more damage compared to the technique described by Donnez applying CO2 laser for vaporization.

Besides investigating new surgical techniques to reduce the amount of iatrogenic damage to the ovarian tissue, a new instrument using argon plasma energy (PlasmaJet™) is introduced to evaporate endometrial cysts/lesions.[72] Use of plasma energy to evaporate endometrial cysts is a feasible and attractive alternative to stripping cystectomy as it seems to result in similar intra- and postoperative outcomes (including a short time to return to work) as previously described.[73] Ablation with the PlasmaJet™ results in less reduction in ovarian volume and antral follicle count compared to cystectomy in a retrospective cohort.[72] A decrease in AMH levels was observed after 3 months, but slightly increased afterwards and it is therefore concluded that this decrease is not progressive in time.[74] A case-control study shows comparable pregnancy rates after ablation with the PlasmaJet™ versus a cystectomy.[75] Whether this new technique is superior to cystectomy and superior to CO2 laser should be investigated in a randomized controlled trial taking into account endometriosis recurrence and pregnancy rates.

Deep endometriosis

Pain

Deep endometriosis is characterized by peritoneal invasion of endometriosis lesions of more than 5 mm in depth. It is most commonly localized at the uterosacral ligaments, the posterior vaginal wall, the bowel, the bladder, or surrounding the ureters. Deep endometriosis is often accompanied with adenomyosis, which is defined by the presence of glandular and stromal endometrial tissue surrounded by reactive hypertrophic myometrium. This definition is often specified by a minimally required (absolute or relative) invasion depth.[76]

Urinary tract endometriosis has been reported in 0.3-12% of women affected by endometriosis. Most patients present with no or unspecific complaints to the urinary tract. Surgery is often necessary to resolve an ureteral obstruction to preserve renal function.[77]

The effect of surgery on pain and quality of life has especially been investigated in women with rectovaginal and colorectal endometriosis, since endometriosis located in those areas is commonly accompanied by pain complaints as dysmenorrhea, dyschezia, haematochezia, tenesmus, diarrhea, constipation, dyspareunia and chronic pelvic pain.[78] When medical treatment is insufficient to treat those symptoms, surgical therapy might be a treatment option. A systematic review and meta-analysis performed by Meuleman and colleagues has shown that surgical treatment of deep endometriosis with colorectal involvement is effective in reducing pain and digestive symptoms.[78] However, most of the included studies had small sample sizes, were heterogenic due to the different patient populations and surgical techniques, and they reported on different outcomes, with short follow up of patients. A variety of surgical procedures are described, such as segmental colorectal resection, discoid resection, shaving and superficial excision of nodules. Complications of surgical treatment of deep endometriosis seem to be more severe after radical surgery. On the other hand, it is thought that recurrence of disease is less common after radical excision (i.e. segmental colorectal resection).[78] Unfortunately, data to support this are lacking, since prospective studies with long-term follow up on recurrence of endometriosis have not been reported yet. Ideally this should be extended with evaluations of the effectiveness of post-surgical hormonal suppression therapy in this regard.

Fertility

Deep endometriosis is also associated with infertility. Since it is often accompanied by ovarian endometriosis, peritoneal endometriosis and/or adenomyosis, the question remains to what extent isolated deep endometriosis contributes to infertility. Some cohort studies report a beneficial effect of (complete) surgery[79,80], whilst others show no improved pregnancy rates or time-to-pregnancy[81-83]. Surgery followed by IVF seems to result in a higher live birth rate compared to IVF only, based on retrospective matched data.[84] A randomized controlled trial currently underway comparing surgery followed by IVF or immediate IVF, will hopefully allow firm conclusions about superiority of one of those treatment strategies (ClinicalTrials.gov; NCT02948972).

In this context it should be noted that presence of adenomyosis is negatively associated with the likelihood of pregnancy after radical surgery for deep infiltrating endometriosis.[85] Prior to IVF the appearance of adenomyosis has a negative impact on clinical pregnancy rates (OR 0.73 95%CI 0.60-0.90), live birth rate (OR 0.59 95%CI0.42-0.82) and is associated with a higher miscarriage rate (OR 2.20 95%CI1.53-3.15) as well.[86] Long-term pituitary down-regulation with a GnRH agonist prior to IVF/ICSI in women with adenomyosis might be beneficial.[86] In general, it is recommended to prescribe long-term pituitary down-regulation with a GnRH agonist to all women with endometriosis receiving IVF/ICSI treatment, since improved pregnancy rates are observed (level B evidence).[16,87] This recommendation is based on a meta-analysis including three small studies performed in another IVF/ICSI era. Nowadays, due to the improved IVF/ICSI stimulation and laboratory protocols resulting in increased pregnancy rates, a single-embryo transfer policy is achieved with cryopreservation of all good-quality embryos. It is unknown to what extent long-term pituitary desensitization with a GnRH agonists improves pregnancy rates in this regard.

Table I Recommendations and level of evidence

Recommendation	Level of evidence
Peritoneal endometriosis	
Treat all visible endometriosis lesions to reduce pain	A
Ablation and excision are comparable in reducing pain	C
Surgery improves naturally conceived pregnancy (NNT 8)	B*
Surgery might improve conception rates after IVF	C
Ovarian endometriosis	
Cystectomy is superior to ablation concerning recurrence of cysts, recurrence of pain and naturally conceived pregnancy	A
Cystectomy might be considered to improve naturally conceived pregnancy rates	D*
A cystectomy prior to ART doesn't improve pregnancy rates	A
A cystectomy might result in a decreased ovarian reserve;	B
This has no detrimental effect on IVF/ICSI pregnancy rates	C
A combination of stripping and ablation might result in less iatrogenic damage to the ovarian tissue compared to a cystectomy	D
Deep endometriosis	
Surgery results in a decrease of complaints and an increased patient satisfaction	B
Surgery combined with IVF improves pregnancy rates compared to IVF alone	D
Adenomyosis is negatively associated with pregnancy rates	B
ART	
IUI might improve pregnancy rates, is advised to be combined with COH and should be started within 6 months after surgery	C
IVF/ICSI should be preceded by long-term pituitary desensitization with a GnRH agonist to improve pregnancy rates	B
Endometriosis recurrence rates are not increased after IVF/ICSI	C

* lower assigned level of evidence as compared to the ESHRE guideline, due to a different interpretation of the available evidence.
Quality of evidence and corresponding level of evidence (adjusted from GRADE[26] and as used in the ESHRE guideline[16]). Level A evidence (high quality): meta-analysis of multiple RCTs of high quality. Level B evidence (moderate quality): meta-analysis of multiple RCTs of moderate quality; single RCT; large non-randomized trials; case control/cohort studies of high quality. Level C evidence (low quality): single RCT; large non-randomized trials; case control/cohort studies of moderate quality. Level D evidence (very low quality): non-analytic studies, case reports/case series of high/moderate quality. Good practice point (GPP): Recommendation based on experts'opinion

NNT: number needed to treat; IUI: intrauterine insemination; IVF: in vitro fertilization; ICSI: intracytoplasmic sperm injection; ART: assisted reproductive techniques; GnRH: gonadotropin releasing hormone

SCOPE OF THIS THESIS

As described above and presented in Table I the available evidence in the treatment of endometriosis related pain and infertility is limited. Only three recommendations are based on level A evidence (Table I); most of the recommendations are based on level B/C evidence. Furthermore, by critically reviewing the available evidence, the level of evidence concerning treatment of endometriosis related pain and infertility might even be lower than adopted. This thesis aims to address various identified gaps of knowledge and focuses on women with moderate to severe (ASRM stage III and IV) and deep endometriosis undergoing surgery and/or assisted reproduction treatment.

Treatment of women with endometriosis associated infertility is challenging taking into account the heterogeneity of this disease and its chronic and progressive character. Besides this, fertility treatment might affect endometriosis related pain complaints and progression of disease. And vice versa, treatment of endometriosis, both medically and surgically, might (in) directly disturb the ability to conceive.

The aim of this thesis was to answer the following questions:

1. What are the long-term surgical and fertility outcomes of women with severe deep endometriosis who received a segmental colorectal resection?
2. What is the efficacy and safety of intrauterine insemination in women with moderate to severe endometriosis?
3. What is the efficacy of long-term pituitary desensitization with a GnRH agonist prior to intrauterine insemination in women with moderate to severe endometriosis?
4. What is the efficacy and safety of in vitro fertilization/intracytoplasmic sperm injection in women with moderate to severe endometriosis?
5. What is the efficacy of long-term pituitary desensitization with a GnRH prior to IVF/ICSI in moderate to severe endometriosis?
6. To what extent are women with moderate to severe endometriosis satisfied with their received assisted reproductive technology treatment? How do they experience the preceding long-term pituitary desensitization with a GnRH agonist?
7. Is it possible to create a treatment algorithm, based on the available evidence concerning surgery and assisted reproduction in endometriosis related infertility? What are the further knowledge gaps concerning treatment of endometriosis related infertility?

OUTLINE OF THIS THESIS

Chapter 2 will focus on long-term surgical outcomes in women with deep endometriosis with bowel involvement, in whom segmental colorectal resections were performed. Long-term outcomes including patients complaints, satisfaction and fertility will be outlined.

In **Chapter 3** the efficacy and safety of intrauterine insemination in women with moderate to severe endometriosis is investigated in a retrospective cohort. The addition of controlled ovarian hyperstimulation and additional value of long-term pituitary desensitization with a GnRH agonist is also evaluated.

In **Chapter 4** a systematic review and meta-analysis is performed to outline the available evidence about performing IUI in moderate to severe endometriosis. Due to the absence of randomized controlled trials, a meta-analysis of observational data is performed. Also the additional value of preceding long-term desensitization with a GnRH agonist is discussed.

In **Chapter 5** the efficacy and safety of in vitro fertilization or intracytoplasmic sperm injection and the additional value of long-term pituitary desensitization with a GnRH agonist are investigated in a retrospective cohort.

In **Chapter 6** patient satisfaction concerning different assisted reproduction techniques is presented. Also, their experience with preceding long-term desensitization with a GnRH agonist is evaluated in a prospective cohort.

In **Chapter 7** a randomized controlled study protocol is presented, to investigate if continuous use of oral contraceptives is non-inferior to long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI in moderate to severe endometriosis patients. It is planned to investigate treatment efficacy, taking into account safety, endometriosis recurrence, patient satisfaction and cost-effectiveness.

In **Chapter 8**, the general discussion, a treatment algorithm is presented including the best available evidence in treatment of endometriosis related subfertility, which will also outline the need for well-established, randomized controlled studies.

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CHAPTER 2

LONG-TERM SURGICAL OUTCOMES AFTER SEGMENTAL COLORECTAL RESECTION IN WOMEN WITH SEVERE ENDOMETRIOSIS

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ABSTRACT

Purpose: The aim of this study is to assess post-operative complications, symptoms, patient satisfaction, and fertility outcome after a long-term follow-up period in patients with severe intestinal endometriosis.

Methods: In this retrospective study (January 1998 - December 2008) patients scheduled for a segmental colorectal resection by laparotomy were identified. Surgery was performed by a multidisciplinary team. Data were obtained from medical records and supplemented by a questionnaire.

Results: A total of 41 patients (median age 30 years [24-45]) were included with a mean follow-up of 50 months. Three patients were lost to follow-up. Chronic pelvic pain, dysmenorrhea, dyschezia, hematochezia, constipation, pencil like stool, diarrhea, and tenesmus decreased, respectively, in 24, 16, 31, 25, 26, 12, 11, and 21 patients. Post-operatively, one patient conceived naturally and eleven out of fifteen patients conceived after in vitro fertilization. The post-operative patient satisfaction rate (mean 7.4) was significantly higher compared to prior to surgery (mean 4.6). Four major complications were reported in the first year after surgery. The cumulative complication rate was 12%.

Conclusions: Segmental colorectal resection by laparotomy in patients with severe intestinal endometriosis effectively reduces symptoms and increases patient satisfaction with an acceptable risk on treatable complications.

Keywords: Colorectal surgery, Intestinal endometriosis, Laparotomy, Segmental resection

INTRODUCTION

Endometriosis is an estrogen-dependent disorder defined by the presence of endometrial glands and stroma outside the uterine cavity. It is a common benign gynecologic disorder, affecting up to 10% of women of reproductive age and nearly 50% of women presenting with subfertility[1]. Within the pelvis, endometriosis commonly manifests as peritoneal tissue implants, endometrial ovarian cysts or fibrotic complications of peritoneal implantation (e.g. adhesions or strictures). The gastrointestinal tract is the most common site of extragenital disease, involving up to 37% of women with endometriosis[2]. The rectum and rectosigmoid junction account for most intestinal endometriosis lesions followed by the sigmoid colon, the appendix, the small bowel, the cecum, and ileocecal junction[3].

Clinical symptoms of endometriosis include subfertility, dysmenorrhea, deep dyspareunia, and chronic pelvic pain. In patients with intestinal endometriosis, cyclic dyschezia, cyclic hematochezia, tenesmus, constipation, and pencillike stool can be present. When severe symptoms cannot be sufficiently treated by hormonal medication and, in particular, in case of complete bowel obstruction surgical therapy is inevitable[4].

Different surgical approaches to manage intestinal endometriosis have been reported, including nodule excision (by shaving, full thickness or disc excision techniques) and colorectal resection by removing the affected segment using laparotomic, laparoscopic, transvaginal or combined approaches[5,6]. There is still no consensus about which surgical technique is superior[5]; in daily practice it depends on the severity of symptoms, extent of intestinal involvement, and surgeons' skills. However, in case of severe intestinal involvement a multidisciplinary approach is recommended[5].

Several studies show that excision of intestinal endometriosis is effective in reducing complaints, improving quality of life and fertility[5,7-16]. However, long-term follow-up data on quality of life, complications, digestive and gynecologic complaints and fertility outcome after laparotomic segmental colorectal resections are still lacking.

In the Endometriosis center of the VU University Medical Center in Amsterdam, a tertiary referral center for patients with severe (multiorgan) endometriosis, long-term experience with laparotomic segmental colorectal resections with a multidisciplinary expert-team has been established. There is little systematically collected data with regard to long-term effect on pain relief and fertility outcome. The aim of our study is to assess peri- and post-operative complications, symptoms, patient satisfaction regarding the outcome of surgery, and fertility outcome in patients with severe intestinal endometriosis during a long-term followup period.

MATERIALS AND METHODS

We performed a descriptive study on clinical follow-up after a laparotomic segmental bowel resection in women with intestinal endometriosis. Patients were identified by means of a retrospective review of medical records of the Endometriosis Center of the VU University

Medical Center, Amsterdam, the Netherlands, over a period of 11 years, from January 1998 to December 2008.

All patients scheduled for a segmental colorectal bowel resection because of intestinal endometriosis were included (n=41). Indication for bowel surgery was based on the clinical suspicion of a partial or total bowel obstruction. In addition, patients with radiologic diagnosis of colorectal endometriosis with insufficient effect of hormonal treatment were also operated. Surgery was performed by a multidisciplinary team, including two gynecologists (VM, PH), one gastrointestinal surgeon (MC), and optionally one urologist, all specialized in treatment of multi-organ endometriosis.

The pelvis was inspected for the presence of endometriosis on the uterus, ovaries, bladder, and intestines by the gynecologists. All genital as well as peritoneal endometriotic lesions were treated by the gynecologic team. Endometriosis spots were evaporated with carbon dioxide laser and/or argon diathermy. If indicated, an urologist performed ureterolysis, ureter neoimplantation, and/ or bladder wall resection. Gynecologists, together with a gastrointestinal surgeon, performed bowel adhesiolysis and a segmental colorectal resection with circular stapler anastomosis. If necessary, in some patients a temporary stoma was constructed.

All information, from the onset of symptoms up to the treatment in our hospital was collected from medical records. For long-term follow-up results we first sent a letter to all patients to inform them about this study and to request their consent to contact them for a telephone questionnaire. Data on pain complaints and fertility status after surgery were collected. All patients were asked to rate their satisfaction regarding the outcome of the operation; before and after surgery on a scale from 1 to 10 where 1 represents the worst condition and 10 excellent overall satisfaction.

The main outcome parameters were short and long-term follow-up results of surgical complications, fertility outcome, and changes in patient satisfaction, comparing pre and post-operative satisfaction rates.

Statistics

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL, USA). Patient satisfaction rate using a 10-point rating scale before and after surgery was compared using a Wilcoxon signed ranked test. $P<.05$ was considered statistically significant.

RESULTS

During the eleven-year period a total of 41 patients underwent a laparotomic segmental colorectal resection. Mean follow-up time after surgery was 50 months [12-128 months]. The questionnaire administered by telephone could not be obtained in three cases: two patients could not be located, one patient was unable to participate.

Patient characteristics

Patient characteristics are presented in Table I.

The diagnostic assessment of endometriosis included transvaginal ultrasound and Ca-125 levels. Magnetic Resonance (MR) Imaging, bowel colonoscopy, barium enema radiography, and X-abdominal were performed in 39 (95%), 36 (88%), 11 (27%), and 10 (24%) patients, respectively. Thirty-two patients had already been surgically assessed before they underwent a segmental colorectal resection in our hospital of which ten patients were treated by a laparotomic approach and fourteen patients have had surgery more than once. Prior to elective segmental colorectal surgery in our hospital, emergency explorative surgery was performed previously elsewhere in seven patients, because of a complete bowel obstruction caused by intestinal endometriosis[4].

Before surgery 17 (42%) and 27 (66%) patients used oral contraceptives (OCs) or GnRH agonists, respectively. Postoperatively, approximately 38 (93%) patients received a GnRH agonist for three to six months.

Table I Pre-operative patient characteristics in 41 patients

Characteristics	
Age *yrs [range]*	30 [24-45]
BMI *kg/m^2 [range]*	23.1 [17.6-35.4]
Subfertility *n (%)*	23 (56)
Primary	16 (70)
Secondary	7 (30)
Duration of subfertility *months [range]*	32 [7-74]
Previous endometriosis surgery *n (%)*	32 (78)
ASRM stage 0	3 (7)
ASRM stage I	3 (7)
ASRM stage II	0 (0)
ASRM stage III	5 (12)
ASRM stage IV	21 (51)
Symptoms *n (%)*	
Dysmenorrhea	40 (98)
Deep dyspareunia	23 (56)
Cyclic dychezia	27 (66)
Cyclic hematochezia	28 (68)
Constipation	29 (71)
Chronic pelvic pain	9 (22)
Dysuria	9 (22)
Hematuria	3 (7)
Pencillike stool	8 (20)

ASRM: American Society for Reproductive Medicine; BMI: body mass index

Surgical data

Surgical data are presented in Table II. Twenty-seven out of 41 patients had a Pfannenstiel incision. A rectosigmoid resection was performed in two-thirds of the cases. In all patients, colorectal endometriosis was confirmed by histologic examination. Nine patients had a temporary ileostomy of which five had previously been constructed elsewhere because of a complete bowel obstruction. In all cases, ileostomy closure was performed within one year.

Table II Surgical data

Surgical data	**n = 41**		
Incision *n (%)*			
Pfannenstiel	27 (66)		
Midline	14 (34)		
Resection *n (%)*			
Rectosigmoid	27 (66)		
Sigmoid	7 (17)		
Rectum	7 (17)		
Number of intestinal sites *n (%)*			
1	38 (93)		
2[a]	3 (7)		
Length resection *cm [range]*	11.5 [4-30]		
Primary anastomosis *n (%)*	32 (78)		
End to side	20 (62.5)		
End to end	12 (37.5)		
Additional surgery *n (%)*			
Ovariectomy[b]	0	3 (7)	2 (5)
Cystectomy[b]	6 (15)	6 (15)	3 (7)
Tubectomy[b]	1 (2)	10 (24)	4 (10)
Salpingo-ovariolysis[b]	3 (7)	8 (20)	24 (59)
Ureterneoimplantation[b]	2 (5)	5 (12)	0
Ureterolysis[b]	3 (7)	8 (20)	0
Bowel adhesiolysis	17 (41)		
Bladderwall resection	3 (7)		
Local excision vaginal wall	3 (7)		
Total amount of bloodloss *ml [range]*	1000 [200-2400]		
Antibiotic profylaxis[c] *n (%)*	39 (95)		
Intra abdominal drain *n (%)*	34 (83)		
Operation time *min [range]*	230 [130-550]		
Hospital admittance *days [range]*	11 [7-21]		

[a] including ileocoecal resection (n = 2) and appendectomy (n = 1)

[b] data presented: right – left – bilateral

[c] administration of antibiotics was unknown in two patients

Post-operative complications

Post-operative complications are listed in Table III. Twenty-two patients had no complications. Twelve patients had one complication and seven patients had two or more.

Major complications were defined as reported previously[5]. Complications requiring a surgical reintervention were also reported as major complications. In total five major complications occurred. The cumulative complication rate at one month, one year, and more than one year was 7.3%, 9.8%, and 12.2% respectively. An anastomotic leak resulting in a pararectal abscess was treated by transrectal drainage; a rectovaginal fistula complicated by a pelvic abscess was treated by drainage and a temporary ileostomy; a wound infection/abscess was treated by drainage and intravenous antibiotics; two patients with a mechanical ileus were surgically treated by a relaparotomy with adhesiolysis.

All other complications were reported as minor complications. A bowel stenosis at the level of anastomosis was treated by rectoscopic dilatation (n = 5). One patient refused (n = 1) this treatment. Patients with a paralytic ileus and one patient with a mechanical ileus were treated conservatively. Infected hematomas were treated by intravenously administered antibiotics. The patient with recurrence of endometriosis at the level of the anastomosis was treated with a GnRH agonist.

Table III Post-operative Complications

	< 1 month	**1 month – 1 year**	**> 1 year**
Surgical	Paralytic ileus (n = 2)	Mechanical ileus (n = 1)	Mechanical ileus (n = 2)
	Infected haematoma (n = 2)	Stenosis (n = 4)	Stenosis (n = 2)
	Wound dehiscention (n = 1)		Hernia cicatricalis at median
	Wound infection/Abscess (n = 1)		incision (n = 1)
	Anastomotic leak (n = 1)		Recurrent endometriosis at
	Fistula (n = 1)		anastomosis (n = 1)
Urologic	Urinary tract infection (n = 4)		
Other	Fever e.c.i. (n = 2)		
	Upper airway infection (n = 1)		

Treatment outcomes

Figure 1 shows post-operative effects on complaints and clinical symptoms. Complaints of chronic pelvic pain, dysmenorrhea, dyschezia, hematochezia, constipation, pencil-like stool, diarrhea, and tenesmus decreased, respectively, in 24 (63%), 16 (42%), 31 (82%), 25 (66%), 26 (68%), 12 (32%), 11 (29%), and 21 (55%) patients. Frequency of defecation increased in 29 patients (76%) from once in four days to eleven times a day with a mean of three times a day. Thirty-four patients (89%) showed an increase in their overall satisfaction. The Wilcoxon Signed Rank Test showed that the post-operative patient satisfaction rate was significantly higher afterwards (mean 7.4) compared to the satisfaction rate prior to surgery (mean 4.6) ($P<.05$). One naturally conceived pregnancy occurred after surgery. One patient had been unsuccessfully

treated with five intrauterine insemination cycles and eleven out of fifteen patients needing IVF treatment conceived. The live birth rate per embryo transfer was 32% (Table IV).

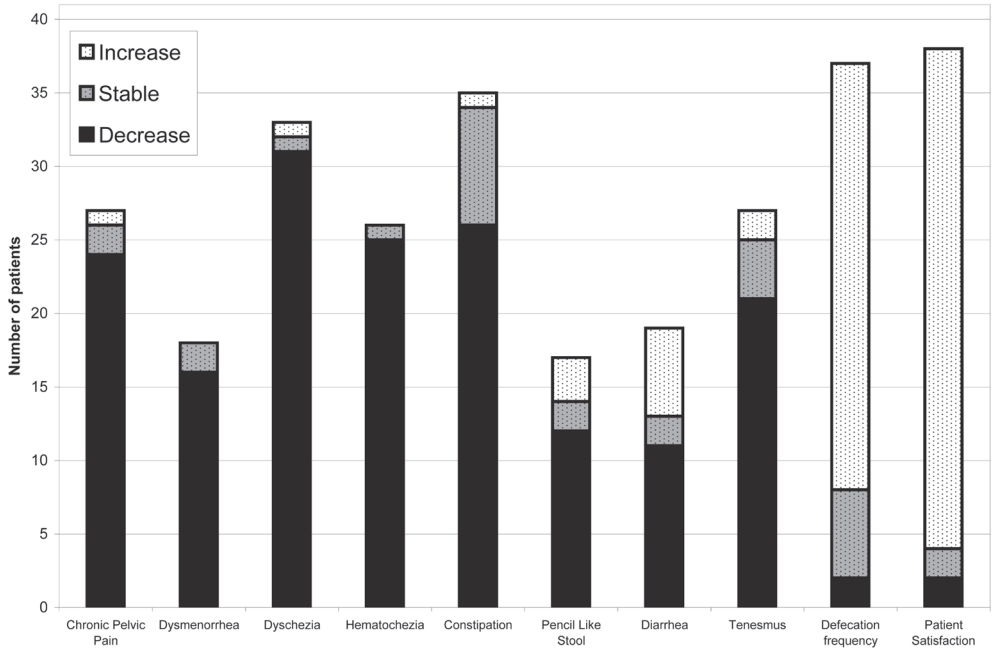

Figure 1 Post-operative long-term effects on complaints and clinical symptoms in 38 interviewed patients

Table IV Post-operative fertility outcomes in 15 patients treated with IVF

Age at surgery	IVF	Cryo	Live birth ratea
< 30 (n = 6)			6/13 (46%)
No. of cycles	11	2	
Conceived	4	2	
Missed abortion	0	1	
Live birth	5[b]	1	
30 – 35 (n = 6)			3/13 (23%)
No. of cycles	12	1	
Conceived	5	0	
Missed abortion	2	0	
Live birth	3	0	
> 35 (n = 3)			3/11 (27%)
No. of cycles	7	4	
Conceived	3	2	
Missed abortion	1	1	
Live birth	2	1	
Total no. of cycles	30	7	
Total no. of live births	10	2	**12/37 (32%)**

[a] Live birth rate per embryo transfer

[b] One patient gave birth to twins

DISCUSSION

Performing colorectal surgery in patients with a benign gynecologic disorder might seem controversial, because of its potential impact as well as the risk of complications. However, patients suffering from severe complaints because of intestinal endometriosis, which often ineffectively or only temporarily react to hormonal medication, can be successfully treated by surgery. Several studies, recently reviewed by Meuleman et al.[5], have confirmed the efficacy of colorectal surgery on digestive and gynecologic complaints in these patients. However, long-term follow-up data on laparotomic segmental colorectal resections are still lacking. In this retrospective long-term follow-up study we assessed the effect of those resections in patients with severe intestinal endometriosis. We demonstrated that these patients experienced a decrease in endometriosis-related symptoms and digestive complaints after treatment. In addition to this, patient satisfaction increased significantly.

To reduce the risk of recurrence or progression of residual disease, we perform, especially in case of extensive bowel wall involvement, a segmental resection to achieve radical removal of all endometriosis lesions[17,18]. Our reported recurrence rate of 2.4% is very low compared to other studies using less radical surgical techniques[9,13,19,20]. Unfortunately, there are no randomized trials comparing the effect of segmental colorectal resection with other techniques. However, it is presumed that incomplete resection of endometriosis lesions will result in more recurrences, which is supported by the fact that studies describing mixed surgical procedures reported higher recurrence rates compared to studies only reporting colorectal resections with anastomosis (17.6 versus 5.8%)[5].

In addition to the degree of completeness of surgery, the surgical approach is a subject of debate. Recently, Darai et al.[7] performed a randomized trial of laparotomic versus laparoscopic colorectal resection in patients with intestinal endometriosis. They found that laparoscopy is a safe option and similar results in improvement of complaints and quality of life were shown. However, in the open surgery group more complications were reported during a follow-up period of only 19 months. Unfortunately, those complications were not specified. Besides this, all patients with former bowel surgery were excluded. In our study seven patients had already had bowel surgery, because of complete bowel obstruction. Besides this, 78% of our patients had been surgically assessed before and 33% had already had more than one operation, which makes a laparoscopic approach unfavorable in this subset of patients[21].

In this study only five major complications occurred; three of them arose in the first month after surgery. Our cumulative complication rate of 12% is comparable with complication rates reported in literature[22,23]. The prevalence of major complications in our present study, such as rectovaginal fistula (2.4%), abscesses (2.4%), and anastomotic leaks (2.4%) are comparable with those reported by Meuleman et al.[5]

Some researchers still recommend less invasive techniques, such as discoid resection[24], nodule excision or shaving (9), associated with less complications and high pregnancy rates. However, even in patients with extensive intestinal endometriosis, in whom a laparotomic segmental bowel resection is performed, live birth rates, are comparable to those reported

in literature[12,25-27]. Most studies are performed in patients undergoing laparoscopic surgery. It is remarkable that in the only randomized controlled trial performed, comparing laparotomy with laparoscopy, no naturally conceived pregnancies were accomplished after laparotomy[7]. However, their mean follow-up of 29 months is, in our opinion, too short to draw conclusions about fertility prospects. Besides this, four out of fourteen women wishing to conceive became pregnant after ART . Unfortunately, the amount of patients undergoing ART and the type of ART is unclear[28], making it difficult to compare those results with our results.

Most of our patients became pregnant after IVF treatment, but naturally conceived pregnancies can still occur after laparotomic surgery. De Ziegler et al. suggested that at least 12 months needs to be awaited after surgery to enable natural conception before commencing ART[29]. However, in patients with (severe) endometriosis the time to pregnancy must be taken into account. For some patients it is unfavorable to discontinue hormonal medication, because of digestive or gynecologic complaints whilst off hormonal medication.

It has been postulated that ovarian hyperstimulation might lead to higher endometriosis recurrence rates. However, we found no recurrences of endometriosis in patients treated with ovarian hyperstimulation. This is in line with the results of a recently published study by Coccia et al.[30] who concluded that recurrence rates were similar between patients with and without ovarian hyperstimulation. In a study by D'Hooghe et al.[31] recurrence rates in patients treated with IVF (7%) were much lower than in patients treated with IUI (70%). This might be because of the fact that IVF was performed, using ovarian hyperstimulation combined with pituitary down-regulation, whilst IUI was performed without pituitary down-regulation. Probably, the negative effect of estrogens on endometriotic lesions might be positively influenced by pituitary down-regulation by GnRH agonists. Another speculative explanation is based on Sampsons theory of retrograde menstruation on the pathogenesis of endometriosis. Women undergoing IVF might be exposed to less retrograde menstruation because of long-term use of GnRH agonist prior to IVF treatment or because of non patent tubes. Unfortunately, circumstantial evidence is still missing. However, IVF with long-term pituitary down-regulation is a good alternative, which effectively improves IVF outcome in patients with endometriosis[32].

We must bear in mind that after surgery GnRH agonists were administered to almost all patients (93%) as recommended by the ESHRE guidelines[33]. Therefore, our results are the combined effect of surgery and post-operative hormonal treatment, shown to be effective in reducing endometriosis- associated pain and recurrence compared to placebo or expectant management. Conversely, Furness et al. concluded that there is no evidence of benefit associated with post-operative hormonal therapy[34]. However, their meta-analysis showed a reduction in pelvic pain at 12 months. In fact, hormonal treatment with GnRH agonists will not cure endometriotic lesions[35], but cessation of hormonal therapy commonly leads to recurrence of symptoms[34]. In addition to this, post-operative administration of GnRH agonists is associated with a decreased adhesion formation and a reduced degree of inflammation postoperatively[36].

In conclusion, in our retrospective study we showed that a laparotomic segmental colorectal resection in patients with severe deep infiltrating endometriosis effectively reduces symptoms and increases patient satisfaction with an acceptable risk on treatable complications. Naturally conceived pregnancies still occur after laparotomic surgery. However, as patient complaints generally increase whilst off hormonal medication, a naturally conceived pregnancy should usually not be awaited. IVF with long-term hormonal suppression is a suitable treatment with high live birth rates.

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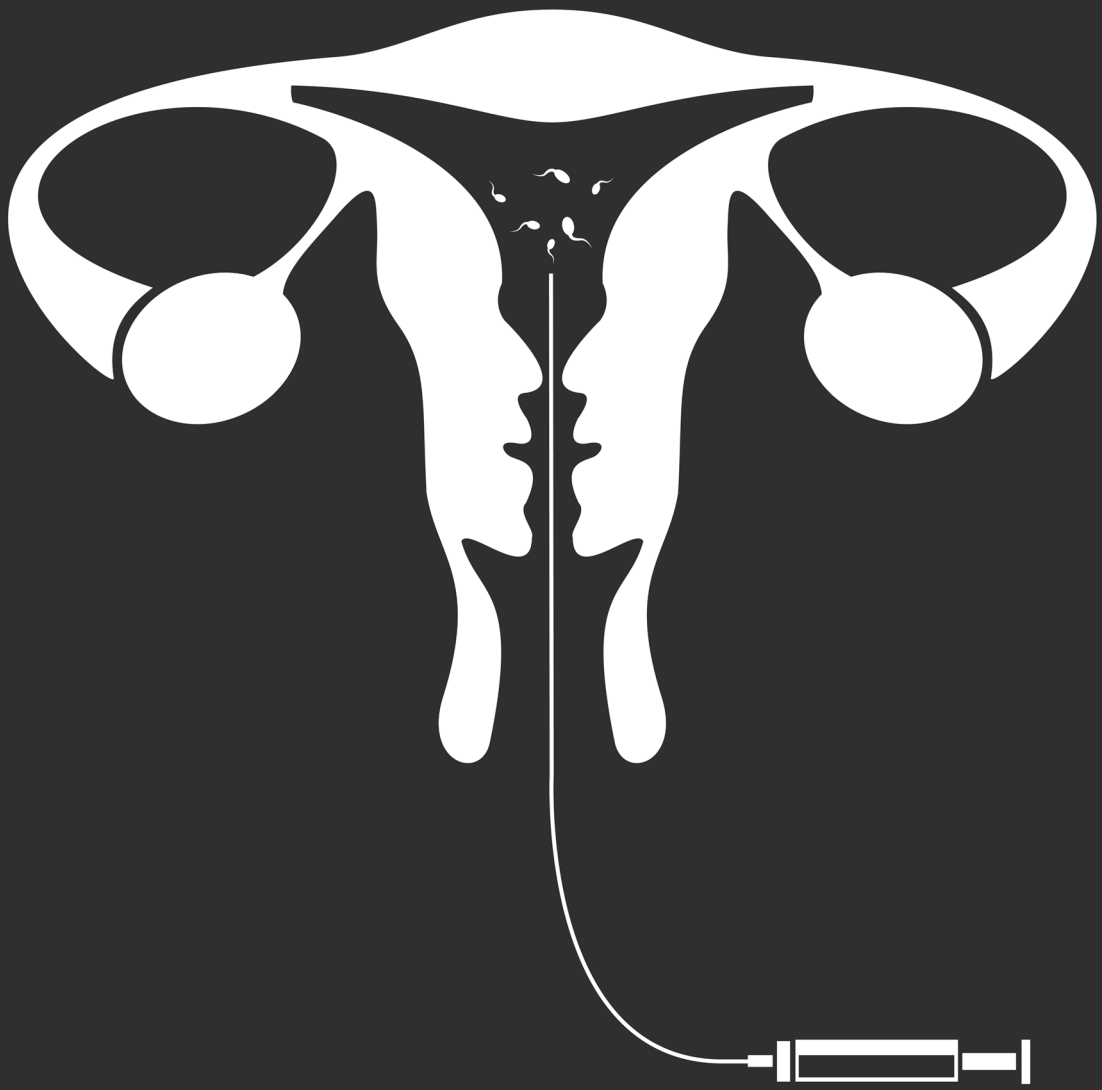

CHAPTER 3

EFFICACY AND SAFETY OF INTRAUTERINE INSEMINATION IN PATIENTS WITH MODERATE TO SEVERE ENDOMETRIOSIS

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ABSTRACT

Performing intrauterine insemination (IUI) in moderate-to-severe endometriosis patients is not implemented in international guidelines, as only limited data exist on treatment efficacy and safety. This retrospective study examined the efficacy and safety of two IUI treatment strategies performed between January 2007 and July 2012 in moderate-to-severe endometriosis patients. Eight (40.0%) versus seven (15.6%) ongoing pregnancies were accomplished in patients undergoing IUI with ovarian stimulation (n = 20, 61 cycles) versus IUI without ovarian stimulation in the first three cycles followed by IUI with ovarian stimulation (IUI with natural/ovarian stimulation; n = 45, 184 cycles). Preceding long-term pituitary down-regulation tended to result in a higher ongoing pregnancy rate (adjusted HR 1.8) and a higher chance of endometriosis recurrence (adjusted HR 2.3). Eight (40.0%) versus 16 (35.6%) recurrences of endometriosis complaints were reported in patients receiving IUI with ovarian stimulation versus IUI with natural/ovarian stimulation. IUI might be a valuable treatment in moderate-to-severe endometriosis patients and IUI with ovarian stimulation should be offered over IUI with natural/ovarian stimulation. Preceding long-term pituitary down-regulation might positively influence the ongoing pregnancy rate and can be considered. Whether this treatment strategy can be structurally offered prior to IVF must be investigated in a randomized controlled trial.

Keywords: complication, endometriosis, GnRH agonist, intrauterine insemination, ongoing pregnancy rate, recurrence

INTRODUCTION

Fecundity is commonly impaired in patients with endometriosis[1]. Since its cause is still not unravelled, management of infertility in endometriosis patients is widely debated in literature[2].

In subfertile patients with moderate-to-severe endometriosis, the anatomy of the pelvic cavity can be disturbed resulting in impaired ovum retrieval or diminished patency of the fallopian tubes, making IVF the first choice of fertility treatment[3]. However, in patients with surgically treated endometriosis in which normal functioning ovum retrieval and patency of at least one fallopian tube has been established, intrauterine insemination (IUI) can be provided prior to IVF.

According to the guidelines of both the European Society of Human Reproduction and Endocrinology[3] and American Society for Reproductive Medicine[4], IUI is only recommended in subfertile women with minimal-to-mild endometriosis. Recommendations with regard to performing IUI in moderate-to-severe endometriosis patients are not formulated, due to the absence of sufficient data[5,6]. Observational, noncomparative studies showed pregnancy rates of 4–32% per cycle[7-14]. In addition, two randomized controlled trials investigated the effect of long-term pituitary down-regulation with a gonadotrophin- releasing hormone (GnRH) agonist prior to IUI in moderate- to-severe endometriosis patients and showed increased clinical pregnancy rates[15,16].

Treatment decision making, including aspects of efficacy and safety, is hard to make due to the lack of sufficient data. Safety of IUI in moderate-to-severe endometriosis patients is reported in only one retrospective study[17], showing a significantly higher risk of developing endometriosis recurrence after IUI compared with IVF treatment. This observation might be explained by a monthly exposure to ovulation and retrograde menstruation in women undergoing IUI. D'Hooghe et al.[17] postulated that the exposure to retrograde menstruation might even be increased by ovarian hyperstimulation, negatively affecting the cumulative endometriosis recurrence rate (CERR). Comparison of IUI with and without ovarian stimulation could further clarify this, but, as far as known, it has not been investigated. Besides this, a possible favorable role of long-term pituitary down-regulation with a GnRH agonist in this regard has not been investigated.

Therefore, this study investigated the efficacy and safety of an IUI treatment strategy, comparing IUI with and without ovarian stimulation in patients with moderate-to-severe endometriosis and the effect on efficacy and safety of long-term pituitary down-regulation with a GnRH agonist prior to IUI.

MATERIALS AND METHODS

This study retrospectively analyzed patients with surgically confirmed moderate-to-severe endometriosis (ASRM stages III and IV) with at least one patent fallopian tube receiving IUI treatment. Patients were selected from the electronic patient database of the IVF centre of the VU University Medical Centre, Amsterdam, The Netherlands. Only patients undergoing their

first IUI treatment between January 2007 and July 2012 were selected. Up to a maximum of six subsequent IUI treatment cycles were included in the analysis. IUI treatment cycles with donor spermatozoa were excluded. The database was validated and completed by two researchers (AS, LH). This study was formally exempted from ethical approval granted by the Institutional Review Board (reference no. 2013/1).

This fertility clinic is reluctant to perform IUI directly combined with ovarian stimulation due to the fear that ovarian hyperstimulation may lead to an increase in or recurrence of endometriosis complaints and also to prevent multiple pregnancies. Therefore, IUI treatments are usually performed as follows: IUI without ovarian stimulation in the first three cycles followed by IUI with ovarian stimulation (IUI with natural/ovarian stimulation). Data are presented for the total study population and the two treatment strategies (IUI with ovarian stimulation versus IUI with natural/ovarian stimulation). The additional effect of long-term pituitary down-regulation with a GnRH agonist is evaluated for the total population as well as for both groups.

Long-term pituitary down-regulation with a GnRH agonist (Leuprolide 3.75 mg depot injections, Lucrin; Abbott, USA) was administered prior to IUI treatment in a subgroup of patients. Ovarian stimulation was accomplished by subcutaneous administration of highly purified human menopausal gonadotrophin (Menopur; Ferring, Denmark) or recombinant FSH (Gonal-F; Merck Serono, Germany; or Puregon; MSD, USA) from cycle day 3, starting with 75 IU in the first IUI treatment cycle. In case of monofollicularity, the dosage was increased in the next treatment cycle by 37.5 IU per cycle. Follicle growth was measured by transvaginal ultrasound. When a follicle reached the size of 17 mm, 10,000 IU human chorionic gonadotrophin (Pregnyl; Organon, the Netherlands) was administered subcutaneously and 42 h later, insemination was performed. According to this centre's protocol, after three IUI treatment cycles, a clinical evaluation was performed and, if a pregnancy did not occur, a diagnostic or therapeutic laparoscopy was performed.

Semen was prepared by this centre's protocol. In summary, after liquefaction, semen was centrifuged through a PureSperm 70% gradient (Nidacon, Mo¨lndal, Sweden) HEPES-human tubal fluid (HTF; Lonza, Basel, Switserland) medium supplemented with human serum albumin (HSA; Albuman, Sanquin, Amsterdam, The Netherlands) at 710g for 15 min. The pellet was washed with HTF/HSA medium at 270g for 7 min. After removal of the supernatant, a maximum of $50 \cdot 10^6$ spermatozoa were resuspended with 0.5–5 ml HTF/HSA medium and incubated at room temperature (5% CO2). Prior to insemination, one last wash step was performed (200g for 7 min). The pellet was concentrated to a volume of 250 ll. Insemination was performed with a total motile sperm count of $0.5 \cdot 10^6$ up to a maximum of $50 \cdot 10^6$ spermatozoa.

The primary outcome measure was the ongoing pregnancy rate (OPR), which was calculated as the total number of ongoing pregnancies divided by the total number of patients included as well as a cumulative OPR calculated by life-table analysis. Secondary outcomes included total number of complications and recurrences as well as the CERR and time to pregnancy including all ongoing pregnancies after treatment (including IUI and IVF) and natural conception up to 1 year after start of IUI treatment. An ongoing pregnancy was

defined as a vital intrauterine pregnancy visualized by transvaginal ultrasound at 12 weeks of gestation. Ovarian hyperstimulation syndrome, infection or hospital admittance occurring within 1 month after treatment were defined as complications. Recurrence of or increase in a patient's complaint within 12 months after the last IUI treatment suspected to be based on endometriosis was stated as endometriosis recurrence.

Baseline measurements included female age, body mass index, type of infertility (primary/secondary), duration of infertility, duration since last therapeutic procedure and the presence of deep infiltrating endometriosis. The presence of deep infiltrating endometriosis was based on MRI findings and included rectovaginal or colorectal endometriosis or endometriosis of the urinary tract.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM SPSS, USA). Data were expressed as mean ± standard deviation (SD) or n (%). Nonparametric data were expressed as medians with range. Differences between the two groups were evaluated using the Students' t-test (continuous data) or Mann–Whitney U-test in case of nonparametric data and chi-squared or Fishers' exact tests for categorical data. A P-value < 0.05 was considered significant.

Life-table analysis was used to calculate the cumulative ongoing pregnancy rate and CERR. Both the number of cycles and duration in the months since first IUI treatment cycle were used as time parameters. The date of entry was the date of the first IUI treatment cycle. Up to a maximum of six subsequent cycles were included. Patients were followed up to 1 year after finishing their last IUI treatment cycle. For measuring the CERR, the endpoint of the study was 12 months after the last IUI treatment cycle, the date of endometriosis recurrence, the date of positive pregnancy test (in ongoing pregnant patients) or the date of patient's last visit (in case of loss to follow up). To plot the time to pregnancy, the endpoint was stated at 12 months after start of IUI treatment. The log rank test was used to compare both groups in cumulative ongoing pregnancy rate and the CERR. Cox regression analysis was performed to estimate hazard ratios (HR) for treatment strategy and long-term pituitary down-regulation on ongoing pregnancy and endometriosis recurrence rates.

RESULTS

This retrospective study selected 65 patients receiving 245 IUI treatment cycles from the electronic database who met the inclusion criteria (Figure 1). Forty-five patients (69.2%) were assigned to the combined IUI with natural/ovarian stimulation treatment strategy. In this group, 125 natural and 59 stimulated IUI treatment cycles were performed. The remaining 20 patients (30.8%) were assigned immediately to IUI with ovarian stimulation and received 61 stimulated IUI treatment cycles.

At baseline, all patient characteristics were not statistically different between the treatment groups (Table I). For IUI with natural/ovarian stimulation versus IUI with ovarian stimulation,

31 and 42 patients were surgically treated within 6 and 12 months, respectively, before commencing IUI treatment (not significant).

Treatment outcomes, recurrences and complications are presented in Table II. Significantly fewer treatment cycles were performed in patients assigned to IUI with ovarian stimulation (P = 0.045). In 13 (28.9%) patients assigned to IUI with natural/ovarian stimulation, completing six IUI treatment cycles was considered to be ineffective: IVF was offered in 10 (22.2%) patients and treatment was completely discontinued in three (6.7%). In six (30.0%) patients assigned to IUI with ovarian stimulation, completing six IUI treatment cycles was considered to be ineffective. In all of them, IVF was offered. Four patients discontinued IUI treatment for personal reasons (IUI with natural/ovarian stimulation: n = 2 (4.4%); IUI with ovarian stimulation: n = 2 (10.0%)).

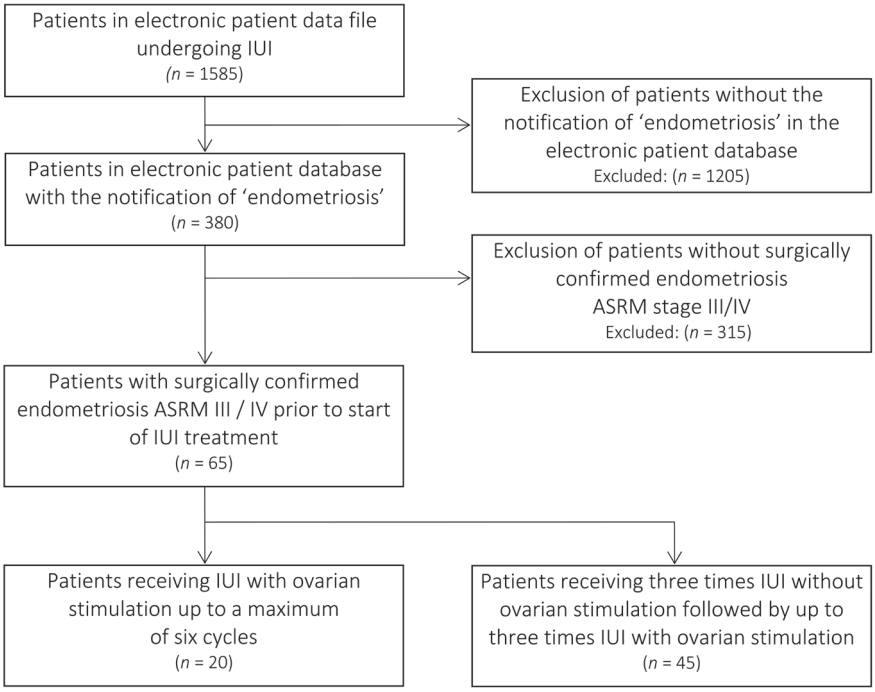

Figure 1 Flowchart of patients

Table I Patient characteristics

	Total group n = 65	IUI with natural/ ovarian stimulation n = 45	IUI with ovarian stimulation n = 20	p-value
Age (y)	33.2 ± 3.8	33.4 ± 3.3	32.8 ± 4.7	0.59
BMI (kg/m^2)	23.4 ± 3.6	23.4 ± 3.5	23.4 ± 3.8	0.99
ASRM				0.58
III	26/65 (40.0%)	17/45 (37.8%)	9/20 (45.0%)	
IV	39/65 (60.0%)	28/45 (62.2%)	11/20 (55.0%)	
Subfertility (months)	26 [3-56]	27 [3-56]	22 [6-51]	0.13
Primary	43/65 (66.2%)	30/45 (66.7%)	13/20 (65.0%)	0.90
Secondary	22/65 (33.8%)	15/45 (33.3%)	7/20 (35.0%)	
Deep infiltrating endometriosis	15/20 (75.0%)	8/12 (66,7%)	7/8 (87.5%)	0.60*

BMI: body mass index; ASRM: American Society for Reproductive Medicine

* Fisher's Exact Test

Table II Treatment outcomes, recurrences and complications

	Total group n = 65	IUI with natural/ ovarian stimulation n = 45	IUI with ovarian stimulation n = 20	p-value
Lucrin prior to first IUI	31/65 (47.7%)	20/45 (44.4%)	11/20 (55.0%)	0.43
Total amount of treatment cycles per patient	3 [1-6]	4 [1-6]	3 [1-6]	0.05
Ongoing pregnancy	15/65 (23.1%)	7/45 (15.6%)	8/20 (40.0%)[b]	0.05
Live birth	12/65 (18.5%)	6/45 (13.3%)[a]	6/20 (30.0%)[c]	0.17*
Recurrence	24/65 (36.9%)	16/45 (35.6%)	8/20 (40.0%)	0.73
Complication	2/65 (3.1%)	1/45 (2.2%)	1/20 (5%)	0.52*

[a] one lost to follow up
[b] one pregnancy concerned a twin pregnancy
[c] two preterm (1 single and 1 twin pregnancy)
* Fisher's Exact Test

Primary outcome

In total, 15 ongoing pregnancies (OPR 6.1% per cycle and 23.1% per patient) were accomplished after IUI treatment: seven (OPR 3.8% per cycle and 15.6% per patient) for IUI with natural/ ovarian stimulation and eight (OPR 13.1% per cycle and 40.0% per patient) for IUI with ovarian stimulation, respectively (P = 0.014 per cycle).

The cumulative ongoing pregnancy rate after six cycles in the total population is shown in Figure 2A. Significantly higher cumulative ongoing pregnancy rates were found in

patients assigned to IUI with ovarian stimulation (45.8%) compared with patients assigned to IUI with natural/ovarian stimulation (19.5%, P = 0.016; Figure 2B). Univariate Cox regression analysis showed a HR of 3.2 (95% CI 1.1–8.8, P = 0.027), reflecting a significantly higher chance of ongoing pregnancy in patients receiving IUI with ovarian stimulation. Multivariate Cox regression analysis showed that long-term pituitary down-regulation with a GnRH agonist could not be identified as a confounding variable in this regard. In patients pretreated with long-term pituitary down-regulation (n = 31), the cumulative ongoing pregnancy rate was 35.0% compared with 21.3% in women (n = 34) who directly started with IUI treatment (Figure 2C). Univariate Cox regression analysis showed a HR of 2.0 (95% CI 0.7–5.5). Adjusted for treatment strategy (IUI with natural/ovarian stimulation or IUI with ovarian stimulation), the HR was 1.8 (95% CI 0.6–5.1).

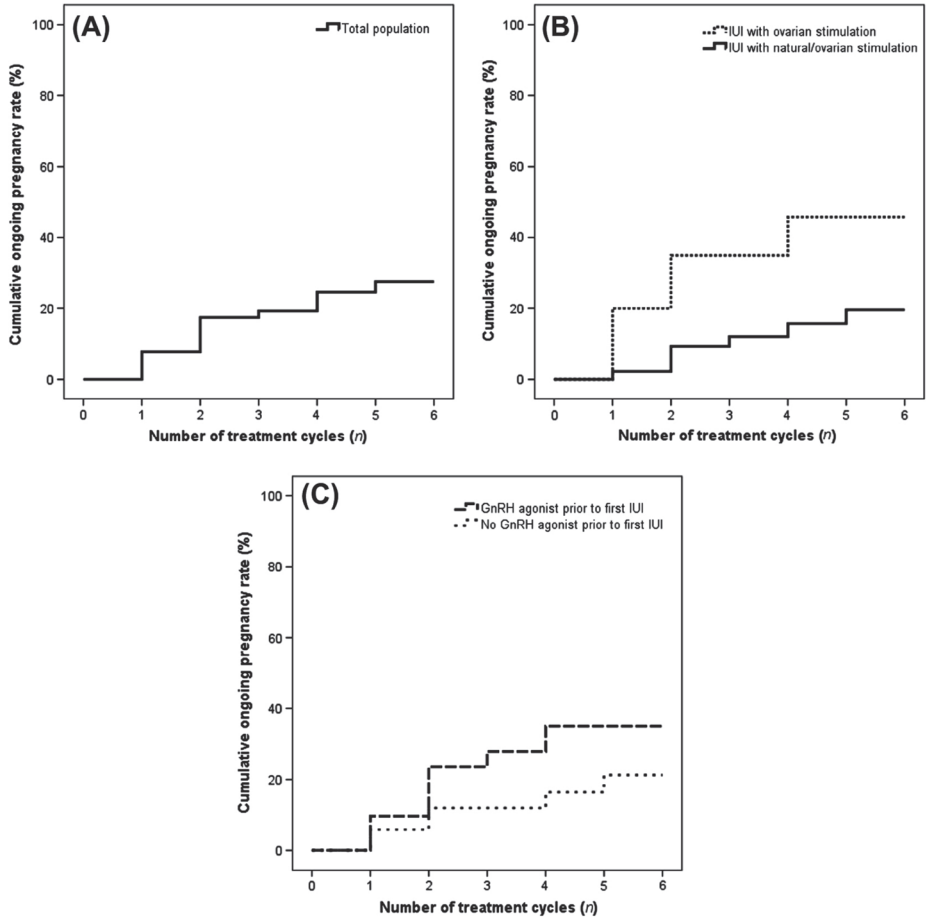

Figure 2 Kaplan-Meier curves of cumulative ongoing pregnancy rates according to IUI treatment cycle for the total population (A), IUI with natural/ovarian stimulation versus IUI with stimulation (B, *P* = 0.016) and with/without GnRH-agonist treatment (C)

Secondary outcomes

The time to pregnancy at 1 year after start of IUI treatment is presented in Figure 3. The cumulative ongoing pregnancy rate, including only ongoing pregnancies accomplished by IUI treatment, was significantly higher in the patients assigned to IUI with ovarian stimulation (41.3%) compared with IUI with natural/ovarian stimulation (16.8%, P = 0.014; Figure 3A). In patients assigned to IUI with natural/ovarian stimulation, two naturally conceived pregnancies were achieved up to 1 year after start of IUI treatment. Sixteen (35.6%) patients underwent at least one IVF attempt, resulting in four ongoing pregnancies. With IUI with ovarian stimulation, no naturally conceived pregnancies were achieved, and up to 1 year after start of IUI treatment, seven (35.0%) patients underwent at least one IVF attempt. Three ongoing pregnancies after IVF were described. The cumulative ongoing pregnancy rate 1 year after start of IUI treatment, including naturally conceived and IVF, ongoing pregnancies was significantly higher in patients assigned to IUI with ovarian stimulation (58.9%) compared to IUI with natural/ovarian stimulation (31.8%, P = 0.008; Figure 3B).

As shown in Table II, 24 patients developed a recurrence of endometriosis complaints. Two (3.1%) patients reported recurrence of their endometriosis complaints, but did not receive an intervention. Five (7.7%) patients started on oral contraception, eight (12.3%) patients started with a GnRH agonist and discontinued IUI treatment and four (6.2%) patients underwent surgery for their endometriosis. Eleven patients had a laparoscopy after three IUI treatment cycles. Cystectomy of endometrioma or extensive adhesiolysis was performed in five (7.7%) and those were considered as recurrences of endometriosis.

The CERR was 60.4% for the total population (Figure 4A). Twelve months after start of first IUI treatment, the CERR was 36.5% for IUI with natural/ovarian stimulation versus 72.3% for IUI with ovarian stimulation (Figure 4B). Univariate Cox regression analysis showed a HR of 2.6 (95% CI 1.1–6.3, P = 0.03), reflecting a significantly higher chance of endometriosis recurrence in patients receiving IUI with ovarian stimulation versus patients receiving IUI with natural/ovarian stimulation. Adjusted for the confounder long-term pituitary down-regulation with a GnRH agonist, the HR became 2.2 (95% CI 0.9–5.3).

A significantly higher 12-month CERR was found in patients who were treated with a GnRH agonist prior to the first IUI treatment cycle (n = 31) versus patients without a GnRH pretreatment ((n = 34; 68.0% versus 26.6%; Figure 4C). Univariate Cox regression analysis showed a HR of 2.6 (95% CI 1.1–6.0, P = 0.024), reflecting a significantly higher chance of endometriosis recurrence in patients treated with long-term pituitary down/regulation with a GnRH agonist. Adjusted for the confounder treatment strategy, the HR became 2.3 (95% CI 0.98–5.3).

Two complications were reported (3.1%): one patient had to be admitted to the hospital for an infected endometriosis cyst and another patient had to be admitted because of an infection of unknown origin (Table II).

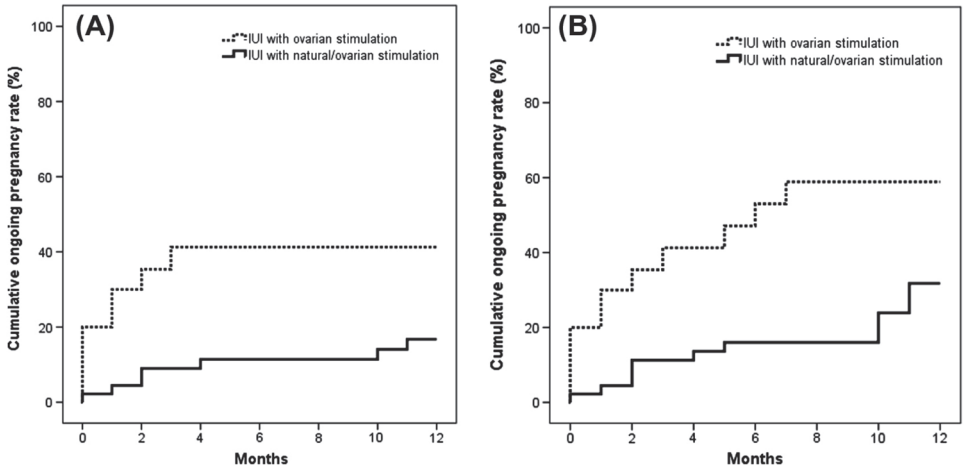

Figure 3 Kaplan-Meier curves of cumulative ongoing pregnancy rates according to time after start of treatment for IUI with natural/ovarian stimulation versus IUI with ovarian stimulation for only IUI-conceived pregnancies (A, $P = 0.014$) and including naturally and IVF-conceived ongoing pregnancies (B, $P = 0.008$).

DISCUSSION

This study demonstrates that IUI treatment in the total population of moderate-to-severe endometriosis patients results in a cumulative ongoing pregnancy rate calculated by life-table analysis of 28% after six subsequent IUI treatment cycles with low complication and modest cumulative endometriosis recurrence rates. A significantly higher cumulative ongoing pregnancy rate calculated by life-table analysis is found in patients receiving IUI with ovarian stimulation versus IUI with natural/ovarian stimulation. Although, as far as is known, this is the first study comparing both IUI treatment strategies in moderate-to-severe endometriosis patients, this observation was not contrary to expectations, since similar results have been reported for minimal-to-mild endometriosis[18] and unexplained infertility[19]. At the same time, the CERR is significantly higher in patients receiving IUI with ovarian stimulation versus IUI with natural/ovarian stimulation. This result supports the hypothesis, stated by D'Hooghe et al.[17], that a monthly exposure to ovulation and retrograde menstruation is the basis of an increased risk of endometriosis recurrence, which might be facilitated by ovarian hyperstimulation.

This study's 1-year CERR after IUI with ovarian stimulation is in line with the reported 1-year CERR of 70% by D'Hooghe et al.[17]; however that study used a different definition of endometriosis recurrence (i.e. surgically confirmed or cytologically proven endometriosis). In total, nine of the current study's patients (13.8%) were surgically treated with confirmation of recurrence of endometriosis. Since the development of endometriosis complaints (presumably based on recurrence of endometriosis) is an important factor in the possibility of continuing IUI treatment, this study used this broad definition of recurrence of endometriosis to calculate the CERR. In a future prospective study, the use of validated questionnaires would be recommended[20].

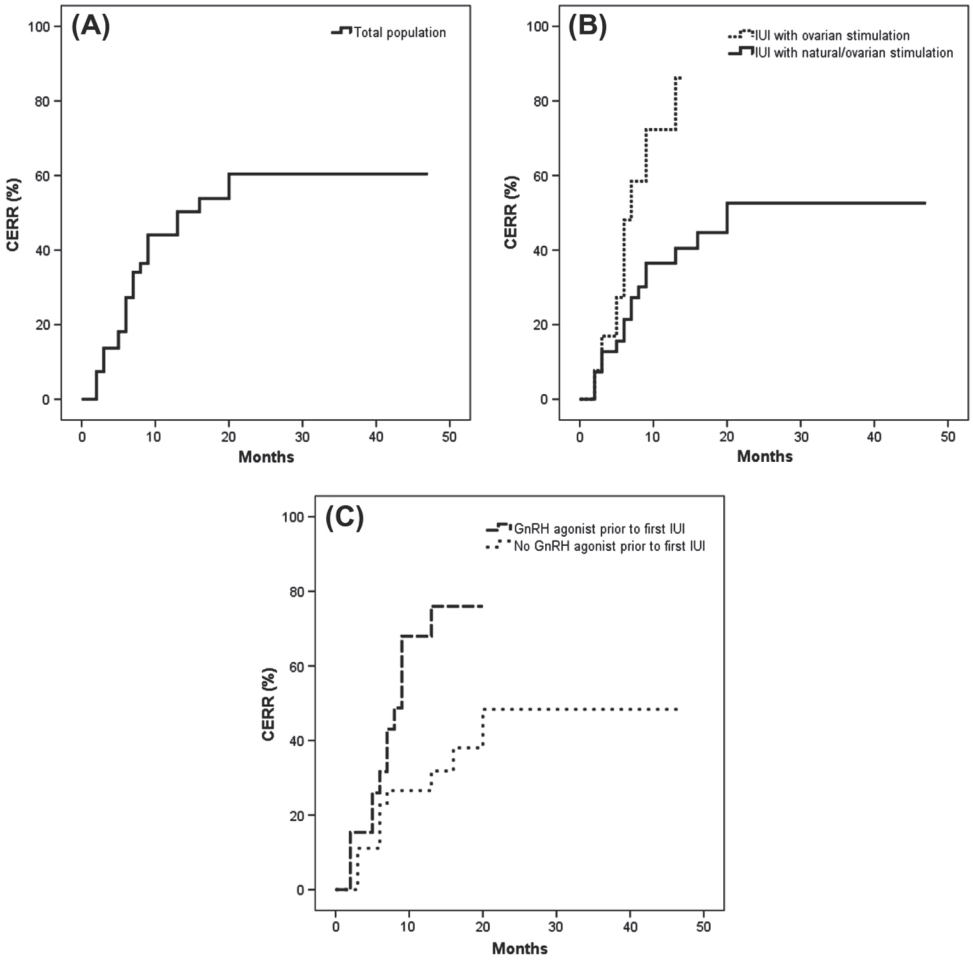

Figure 4 Kaplan-Meier curves of cumulative endometriosis recurrence rate (CERR) per month after start of IUI treatment for the total population (A), IUI with natural/ovarian stimulation versus IUI with ovarian stimulation (B, $P = 0.021$) and with/without GnRH-agonist treatment (C, $P = 0.016$)

An important advantage of calculating the CERR by using life-table analysis is achieved by the opportunity to take the variable 'time of follow up' into account[21]. However, one assumption in life-table analysis is that censored patients have the same risk of endometriosis recurrence as noncensored patients[22]. A discrepancy between cumulative and absolute number can be explained by a large number of early censored patients. In this study, the high discrepancy between the CERR and absolute number of endometriosis recurrence can be explained by, in particular, early censored pregnant patients. For them, the endpoint was stated as the date of a positive pregnancy test. This conforms with the definition used by D'Hooghe et al.[17]. However, these patients presumably have a lower risk of endometriosis recurrence[23], meaning that the CERR is an overestimation of the endometriosis recurrence risk.

This study also investigated the additional effect of long-term pituitary down-regulation with a GnRH agonist prior to the first IUI treatment cycle, which resulted in nonsignificantly higher odds of achieving an ongoing pregnancy. This observation is in line with two randomized controlled trials investigating the effect of GnRH administration prior to IUI. Rickes et al.[16] investigated the effect of long-term pituitary down-regulation with a GnRH agonist for 6 months after surgery before commencing IUI treatment in patients with endometriosis ASRM stages II–IV. They found a significantly higher pregnancy rate in the long-term pituitary down-regulation group (89%) versus no prior GnRH treatment group (61%). Kim et al.[15] compared standard down-regulated IUI cycles (2 weeks GnRH agonist) versus an ultralong down-regulated IUI cycle (6 weeks GnRH agonist) and found a significantly increased clinical pregnancy rate. Before long-term pituitary down-regulation with a GnRH agonist for 3–6 months prior to IUI can be routinely offered, a well-powered randomized controlled trial should be performed.

Although positive effects of long-term pituitary down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist on pregnancy rate after IUI[15,16] and IVF[24] have been described, data on endometriosis recurrence is limited. D'Hooghe et al.[17] postulated that short-term administration of GnRH analogues might protect against recurrence of endometriosis. Against all odds, in the current study, long-term pituitary down-regulation with a GnRH agonist resulted in a nonsignificant 2.3-fold increase in the adjusted odds on endometriosis recurrence. It is inconceivable that GnRH agonists directly increase the risk on endometriosis recurrence, since GnRH agonists have positive effects on endometriosis complaints by lowering the oestrogen concentrations[25]. Indirectly, cessation of GnRH-agonist suppression therapy can result in a quick relapse of endometriosis symptoms[26], which can explain the higher amount of recurrences in this group of patients. Besides this, patients receiving long-term pituitary down-regulation with a GnRH agonist probably had more severe complaints of endometriosis prior to start of GnRH-agonist treatment.

Due to the retrospective design of this study, a selection bias might be achieved by the uncertainty about the assignment of patients to one of the two treatment groups. However, both groups had comparable baseline patient characteristics. Still, it is possible that the included patients represent a negative selected group, because patients with a strong suspicion of endometriosis without a surgical confirmation were not included. Those patients may have started IUI with or without ovarian stimulation before they are scheduled for a laparoscopic therapeutic procedure. In case of an ongoing pregnancy, those patients were missing in the database.

This study showed that patients assigned to IUI with ovarian stimulation not only conceived more but also had a shorter time to pregnancy compared with patients receiving IUI with natural/ovarian stimulation. Although the number of patients who discontinued IUI treatment and started IVF was not different between the groups, patients receiving IUI with ovarian stimulation switched to IVF earlier, which resulted in a higher cumulative ongoing pregnancy rate at 1 year after start of IUI treatment. This might be explained by this centre's standard

evaluation after three IUI with ovarian stimulation cycles of whether or not to stop treatment, continue IUI with ovarian stimulation or switch to IVF.

From these data, it is concluded that IUI might be a valuable treatment for achieving an ongoing pregnancy in this group of patients. IUI with ovarian stimulation should be offered over IUI with natural/ovarian stimulation, since this study found a significantly higher cumulative ongoing pregnancy rate in patients immediately starting ovarian stimulation. Taking into account an acceptable cumulative recurrence rate at 6 months after start of treatment, IUI with ovarian stimulation should be offered with a maximum of three cycles, providing that IUI treatment is completed within half a year after start of treatment. Long-term pituitary down-regulation with a GnRH agonist prior to the first IUI treatment cycle might positively influence the ongoing pregnancy rate and can be considered. Although conclusions can only be made with some degree of uncertainty, the results highlight the need for prospective trials with regard to the efficacy and safety of IUI in moderate-to-severe endometriosis. Since IUI is less radical and less expensive than an IVF procedure, the possibility to offer IUI with ovarian stimulation in patients with at least one patent fallopian tube, for a maximum of three cycles prior to start of IVF treatment, should be further investigated in a randomized controlled trial, taking into account the efficacy, safety and cost-effectiveness of both treatment strategies.

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CHAPTER 4

PREGNANCY RATES AFTER INTRAUTERINE INSEMINATION IN MODERATE TO SEVERE ENDOMETRIOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS OF OBSERVATIONAL STUDIES

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ABSTRACT

To evaluate the efficacy and safety of intrauterine insemination (IUI) in moderate to severe endometriosis patients, a systematic review and meta-analysis was conducted since the role of this treatment strategy in these patients is a matter of debate in the literature. Systematic searches were performed in PubMed, EMBASE, Cinahl, and The Cochrane Library from inception to September 1, 2016. Studies including moderate to severe endometriosis patients reporting pregnancy rates after IUI were selected. The primary outcome was live birth after IUI treatment compared to expectant management. Secondary noncomparative outcomes were live birth and clinical pregnancy, which were presented as weighed mean pregnancy rates. Nineteen articles (2 unclear design, 11 retrospective, 6 prospective) were included for the analysis. Our primary outcome measure was only addressed by one study, showing an odds ratio of 1.77 (95% confidence interval [CI], 0.86-3.63) on live birth favoring IUI versus no treatment. The calculated weighed mean live birth and clinical pregnancy rate per patient was 20.3% (95% CI, 11.2-29.4) and 32.7% (95% CI, 21.3- 44.0), respectively. This meta-analysis of observational data showed that IUI could be a feasible treatment in moderate to severe endometriosis. Whether this treatment should be structurally offered prior to in vitro fertilization needs to be investigated in a randomized, controlled trial, including time-to-pregnancy, safety, and cost-effectiveness.

Keywords: Endometriosis, Intrauterine insemination, Meta-analysis, Pregnancy, Recurrence

INTRODUCTION

Endometriosis is a benign, estrogen-dependent gynecological disease in which fecundity is commonly impaired[1]. Treatment of endometriosis-related subfertility is widely debated in literature[2-5]. The evidence to perform surgery and/or use medically assisted reproduction (MAR) techniques, including intrauterine insemination (IUI) and in vitro fertilization (IVF), was updated in 2014[6].

In women with moderate to severe endometriosis, surgery or IVF might be advised, especially when tubal function is impaired[6]. However, this recommendation is based on experts' opinion only.

In minimal to mild endometriosis-related subfertility (American Society for Reproductive Medicine [ASRM] stages 1-2), IUI is shown to be superior to expectant management[7], and IUI preceded by controlled ovarian hyperstimulation results in higher pregnancy rates compared to IUI alone[8]. In moderate to severe endometriosis-related subfertility (ASRM stages 3-4), firm recommendations on performing IUI are lacking in both the European and American guidelines[6,9]. Therefore, IUI as an MAR treatment option is not structurally offered prior to IVF in this subgroup of patients.

However, in our experience, IUI (with controlled ovarian hyperstimulation) might be a valuable treatment option in moderate to severe endometriosis patients with normal tubal-ovarian function. This is supported by recent observational data showing cumulative ongoing pregnancy rates of 41.3% after 6 treatment cycles[10]. In addition, it is also suggested that long-term pituitary desensitization with a gonadotropinreleasing hormone (GnRH) agonist prior to the start of IUI should be considered[10], since this may improve pregnancy rates[11,12].

In view of the current lack of guidance, we aimed to perform a systematic review and meta-analysis of observational data, investigating the efficacy and safety of IUI (with ovarian stimulation) and the additional effect of preceded long-term pituitary desensitization with a GnRH agonist in patients with moderate to severe endometriosis to endorse future randomized trials.

METHODS

Search strategy

Both MOOSE[13] and PRISMA[14] guidelines were used to conduct this meta-analysis. To identify all relevant publications, we performed systematic searches in the bibliographic databases PubMed, EMBASE.com, Cinahl, and The Cochrane Library (via Wiley) from inception to September 1, 2016. The search terms included controlled terms (e.g., MeSH in PubMed, EMtree in EMBASE.com, Mesh Headings in Cinahl) and free-text terms. We used free-text terms only in The Cochrane Library. Search terms expressing "endometriosis" were used in combination with search terms comprising "intra-uterine insemination (IUI) treatment." No limitations were used. The Medline search strategy is presented as supplementary data (Supplement 1); the

search strategies for the other databases were based on this strategy. The references of the identified articles were also searched for relevant publications.

Selection process

L.H. and A.S. independently selected articles by title and abstract, which were then coded, but did not show author, year, or journal, to limit selection bias by investigators. To be included, peer reviewed articles, including randomized, controlled trials (RCT) and observational studies with and without a control group of patients receiving no treatment, needed to report on absolute pregnancy numbers per patient and/or per IUI treatment cycle in specifically moderate to severe endometriosis patients. To prevent a limited selection of papers, all IUI treatment strategies (i.e., with ovarian hyperstimulation with clomiphene citrate, recombinant folliclestimulating hormone [FSH] or human menopausal gonadotrophins, and unstimulated cycles) were included. Only articles reporting primary data were selected. Studies were excluded if they (i) presented nonprimary data; (ii) were in languages other than English, Dutch, German, French, or Spanish; and (iii) included IUI treatment cycles performed with donor semen. Through discussion, consensus was formed regarding doubtful articles.

Data assessment

The full texts of the selected articles were obtained for further review. Two reviewers (L.H. and A.S.) independently evaluated the papers using a standardized record form, checking whether all the necessary data were provided in the article. Disagreement between the reviewers on individual items were identified and solved during a consensus meeting.

Data extraction

Details about the following elements were extracted and tabulated independently by two investigators (L.H. and A.S.) from the publications: study design, treatment outcomes, number of patients with moderate to severe endometriosis, number of treatment cycles, IUI treatment characteristics (i.e., medication used for controlled ovarian hyperstimulation, use of preceding long-term pituitary desensitization and its duration), and treatment outcomes (definition of pregnancy, number of pregnancies, pregnancy rate per cycle and per patient). No unpublished data were used.

Outcomes

The primary outcome concerned the efficacy of IUI treatment defined as live birth rate after IUI compared to expectant management. Secondary outcomes were biochemical; clinical; ongoing pregnancy per patient and per cycle; the efficacy of preceded treatment with a GnRH agonist; and recurrence of endometriosis.

Statistical analysis

To calculate the odds ratio (OR) of live birth in RCTs and observational (comparative) studies, forest plots were conducted with a 95% confidence interval (95% CI) by using Review Manager (version 5, The Cochrane Library). In case of observational, noncomparative studies, statistical analysis was performed to calculate and plot the weighed mean pregnancy rate with a 95% CI of the included studies by using Microsoft Excel[15]. Plots of weighed mean clinical pregnancy and live birth were composed. Heterogeneity was tested using the Q test and I^2 test[16].

RESULTS

Search results

Figure 1 presents the selection process of the literature search. The search generated a total of 913 references: in PubMed, in EMBASE.com, in Cinahl, and in The Cochrane Library. After removing duplicates of references that were selected from more than one database, 646 titles and abstracts were examined. Of these titles and abstracts, 259 full texts were selected for further investigation. After reading the full texts, 18 articles were selected. An additional 2 articles were added to the selection after screening references. One article[17] was excluded due to overlapping data resulting in a final selection of 19 articles.

Overview of studies

Characteristics of the retrieved articles are presented in Table I. No RCTs were found comparing IUI treatment with expectant management in moderate to severe endometriosis patients. One prospective observational study published by Keresztúri et al[18] compared IUI treatment with expectant management in surgically treated endometriosis patients. From all other included studies, noncomparative data concerning IUI treatment in moderate to severe endometriosis patients were extracted. One RCT compared an ultralong GnRH agonist protocol with 2 weeks of GnRH agonist treatment prior to ovarian hyperstimulation with IUI[11]. In 5 studies, inclusion was limited from moderate to severe endometriosis patients[10,19-22]. In all other studies, moderate to severe endometriosis patients were a subgroup of included patients[18, 23-34].

Primary outcome

Keresztúri et al[18] performed the only prospective nonrandomized study that was included in our meta-analysis, which investigated the benefit of surgery followed by IUI with controlled ovarian hyperstimulation over surgery followed by no treatment during a follow-up period of 12 months. No significant difference was shown between the groups with an OR of 1.77 (95% CI, 0.86-3.63) (Figure 2). In this study, no long-term pituitary desensitization with a GnRH agonist was performed.

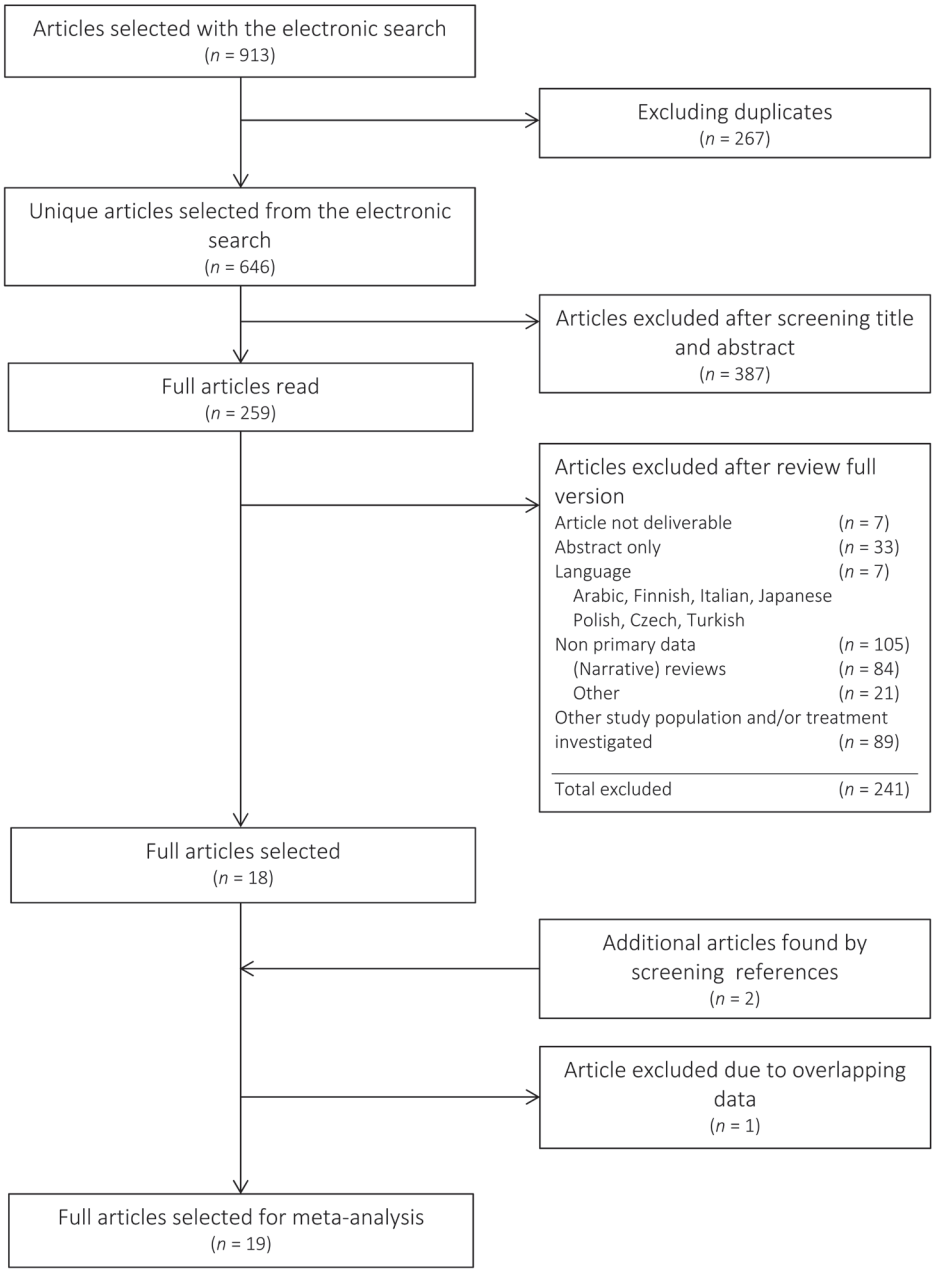

Figure 1 Flowchart

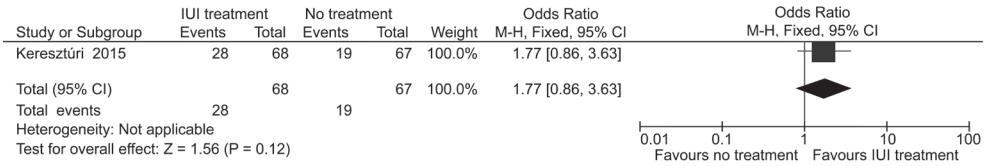

Figure 2 Forest plot on live birth rate

Secondary outcomes

Treatment outcomes are presented in Table II. Twelve studies reported on clinical pregnancies[11,18,19,21,23,25,26,28-31,33]. The calculated weighed mean clinical pregnancy rate was 13.4% per treatment cycle and 32.7% per patient with a 95% CI of 7.4-19.4 and 21.3-44.0, respectively (Figure 3). The test for heterogeneity showed a Q of 11.5 and 7.8 per cycle and per patient, respectively, and an I2 of 39.0% and 0% on pregnancy rate per cycle and per patient, respectively, using the random effects model for both values.

Nine studies reported on live births[10,11,18,19,23,25,26,28,29]. The calculated weighed mean live birth rate per cycle and per patient was 5.6% (95% CI, 3.0-8.2) and 20.3% (95% CI, 11.2-29.4), respectively (Figure 4). The test for heterogeneity showed a Q of 8.1 and 7.4 per cycle and per patient, respectively, and an I2 of 25.9% and 5.4% on pregnancy rate per cycle and per patient, respectively, using the random effects model for both values.

Seven studies included patients undergoing long-term pituitary desensitization using GnRH agonists prior to IUI treatment[10,11,21,22,24,28,33]. However, no studies included a control group of IUI treatment with no preceding GnRH agonist use. One trial[11], which used a randomized, controlled setting to compare ultra-long treatment of at least 6 weeks with 2 weeks of GnRH agonist pre-treatment, showed an OR of 3.53 (95% CI, 0.34-37.15; p = 0.29).

The rate of recurrence of endometriosis was reported in 1 study[10]. Recurrence of endometriosis, which was defined as recurrence of or increase in patient's complaints within 12 months after the last IUI treatment attempt, was seen in 24 out of 65 patients (36.9%), requiring no intervention (n = 2), medical intervention (n = 13), and interference with the continuation of IUI treatment or laparoscopic surgery (n = 9).

Table I Characteristics of included studies

Reference	Design	Population	Purpose	IUI strategy	GnRH analogue
Abuzeid et al.[19]	Retrospective cohort	Moderate to severe endometriosis patients receiving surgery for infertility	To investigate the effect of unilateral versus bilateral adnexal involvement on pregnancy	Not specified; IUI was performed in a subgroup of patients after surgery in male factor infertility, or ovulatory disorder (resistant to CC) or after six months of natural conception. Some patients opted to directly start with IUI with COH.	Not specified
Alborzi et al.[20]	Prospective RCT	Endometriosis with uni- or bilateral cysts receiving different methods of laparoscopic surgery	To compare the response to COH after 1) fenestration and coagulation of an unilateral endometrioma, 2) cystectomy of an unilateral endometrioma, 3) cystectomy at one side and fenestration and coagulation at the other side in bilateral endometrioma	COH with CC and hMG Ovulation: 10.000 IU hCG Insemination: 34-36 h after hCG Luteal support: not specified	Not specified
Amrani et al.[21]	Retrospective cohort	Patients with endometriosis ASRM III or IV receiving surgery for infertility	To define the best surgical strategy in moderate to severe endometriosis patients with infertility	Not specified; IUI was performed in a subgroup of patients after 2 months of GnRH anologue treatment after surgery. Other patients waited on a spontaneous conception or received IVF. Treatment allocation dependend on age, the presence of male factor infertility and surgical findings.	Two months
Burwinkel et al.[23]	Retrospective cohort	Infertile couples receiving IUI	To determine a relationship of basal FSH and age to ovarian responsiveness and pregnancy	COH with hMG Ovulation: ? IU hCG Insemination: 36-40 h after hCG Luteal support: not specified	Not specified

Daru et al.[24, a]	Unclear	Infertile patients with endometriosis receiving surgery and GnRH agonist treatment	To investigate if IUI with COH following surgery and GnRH agonist treatment increases pregnancy rate in infertile patients with endometriosis	COH with FSH and hMG. Ovulation: 10.000 IU hCG Insemination: 36 h after hCG Luteal support: not specified	GnRH agonist for six months
Dickey et al.[25, b]	Prospective cohort	Couples receiving IUI with hMG	To determine characteristics associated with pregnancy and multiple gestationafter IUI with hMG	COH with hMG alone, with or after CC Ovulation: 10.000 IU hCG or LH surge Insemination: 24-36 h after hCG or LH surge Luteal support: not specified	Not specified
Dickey et al.[26]	Prospective cohort	Couples receiving IUI with CC (anovulatory cycles or luteal insufficiency)	To determine characteristics associated with pregnancy and multiple gestationafter IUI with CC	COH with CC cycle day 3-7 Ovulation: 5.000-10.000 IU hCG or LH surge Insemination: 2-40 h after hCG, 2-28 h after LH surge. Luteal support: Not specified	Not specified
Dodson and Haney[27]	Review including retrospective cohort	Infertile couples receiving IUI	To determine cycle fecundity of IUI with hMG in couples without anatomic pelvic distortion	COH with hMG Ovulation: 5.000 IU hCG Insemination: 36-40 h after hCG Luteal support: 2.500 IU hCG day 3 and 6	Not specified
van der Houwen et al.[10]	Retrospective cohort	Moderate to severe endometriosis patients receiving IUI	To investigate the efficacy and safety of two different IUI treatment strategies; A) three times IUI in the natural cycle followed by up to three cycles IUI with COH, B) IUI directly combined with COH	COH with hMG or FSH Ovulation: 10.000 IU hCG Insemination: 42 h after hCG Luteal support: not specified	A subgroup of patients received a GnRH agonist for at least three months
van der Houwen et al.[22]	Prospective cohort	Patient satisfaction moderate to severe endometriosis patients receiving IUI/IVF/IVF ultralong	To investigate patient satisfaction concerning one ART treatment cycle	COH with or without hMG or FSH Ovulation: 10.000 IU hCG Insemination: 42 h after hCG Luteal support: not specified	A subgroup of patients recieved GnRH agonist for at least three months

Table I Characteristics of included studies (continued)

Reference	Design	Population	Purpose	IUI strategy	GnRH analogue
Keresztúri et al.[18]	Prospective cohort	Patients with endometriosis receiving IUI versus no treatment following surgery (non random allocation)	To investigate if IUI has a significant effect on pregnancy in infertile patients with endometriosis after laparoscopic surgery	COH with CC and hMG Ovulation: 10.000 IU hCG Insemination: 36 h after hCG and subsequent day (double insemination) Luteal support: no luteal support	No GnRH agonist pre-treatment
Kim et al.[11]	RCT ultralong versus short GnRH agonist desensitization	Patients with endometriosis (ASRM I-IV) undergoing IUI	To compare the ultralong protocol (ULP) and long protocol (LP) with GnRHa desensitization for ovulation induction with IUI	COH with FSH and hMG Ovulation: 10.000 IU hCG Insemination: 36-40 h after hCG Luteal support: 50 mg progesterone daily	ULP: ≥ 6 weeks GnRHa desensitization LP: 2 weeks GnRHa desensitization
Lodhi et al.[28]	Retrospective cohort	Endometriosis patients receiving GIFT or IUI	To compare the effectiveness of GIFT and IUI with COH in endometriosis patients	COH with FSH or hMG Ovulation: 10.000 IU hCG Insemination: 42 h after hCG Luteal support: not specified	Midluteal pituitary desensitization with a GnRH agonist
Stepniewska et al.[29]	Retrospective cohort	Infertile patients with bowel endometriosis	To determine the influence of bowel endometriosis on fertility in patients who A) underwent colorectal segmental resection, B) had evidence of bowel endometriosis without bowel resection and C) underwent surgery for moderate to severe endometriosis with DIE without bowel involvement	Not specified; A subgroup of patients tried to conceive after surgery; those patients tried to conceive spontaneously, received IUI or IVF.	Not specified
Tavmergen Göker et al.[30]	Retrospective cohort	Patients with endometriosis, male factor, tubal factor or unexplained infertility	To evaluate the efficacy of IUI with COH in endometriosis	COH with FSH or hMG Ovulation: 10.000 IU hCG Insemination: 24 h after hCG Luteal support: not specified	Not specified

Tay et al.[31]	Retrospective cohort	Infertile couples receiving IUI	To analyze the influence of patient and treatment characteristics on the cumulative pregnancy rate	COH with CC and FSH Ovulation: 5.000 IU hCG Insemination: 36 h after hCG Luteal support: 200 mg twice daily vaginally administered progesterone	Not specified
Vollenhoven et al.[32]	Retrospective cohort	Infertile couples receiving IUI	To determine the effectiveness of IUI with hMG and to identify prognostic factors for pregnancy	COH with hMG Ovulation: 10.000 IU hCG Insemination: 18-24 h and/or 36-48 h after hCG Luteal support: 25 mg twice daily progesterone vaginally	Not specified
Wu et al.[33]	Retrospective cohort	Endometriosis patients receiving IUI after laparoscopic treatment of endometriosis	To investigate if the presence and amount of peritoneal fluid is correlated to severity of endometriosis and pregnancy outcome of IUI treatment	COH with FSH Ovulation: 250ugr hCG Insemination: 36 h after hCG Luteal support: progesterone 600mg/day during 2 weeks and 1500 IU hCG on day 6	Two months
Yovich and Matson[34]	Unclear	Non-tubal infertility couples receiving IUI	To determine any relationship between pregnancy rate after IUI and the underlying disorder	COH with hMG and/or CC Ovulation: 5.000 IU hCG or LH surge Insemination next three mornings Luteal support: non specified	Not specified

[a] overlap of patients with Keresztúri et al.[18] cannot be excluded
[b] overlap of patients with Dickey et al.[26] cannot be excluded
ART = assisted reproductive technology; ASRM = American Society of Reproductive Medicine; CC = clomiphene citrate; COH = controlled ovarian hyperstimulation; DIE = deeply infiltrating endometriosis; FSH = follicle-stimulating hormone; GIFT = gamete intrafallopian transfer; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotrophin; hMG = human menopausal gonadotrophin; IU = international units; IUI = intrauterine insemination; LH = luteinizing hormone; LP = long protocol; RCT = randomized controlled trial; ULP = ultra-long protocol

Table II Pregnancy rates

Reference	Patients	Cycles	Biochemical pregnancy			Clinical pregnancy			Ongoing pregnancy			Live birth		
	n	*n*	n	per pt	per cycle	n	% / pt	% / cycle	n	% / pt	% / cycle	n	% / pt	% / cycle
Abuzeid et al.[19]	29	51	-	-	-	14	48,3%	27,5%	-	-	-	11	37,9%	21,6%
Alborzi et al.[20, a]	81	149	48	59,3%	32,2%	-	-	-	-	-	-	-	-	-
Amrani et al.[21]	22	-	-	-	-	15	68,2%	-	-	-	-	-	-	-
Burwinkel et al.[23]	15	37	-	-	-	3	20,0%	8,1%	-	-	-	3	20,0%	8,1%
Daru et al.[24, a]	38	-	17	44,7%	-	-	-	-	-	-	-	-	-	-
Dickey et al.[25]	-	114	-	-	-	6	-	5,3%	-	-	-	5	-	4,4%
Dickey et al.[26]	82	213	12	14,6%	5,6%	10	12,2%	4,7%	-	-	-	7	8,5%	3,3%
Dodson and Haney[27]	-	65	9	-	13,8%	-	-	-	-	-	-	-	-	-
van der Houwen et al.[10]	65	245	-	-	-	-	-	-	15	23,1%	6,1%	12	18,5%	4,9%
van der Houwen et al.[22]	25	25	4	16,0%	16,0%	-	-	-	2	8,0%	8,0%	-	-	-
Keresztúri et al.[18]	68	-	-	-	-	31	45,6%	-	-	-	-	28	41,2%	-
Kim et al.[11]	41	41	-	-	-	14	34,1%	34,1%	10	24,4%	24,4%	4	9,8%	9,8%
Lodhi et al.[28]	14	16	-	-	-	5	35,7%	31,3%	-	-	-	2	14,3%	12,5%
Stepniewska et al.[29]	6	-	-	-	-	4	66,7%	-	-	-	-	3	50,0%	-
Tavmergen Göker et al.[30]	17	-	-	-	-	4	23,5%	-	-	-	-	-	-	-
Tay et al.[31]	-	48	-	-	-	5	-	10,4%	-	-	-	-	-	-
Vollenhoven et al.[32]	8	15	3	37,5%	20,0%	-	-	-	-	-	-	-	-	-
Wu et al.[33]	47	47	-	-	-	11	23,4%	23,4%	-	-	-	-	-	-
Yovich and Matson[34]	23	49	2	8,7%	4,1%	-	-	-	-	-	-	-	-	-

[a] Unclear definition of pregnancy used, stated in this table as biochemical pregnancy
n = number, pt = patients

Study	events	cycles	patients
Abuzeid et al.[19]	14	51	29
Amrani et al.[21]	15		22
Burwinkel et al.[23]	3	37	15
Dickey et al.[25]	6	114	
Dickey et al.[26]	10	213	82
Keresztúri et al.[18]	31		68
Kim et al.[11]	14	41	41
Lodhi et al.[28]	5	16	14
Stepniewska et al.[29]	4		6
Tavmergen Göker et al.[30]	4		17
Tay et al.[31]	5	48	
Wu et al.[33]	11	47	47
Weighed mean clinical pregnancy rate		567	341

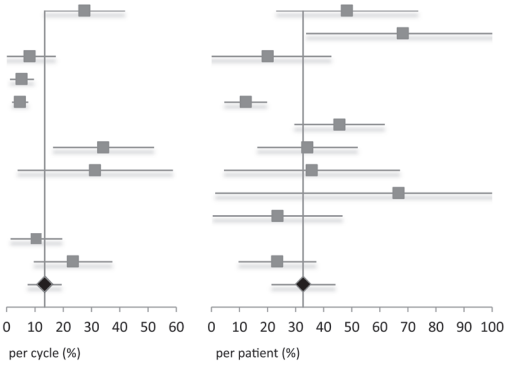

Figure 3 Weighed mean clinical pregnancy rate

Study	events	cycles	patients
Abuzeid et al.[19]	11	51	29
Burwinkel et al.[23]	3	37	15
Dickey et al.[25]	5	114	
Dickey et al.[26]	7	213	82
van der Houwen et al.[10]	12	245	65
Keresztúri et al.[18]	28		68
Kim et al.[11]	4	41	41
Lodhi et al.[28]	2	16	14
Stepniewska et al.[29]	3		6
Weighed mean live birth rate		717	320

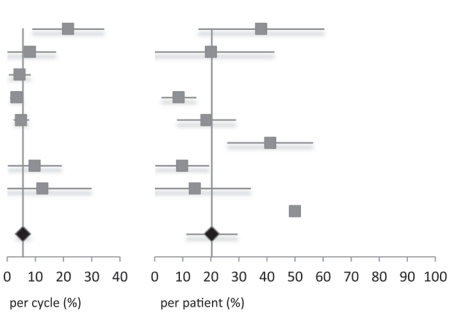

Figure 4 Weighed mean live birth rate

DISCUSSION

In our meta-analysis, observational (noncomparative) data were plotted by calculation of the weighed mean pregnancy rate, showing favorable pregnancy rates after IUI in this group of endometriosis patients. To our knowledge, this is the first systematic search and meta-analysis that has investigated the pregnancy rates of patients with moderate to severe endometriosis undergoing IUI treatment. We were able to combine a reasonable amount of articles for this specific research goal. Unfortunately, no RCTs could be identified. Therefore, our primary outcome measure could only be addressed by 1 study, showing a nonsignificant difference favoring IUI with controlled ovarian hyperstimulation compared with expectant management[18].

Interpretation of the study results is difficult, since the included studies investigated a variety of treatment strategies and populations as presented in Table I. The best available evidence was provided by Keresztúri and colleagues[18] investigating a treatment strategy of laparoscopic surgery followed by IUI with controlled ovarian hyperstimulation in all stages of endometriosis in a prospective cohort compared to no treatment after surgery. For the total

group of endometriosis patients (all ASRM stages), surgery followed by IUI with controlled ovarian hyperstimulation was more beneficial than surgery alone in terms of live birth (OR 1.85; 95% CI, 1.09- 1.34; p = 0.02). For patients with stage III/IV endometriosis, this effect was less pronounced (41.2% vs. 28.4%; p = 0.29). This difference, favoring IUI treatment, did not reach statistical significance, which was possibly due to a lack of power.

Surgery in moderate to severe endometriosis patients seeking for natural conception is recommended by the The European Society of Human Reproduction and Embryology (ESHRE) guideline[6], since surgery compared to expectant management improves spontaneous pregnancy rates (level B evidence). However, prior to IVF/intracytoplasmic sperm injection (ICSI) surgical treatment of moderate to severe endometriosis (i.e., performing cystectomy) should be carefully considered, taking into account the lack of evidence that performing a cystectomy improves pregnancy rates; the possible loss of functional ovarian tissue (especially in repetitive ovarian surgery); the accessibility of follicles; and patients' pain complaints. Whether surgery of moderate to severe endometriosis prior to IUI affects pregnancy rates has not been investigated. However, it can be hypothesized that laparoscopically treating peritoneal disease in moderate to severe endometriosis patients (without performing cystectomy in the absence of endometriosis-related pain complaints), may be more beneficial in improving pregnancy rates with IUI compared to IUI alone, as it is already shown for natural conception[35] (level A evidence) and pregnancy after IVF[36] (level C evidence). Unfortunately, the studies included in our meta-analysis reported no data on surgical interventions.

Performing surgery also results in the ability to calculate the endometriosis fertility index (EFI) score as described by Adamson and Pasta to predict pregnancy rates in patients attempting nonIVF conception[37]. This fertility index is already externally validated[38], and recent studies focus on the possibility to use this tool to select patients who should be offered IVF/ICSI[39, 40]. Whether IUI can be performed prior to IVF/ICSI at specific cut-off values of the EFI score has not yet been investigate.

Next to the variety of strategies and populations, different IUI treatment strategies have been described in the included studies, such as those concerning IUI in a natural cycle and IUI with controlled ovarian hyperstimulation, including antiestrogens (clomifenecitrate), recombinant follicle stimulating hormone (FSH) and/or human menopausal gonadotropin (hMG). It is worth noting that in subfertile couples, gonadotrophins are superior to antiestrogens regarding pregnancy rates after IUI[41], but this has never been evaluated in moderate to severe endometriosis patients.

It has been shown that prior long-term pituitary desensitization promotes pregnancy rates after IUI in endometriosis patients ASRM stage 2-4[12]. Besides this, the beneficial effect in this specific subgroup of ASRM 2-4 endometriosis patients (100% vs. 70% pregnancy rate) was not significantly different, which is possibly due to a lack of power. This is in line with the results published by Kim and colleagues[11], investigating a modified ultra-long desensitization with a GnRH agonist for 6 weeks in an RCT showing an OR on live birth of 3.53 (95% CI, 0.34-37.15). Besides this, our recently published retrospective study on IUI in moderate to severe

endometriosis patients showed a hazard ratio of 1.8 (95% CI, 0.6-5.1) in favor of long-term pituitary desensitization (nonsignificantly) for at least 3 months[10]. Those results ask for more research regarding the possible beneficial effect of long-term pituitary desensitization with a GnRH agonist.

Differences in stimulation protocols, (duration since) surgical interventions, and the use of preceding treatment with a GnRH agonist might have influenced the outcome of our metaanalysis, and most of the included studies were not designed to specifically investigate the effect of IUI in moderate to severe endometriosis patients. However, despite this clinical heterogeneity, calculation of the weighed mean pregnancy rate was statistically the best method to combine observational data and calculate the effect of intrauterine insemination on pregnancy rates, resulting in a level 4 evidence (grade C) recommendation.

Next to efficacy, the safety of treatment in terms of complications and the recurrence of endometriosis should be taken into account, especially in moderate to severe endometriosis patients. Recurrence of endometriosis complaints may lead to discontinuation of fertility treatment due to the need to start hormonal suppression therapy or surgical intervention. This directly results in postponement or cancellation of the possibility to conceive[10], which negatively affects time to pregnancy. D'Hooghe and colleagues[42] have shown that the endometriosis recurrence rate is higher in patients undergoing IUI than in IVF, which is explained by the result of a more frequent exposure to ovulation and subsequent retrograde menstruation in IUI treatment. By limiting the amount of IUI treatment cycles to 3 per patient, this negative effect might be negligible[10].

CONCLUSION

This meta-analysis of observational data has shown that IUI could be a feasible treatment in moderate to severe endometriosis. Due to the lack of RCTs, no clear recommendation can be made in offering IUI treatment in moderate to severe endometriosis patients. Whether this treatment should be structurally performed prior to IVF must be investigated in a RCT, including time-to-pregnancy, safety, and cost effectiveness.

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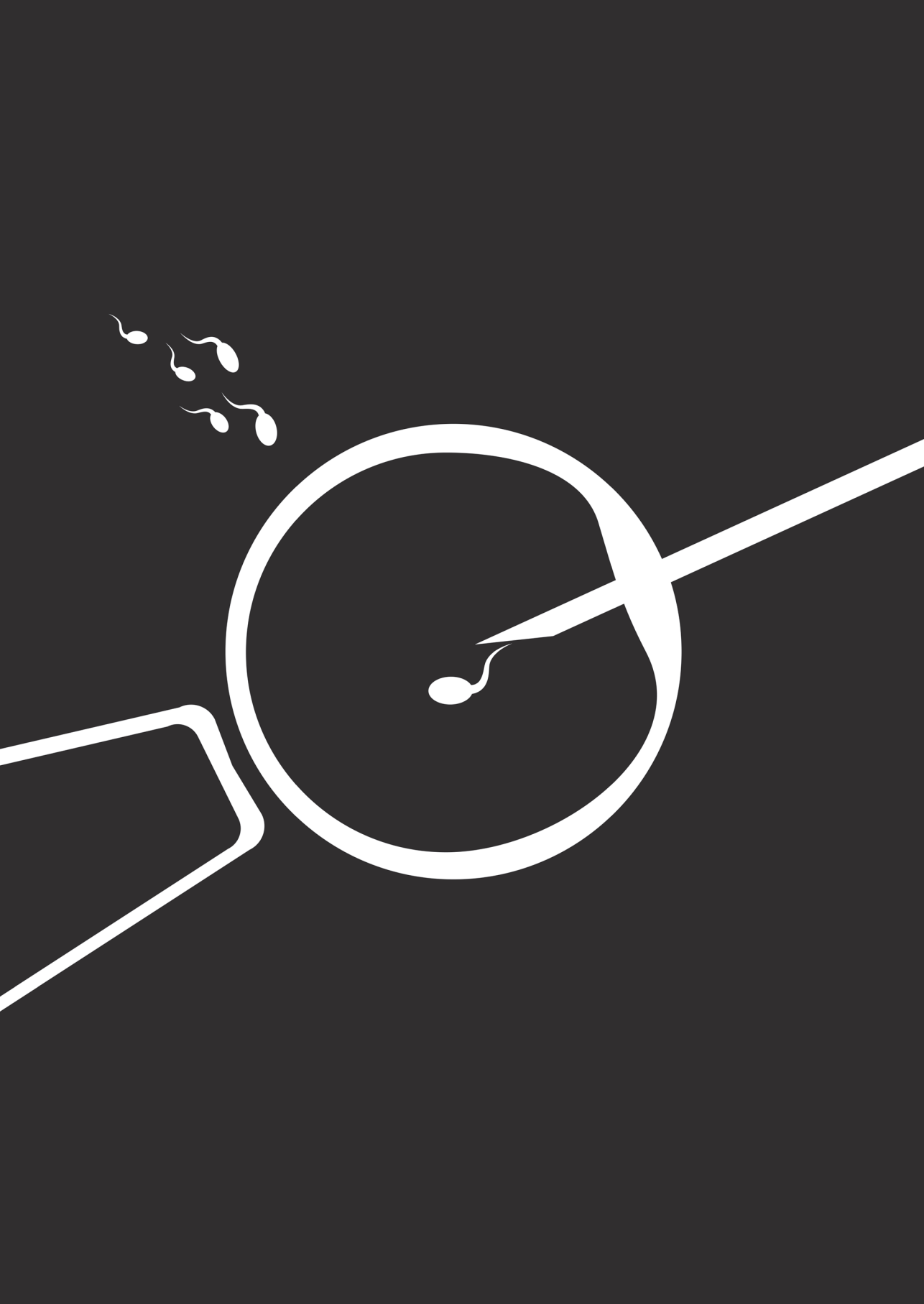
SUPPLEMENT 1 SEARCH STRATEGY

"Endometriosis"[Mesh] OR "Endometriosis"[tiab] OR "Endometrioses"[tiab] OR "Endometrioma"[tiab] OR "Endometriomas"[tiab] OR "Endometriotic"[tiab] OR "endometriosis externa"[tiab] OR "ASRM 3"[tiab] OR "ASRM III"[tiab] OR "ASRM 4"[tiab] OR "ASRM IV"[tiab] OR "AFS III"[tiab] OR "AFS 3"[tiab] OR "AFS IV"[tiab] OR "AFS 4"[tiab]

AND

"Insemination, Artificial, Homologous"[Mesh] OR "Intra-uterine insemination"[tiab] OR "Intra-uterine inseminations"[tiab] OR "Intrauterine insemination"[tiab] OR "Intrauterine inseminations"[tiab] OR "Insemination, Homologous"[tiab] OR "Insemination, Artificial, Husband"[tiab] OR "Homologous Insemination"[tiab] OR "AIH"[tiab] OR "Husband Artificial Insemination" OR "uterine insemination"[tiab] OR "IUI"[tiab]



CHAPTER 5

EFFICACY AND SAFETY OF IVF/ICSI IN PATIENTS WITH SEVERE ENDOMETRIOSIS AFTER LONG-TERM PITUITARY DOWN-REGULATION

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ABSTRACT

Long-term pituitary down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist for 3–6 months prior to IVF/intracytoplasmic sperm injection (ICSI) improves clinical pregnancy rates in endometriosis patients. However, some discussion about this treatment strategy still exists. This retrospective study from a tertiary-care university hospital examined the efficacy and safety of IVF/ICSI with and without long-term pituitary down-regulation in severe endometriosis patients (surgically confirmed American Society for Reproductive Medicine stages III and IV). All first IVF/ICSI treatment cycles between January 2009 and January 2012 were analysed. In patients treated with (n = 68) and without (n = 45) long-term pituitary down-regulation, 13 (19.1%) versus nine (20.0%) ongoing pregnancies after fresh embryo transfer (adjusted OR 0.58, 95% CI 0.18–1.86,) and 24 (35.3%) versus 10 (22.2%) ongoing pregnancies after fresh and cryopreserved embryo transfers (adjusted OR 1.62, 95% CI 0.60–4.38) were accomplished, respectively. Three complications (2.7%) and three recurrences (2.7%) were reported, only in patients treated with long-term pituitary down-regulation. The 1-year cumulative endometriosis recurrence rate was 7.3%. IVF/ICSI in patients with severe endometriosis is safe with low complication and recurrence rates. A favourable effect, albeit non-significant, of long-term pituitary down-regulation in achieving an ongoing pregnancy was observed only after including cryopreserved embryo transfers.

Keywords: Complication, Endometriosis, IVF, Long-term pituitary down-regulation, Ongoing pregnancy rate, Recurrence

INTRODUCTION

Endometriosis, a benign gynaecological disorder, occurs in up to 50% of patients associated with subfertility[1]. Although the exact mechanisms are still not unravelled, it has been postulated that endometriosisassociated subfertility is based on a disturbed pelvic anatomy, a hostile peritoneal environment, a diminished ovarian reserve and an altered endometrial receptivity, or combinations of those[2,3].

In subfertile patients with severe endometriosis, embryo transfer after IVF or intracytoplasmic sperm injection (ICSI) is an appropriate treatment, especially in case of nonpatent tubes, but also in male factor or unexplained infertility[4]. Although a few recent studies[5,6] showed comparable IVF/ICSI treatment outcomes between patients with endometriosis and patients with tubal factor infertility, other studies report significantly decreased pregnancy rates in patients with endometriosis[7,8]. In particular, this seems to be the case in patients with severe endometriosis, American Society for Reproductive Medicine (ASRM) stage III and IV[8] and in patients with endometriomas present at the time of ovarian stimulation[6].

Several nonrandomized trials[9-13] and one Cochrane systematic review[14] have shown that long-term pituitary down-regulation with a GnRH agonist for 3–6 months prior to IVF/ICSI improves clinical pregnancy rates in endometriosis patients. Still, some discussion about this treatment strategy exists, as the Cochrane recommendation was based on only three small studies[15-17]. Nowadays, less aggressive stimulation protocols are used to minimize the risks of ovarian hyperstimulation syndrome and (elective) single-embryo transfer is preferred to prevent the development of multiple pregnancies and its known complications. Since cryopreserved embryo transfers are an important additional benefit of IVF/ICSI in achieving a pregnancy, the question becomes relevant if the prolonged use of a GnRH agonist prior to IVF/ICSI has any effect on the consequential cryopreserved embryo transfers.

Besides this, it is not inconceivable that clinicians are sceptical about long-term pituitary down-regulation, possibly being afraid that it may lower ovarian response to ovarian stimulation, especially in poor responders. In addition, as uncomfortable side effects, such as vasomotor instability, are often related to this treatment strategy, patients are frequently unwilling to use GnRH agonists for a longer period of time. As a result, other IVF/ICSI treatment strategies are offered, although they are not demonstrated to be effective in this specific group of (severe) endometriosis patients. Recently, continuous use of oral contraceptives is suggested to be an appropriate treatment in those patients, but unfortunately a comparison with the standard long-term pituitary down-regulation with a GnRH agonist regime has not been made[18].

Besides IVF/ICSI treatment efficacy, safety is a key clinical issue in treatment decision making. Only a few studies have reported complications19-21 and recurrences22-24 of endometriosis after IVF/ICSI. In general, they showed reassuring results. Still, fear exists among clinicians about serious complications, such as development of pelvic inflammatory disease or pelvic organ dysfunction through recurrence of endometriosis. Therefore, there is urgent need for

more data on complications and endometriotic recurrence in IVF/ICSI in severe endometriosis patients and a possible protective role of prolonged use of a GnRH agonist in this regard.

Therefore, this study aimed to investigate the efficacy and safety of IVF/ICSI with and without long-term pituitary down-regulation with a GnRH agonist in severe endometriosis patients.

MATERIALS AND METHODS

This study retrospectively analysed endometriosis patients who underwent IVF/ICSI treatment in the period between January 2009 and January 2012. All patients were selected by using the electronic patient database of the IVF centre of the VU University Medical centre. Only patients diagnosed with surgically confirmed severe endometriosis (ASRM stage III and IV) undergoing their first IVF/ICSI treatment cycle were included (Figure 1). The database was validated and supplemented by two researchers (EL, LH). The study was approved by the Medical Ethics Review Committee of VU University Medical Centre (reference no. 2013/2, approved 17 January 2013).

The primary outcome was ongoing pregnancy rate, including fresh as well as cryopreserved embryo transfer procedures. Secondary outcomes were complication, cycle cancellation and recurrence rates, clinical pregnancy rate per started cycle, total number of oocytes retrieved, total number of embryos and total number of cryopreserved embryos. An ongoing pregnancy was defined as an intact intrauterine pregnancy confirmed by ultrasound at 12 weeks of gestational age. A clinical pregnancy was defined as the confirmation of at least one gestational sac visualized by ultrasound. A miscarriage was defined as the loss of a clinical pregnancy before 12 weeks of gestational age. Ovarian hyperstimulation syndrome, infection, pelvic organ dysfunction and/or hospital admittance within 3 months after IVF/ICSI treatment were defined as complications. Recurrence of endometriosis was defined as the presence of visually/histologically confirmed endometriosis during surgery within 1 year after IVF/ICSI ovum retrieval[24]. An indication for surgery was based on: (i) recurrence/increase of complaints suspicious for endometriosis recurrence insufficiently reacting on hormonal suppression therapy; or (ii) need for pelvic surgery in acute situations. Recurrence of complaints without a surgical confirmation of endometriosis was considered to be insufficient evidence to reflect recurrence of endometriosis.

Data are presented for the total study group. Subgroup analysis was performed to compare patients treated with and without long-term pituitary down-regulation with a GnRH agonist for at least 3 months prior to IVF/ICSI. Down-regulation was performed with leuprolide 3.75 mg depot injections (Lucrin; Abbvie, Hoofddorp, The Netherlands). Exactly 28 days after the last injection, daily subcutaneous injec tions of triptoreline (Decapeptyl; Ferring, Copenhagen, Denmark) was started and tions of triptoreline (Decapeptyl; Ferring, Copenhagen, Denmark) was started and 1 day later followed by the administration of recombinant FSH (Gonal F; Serono, Geneva, Switzerland; or Puregon; MSD, Oss, The Netherlands). In patients treated

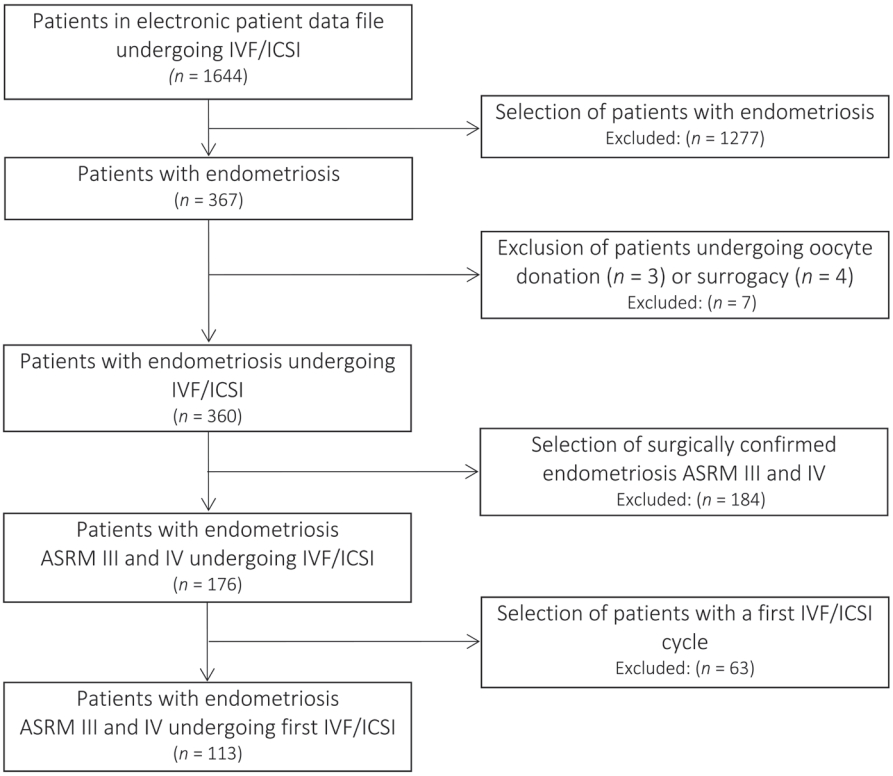

Figure 1 Flowchart of patient selection. ASRM: American Society for Reproductive Medicine; ICSI: intracytoplasmic sperm injection.

without long-term pituitary down-regulation, a standard stimulation protocol was performed as previously described[25]. Briefly, those patients underwent a standard long agonist protocol (n = 28) or short agonist protocol (n = 17) preceded by continuous use of oral contraceptives (n = 20) or not (n = 25). Long-term pituitary down-regulation is this study centre's first choice of treatment. Deviation of this treatment strategy was based on patient request (patient was unwilling to use GnRH agonists), practical reasons (patient's symptoms were already effectively treated with continuous use of oral contraceptives) or the anticipation of a poor ovarian response (because of an increased FSH and/or diminished antral follicle count). Dose of recombinant FSH was determined individually. Follicle growth monitoring, oocyte retrieval, the luteal phase and laboratory's insemination procedure were performed as previously described[25]. Cryopreserved embryo transfers were either performed in a spontaneous or an artificial cycle. In a spontaneous cycle, human chorionic gonadotropin (Pregnyl; MSD, Oss, The Netherlands) was administered when a follicle reaches the size of at least 17 mm in combination with an adequate endometrial thickness of at least 7 mm. An artificial cycle was carried out by administering oestradiol (Progynova; Bayer Schering Pharma, Berlin, Germany) and progesterone (Utrogestan; Bessins Healthcare, Bangkok, Thailand) to prepare

the endometrium for implantation. Six days after Pregnyl (spontaneous cycle) or start with progesterone administration (artificial cycle), the embryo transfer was performed.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 16.0 (IBM SPSS, USA). Data were expressed as means ± standard deviations or n (%). Differences between the two subgroups were evaluated with chi-squared or Fisher's exact tests in categorical data and Students' t-test in parametric continuous data or Mann–Whitney test in nonparametric data. Multiple logistic regression analysis was performed to evaluate the effect of different confounders (i.e. patient and cycle characteristics) on the primary outcome.

Life table analysis was used to calculate the cumulative endometriosis recurrence rate (CERR)[26]. For each patient, date of oocyte pick up was set as date of entry. The endpoint was exactly 12 months after the date of entry or the date of surgical reintervention (in recurrent endometriosis patients), the date of the positive pregnancy test (in ongoing pregnant patients) or the date of patient's last visit. The log rank test was used to compare the CERR between the two groups.

RESULTS

This study included 113 patients, of whom 68 patients were treated with long-term pituitary down-regulation using a GnRH agonist for at least 3 months (median 3 months, range 3–14 months). Patients treated with long-term pituitary down-regulation were significantly younger ($P < 0.01$), more frequently diagnosed with endometriosis ASRM stage IV ($P < 0.01$) and obese (BMI _30 kg/m2, $P = 0.02$) (Table I). Ovarian stimulation was more frequently started with lower dosages of FSH and resulted in lower oestradiol concentrations on the day of human chorionic gonadotrophin administration in patients treated with long-term pituitary down-regulation versus without. Mean number of oocytes, embryos and cryopreserved embryos was equal for both groups (Table II).

In total, 22 ongoing pregnancies were accomplished after fresh embryo transfer (19.5% per started cycle); 13 after long-term pituitary down-regulation (19.1%) versus nine after treatment without (20.0%). In total, 64 patients had cryopreserved embryos, of whom 12 achieved an ongoing pregnancy (10.6%). Including all cryopreserved embryo transfers, 34 ongoing pregnancies were accomplished (30.1%); 24 (35.3%) after treatment with long-term pituitary down-regulation versus 10 (22.2%) after treatment without (Table II).

Table I Patient and cycle characteristics

	Total group (n = 113)	No long-term pituitary down-regulation (n = 45)	Long-term pituitary down-regulation (n = 68)	P-value
Age (years)	33.4±3.6	34.7±3.8	32.5±3.2	<0.001
BMI (kg/m^2)	23.8±3.9	23.3±2.9	24.2±4.5	0.17
< 25	76 (67.2%)	32 (71.1%)	44 (64.7%)	0.02
25 – 30	28 (24.8%)	13 (28.9%)	15 (22.1%)	
≥ 30	9 (8.0%)	0 (0%)	9 (13.2%)	
Subfertility				0.01
Primary	71 (62.8%)	22 (48.9%)	49 (72.1%)	
Secondary	42 (37.2%)	23 (51.1%)	19 (27.9%)	
Duration (months)	37±24	37±28	36±21	0.76
ASRM stage				<0.01
III	30 (26.5%)	19 (42.2%)	11 (16.2%)	
IV	83 (73.5%)	26 (57.8%)	57 (83.8%)	
Semen (million)	30.5±31.4	27.0±38.3	32.7±26.0	0.09[a]
AB profylaxis[b]	17 (15.0%)	3 (7.1%)	14 (23.0%)	0.03
Fertilization protocol				0.11
IVF	102 (90.3%)	38 (84.4%)	64 (94.1%)	
ICSI	11 (9.7%)	7 (15.6%)	4 (5.9%)	
Duration of stimulation (days)	11±2.6	10.8±2.5	11.2±2.7	
Start dose FSH (IU)				<0.001
125 IU	1 (0.9%)	1 (2.2%)	0	
150 IU	43 (38.1%)	10 (22.2%)	33 (48.5%)	
225 IU	32 (28.3%)	9 (20.0%)	23 (33.8%)	
300 IU	36 (31.9%)	25 (55.6%)	11 (16.2%)	
450 IU	1 (0.9%)	0	1 (1.5%)	
Total FSH (IU)	2440±979	2697±982	2270±945	0.02
Endometrial thickness on HCG day (mm)	9.3±2.4	9.6±2.8	9.1±2.1	0.35
Estradiol concentration on HCG day (pmol/l)	4952±3867	5902±4494	4328±3283	0.12[a]
Cancelled cycles				
No oocyte retrieval[c]	10 (8.8%)	3 (6.7%)	7 (10.3%)	0.74
No oocytes after oocyte retrieval	2 (1.8%)	1 (2.2%)	1 (1.5%)	1.00
Total fertilization failure[d]	4 (3.5%)	2 (4.4%)	2 (2.9%)	1.00
Primary cryopreservation[e]	3 (2.7%)	0	3 (4.4%)	0.28

Values are mean ± SD or n (%). AB = antibiotics.
[a] Mann–Whitney test.
[b] Number of patients per oocyte retrieval.
[c] Reasons: low response (long-term pituitary down-regulation n = 4; no long-term pituitary down-regulation n = 3; in four out of these seven patients an intrauterine insemination was performed); personal reasons (n = 1); presence of intracavity fluid due to a hydrosalpinx (n = 1); incorrect use of Pregnyl (n = 1).
[d] Including one patient who underwent embryo transfer without the notification of 2PN stage.
[e] Because of the risk of severe OHSS (n = 2) and due to being unable to puncture one ovary (n = 1).

Table II Outcome parameters

	Total group (n = 113)	**No long-term pituitary down-regulation (n = 45)**	**Long-term pituitary down-regulation (n = 68)**	**P-value**
Total oocytes	8.9 ± 6.2	9.0 ± 6.4	8.9 ± 6.2	0.97
Fertilization	0.57 ± 0.24	0.56 ± 0.25	0.58 ± 0.24	0.70
Total embryos	5.1 ± 4.1	5.2 ± 4.5	5.1 ± 3.8	0.92
Total cryo preserved embryos[a]	3.3 ± 3.4	3.2 ± 3.2	3.2 ± 3.6	0.87
Embryo transfer[b]				1.00
Single-embryo transfer	86 (92.5)	35 (92.1)	51 (92.7)	
Double-embryo transfer	7 (7.5)	3 (7.9)	4 (7.3)	
Implantation[a,b]	0.29 ± 0.46	0.28 ± 0.45	0.30 ± 0.47	0.72
Clinical pregnancy	27 (23.9)	10 (22.2)	17 (25.0)	0.74
Miscarriage	5 (4.4)	1 (2.2)	4 (5.9)	0.65
Ongoing pregnancy	22 (19.5)	9 (20.0)[c]	13 (19.1)	0.91
Patients with ≥ 1 cryopreserved embryo	64 (56.6)	24 (53.3)	40 (58.8)	0.56
Ongoing pregnant after fresh ET	19 (29.7)	8 (33.3)	11 (27.7)	0.77
Not ongoing pregnant after fresh ET	45 (70.3)	16 (66.7)	29 (72.3)	
Cryopreserved ET cycles/no. of patients	58 / 42	23 / 15	35 / 27	
Natural cycle	54 (93.1)	23 (100)	31 (88.6)	
Artificial cycle[d]	4 (6.9)	0	4 (11.4)	
Total cryopreserved ET cycles per woman[a]	1 [0-4]	2 [0-3]	1 [0-4]	0.17
Total cryopreserved embryos transferred[a,e]	1 [0-4]	2 [0-3]	1 [0-4]	0.11
Ongoing pregnancy after cryopreserved ET cycles	12 (10.6)	1 (2.2)	11 (16.2)	0.03
Ongoing pregnancy fresh + cryopreserved ET cycles	34 (30.1)	10 (22.2)[c]	24 (35.3)	0.14
Patient with ≥ 1 cryopreserved embryo left[f]	11 (24.4)	3 (18.8)	8 (27.6)	0.72
Complication[b]	3 (2.7)	0	3 (4.4)	0.28
Recurrence	3 (2.7)	0	3 (4.4)	0.28

Values are mean ± SD, n (%) or median [range]
[a]Mann–Whitney test
[b]After fresh embryo transfer
[c]Three ongoing pregnancies were accomplished in patients pretreated with continuous use of oral contraceptives
[d]An artificial cycle is carried out with oestradiol and progesterone after long-term pituitary down-regulation with a GnRH agonist for at least 3 months
[e]In four cryo-embryo transfer cycles, a double-embryo transfer was performed
[f]Per number of non-pregnant patients at 1 January 2012.

Multiple logistic regression analysis showed a nonsignificant, slightly lower odds on ongoing pregnancy per started cycle after fresh embryo transfer in patients treated with long-term pituitary down-regulation (OR 0.95, 95% CI 0.37–2.44). Adjusted for baseline patient characteristics (confounders age, primary or secondary infertility, BMI and start dose of FSH), the OR was 0.58 (95% CI 0.18–1.86). Including cryopreserved embryo transfers, a nonsignificant higher ongoing pregnancy rate per started cycle in patients treated with long-term pituitary

down-regulation was found (OR 1.91, 95% CI 0.81–4.52). Adjusted for baseline patient characteristics (confounders age, BMI and start dose of FSH) the OR was 1.62 (95% CI 0.60–4.38).

This study also investigated the effect of treatment on complications and recurrences. Three complications were reported (complication rate of 2.7% per started cycle), occurring only in patients (ASRM stage IV) treated with long-term pituitary down-regulation. In two patients, mild ovarian hyperstimulation syndrome was reported. One of those patients recovered by expectant management. The other patient was admitted and treated with intravenous administration of saline and antibiotics. One patient suffered from gastrointestinal blood loss during follicle stimulation, which did not require an intervention. Three recurrences (recurrence rate of 2.7%) have been reported, all of them in patients treated with long-term pituitary down-regulation. Two patients (ASRM stage III and IV) were treated with a segmental colorectal resection by laparotomy, because of a (partial) stenosis in the rectosigmoid colon of both patients. In one of them, this surgery was combined with neoimplantation of the left ureter. In one patient (ASRM stage IV), salpingoovariolysis, a left tubectomy, cystectomy and appendectomy were performed by laparoscopy, because of the appearance of endometriosis. The overall CERR was 7.3% after a follow up of 12 months; the CERR was 11.4% versus 0.0% (log rank test, not significant) in patients treated with and without long-term pituitary down-regulation, respectively (Figure 2).

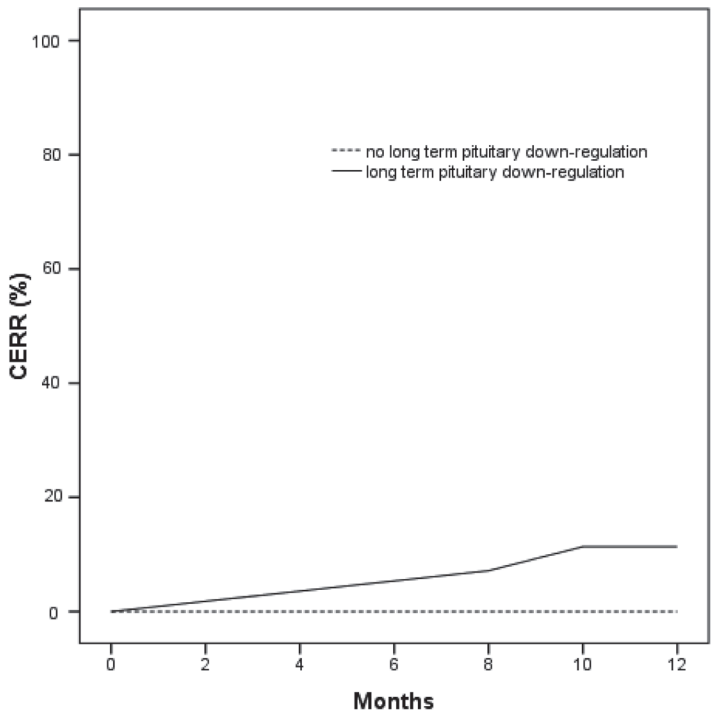

Figure 2 Cumulative endometriosis recurrence rate (CERR) after IVF/intracytoplasmic sperm injection.

DISCUSSION

This study demonstrates that IVF/ICSI is a safe procedure with low complication and recurrence rates in patients with severe endometriosis, which is in line with recent studies of Benaglia et al.[22,23] and D'Hooghe et al.[24]. The ongoing pregnancy rate after fresh embryo transfer in patients with severe endometriosis is lower than found for all IVF/ICSI treatment cycles in this IVF clinic during the same period (2520 treatments started, 649 ongoing pregnancies after fresh embryo transfer (25.8%), 995 ongoing pregnancies including cryopreserved embryo transfers (39.5%)) which supports earlier observations of significantly decreased pregnancy rates in IVF patients with endometriosis compared with IVF patients with other treatment indications[7,8]. On the other hand, it is in line with this study centre's recently published data on IVF outcome in patients with severe endometriosis who underwent a segmental bowel resection, showing an ongoing pregnancy rate of 32% per embryo transfer[27].

This retrospective study has insufficient statistical power to draw firm conclusions about the amount of effect of long-term pituitary down-regulation on ongoing pregnancy after fresh and after fresh including cryopreserved embryo transfers. Nevertheless, the outcomes of this study generate a new and intriguing perspective with regard to the short- and long-term effects of long-term pituitary down-regulation with a GnRH agonist because, after including cryopreserved embryo transfers, the odds ratio on ongoing pregnancy changed to the opposite (favourable) direction. First, does long-term pituitary down-regulation with a GnRH agonist have a short-term negative effect on implantation? Secondly, does long-term pituitary downregulation with a GnRH agonist improve oocyte quality? Apparently, the possibility exists that among severe endometriosis patients, long-term pituitary down-regulation prior to IVF/ICSI improves oocyte quality given the remarkable positive effect seen in the ongoing pregnancy rate after cryopreserved embryo transfer over patients treated without long-term pituitary down-regulation.

In contrast to these findings, a Cochrane systematic review[14] showed a significant improvement of pregnancy rates after long-term pituitary down-regulation prior to IVF/ICSI in endometriosis patients. Unfortunately, the mechanism to explain favourable results after long-term pituitary down-regulation with a GnRH agonist is lacking and one may only speculate in order to understand this observed improvement in IVF outcome: it may be based on an improved endometrial receptivity or improved oocyte quality[14]. However, the results of the systematic review might be influenced by the inclusion of patients with minimal to mild endometriosis, because in patients with severe endometriosis lower IVF/ICSI pregnancy rates have been observed[7]. In our current study, only patients with severe endometriosis were included and, in advance, especially in this subgroup of patients improved ongoing pregnancy rates after long-term pituitary down-regulation were expected. However, the current study's expectations could not be completely confirmed as the odds on ongoing pregnancy after fresh embryo transfer is remarkably not in favour of this treatment strategy. Remarkably, in patients treated with long-term pituitary down-regulation, the ongoing pregnancy rate substantially increased after including cryopreserved embryo transfers.

This observation supports the idea of an impaired endometrial receptivity directly after using GnRH agonists in ovarian stimulation cycles[28], which is probably the result of a decreased endometrial expression of genes involved in successful implantation[29]. Those findings are not only related to patients with endometriosis. However, it is shown in patients with endometriosis in unstimulated cycles that the mid-luteal rise of two specific genes (HOXA10 and HOXA11), both well known to be involved in successful implantation, is already altered compared with controls[30-33]. Although a GnRH agonist seems to diminish the endometrial receptivity, in the meantime this treatment regime might improve oocyte (and thus embryo) quality, because of the observation of increased ongoing pregnancy rates after cryopreserved embryo transfers in patients treated with long-term pituitary down-regulation. Since the reduced embryo implantation in moderate to severe endometriosis patients is assumed to be mainly based on a diminished oocyte quality[34], it is very important to further investigate the impact and mechanism of action of a GnRH agonist on the oocyte/embryo quality.

Although IVF/ICSI with long-term pituitary downregulation is the first-choice treatment in patients with severe endometriosis, almost 40% of these patients surgically diagnosed with severe endometriosis did not receive this treatment regime, which illustrates the need for studies investigating the efficiency of other treatment strategies, such as continuous use of oral contraceptives prior to IVF/ICSI in this specific group of severe endometriosis patients which is supposed to be as effective as long-term pituitary down-regulation[18]. Unfortunately, the subgroup in this study was too small to calculate reliable (adjusted) odds ratios for the different subgroups.

As the Cochrane systematic review recommendation is only based on three small studies [15-17] a randomized controlled trial is needed. The studies only reported the endpoint as clinical pregnancy rate, which is no longer an acceptable outcome measure in the literature and should be replaced by (at least) the ongoing pregnancy rate[35]. This is also in line with their recommendation for future research. Additionally, the three studies were performed in another IVF/ICSI treatment era with overall lower outcomes than today. In the last decade, new stimulation and IVF/ICSI techniques have resulted in steeply improved ongoing pregnancy rates, which resulted in the preference to perform (elective) single-embryo transfers and cryopreserve all good-quality embryos. A restrained policy on double-embryo transfers is incorporated in our IVF clinic to prevent multiple pregnancies and its complications.

To investigate the amount of effect of long-term pituitary down-regulation, a well-powered randomized study in severe endometriosis patients undergoing IVF/ICSI with and without long-term pituitary down-regulation should be performed. The ongoing/live birth rate after all embryo transfers of one treatment cycle should be analysed and at least embryo quality and time to pregnancy should be taken into account. Based on these findings, it might be suggested to only perform this treatment strategy in patients with a high potential of cryopreservation. Patients with a poor response after a former IVF/ICSI attempt, signs of imminent ovarian failure (raised basal FSH concentrations beyond 10 IU/l, an antral follicle count lower than 5), or an inability to perform cryopreservation (e.g. because of the presence

of hepatitis B/C or HIV infection) should probably be offered an IVF/ICSI treatment without the long-term pituitary down-regulation regime. The question remains whether or not to only perform cryopreserved embryo transfers as stated by Mohamed et al.[36]. However, ongoing pregnancy rates after fresh embryo transfer are still higher compared with cryopreserved embryo transfers[36].

Concerns on the risk of complications, such as developing pelvic abscesses after oocyte retrieval in patients with endometrioma, still exist[19-21]. The current study found a complication rate of only 2.7%, including general IVF/ICSI-related complications, which is in line with the reported complication rate of 1.4% by Benaglia et al.[19]. No pelvic abscesses have been reported, probably because in most patients ovarian endometrioma have been surgically removed prior to IVF/ICSI. Patients with endometrioma in situ have been prophylactically treated with antibiotics.

Only a few studies investigated the effect of IVF on endometriosis recurrence rates[22-24]. Benaglia et al.[22] was unable to find an association between number of IVF cycles and endometriosis recurrence and their prospective study showed no consistent risk of IVF on endometriosis-related symptoms[23]. Another method to describe recurrences is by assessing the CERR by using life table analysis, which allows taking into account the variable time of follow up[26]. Overall, the current study showed a CERR of 7.3% at 12 months after IVF. Only the study by D'Hooghe et al.[24] assessed the CERR and reported a CERR of 7.0% at 21 months after IVF. Although the current duration of follow up is shorter, the CERR is probably overestimated, as some patients had intrauterine insemination before IVF, which is associated with higher recurrence rates[24]. Due to the lack of a control group, it is not possible to conclude from these data whether IVF/ICSI in endometriosis patients has an adverse or even protective effect on endometriosis recurrence, as postulated by D'Hooghe et al.[24]. Remarkably, all recurrences were seen in patients treated with long-term pituitary downregulation, which is thought to protect patients from endometriosis recurrence. However, this is probably due to the fact that patients treated with long-term pituitary down-regulation were more frequently diagnosed with more severe forms of endometriosis.

In conclusion, IVF/ICSI in patients with severe endometriosis is a safe procedure. In patients treated with long-term pituitary down-regulation, it seems that ongoing pregnancy rates are diminished after fresh embryo transfer. However, including cryopreserved embryo transfers, long-term pituitary down-regulation is beneficial in achieving an ongoing pregnancy.

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CHAPTER 6

PATIENT SATISFACTION CONCERNING ASSISTED REPRODUCTIVE TECHNOLOGY TREATMENTS IN MODERATE TO SEVERE ENDOMETRIOSIS

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ABSTRACT

A prospective observational cohort study was performed to examine patient satisfaction after one Assisted Reproductive Technology (ART) treatment cycle in moderate to severe endometriosis patients. From May 2012 till September 2013, 25 patients with surgically proven endometriosis stage III-IV were included per group and received intrauterine insemination (IUI), in vitro fertilization (IVF) or IVF preceded by long-term pituitary downregulation (IVF-ultralong). The median patient satisfaction scores were 8.3, 7.9 and 8.0 in patients receiving IUI (n = 22), IVF (n = 24) and IVF-ultralong (n = 23), respectively (p = 0.89). Both deterioration in pain and quality-of-life could not be identified as determinants of decreased patient satisfaction scores. Satisfaction was higher in women receiving their first ART treatment attempt (p = 0.002), after treatment accomplishment (p = 0.04) and after a positive pregnancy test (p = 0.04). A median satisfaction score concerning preceding long-term pituitary down-regulation of 6.1 (IVF-ultralong n = 25, IUI n = 8) was reported. Only three patients would refrain from this preceding therapy in a next treatment attempt. We concluded that patient satisfaction scores were comparable between the three different ART treatments. Since patient satisfaction was in particular dependent on treatment outcomes, it is recommended to compare those three ART treatments in a randomized controlled trial investigating the efficacy, safety and cost-effectiveness.

Keywords: Endometriosis, Pain, Patient satisfaction, IUI, IVF, Quality-of-life

INTRODUCTION

Endometriosis is a benign, estrogen-dependent, gynaecological disease, which is associated with subfertility[1]. Best practice of treating moderate to severe endometriosis associated subfertility is widely debated[2-4]. In vitro fertilization (IVF) is assumed as a successful treatment in moderate to severe endometriosis patients[4]. Long-term pituitary down-regulation with a GnRH agonist for at least 3 months prior to IVF (IVF-ultralong) is recommended, as this was shown to improve clinical pregnancy rates[5,6]. Since a lack of sufficient data exists on efficacy and safety of intra-uterine insemination (IUI) in this group of patients, this treatment option is disputed[4]. However, IUI may be a valuable treatment option, since observational studies reported pregnancy rates of 4–32% per cycle[7–15] and our recently performed retrospective study showed a cumulative ongoing pregnancy rate of 45.8% after six cycles in moderate to severe endometriosis patients who underwent IUI with controlled ovarian hyperstimulation (COH)[16].

Especially in this group of moderate to severe endometriosis patients it is expected that the fulfilment of ART can be complicated due to the severity of endometriosis and endometriosis related medical history. In addition, ART might influence endometriosis pain complaints and quality-of-life, which both are clinically relevant in the ability to continue with ART, and which in turn might be related to the level of patient satisfaction.

Due to the elimination of the ovum pick-up and the requirement of lower dosages of follicle stimulating hormone (FSH), IUI is less invasive compared to IVF. This less invasive treatment option is hypothesized to be associated with higher patient satisfaction scores. Since long-term pituitary down-regulation with a GnRH agonist for at least three months is mostly accompanied with discomfort through side effects[17], IVFultralong is assumed as most burdensome and therefore assumed most negatively correlated with patient satisfaction.

A better understanding of patient satisfaction with respect to the received ART treatment may lead to better counselling and better substantiated choices. Therefore, the aim of our study is to investigate patient satisfaction in moderate to severe endometriosis patients receiving ART treatment.

METHODS

This prospective observational cohort study was performed at the VU University Medical Center, Amsterdam, The Netherlands, from May 2012 to September 2013. Eighty-one patients with surgically proven moderate to severe endometriosis (stage III and IV) receiving ART treatment (IUI, IVF or IVF-ultralong) were asked to participate and 75 patients were subsequently included once they signed up to start their treatment cycle. Six eligible patients refused to participate. Patients could only participate once. Non-Dutch speaking patients and patients receiving donor semen or donor eggs were excluded. This study has been formally exempted from ethical approval granted by the Institutional Review Board of the VU University Medical Center.

Stimulation protocols were performed as previously described[16,18]. In summary, IUI was performed in a natural cycle or with COH (highly purified human menopausal gonadotropin

{Menopur®, Ferring, Copenhagen, Denmark} or recombinant FSH {Gonal F®, Serono, Geneva, Switserland or Puregon®, Organon, Oss, The Netherlands}) started on cycle day (CD) 3. Follicle growth was monitored by transvaginal ultrasound until at least one follicle reached the size of _17 mm. Forty-two hours after injection of 10.000 IU of human chorionic gonadotrophin (hCG) the insemination was performed. Patients receiving IVF, underwent a standard long (n = 16) or short (n = 9) agonist protocol. The long agonist protocol was preceded by the use of oral contraception combined with daily subcutaneous administration of triptoreline (Decapeptyl®, Ferring, Copenhagen, Denmark) starting on CD17. After withdrawal bleeding recombinant FSH was started on CD3. In the short agonist protocol injections of triptoreline were administered from CD2 and recombinant FSH was started on CD3. In patients receiving IVF-ultralong, long-term pituitary down-regulation was performed with Leuprolide 3.75 mg depot injections (Lucrin®, Abbvie, Hoofddorp, The Netherlands) for at least three months. Exactly 28 days after the last injection, daily administration of subcutaneous injections of triptoreline was started and one day later followed by the administration of recombinant FSH. For all treatments, dose of recombinant FSH was determined individually. Follicle growth monitoring, oocyte retrieval, the luteal phase and laboratory's insemination procedure were performed as previously described[19].

The primary outcome was patient satisfaction concerning one ART treatment cycle. Secondary outcomes were patient satisfaction with regard to preceding long-term pituitary down-regulation. Positive pregnancy test (b-hCG45 IU/ml), treatment accomplishment (in IUI defined as performing the insemination; in IVF as execution of the embryo transfer), complications (defined as hospitalization, ovarian hyperstimulation syndrome (OHSS) or infection), alterations in endometriosis pain complaints (i.e. dysmenorrhea, dyschezia, dysuria, dyspareunia and chronic pelvic pain), and health-related-quality-of-life were registered. Health-related-quality-of-life was measured with the Dutch validated Endometriosis-Health-Profile-30 (EHP-30) questionnaire[20]; lower EHP-30 scores reflect a better health status.

The first measurement was performed by LvH/AS directly prior to start of ovarian hyperstimulation. Patients completed the EHP-30 questionnaire and graded the amount of pain complaints on a visual analogue scale (VAS) from 0 (no pain) to 100mm (maximum amount of pain; VAS-pain, presented in decimals). Satisfaction with regard to preceding long-term pituitary downregulation was scored on a VAS-satisfaction ranging from 0 (no satisfaction) to 100mm (fully satisfied)[21] and a short Likert scale questionnaire was completed. Twenty-two days after insemination or oocyte retrieval, a b-hCG blood test was performed. A second measurement was performed approximately one week hereafter by LvH/AS. VAS-pain, VAS-satisfaction and the EHP-30 questionnaire were completed.

The sample size calculation was based on the minimal clinically significant difference (MCSD) of 10mm in VAS satisfaction[21]. To investigate a clinically relevant difference in satisfaction between groups, 22 patients per group were needed (power 90%, a 0.05). With an estimated dropout rate of 10%, the inclusion target was 25 patients per group.

Statistical analysis was performed using SPSS version 20.0 (IBM SPSS, Armonk, NY). Categorical data were expressed as numbers (percentages) and continuous data as medians

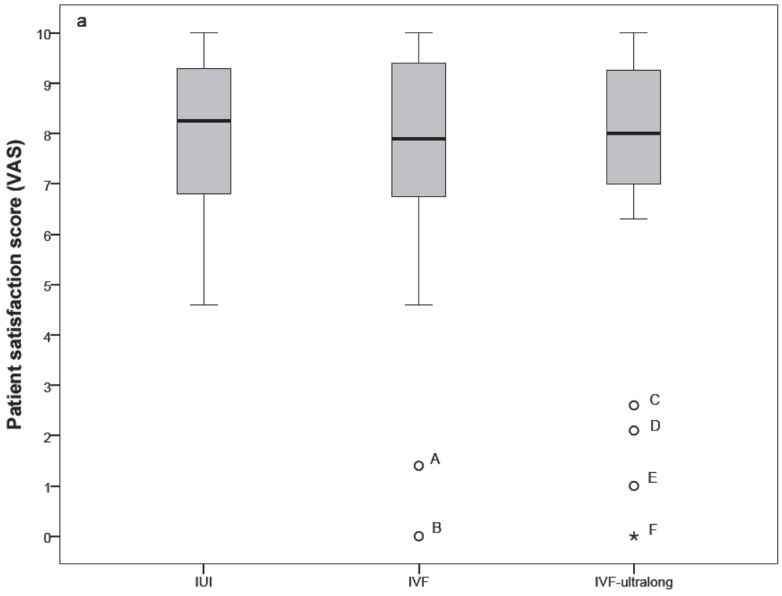
(range). Differences between the groups were calculated with Chi-square, Fishers' exact, Mann–Whitney U and Kruskal–Wallis test. Differences in VAS-pain scores were classified as improved, unchanged and deteriorated by using the MCSD of 10mm[21]. Since VAS-pain-scores of less than 40mm present 'mild pain'[22], the combination of a baseline and follow-up VAS-painscores below 40mm were classified as 'unchanged'. EHP-30 scores were classified as improved, unchanged and deteriorated by using the minimal clinical important difference[23].

RESULTS

Patient characteristics are presented in Table I. Except from the duration of sub-fertility, there are no statistically significant differences between the three ART groups at baseline.

Table I Patient characteristics

	IUI n = 25	**IVF n = 25**	**IVF-ultralong n = 25**	**P-value**
Age	32 [27-40]	34 [28-42]	34 [27-40]	0.11
BMI	23.1 [18.6-30.5]	21.9 [16.8-28.1]	24.5 [19.4-36.8]	0.07
Indication ART				
Endometriosis only	21 (84%)	21 (84%)	19 (76%)	0.81
Including other	4 (16%)	4 (16%)	6 (24%)	
Male factor infertility	1 (4%)	3 (12%)	3 (12%)	
Imminent ovarian failure	2 (8%)	-	2 (8%)	
Polycystic ovary syndrome	1 (4%)	-	1 (4%)	
Non-patent tubes	-	1 (4%)	-	
Etnicity				
Caucasian	16 (64%)	19 (76%)	20 (80%)	0.68
Asian	3 (12%)	5 (20%)	3 (12%)	
Mediterrean	2 (8%)	1 (4%)	-	
Creole	1 (4%)	-	1 (4%)	
Hindu	2 (8%)	-	1 (4%)	
Other	1 (4%)	-	-	
Smoking	3 (12%)	2 (8%)	1 (4%)	0.87
Subfertility (months)	21 [5-53]	37 [4-99]	24 [2-79]	0.02
Primary	15 (60%)	12 (48%)	16 (64%)	0.49
Secondary	10 (40%)	13 (52%)	9 (36%)	
ASRM				
III	7 (28%)	7 (28%)	6 (24%)	1.00
IV	18 (72%)	18 (72%)	19 (76%)	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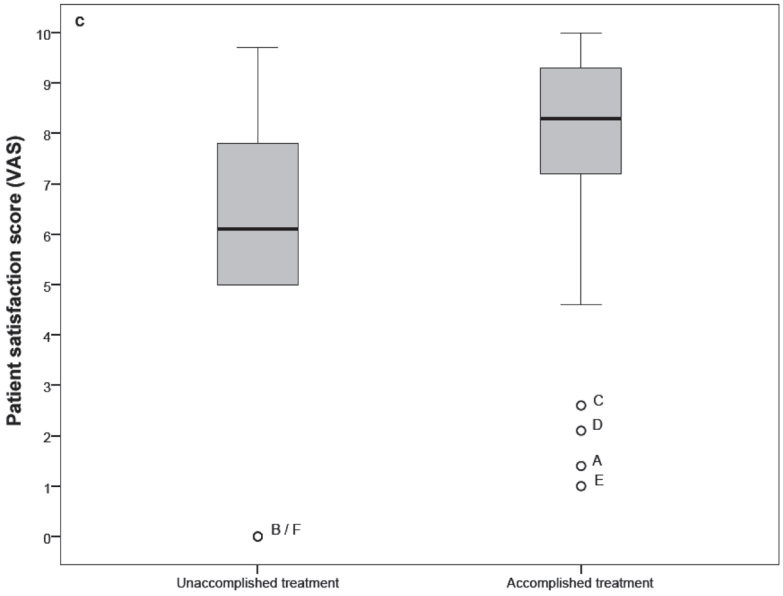
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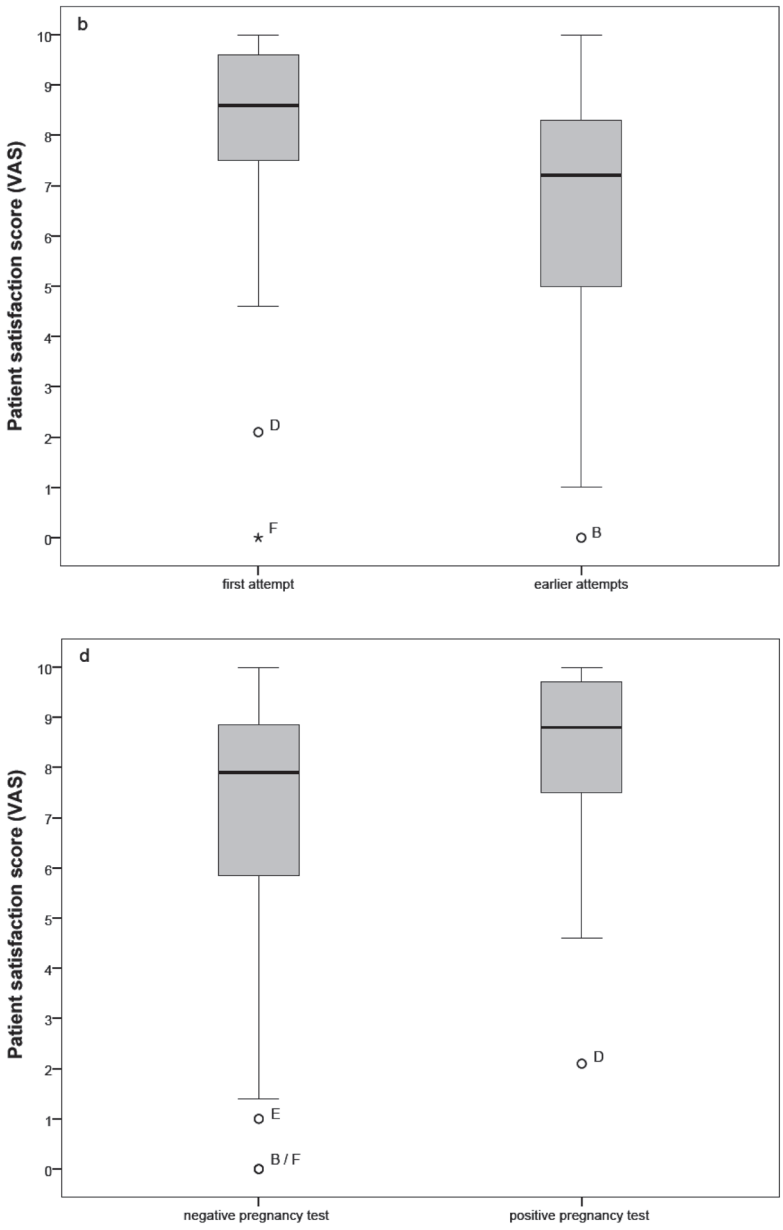

Figure 1 represents patient satisfaction scores of IUI, IVF and IVF-ultralong (a), number of previous treatment attempts (b, $P = 0.002$), the accomplishment of treatment (c, $P = 0.04$) and the outcome of the pregnancy test (d, $P = 0.04$). Circles and stars represent outliers and extreme outliers, respectively. (A) patient with a poor respons (no oocyte pick up carried out), (B) patient without the opportunity to cryopreserve embryos due to low embryo quality scores, (C) patient with a very painful oocyte pick-up procedure, (D) patient with a biochemical pregnancy, (E) patients with one oocyte after ovum pick up, (F) patient without oocytes found after ovum pick-up (an insemination procedure was carried out).

In Table II treatment characteristics and outcomes are listed. Fourteen patients did not accomplish their treatment cycle. Four out of them were lost to follow up. Another two patients were lost to follow-up: one had a missed abortion (IVF-ultralong), and one patient was unwilling to evaluate her IUI treatment attempt. Two complications were reported; one patient was hospitalized for one day due to severe pain after oocyte retrieval and one patient had an increased risk on OHSS (estradiol 19 846 pMol/l, 14 oocytes) and developed complaints (fever, vomiting, diarrhoea), starting one day after ovum pick-up lasting for two days. No embryo transfer was carried out in both patients.

Table II Treatment characteristics and outcomes

	IUI[a]	**IVF**	**IVF-ultralong**	**p-value**
First treatment attempt	16 (64%)	8 (32%)	20 (80%)	0.002
Fertilization protocol				
IVF	-	18 (81.8%)	21 (87.5%)	0.69
ICSI	-	4 (18.2%)	3 (12.5%)	
Oocytes	-	7 [1-22]	8 [0-19]	0.68
Embryos	-	3.5 [0-16]	6 [0-17]	0.22
Cryo preserved embryos	-	2 [0-14]	4 [0-14]	0.23
Uncompleted treatment cycle	5[b] (20%)	6[c] (24%)	3[d] (12%)	0.66
Positive pregnancy test	4 (16%)	10 (40%)	13 (52%)	0.03
Ongoing pregnancy	2 (8%)	6 (24%)	8 (32%)	0.11

[a]IUI in natural cycle n = 11, IUI with COH n = 14, preceding long-term pituitary down-regulation n = 8.
[b] Due to premature ovulation (n=2), low semen quality (n=2) and personal reasons (n=1)
[c] Due to poor respons (n=3), total fertilization failure (n=2) and increased risk on ovarian hyperstimulation syndrome (n=1)
[d] Due to no oocytes found after ovum pick-up (n=1), total fertilization failure (n=1) and no embryo transfer due to severe pain after ovum pick-up (n=1)

The median patient satisfaction scores concerning the ART treatment attempts were 8.3, 7.9 and 8.0 in patients who received IUI, IVF and IVF-ultralong, respectively (p = 0.89; Figure 1). Patient satisfaction scores were significantly higher in women receiving their first treatment attempt (p = 0.002), after treatment accomplishment (p = 0.04) and a positive pregnancy test (p = 0.04; Figure 1). Deterioration in VAS-pain scores and EHP-30-scores could not be identified as determinants of decreased patient satisfaction scores.

The number of women with an improvement or deterioration of VAS pain scores were as follows: dysmenorrhea 7 (22.6%) and 8 (25.8%), dyschezia 8 (11.8%) and 9 (13.2%), dysuria 4 (5.8%) and 4 (5.8%), dyspareunia 7 (14.3%) and 5 (10.2%), and chronic pelvic pain 9 (13.0%) and 10 (14.5%), respectively. Differences of VAS pain scores are illustrated in Figure 2 for the three different ART treatments.

Differences in EHP-30-scores for the three ART treatments are illustrated in Figure 3 and 4.

The median patient satisfaction score concerning preceding long-term pituitary down-regulation with a GnRH agonist was 6.1 (0.7–9.3). Three patients (9%) would refrain from this preceding therapy in a next ART treatment attempt. Twenty-one (64%) patients experienced a decline of endometriosis pain complaints and 30 (91%) patients suffered from side-effects.

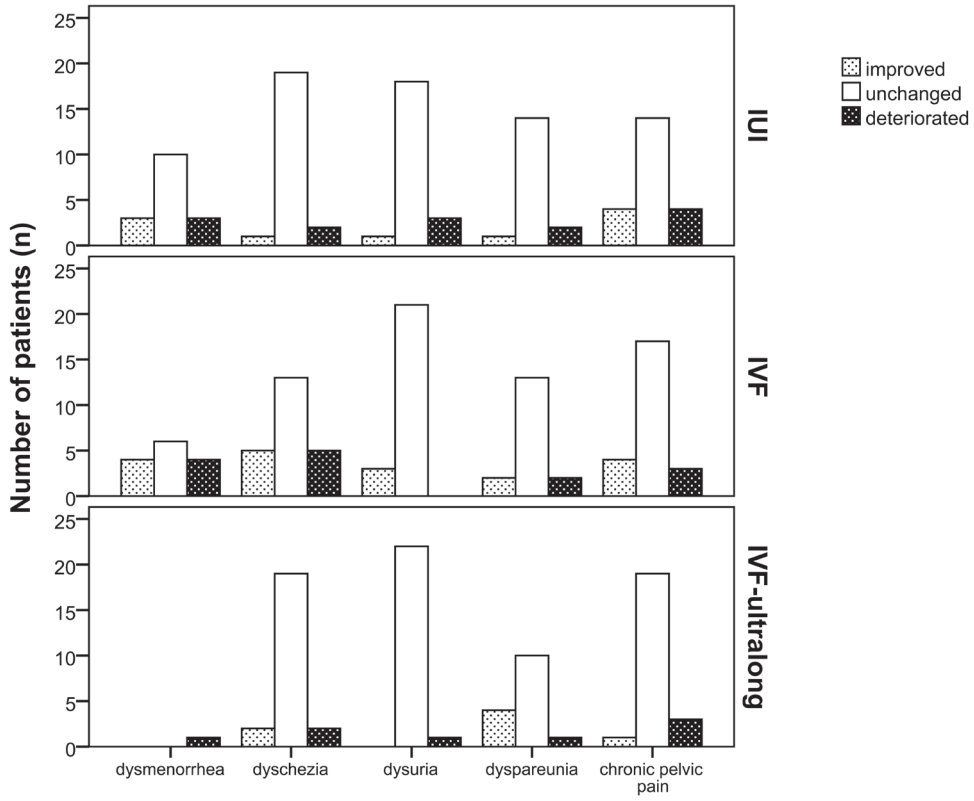

Figure 2 illustrates the difference in endometriosis complaints before and after ART treatment for the three different ART treatments. There were no significant differences.

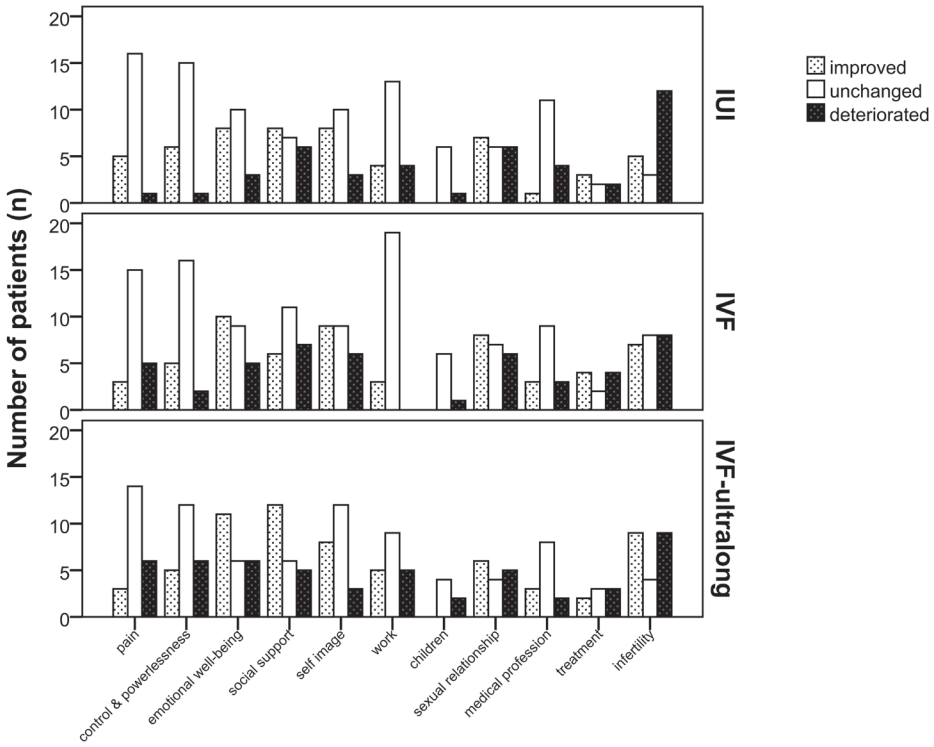

Figure 3 illustrates the difference in all EHP-30 scores before and after ART treatment for the three different ART treatments.

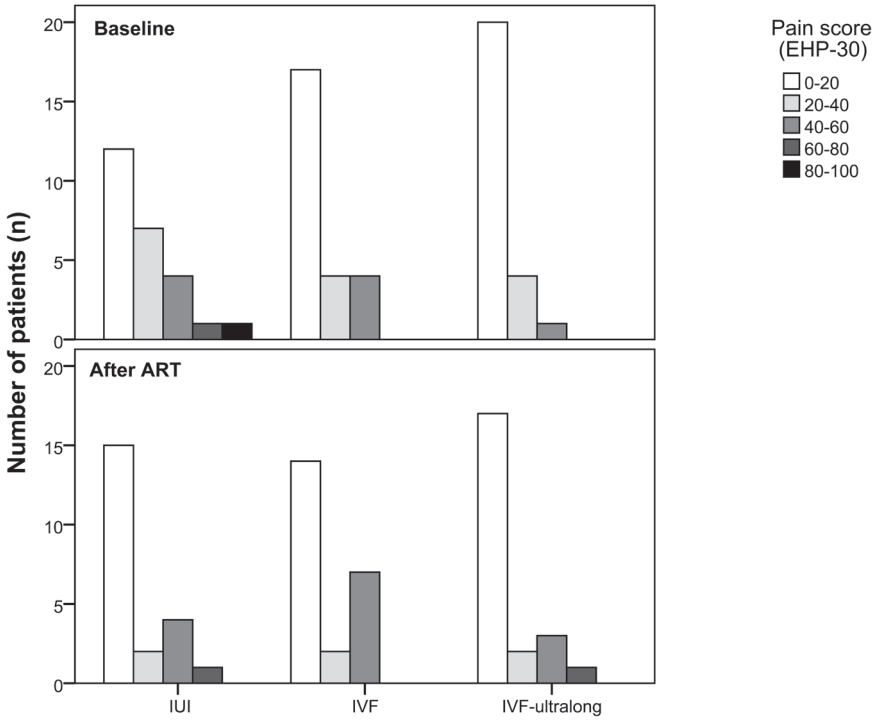

Figure 4 illustrates the difference in EHP-30 Pain scores at baseline and after ART treatment for the three different ART treatments.

DISCUSSION

This prospective observational cohort study in moderate to severe endometriosis patients receiving ART treatment showed that patient satisfaction scores were comparable between three different ART treatments.

Although treatment invasiveness did not affect satisfaction, treatment accomplishment and a positive pregnancy test did. In a population of infertile patients seeking ART treatment, conceiving[24] and the hope to conceive soon after treatment are important factors influencing treatment satisfaction. A review of women's emotional adjustment to IVF showed higher anxiety and depression scores after an unsuccessful IVF treatment[25], which were shown to be related to lower patient satisfaction scores in an outpatient population[26]. Similarly we observed a lower satisfaction score after an unaccomplished treatment cycle and a lower score in patients with previous treatment attempts. Both factors are indirectly related to the ability to conceive in the near future.

Pain severity was reported to be strongly related to patient satisfaction[26]. In contrast, in our study the deterioration of endometriosis complaints could not be identified to correlate with diminished patient satisfaction scores. This can be the result of a relatively low number of patients with a deterioration of endometriosis pain complaints. Apparently, the direct effect of ART on endometriosis pain complaints after a short duration of follow-up is low.

No significant differences were found in VAS-pain-scores between the three treatment groups. Due to our follow-up of 1 month, it is difficult to compare our results with other studies with a longer follow-up duration[27–29] concluding that endometriosis recurrence is not influenced by IVF[27,28] or COH[29]. However, d'Hooghe et al. reported a 1-year-cumulative endometriosis recurrence rate (CERR) after IUI of 70% compared to 7% after IVF[30]. This is in line with our recently performed retrospective study in moderate to severe endometriosis patients showing a 1-year-CERR of 72.3% after IUI with COH[16]. Still, prospective data with a longer follow-up including a control group receiving no ART are needed to investigate the effect of ART on endometriosis recurrence taking into account relevant confounding factors.

Quality-of-life was measured with the Dutch EHP-30 questionnaire. This outcome measure was only presented as descriptive data for the three different ART treatments, since the number of patients included was too small to perform statistical comparative analysis (Figure 3). Our study was conducted to evaluate the level of patient satisfaction in three different ART treatments. To investigate differences in EHP-30 scores between different treatment groups more patients need to be included, which highly depends on the level of responsiveness[31].

Although the Dutch EHP-30 is a validated questionnaire[20,23] difficulties have been noticed in completing this questionnaire in our study. First, patients receiving long-term pituitary down-regulation experienced problems as side effects were frequently not considered as endometriosis related complaints. As van den Burgt et al.[20] already discussed it might be better to start all questions with 'how often did you...' instead of 'because of your endometriosis, how often did you...' to make sure that all patients complaints are registered. Second, many patients did not complete the E section, which questions about current treatment for endometriosis.

Therefore, it can be concluded that ART is not seen as endometriosis treatment. Overall our patients had lower EHP-30-pain-scores (Figure 4) compared to the scores published by van de Burgt et al.[20,23], possibly because our patients were required to have controlled disease before entering ART. Since validation was performed by sending questionnaires to patients with all stages of endometriosis by van de Burgt et al.[20,23] this may have led to a selection bias as patients with (pain) complaints are more likely to complete the questionnaire. Therefore, before structurally using the EHP-30 in endometriosis patients receiving ART treatment in future studies, we recommend to adapt and validate this adapted questionnaire.

Due to a spectrum of frequently reported side-effects[17], clinicians are often reluctant to offer long-term pituitary downregulation prior to ART. Most patients however, reported to be motivated to use this treatment strategy prior to a next attempt, despite side-effects. Apparently, women take these side-effects for granted for a certain period of time, since the treatment strategy increases the chance on pregnancy[5,6].

The ongoing pregnancy rates are similar to our earlier published ongoing pregnancy rates after IVF[18] and IUI[16]. Although the ongoing pregnancy rate after one IUI treatment is remarkably lower than after one IVF treatment attempt, an earlier published study showed that in a population of subfertile patients four IUI treatments result in similar pregnancy rates as one IVF treatment[32]. To our knowledge no such data exists in moderate to severe endometriosis patients.

In conclusion, patient satisfaction scores were comparable between the three ART treatments. Despite low satisfaction concerning preceding long-term pituitary down-regulation, most patients were motivated to use this preceding therapy in a next treatment attempt. Since patient satisfaction scores were in particular dependent on treatment outcomes (i.e. conceiving and the ability to conceive in the near future), it is recommended to compare those three ART treatments in a randomized controlled trial investigating the efficacy, safety and cost-effectiveness.

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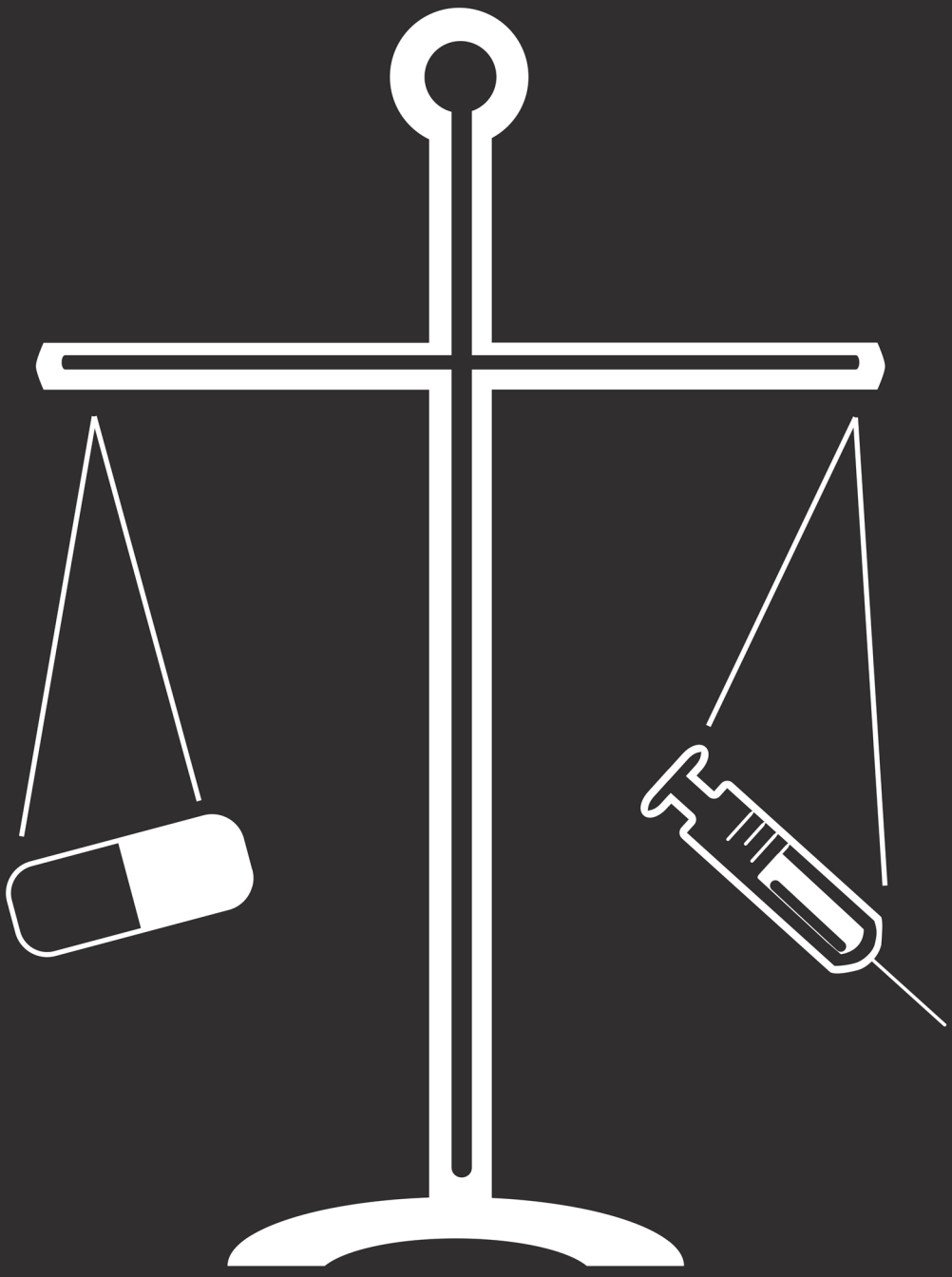

CHAPTER 7

CONTINUOUS ORAL CONTRACEPTIVES VERSUS LONG-TERM PITUITARY DESENSITIZATION PRIOR TO IVF/ICSI IN MODERATE TO SEVERE ENDOMETRIOSIS: STUDY PROTOCOL OF A NON-INFERIORITY RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Study questions: The primary objective is to investigate if continuous use of oral contraceptives is non-inferior compared to long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI in patients with moderate to severe endometriosis with regard to treatment efficacy. Secondary objectives concern treatment safety and cost-effectiveness.

What is known already: Long-term pituitary desensitization with a GnRH agonist for 3-6 months prior to IVF/ICSI improves clinical pregnancy rates in women suffering from endometriosis. However, discussion about this treatment strategy exists because of its uncomfortable side effects. Alternatively, IVF/ICSI pre-treatment with continuously administered oral contraceptives may offer fewer side-effects, lower (in)direct costs, as well as encouraging IVF outcomes in women with endometriosis. To date, these two different IVF/ICSI pre-treatment strategies in women with endometriosis have not been directly compared.

Study design, size, duration: An open-label, parallel two-arm randomized controlled multicenter trial is planned, including patients with moderate to severe endometriosis. To demonstrate an absolute difference of 13% (delta of 10% with non-inferiority margin of 3%) with a power of 80% 137 patients per group are sufficient. Taking into account a withdrawal of patients of 10% and a cancelation rate of embryo transfer after ovum pick up of 10% (for instance due to fertilization failure), the sample size calculation is rounded off to 165 patients per group; 330 patients in total will be included. After informed consent, eligible patients will be randomly allocated to the intervention or reference group by using web based block randomization stratified per center. Study inclusion is expected to be complete in 3-5 years.

Participants/materials, setting, methods: The research population consists of patients with moderate to severe endometriosis (ASRM III/IV) who are scheduled for their first, second or third IVF/ICSI treatment attempt. Women aged over 41 years, younger than 18 years, with a known contraindication for the use of oral contraceptives and/or GnRH agonists or with severe male factor infertility will be excluded from participation. After informed consent patients are allocated to the intervention group (one-phase oral contraceptive continuously during three subsequent months) or the reference group (three Leuprorelin 3.75mg i.m./s.c. depot injections during three subsequent months). Tibolon 2,5mg can be given daily as add-back therapy in the reference group. After 3 months of pre-treatment the IVF/ICSI stimulation phase will be started. The primary outcome is live birth rate after fresh embryo transfer. Secondary outcomes are cumulative live birth rate after one IVF/ICSI treatment cycle (including fresh and frozen embryo transfers up to 15 months after randomization), ongoing pregnancy rate and time to pregnancy. In addition, treatment outcome parameters, adverse events, side-effects during the first 3 months, complications, recurrence of endometriosis (complaints), quality of life, patient preferences, safety and costs effectiveness will be reported. Measurements will be performed at baseline and at 3, 6, 9, 12 and 15 months after randomization.

Study funding/competing interest(s): All authors have no conflict of interest related to this manuscript. The department of reproductive medicine of the Amsterdam AMC location VUmc has received several research and educational grants from Guerbet, Merck and Ferring not related to the submitted work.

Trial registration number: The trial is registered as the COPIE trial (Continuous use of Oral contraceptives as an alternative for long-term Pituitary desensitization with a GnRH agonist prior to IVF/ICSI in Endometriosis patients) in the Dutch Trial Register (Ref. No. NTR6357, http://www.trialregister.nl).

Trial registration date: 16 March 2017

Date of first patient's enrolment: Enrolment of patients started at November 2018.

Key words: Endometriosis, Assisted Reproduction, IVF/ICSI outcome, Pregnancy, Cost Effectiveness, Infertility, GnRH agonist

INTRODUCTION

Endometriosis is in up to 50% of patients associated with subfertility[1]. In patients with severe endometriosis, subfertility is presumed to be based on a distortion of the pelvic anatomy, a hostile peritoneal environment, a decreased oocyte quality, a diminished ovarian reserve (due to the presence of endometrioma or prior ovarian surgery) and/or an impaired implantation due to an altered endometrial receptivity[2,3].

Especially in cases of tubal dysfunction, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) are stated as appropriate treatments for subfertility in endometriosis patients by the European Society of Human Reproduction and Embryology (ESHRE) guideline[4]. However, inferior success rates are especially described in patients with moderate to severe endometriosis (American Society for Reproductive Medicine (ASRM) stage III and IV) and in patients with endometrioma(s)[5-8].

To improve pregnancy rates after IVF/ICSI, it is recommended to precede IVF/ICSI by long-term pituitary desensitization with a GnRH agonist for 3-6 months, since this is shown to improve clinical pregnancy rates (CPR)[9-17]. However, the mechanism responsible for this increase in clinical pregnancy rate is not yet clarified and more research is needed.

Furthermore, as both the Cochrane and ESHRE recommendations are based upon only three small randomized studies (N=165)[12,15,17], executed in a different IVF/ICSI treatment era in which more aggressive stimulation was used and multiple embryos were transferred, debate about this treatment strategy exists. Additionally, different study-populations with varying degrees of endometriosis (ASRM stage II – IV) were included in these trials[12,15,17], which could have influenced the results.

It is also postulated that the use of a long-term pituitary desensitization regime may lower ovarian response to ovarian stimulation, especially in poor responders[18]. In addition, uncomfortable side effects, such as vasomotor instability, are often reported by patients. These side effects might result in a restrained attitude in prescribing this treatment strategy for a longer period of time, although add-back therapy is available to diminish these vasomotor side-effects[19,20]. On the other hand, patients who used long-term GnRH agonists prior to IVF reported to be motivated to use this treatment strategy again, despite side-effects, in a next IVF/ICSI attempt[21].

Alternatively, the effect of continued use of oral contraceptives (OCs) for 6-8 weeks prior to IVF/ICSI has been investigated[22]. Non-randomized data show that this treatment is favorable in patients with severe endometriosis undergoing IVF/ICSI, as clinical pregnancy rates were higher compared to endometriosis patient treated without OCs and comparable to that of control patients without endometriosis[22]. However, a randomized comparison between continuous use of OCs and long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI in patients with endometriosis has not yet been made.

The daily uncomfortable vasomotor side-effects that are associated with a GnRH agonist treatment without add-back therapy, are negatively associated with work-ability and increase

the risk of sickness absence[23-26]. It is currently unknown if this can be positively influenced by using add-back therapy.

Although the tolerability of OC is higher compared to GnRH agonists (with or without add-back therapy)[27], its use is known to be often associated with migraine, weight gain, depression and with a higher risk on venous and arterial thromboembolism.[28,29] By using OC continuously, a reduction in monthly blood loss is expected combined with a decrese in dysmenorrhea compared to cyclic use of OCs. However, this seems to be related with a higher risk on spotting.[28]

Due to potentially fewer side effects, improvement of societal productivity can be expected in women receiving continuous OC treatment instead of GnRH agonist treatment. Moreover, since GnRH agonists are over 40 times more expensive than OCs, a reduction in directs costs of medication used in IVF/ICSI can be achieved by prolonged use of OCs prior to IVF/ICSI treatment.

Therefore, this study is conducted to investigate if continuous use of OCs is non-inferior to long-term pituitary desensitization with a GnRH agonist (as standard care) combined with add-back therapy (if necessacy) prior to IVF/ICSI treatment, with regard to treatment efficacy, safety and cost-effectiveness.

OUTCOMES

The primary outcome is live birth rate after fresh embryo transfer (ET). Secondary outcomes are listed in Table I. Measurements will be performed at baseline (t0), three (t1), six (t2), nine (t3), twelve (t4) and fifteen (t5) months after randomization.

MATERIALS AND METHODS

The study will have a parallel two-arm randomized controlled non-inferiority design and will be open-label. Recruitment of patients will be performed in two tertiary care centres in the Netherlands. The research population will consist of women with endometriosis ASRM Stage III or IV who are scheduled for their first, second or third IVF/ICSI treatment. The diagnosis of endometriosis has to be surgically confirmed or likely to be present based on transvaginal sonography (TVS) or magnetic resonance imaging (MRI) findings, including the presence of uni- or bilateral ovarian endometrioma and deep endometriosis. For diagnosing endometrial cysts and/or deep endometriosis diagnostic classification systems for imaging modalities like sonography and/or MRI do not exist, although guidelines help clinicians in describing sonographic findings in a structural way.[30] Clinics involved in this study will use the systematic approach for sonography as presented by the IDEA group.[30] Sonography and MRI are both shown to be accurate enough to diagnose endometrial cysts in the ovaries and deep endometriosis in the lower bowel and other pelvic structures.[31] Also women with surgically treated (i.e. remediated) moderate to severe endometriosis will be included. Excluded

from participation will be women aged under 18 and over 41 years, women with a known contraindication for the use of OCs (history of venous thromboembolism (VTE), hepatic adenoma(s), positive family history for VTE and/or known thrombophilic abnormalities[32]) or for the use of GnRH agonists (severe side-effects and/or allergic reaction to GnRH agonists), pregnant women, women with a malignancy or severe male factor infertility (i.e. azoospermia). Non-Dutch speaking women will be excluded. Women can only participate once in the study.

Table I Secondary outcomes

Clinical	Cumulative live birth rate after one IVF/ICSI treatment *(number of live births per initiated cycle, including fresh and frozen ETs up to 15 months after randomization)*
	Ongoing pregnancy rate *(positive heart action, confirmed ≥ 10 weeks after ET by TVS)*
	Cumulative ongoing pregnancy rate (*including fresh and frozen ETs up to 15 months after randomization)*
	Time to pregnancy *(months)*
Treatment	Follicular development *(follicle size distribution at the time of hCG administration)*
	Total dose and duration of gonadotrophin treatment
	Number of oocytes and (top-quality) embryos *(morphological assessment of embryos: combining number of blastomeres and percentage of fragmentation)*
	Fertilization rate *(number of fertilized oocytes per number of retrieved oocytes)*
	Implantation rate *(number of embryonic sacs observed by TVS per number of transferred embryos)*
	Multiple pregnancy rate, miscarriage rate, ectopic pregnancy rate
	Endometrial thickness (*measured by TVS at the time of hCG administration)*
	Pain during oocyte pick up *(VAS 0-10 cm)*
	Adverse events, complications, side-effects
	Cancellation rate
Endometriosis	Recurrence of endometriosis complaints within 15 months after randomization
	Need for surgical/medical treatment within 15 months after randomization
	Quality of life *(EHP-30)*
	Patients' preference of treatment and treatment-satisfaction *(VAS 0-10 cm)*
Cost-effectiveness and BIA	Direct and indirect costs within 15 months after randomization (*measured by the iMCQ and iPCQ validated questionnaires).*
Factors to be taken into account	Patient characteristics (age; BMI; smoking; alcohol use; hormonal treatment prior to start of study; duration until latest therapeutic surgery prior to start of study; prior surgical procedure; complete or incomplete remediation of endometriosis with prior surgery; presence of endometrioma and/or deep endometriosis on ultrasound and/or MRI; presence of adhaesions on ultrasound and/or MRI and/or during previous pelvic surgery; presence of adenomyosis diagnosed conform the MUSA criteria)
	Treatment characteristics (first/second/third IVF/ICSI attempt; other indications for IVF/ICSI)

IVF = In Vitro Fertilization; ICSI = Intracytoplasmic Sperm Injection; EHP-30 = Endometriosis Health Profile 30; ET= Embryo Transfer; hCG = human Chorionic Gonadotrophin; TVS = Transvaginal Sonography; VAS = Visual Analogue Scale; BIA = budget impact analysis; iMCQ = iMTA Medical Consumption Questionnaire; iPCQ = iMTA Productivity Cost Questionnaire; iMTA = institute for Medical Technology Assessment; MUSA = Morphological Uterus Sonographic Assessment[49]

The study schedule is presented in the Consort Flow Diagram (Figure 1). Before study entry, women will be screened for eligibility. Women who comply with all selection criteria will be informed about the trial during a visit at the outpatient clinic or IVF center. Information will be handed out by a gynecologist, resident, fertility physician or research nurse offering a reflection time of minimally 7 days. Informed consent must be signed before any study-related procedures can be carried out. After informed consent is obtained, women will be randomly assigned to the intervention group (one-phase oral contraceptive continuously administered during three subsequent months) or the reference group (three GnRH agonist depot injections during three subsequent months combined with add back therapy if necessay). Randomization will be performed via web based randomly permuted blocks with variable, randomly chosen sizes (4-6-8 patients) stratified by participating center. Drop outs after randomization will not be replaced.

After randomization, at baseline (t0) a TVS will be performed, to determine the presence of endometrioma and signs of deep endometriosis. Baseline characteristics and medical history will be listed in the case report file (CRF). Participants will be asked to fill in different questionnaires at baseline (t0), three (t1), six (t2), nine (t3), twelve (t4) and fifteen (t5) months after randomization. These validated questionnaires measure quality of life of women with endometriosis (Endometriosis Health Profile 30 (EHP-30)[33]), direct and indirect costs (the Medical consumption Questionnaire (iMCQ)[34] and the Productivity Cost Questionnaire (iPCQ)[35]).During the first 3 months of treatment medical consultation, side-effects and absence of work will also be recorded in a patients' diary.

All women in the intervention group will receive one-phase oral contraceptives (sub-50 OCs) continuously administered during three subsequent months (i.e. 3x28 days). Preferably ethinylestradiol/levonorgestrel 30/150µg is prescribed. Since a lot of patients already use specific types of OCs, other one-phase sub-50 OCs will be accepted as well. Women will be instructed to contact the IVF department on the first day of bleeding after stopping the oral contraceptives (after 3 months) treatment. On day two of the withdrawal bleeding women will visit the IVF center and Triptorelin "Decapeptyl" s.c. will be started for suppression of the luteinizing hormone (LH) peak. One day later ovarian stimulation will be started with subcutaneously injected gonadotrophins (follicle stimulation hormone (FSH)) in an individually determined dosage.

All women in the reference group will receive three Leuprorelin "Lucrin" 3.75mg i.m. or s.c. depot injections during three subsequent months. During these months Tibolon "Livial" 2,5mg tablets can be given daily as add-back therapy. Women will have an appointment at the IVF department exactly 28 days after the last Leuprorelin injection. According to protocol, daily administration of Triptorelin "Decapeptyl" s.c. will then be started. One day later ovarian stimulation will be started with subcutaneously injected gonadotrophins (FSH) in an individually determined dosage.

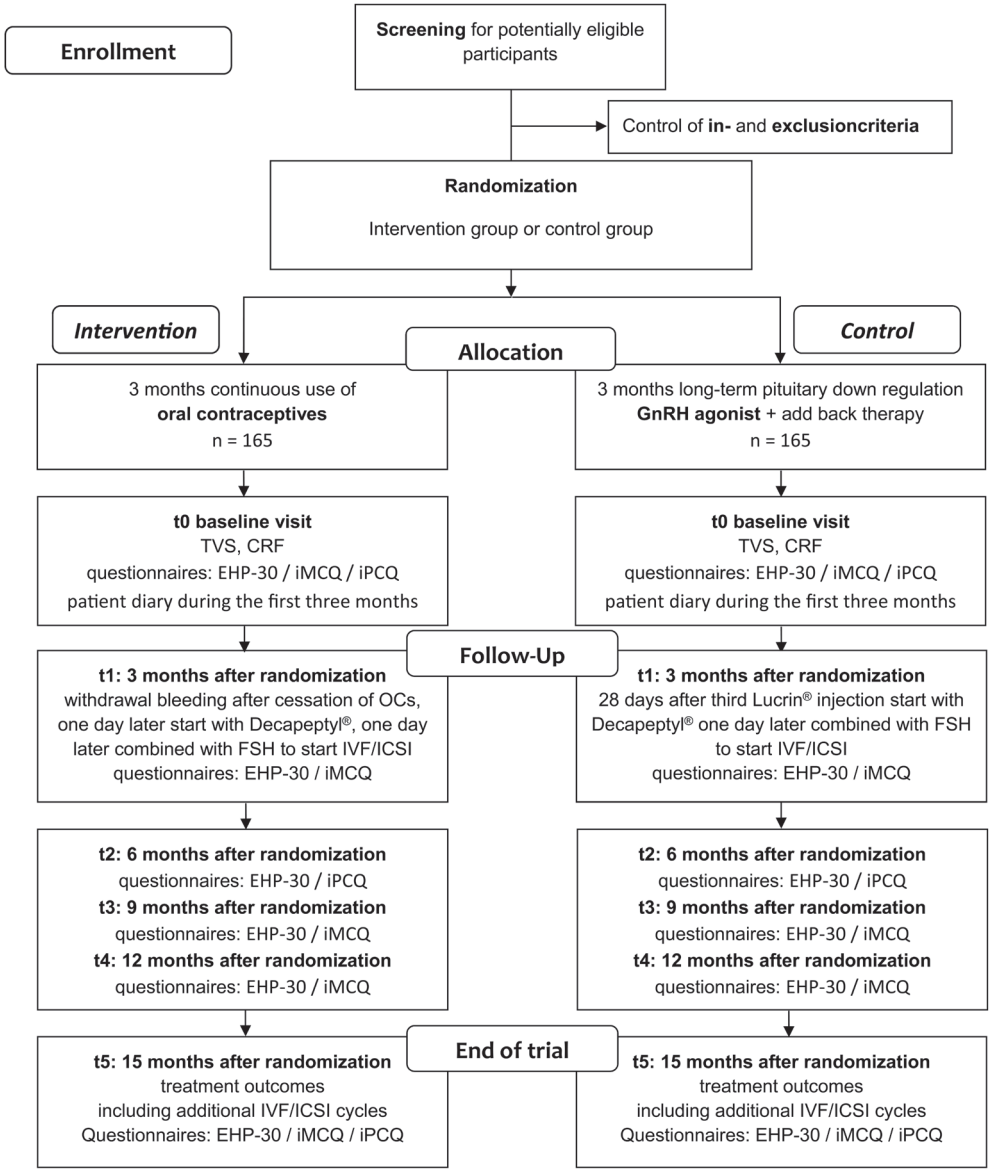

Figure 1. Consort Flow Diagram and study schedule. CRF = case record form; EHP-30 = Endometriosis Health Profile 30; GnRH = gonadotropin releasing hormone; ICSI = intracytoplasmic sperm injection; iMCQ = iMTA Medical Consumption Questionnaire; iMTA = institute for Medical Technology Assessment; iPCQ = iMTA Productivity Cost Questionnaire; IVF = in vitro fertilization; n = number; t = time point; TVS = transvaginal sonography

When the ovarian stimulation cycle is started women in both groups will be monitored routinely by standard (local) protocols, depending on follicle growth monitored by TVS. FSH dose adjustments during the stimulation cycle are allowed. Monitoring will be continued until the criteria for human chorionic gonadotrophin (hCG) injection are met (three or more follicles of 17mm), to achieve final oocyte maturation. Oocyte retrieval will be carried out 34-37 h after hCG injection. Embryos will be cultured and incubated. Embryos will be morphologically assessed by combining the highest number of blastomeres and the percentage of fragmentation. The embryo with the highest number of blastocysts and the least fragmentation rate will be transferred 48-80 h after oocyte retrieval. The number of morphologic top-quality embryos (TQE) will be assessed and elective single embryo transfer (eSET) will be performed in the first IVF/ICSI cycle and $\leq$2 embryos will be selected for transfer to the uterus in the second or third cycle of IVF/ICSI. Remaining embryos of good quality will be cryopreserved according to local protocols. Luteal support and pregnancy testing will be accomplished by local protocols.

All additional IVF/ICSI treatment cycles (including subsequent pregnancies) up to 15 months after randomization (t5) will be registered in both intervention and control groups.

Sample size

We performed a retrospective study[36] regarding the efficacy and safety of IVF/ICSI in patients with moderate to severe endometriosis, showing ongoing pregnancy rates of 20% after fresh embryo transfer. De Ziegler *et al.*[22] reported clinical pregnancy rates of almost 40% in patients with moderate to severe endometriosis with or without the presence of an endometrioma during IVF with OCs as a pretreatment. Taking into account a miscarriage rate of 20%[37], an ongoing pregnancy rate of 30% can be expected after continuous use of OCs. Therefore, assuming that the ongoing pregnancy rate in patients treated with long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI is 20% and in patients treated with continuous use of OCs prior to IVF/ICSI is 30%, 137 patients per group are sufficient to demonstrate an absolute difference of 13% (i.e. a non-inferiority margin of 3%) with an 80% power that the live birth rate in the continuous use of OCs group is not inferior to the live birth rate in the long-term-pituitary desensitization with a GnRH agonists group. The non-inferiority margin of 3% is arbitrary chosen. Justification can be arranged by performing a discrete choice experiment taking into accout efficacy, safety and burden of treatment. For instance, an earlier published trial concerning patients' preferences regarding GnRH agonist or antagonists in IVF/ICSI showed that with a trade-off of 2.0% increase in pregnancy rate patients would switch from antagonists to GnRH agonists.[38] Therefore, taking into account more benefits of oral contraceptives over GnRH agonists, a non-inferiority margin of 3% appears to be justified. The significance level is set at α 0.05, one sided. To take into account loss to follow-up due to withdrawal of patients of 10% and a cancelation rate of embryo transfer (for instance due to fertilization failure) the sample size is rounded off to 165 patients per group. In total, 330 patients need to be included in this study.

Statistical analysis

SPSS will be used for statistical analysis. Continuous data will be presented as means and standard deviations (normally distributed data) or medians and ranges (non-parametrical data). In case of dichotomous or categorical data numbers with percentages will be used.

The primary analysis (live birth rate after fresh embryo transfer) will be performed according to the intention to treat (ITT) principle including all randomized patients. The effectiveness of the interventional treatment versus the reference treatment will be expressed as a rate for live birth with corresponding 95% confidence interval. We will consider the intervention inferior when the absolute difference in success rate exceeds 13% compared to the expected success rate of 30% - this is comparable to a relative difference of 0.17/0.30 is 0.57. If the left border of the 95% CI of the RR does not exceed the pre-defined threshold of 0.57 for inferiority we will consider the intervention to be non-inferior to the reference treatment. A secondary analysis for effectiveness will be done on the per-protocol (PP) population. Non-inferiority of the intervention is stated if non-inferiority is shown in both the ITT and PP population.

All secondary outcomes will be compared in both the ITT and PP analysis. The live birth rates in both groups will be compared using Kaplan-Meier analysis. Dichotomous and categorical data will be analyzed using either Fisher Exact or chi-square as appropriate. For continuous outcomes, the confidence interval will be based on (the Welch version of) the t-test if the observations are normally distributed. If continuous outcomes are non-normally distributed, the Mann-Whitney-U test will be employed. A probability (P) of less than 0.05 will be considered statistically significant. Because of the non-inferiority design of this study, for a better interpretation of the findings, confidence intervals around point estimates will also be provided.

An economic evaluation will be performed alongside the randomized controlled trial from a societal and a health care perspective perspective according to Dutch guidelines with a time horizon of 15 months after randomization (i.e. 12 months after start of hormonal stimulation for IVF/ICSI treatment).[39]

Cost categories that will be included are: 1) healthcare costs (primary and secondary care, complementary care and home care); 2) lost productivity costs (absenteeism from paid and unpaid work, and presenteeism); and 3) patient costs (informal care and other care services paid for by patients themselves). Valuation will be done according to Dutch costing guidelines[40]. For the valuation of health care utilization, lost productivity and informal care Dutch standard costs will be used. Medication use will be valued using prices of the Royal Dutch Society for Pharmacy. Patient and family costs other than informal care will be valued using self-reported prices. For the valuation of absenteeism from paid work, the friction cost approach will be used. To document absence from paid work the iPCQ[35] will be used at t0, t2 and t5. Besides, absence of work will be evaluated with a patient diary during the first 3 months of treatment.

The economic evaluation will be analysed by the ITT principle. Missing cost and effect data will be imputed using multiple imputation according to the MICE algorithm[41]. Rubin's rules will be used to pool the results from the different multiply imputed datasets. Multiple regression analyses will be performed to estimate cost and effect differences between OC pre-treatment

and the reference treatment of long-term pituitary desensitization with a GnRH agonist, and adjusted for confounders. Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in the mean total costs by the difference in mean effect between the two groups. Bias-corrected and accelerated bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around the cost differences and statistical uncertainty surrounding the ICERs. Cost-effectiveness acceptability curves will also be estimated for a range of different ceiling ratios, thereby showing decision uncertainty.[42]

In sensitivity analyses we will evaluate the effect of 50% higher or lower endometriosis-related complaints and/or side effects requiring surgery.

A budget impact analysis (BIA) is planned to be performed. The time horizon for the BIA will be 15 months after randomization up to the birth of a child. For our final BIA we will evaluate (I) a scenario where OCs will be implemented in all cases, (II) a scenario where OCs will be implemented in 70% of the cases, and (III) sensitivity analyses on productivity loss.

Data management and monitoring

The datasets generated or analyzed during the current study will be available from the corresponding author on reasonable request. An interim analysis for efficacy will not be performed. All Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the Medical Ethics Committee (METc). All Adverse Events (AEs) will be recorded and followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. An annual safety report will be send to the accredited METc and the competent authority. A Data Safety Monitoring Board (DSMB) will not be installed since all medication used in this study is registered for the given indication and used in clinical practice for years.

Ethical approval

This study is approved by the National Central Committee on Research involving Human Subjects (CCMO – NL 59874.026.16) and by the METc of the VU University Medical Center (Ref. No. 2016.570). The trial is registered as the COPIE trial (Continuous use of Oral contraceptives as an alternative for long-term Pituitary desensitization with a GnRH agonist prior to IVF/ICSI in Endometriosis patients) in the Dutch Trial Register (Ref. No. NTR6357, http://www.trialregister.nl). From all participants written informed consent will be obtained before they will be enrolled in the study.

DISCUSSION

In women with moderate to severe endometriosis, IVF/ICSI treatment is frequently applied to overcome endometriosis-associated infertility[43]. This randomized controlled trial is the first to investigate the non-inferiority and cost-effectiveness of continuous use of OCs compared to long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI treatment in women with endometriosis ASRM Stage III/IV. An IVF/ICSI treatment strategy with continuous use of OCs holds promise to be more patient friendly as well as cost-effective compared with long-term pituitary desensitization with a GnRH agonist. To our knowledge there are currently no other (registered) ongoing trials that evaluate both treatment regimens.

The COPIE trial is an adequately powered trial. Since a new treatment regime (OCs) will be compared with the currently used standard treatment (GnRH agonist) a non-inferiority design is appropriate[44]. In case of a superiority design, a larger sample size (i.e. 650 women in total) would be needed, but this would not necessarily lead to different conclusions. If OC prior to IVF/ICSI is non-inferior, the current standard can be replaced and less women have to experience the discomforts that are related to the use of a GnRH agonist.

Due to the different application forms of GnRH agonist (subcutaneously or intramuscularly administered) and OCs (orally administered) the study will be open-labelled. This may influence the outcomes reported by the patient, like quality of life and the experienced side-effects of both treatment regimens, but we do not expect the primary outcome to be influenced.

The risk of bias is reduced by random allocation of patients to the intervention or control group. Block-randomization, stratified for each participating centre, will be web based through which chance of allocation bias will be reduced.

To our best knowledge, it is unknown if add-back therapy has an effect on pregnancy rates after IVF/ICSI. Since the duration of pituitary desensitization is limited to 3 months, it is not obligatory to start with add-back therapy to reduce long-term side effects on bone mineral density. However, in clinical daily practice, add-back therapy can be necessary in patients receiving GnRH analogues, because of severe side effects (e.g. vasomotor complaints). Though, the hypothesis postulated by Barbieri[45] supports the idea that endometriosis is effectively reduced in terms of endometrial growth and pain reduction by taking into account a threshold for serum estradiol of 30-50 pgrom/ml. By using Tibolone 2.5mg daily, as usually applied in add-back therapy, it is not expected that this threshold will be exceeded.[46]

For this trial we use validated questionnaires in the Dutch language. The EHP-30 is a validated and frequently used instrument to measure quality of life in women diagnosed with endometriosis[33,47]. The iMCQ[34] and iPCQ[35] are validated questionnaires to measure medical consumption, absence from (paid) work and loss of productivity due to health problems and are both suitable to be used in chronic conditions like endometriosis.

The study is expected to guide future management of women with severe endometriosis undergoing IVF/ICSI, either (when continuous use of OCs is the preferred strategy) improving quality of life and treatment compliance or (when continuous use of OCs is inferior to GnRH agonists) preventing the use of strategy that reduces pregnancy rates. Women and clinicians

can use the results in shared-decision making, increasing the chance of pregnancy and with the potential to reduce healthcare expenditures. To improve counselling, a discrete choice experiment is planned to investigate patient preferences. We will evaluate the indirect costs of patients' loss of societal productivity, due to endometriosis-related symptoms or medication associated side effects. The trial will be supported and promoted by the Dutch Endometriosis Foundation, the patient association for women with endometriosis in The Netherlands. By the intense collaboration with the Dutch Endometriosis Foundation and the NVOG (Dutch Society of Obstetrics & Gynaecology) Working Group on Endometriosis, the results of this trial should stimulate a prompt incorporation in guideline and daily practice. In 2015 this study was recognized by the NVOG as a first priority knowledge gap in reproductive medicine and is listed in the group of studies which are supported by the NVOG[48].

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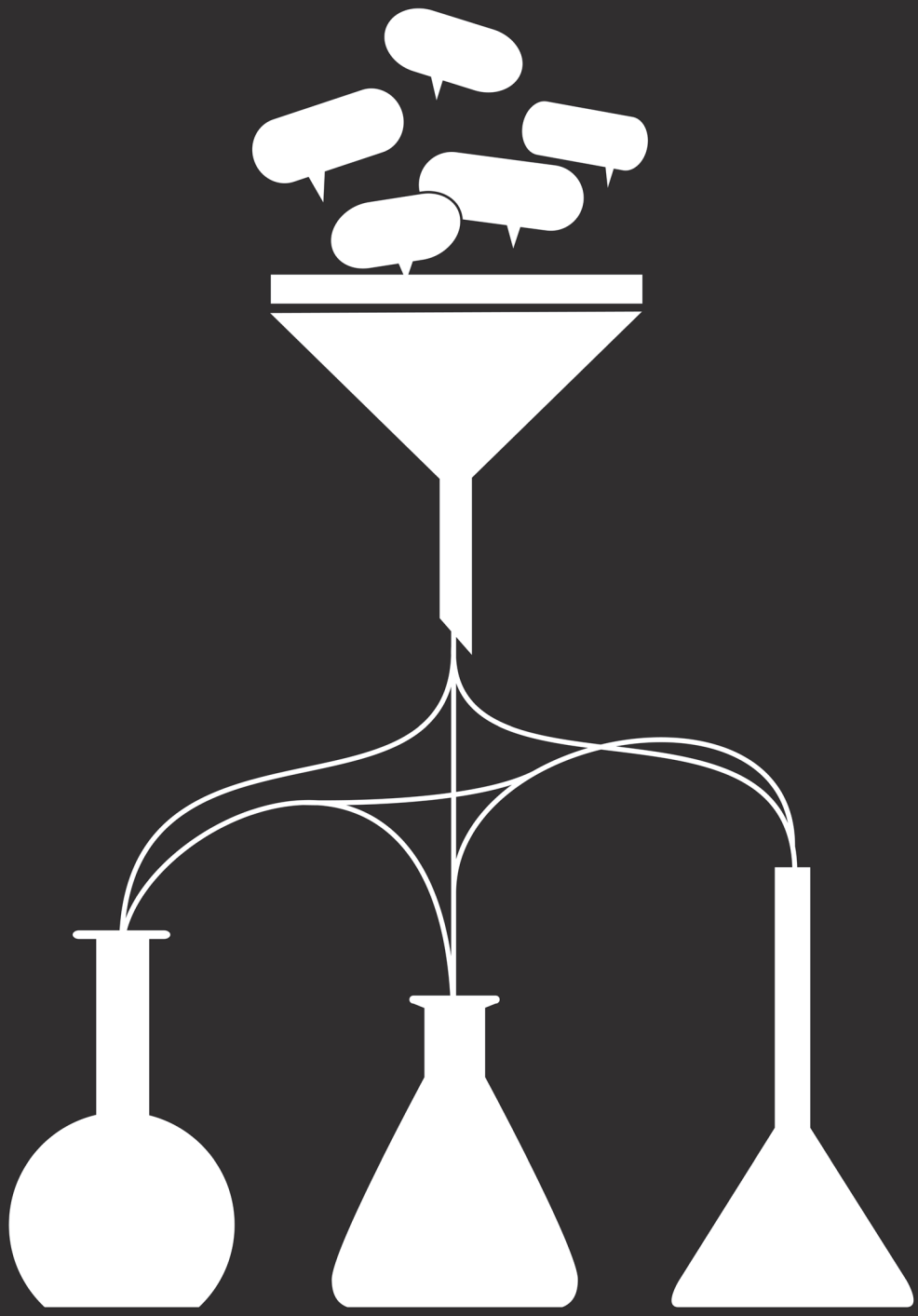


CHAPTER 8

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

This thesis focuses on surgical treatment and assisted reproduction techniques in patients with moderate to severe and deep endometriosis.

Surgery in deep endometriosis (Chapter 2)

We showed that in women with intestinal endometriosis segmental colorectal resection reduces pain and improves patient satisfaction after a long-term follow up. Surgery was performed because of severe pain complaints and defaecation disorders related to a partial or complete bowel obstruction due to deep endometriosis of the bowel wall. After surgery, we reported favorable live birth rates accomplished by natural conception and after IVF/ICSI.[1]

It is reassuring that long-term effects on pain and infertility are favorable even after extensive (intestinal) surgery. But whether surgery should be performed as first line therapy for improvement of fertility is not answered with our study, nor in all the other observational studies published up till now on this topic.[2] Importantly, the risk of surgery associated morbidity including neurogenic bladder, rectovaginal fistulae, pelvic abscesses and anastomotic dehiscence, has to be taken into account when counseling patients for such operative treatments. Robust randomized trials are needed to establish whether colorectal endometriosis should be removed in infertile patients to enhance fertility, taking into account benefits, harm and costs. And while awaiting the results, colorectal surgery with the sole intent of improving reproductive performance of infertile endometriosis patients with intestinal disease should not be offered in routine clinical care.

Intrauterine insemination (IUI) in moderate to severe endometriosis (Chapter 3 and 4)

We showed that in women with moderate to severe endometriosis promising live birth rates after IUI were reported, especially after controlled ovarian hyperstimulation.[3] Those results, in combination with the outcomes of our meta-analysis of observational data, support that IUI might be a feasible treatment strategy in infertile women with moderate to severe endometriosis.[4] Whether a treatment strategy of three cycles IUI with controlled ovarian hyperstimulation is more beneficial compared to immediate IVF/ICSI is unknown and needs to be investigated in a randomized controlled trial, taking cost-effectiveness, time-to-pregnancy and burden of treatment into account. Besides this, a possible beneficial effect of long-term pituitary desensitization with a gonadotrophin releasing hormone (GnRH) agonist prior to IUI must be further investigated, since high quality evidence (defined by using the Grades of Recommendation Assessment, Development and Evaluation (GRADE)[5]) is not available yet.

In vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) in moderate to severe endometriosis (Chapter 5, 6 and 7)

Prior to IVF/ICSI a beneficial effect of long-term pituitary desensitization with a GnRH is acknowledged in a Cochrane meta-analysis[6] and advised as such in the current ESHRE

guideline[7]. However, it is debated whether or not this treatment strategy increases live birth rates after IVF/ICSI, since the Cochrane meta-analysis is based on only three small studies reporting on clinical pregnancy rates, which is currently no longer accepted as primary outcome measure. More aggressive IVF/ICSI stimulation and transfer protocols were used, which cannot be compared to the currently used protocols.

Nowadays, due to improved IVF/ICSI procedures, it is recommended to perform a single embryo transfer and cryopreserve all remaining high-quality embryos, resulting in less multiple pregnancies and higher overall (cumulative) live birth rates. To investigate the efficacy of long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI in those currently used protocols, we performed a retrospective study and showed that the ongoing pregnancy rate substantially increased after including frozen embryo transfers.[8] Therefore, we postulated that long-term pituitary desensitization with a GnRH agonist negatively influences embryo implantation, but might improve oocyte quality. This is also supported by observations of an impaired endometrial receptivity after GnRH agonist treatment, due to decreased endometrial expression of genes involved in successful implantation.[9] Contrary to these findings, pituitary desensitization with a GnRH agonist in adenomyosis results in improved pregnancy rates[10,11], which is probably related to a reduced inflammatory reaction at the endometrium[12]. Possibly, another pathophysiological mechanism causes a reduced pregnancy rate in women with endometriosis versus adenomyosis explaining those different effects of long-term pituitary down-regulation on pregnancy rates. Therefore, the presence of adenomyosis should be taken into account in future studies investigating pregnancy rates in women with endometriosis.

Unfortunately, the retrospective design of our study without any notification of the presence of adenomyosis does not allow firm conclusions, but it supports the need for high quality studies investigating the effect of long-term pituitary desensitization with GnRH agonists on live birth rates, implantation, oocyte quality, and recurrence of endometriosis.

Since women with moderate to severe endometriosis are willing to use GnRH agonists prior to assisted reproduction to increase their chances to become pregnant[13], well established information on the exact beneficial effect and harm is needed.

As an alternative, IVF/ICSI pre-treatment with continuously administered oral contraceptives may offer less side effects as well as encouraging pregnancy rates compared to preceding long-term pituitary desensitization with a GnRH agonist. A randomized controlled non-inferiority trial, which is currently conducted in the Netherlands, will investigate if continuous use of oral contraceptives is non-inferior compared to long-term pituitary desensitization with a GnRH combined with add-back therapy prior to IVF/ICSI with regard to treatment efficacy, safety, patient satisfaction, patient preferences and cost-effectiveness.[14] In 2015 the objective of this study is acknowledged by the 'Nederlandse Vereniging voor Obstetrie en Gynaecologie' (NVOG) as a first priority knowledge gap in reproductive medicine and is endorsed by the Dutch Endometriosis Foundation, the patient association for women with endometriosis in The Netherlands.

ALGORITHM FOR TREATMENT OF SUBFERTILITY

How to treat women with endometriosis wishing to conceive is still challenging taking into account the heterogeneity, chronic and progressive character of this disease, and the limited quantity of high quality evidence. This applies to all stages of endometriosis disease, as well as deep endometriosis and adenomyosis. With this in mind, by using the ESHRE[7] and ASRM[15] guidelines an evidence based treatment algorithm for individually tailored treatment for endometriosis related subfertility has been developed (figure 1).

Since the severity of endometriosis (classified by the ASRM as minimal, mild, moderate or severe) is not related to pregnancy rates[16], the algorithm is centered around the need for hormonal suppression therapy. Since this directly interferes with the ability to conceive, this should play a central role in shared decision making on fertility treatment. Women with (suspicion of) any stage of endometriosis disease are assigned to box 1, 2 or 3, which is dependent on need for hormonal suppression therapy due to endometriosis related pain or the expectation of progression of endometriosis related complaints.

Box 1

Box 1 represents patients with endometriosis with absence of endometriosis related pain and without the expectation of progression of endometriosis related complaints. Those patients do not necessarily need hormonal suppression therapy. Choice of treatment is dependent on the patency of the fallopian tubes, duration of subfertility, the co-existence of semen pathology and ability to have regular intercourse. Care must be taken to prevent over-treatment by advising immediate IVF to this group of women with endometriosis. Evidence exists that the presence of endometriosis is related with lower fertilization rates (stage I-II endometriosis), decreased implantation rates (stage III-IV endometriosis) and decreased clinical pregnancy rates (stage III-IV endometriosis) after IVF compared to women without endometriosis[17]. However, whether immediate IVF is superior to IUI or expectant management in this group of women with endometriosis has not been investigated so far.

Box 2

Box 2 represents patients needing hormonal suppression therapy due to endometriosis related pain or the expectation of progression of endometriosis related complaints. Assisted reproduction (i.e. IUI or IVF/ICSI) should be performed immediately after cessation of hormonal suppression therapy. The patency of the fallopian tubes determines whether or not to perform IUI with controlled ovarian hyperstimulation or immediately start IVF/ICSI. To reduce the risk on recurrence of endometriosis related pain and/or disease, the duration of cessation with hormonal therapy has limits. In this regard, one could consider to perform maximally three IUI treatment cycles preceded by long-term pituitary desensitization with a GnRH agonist followed by IVF/ICSI (preceded by long-term pituitary desensitization with a GnRH agonist as well).

Unfortunately it has not been investigated yet whether or not a treatment strategy of three IUI treatment cycles prior to IVF/ICSI is superior (or at least non-inferior) compared to immediate

start with IVF/ICSI. Therefore, well-established randomized controlled trials (RCTs) are needed to investigate which treatment strategy should be advised. Such future studies must take time-to-pregnancy, burden of treatment, recurrence of endometriosis related complaints requiring an intervention (i.e. hormonal suppression therapy and/or surgery), patient satisfaction and patient preferences into account. In absence of such studies one can consider to immediately start IVF/ICSI in women at high risk of progression of complaints, which is estimated based on earlier recurrence or persistence of endometriosis related complaints whilst being on hormonal medication.

Box 3

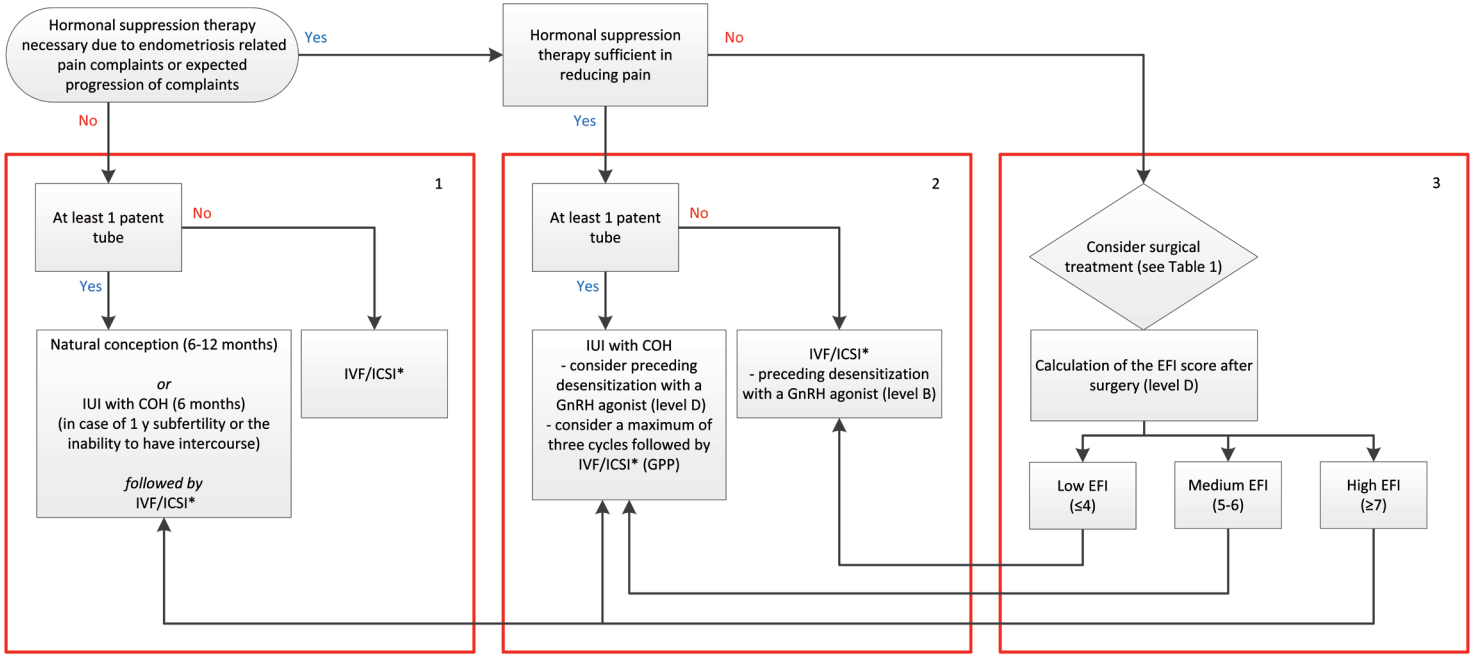
Box 3 represents patients with recurrence or progression of endometriosis related pain. Also patients who refuses hormonal suppression therapy (due to severe side-effects or the presence of contraindications for hormonal suppression therapy) might be assigned to this box. Therapeutic surgery should be considered to reduce the amount of complaints and to restore pelvic organ dysfunction. If IVF/ICSI is technically impossible to be performed safely, surgery should be considered to improve the accessibility of the ovaries and to reduce the risk of IVF related complications.

The level of evidence concerning treatment of peritoneal, ovarian and deep endometriosis to improve fertility is described in the introduction of this thesis and summarized in Table I. Whether or not surgery improves fertility (naturally conceived or by ART) has insufficiently been investigated.

ENDOMETRIOSIS FERTILITY INDEX

One advantage of a surgical procedure is that the endometriosis fertility index (EFI) score can be calculated, which can be used in treatment decision making. The EFI score has been developed to predict pregnancy rates in surgically diagnosed women with endometriosis.[18] A combination of historical factors (i.e. age, duration of infertility and prior pregnancy) and surgical factors (i.e. least function score after surgery, the pre-surgical ASRM endometriosis score and ASRM total score) provide the endometriosis fertility index score. The higher the score, the higher the change of non-ART[19] and ART[20] pregnancy. It is a clinical tool, which is already externally validated in various countries.[21-24] It has also been proposed to use the EFI score to counsel patients to attempt to conceive naturally in women with good prognosis or to immediately start ART in case of poor prognosis.[25] An EFI score ≤ 4 is associated with low naturally conceived pregnancy rates and might be a reason to refer immediately to IVF/ICSI (level D evidence).[24,25] In medium EFI scores (5-6) patients can be advised to IUI (with COH) (GPP).[26] In patients with high EFI scores (7 or higher) choice of treatment should depend on the amount of endometriosis related complaints and perceived progression of the disease (i.e. differentiate between box 1 and 2, GPP). However, the proposed cut-off levels should be validated, since comparative studies or large (non-comparative) cohort studies are not available yet.

Figure 1 Algorithm for treatment of endometriosis related subfertility



Box 1 represents patients with (suspicion of) endometriosis without significant endometriosis related pain complaints or without the expectation of progression of complaints (i.e. patients who do not necessarily need hormonal suppression therapy). Choice of treatment is dependent on the patency of the fallopian tubes, duration of infertility, quality of semen, and ability to have intercourse.

Box 2 represents patients with (suspicion of) endometriosis with the need for hormonal suppression therapy due to endometriosis related pain complaints or the expectation of progression of complaints. Assisted reproduction should be performed immediately after cessation of hormonal suppression therapy. If the function of both fallopian tubes is impaired, IVF/ICSI is advised. If at least one fallopian tube is patent IUI could be considered, preceded by long-term pituitary desensitization with a GnRH agonist, and with a maximum of three IUI treatment cycles, to reduce the risk on recurrence of pain/disease.

Box 3 represents patients with recurrence of endometriosis related pain, or progression of complaints during hormonal suppression therapy. A therapeutic surgery should be considered to reduce the amount of complaints. After surgery the EFI score can be calculated. Then, dependent on the EFI score immediate IVF/ICSI (EFI≤4) or IUI with COH (EFI 5-6) can be advised. In patients with EFI ≥7 choice of treatment is dependent on the amount of endometriosis related complaints and expected progression of complaints (i.e. differentiate between Box 1 and 2).

* If IVF/ICSI is technically impossible, surgical treatment should be considered to improve the accessibility of the ovaries for aspiration.

IUI intrauterine insemination; COH controlled ovarian hyperstimulation; IVF in vitro fertilization; ICSI intracytoplasmic sperm injection; EFI endometriosis fertility index; RCT randomized controlled trial

Table I Evidence of surgical treatment of endometriosis related subfertility

Peritoneal endometriosis	**Ovarian endometriosis**	**Deep endometriosis**
Ablation/excision and adhesiolysis:	Cystectomy:	Surgical treatment:
• impoves pain (level A) • improves naturally conceived pregnancy rates (level B) • might improve pregnancy after IUI (level D) • might improve pregnancy after IVF/ICSI (level C)	• is superior to drainage and coagulation in terms of pain and naturally conceived pregnancy rates (level A) • might reduce ovarian function and might lead to ovarian insufficiency, especially in repeated ovarian surgery (level C) • might result in more ovarian damage compared to a combination of stripping and ablation of the cystwall (level D) • doesn't improve ART pregnancy rates (level A) • can be considerd to improve pain and accessibility of follicles and to reduce IVF related complications (GPP)	• improves pain and quality of life (level B) • might improve pregnancy rates after IVF (level D) • effect on pregnancy rates in not well established (level C) • is advised to be performed in a centre of expertise (GPP)

IUI intrauterine insemination; IVF in vitro fertilization; ICSI intracytoplasmic sperm injection; ART assisted reproductive techniques

Quality of evidence and corresponding level of evidence (adjusted from GRADE[5] and as used in the ESHRE guideline[7]):

Level A evidence (high quality evidence), level B evidence (moderate quality evidence), level C evidence (low quality evidence), level D evidence (very low quality evidence), Good Practice Point (GPP) recommendation based on experts' opinion. Good practice point (GPP): Recommendation based on experts'opinion

SURGICAL TREATMENT TO IMPROVE ENDOMETRIOSIS RELATED FERTILITY

The evidence on surgical treatment of endometriosis is discussed in the introduction of this thesis and visualized in Table I. Ablation or excision of peritoneal endometriosis and adhaesiolysis reduce pain and improve naturally conceived pregnancy rates.[7] Due to the invasiveness of surgery, it can be questioned whether or not to surgically treat all visible peritoneal lesions in asymptomatic women prior to conceive naturally (i.e. women in box 1). Does the number needed to treat (NNT of 8) justify surgically related risks and costs? Due to a potential publication bias the beneficial effect of surgical treatment of peritoneal endometriosis might be overestimated. But for the time being it seems justified to treat all visible peritoneal endometriosis lesions in case a laparoscopy is already indicated (for instance to test tubal patency). To what extent treatment of peritoneal endometriosis relates to the odds of becoming pregnant after IUI[27] or IVF/ICSI[28] is insufficiently investigated, but possibly has a beneficial effect (level C and D, respectively).

It can be considered to perform a cystectomy of endometrial cysts to improve naturally conceived pregnancy rates as recommended by the ESHRE guideline[7]. However, randomized controlled trials have not been performed. Therefore, it remains the question whether the risk of surgery related complications in asymptomatic women and a potential negative effect of a cystectomy on ovarian reserve (level C) outweighs a possible (not determined) beneficial effect on pregnancy rates. Since a cystectomy does not improve IVF/ICSI pregnancy rates (level A), and no randomized trials are available concerning surgical treatment of deep endometriosis to improve (naturally conceived and ART) pregnancy rates (level C and D, respectively), it is advised to be reluctant to perform surgery in women with ovarian endometriosis without endometriosis related symptoms. Surgery can be considered to improve the accessibility of follicles, especially if IVF/ICSI is technically impossible or to reduce the risk of IVF related complications.

Possibly, new surgical techniques might be less detrimental to the ovary, for instance using laser or argon plasma energy for vaporisation instead of diathermal coagulation, and/or performing a combined approach of stripping and ablation of the hilus instead of a cystectomy[29]. However, to what extent those techniques result in a better ovarian reserve, with a positive effect on pregnancy rates must be further investigated.

Whether or not treating women assigned to box 2 by starting IUI or IVF immediately after cessation of hormonal therapy can be discussed, since these women do not benefit from a potentially positive effect of surgery. The level of evidence to perform surgery structurally prior to IUI or IVF/ICSI to improve pregnancy rates is limited (see Table I). It should be mentioned that not only the effect on pregnancy rates, but also complications of surgery, as well as time to pregnancy should be taken into account in treatment decision making. Furthermore, since endometriosis is a chronic disease, often former surgery has been performed. It is generally accepted to limit repeated surgery in order to reduce the risk of adhesion formation and iatrogenic damage to the ovaries.

RECURRENCE OF ENDOMETRIOSIS

It is still unclear to what extent assisted reproduction techniques influence recurrence of endometriosis. Our study showed no negative effect of IUI and IVF/ICSI on pain scores after a short follow up of 1 month.[13] This is in line with the results reported by Santulli.[30] In their prospective cohort study it was shown that IVF/ICSI did not negatively impact pain scores and quality of life in women with peritoneal, ovarian and deep endometriosis. After a longer follow up of 3-6 months, no association was found between the total number of IVF/ICSI cycles and endometriosis recurrence.[31] It was shown that there was no consistent risk of IVF/ICSI ovarian hyperstimulation on endometriosis related complaints.[32]

Recurrence of endometriosis can be more precisely described by the cumulative endometriosis recurrence rate (CERR) employing life table analysis. We showed a CERR of 7.3% at 12 months after IVF[8], which is comparable to the reported CERR by d'Hooghe (2006).[33] D'Hooghe postulated that IVF/ICSI might even have a protective effect on endometriosis recurrence, since a higher CERR was found in women who underwent IUI prior to IVF. It is hypothesized that a monthly exposure to ovulation and retrograde menstruation, as is the case in IUI treatments, is the basis of an increased risk of endometriosis recurrence. This might be facilitated by ovarian hyperstimulation, since higher recurrence rates were described after IUI with controlled ovarian hyperstimulation compared to IUI in the natural cycle as shown in our retrospective cohort study.[3] However, the risk on endometriosis recurrence is limited if the number of IUI treatment cycles is restricted to three cycles. If a woman develops recurrence of endometriosis, cessation of assisted reproductive treatment should be considered by restarting hormonal suppression therapy. From that point of view it should be reconsidered to continue assisted reproduction after successful suppression of endometriosis related pain (box 2) or to perform a therapeutic surgery (box 3).

CONCLUSION

Treatment of women with endometriosis related subfertility is challenging, especially in moderate to severe and deep endometriosis. Different surgical and assisted reproduction techniques are available, but the efficacy and safety of those treatment options are not clearly investigated in high quality studies. In this thesis, we have shown that even in moderate to severe and deep endometriosis patients favorable pregnancy rates after natural conception, IUI and IVF/ICSI are described. Whether or not IUI and IVF/ICSI should be preceded by long-term pituitary desensitization with a GnRH agonist should be further investigated. However, although its severe side-effects, patients are willing to use this pre-treatment to improve their pregnancy rate.

It is also introduced not to focus on severity of endometriosis disease in women with endometriosis trying to conceive, but to focus on endometriosis related symptoms (i.e. pain) in treatment decision making. This is argued, because severity of endometriosis disease is poorly correlated to the ability to conceive and to endometriosis related symptoms as well.

However, the need for hormonal suppression therapy is highly dependent on the existence of endometriosis related complaints. As a result, the ability to conceive is highly dependent on the necessity of using hormonal suppression therapy.

Therefore, an algorithm for treatment of endometriosis related subfertility is developed, which is based on the amount of endometriosis related complaints instead of severity of endometriosis disease. This algorithm visualizes a structured basis in treatment decision making, and can be individually used and tailored by using shared decision making techniques.

In shared decision making, the following challenges can be weighed: 1) The effect of discontinuation of hormonal suppression or surgical therapy on recurrence of endometriosis related pain complaints in combination with or without impaired pelvic organfunction while pursuing natural conception and/or using assisted reproductive techniques (i.e. IUI or IVF/ICSI). 2) The impact of (repeated) surgery on natural conception and assisted reproduction conception rates and its (negative) effect on ovarian reserve. 3) Contra-indications, side-effect and complications of hormonal suppression and surgical treatment. 4) Time-to-pregnancy, since couples might deal with family planning, besides the desire to conceive.

The algorithm also visualizes the existing knowledge gaps and can be used to develop randomized clinical trials and/or large (prospective, comparative) cohort studies of high quality. Implementation of clinical studies can be easily achieved by adapting the algorithm directly improving treatment of endometriosis related subfertility.

FUTURE PERSPECTIVES

The algorithm is based on the currently available evidence and implementation of this algorithm in daily practice should be formally evaluated. The algorithm forms the basis in treatment decision making and can be individually tailored. So far, it can be used as a guideline instead of a fixed treatment protocol.

It also highlights important knowledge gaps. By investigating the efficacy and safety of different treatment options the algorithm can be adjusted in advance. For instance, randomized controlled trials can be developed to increase the level of evidence of different surgical procedures (see Table II).

Up till now, the impact of bowel surgery for colorectal endometriosis on reproductive performance of infertile patients has been exclusively investigated in observational studies with a high amount of heterogeneity and bias. High quality controlled studies are needed to determine the effect size as well as the risk of harms. Currently, a multicentre RCT is ongoing in France comparing the reproductive performance of infertile women with colorectal endometriosis undergoing IVF with or without prior radical bowel surgery including disk excision and segmental bowel resection (https://www.clinicaltrials.gov). Recruitment is expected to be completed before 2021. Therefore, the results will not be available until another two years from now.

In addition, different assisted reproduction treatments can be compared as well. For instance, comparing long-term pituitary desensitization with a GnRH agonist and long-term continuous oral contraceptives prior to IVF/ICSI.[14] Probably more interestingly, but also more challenging, different treatment strategies can be compared (see figure 1). A well designed research proposal to randomize women assigned to box 2 to surgery (i.e. box 3) or no surgery (stay in box 2) prior to start with assisted reproduction will create the answer whether or not structurally perform surgery prior to the wish to conceive. The primary outcome should be life birth rate; secondary outcomes should include, at least, time-to-pregnancy, complications, recurrence of endometriosis (complaints) and cost-effectiveness.

It is not inconceivable that IVF/ICSI treatment procedures will change and as a consequence be improved as well. Possibly, in the future a freeze all strategy with embryo transfer in a natural (or artificial) cycle will be the gold standard. By using a freeze all strategy, ovulation might also be suppressed by using daily progesterone during controlled ovarian hyperstimulation.[34] Therefore, in the near future, women might continue with their hormonal suppression therapy and no longer need to switch or stop their medication prior to start with ovarian hyperstimulation.

Another important issue will be fertility preservation in women with endometriosis. Especially women with bilateral endometrial cysts and the need for repeated ovarian surgery are at risk for reduced ovarian reserve. They may benefit from techniques such as oocyte and ovarian cortex freezing which have improved over time and will be applied more widely in the near future. Before routinely take fertility preservation in consideration, studies are needed to provide data on efficacy, safety and costs.[35]

Since endometriosis is a chronic disease and interferes with fertility and the ability to conceive naturally, this often has an important effect on quality of life. It is shown that health related quality of life is associated with patient centeredness of endometriosis care (which is an important dimension of quality of care). Therefore, it is hypothesized that improving patient centered endometriosis care might improve health related quality of life, which should be further investigated.[36] By identifying targets for improvement in patient centered endometriosis care,[37] strategies to improve those targets can be created. By implementation of those improvement strategies, the effect on quality of care and, as a consequence, on health related quality of life can be investigated as well. This will be further investigated by our study group.

Table II Knowledge gaps and (potential) research proposals

Knowledge gap	Research proposal
Surgery	*Surgery*
1. The effect of colorectal surgery on pregnancy rates	1. Large prospective cohort study including women with deep endometriosis with/without complaints and with/without surgery performed
2. The effect of stripping cystectomy versus ablation with plasma energy on ovarian reserve	2. RCT on stripping cystectomy versus ablation with plasma energy
3. Effect of surgical treatment of peritoneal endometriosis on pregnancy rates in women with a prior diagnosis of endometriosis without disease related complaints	3. RCT including women without endometriosis related complaints trying to conceive naturally, starting IUI or IVF/ICSI randomly allocated to a diagnostic or therapeutic laparoscopy to treat all visible peritoneal endometriosis and perform adhaesiolysis.
Treatment strategy	*Treatment strategy*
1. The effect of a standard surgical treatment in women with hormonal suppression therapy sufficiently treating symptoms (i.e. women assigned to box 2) prior to try to start assisted reproduction	1. RCT including women assigned to box 2 randomly allocated to box 2 or box 3
2. Efficacy and safety of immediate IVF/ICSI compared to three times IUI in women assigned to box 2	2. RCT including women eligibe to start with IUI randomly allocated to three times IUI versus immediate IVF/ICSI
3. Efficacy and safety of long-term pituitary desensitization with a GnRH agonist prior to IUI and IVF/ICSI	3. RCT including all women with endometriosis related complaints (i.e. women assigned to box 2) starting with IUI or IVF/ICSI randomly allocated to long-term pituitary desensitization with a GnRH agonist versus no treatment
4. Efficacy and safety of continuous oral contraceptives as an alternative to long-term pituitary desensitization prior to IVF/ICSI	4. RCT including women eligible to start with IVF/ICSI randomly allocated to continuous oral contraceptives versus long-term pituitary desensitization with a GnRH agonist prior to IVF/ICSI (COPIE protocol / chapter 7)
5. Use of the EFI score in treatment decision making	5. Validation studies of the proposed cut-off values of the EFI scores (figure 1) to be used in treatment decision making with the outcome live birth or time to live birth

EFI Endometriosis Fertility Index; GnRH gonadotropin releasing hormone; ICSI intracytoplasmic sperm injection; IVF in vitro fertilization; IUI intrauterine insemination; RCT randomized controlled trial

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APPENDICES

NEDERLANDSE SAMENVATTING

LIST OF PUBLICATIONS

DANKWOORD

CURRICULUM VITAE

NEDERLANDSE SAMENVATTING

Endometriose geassocieerde subfertiliteit

Chirurgische behandeling en geassisteerde voortplantingstechnieken

Endometriose is een goedaardige, gynaecologische aandoening, waarbij endometrium cellen buiten het cavum uteri uitgroeien onder invloed van oestrogenen. De aandoening komt ongeveer bij 35% van de vrouwen met een verminderde vruchtbaarheid voor en kan daarnaast gepaard gaan met een verscheidenheid aan pijnklachten, zoals dysmenorroe, dyschezie, haematochezie, dysurie, haematurie, dyspareunie en chronische buikpijn.[1]

Tot op heden bestaat nog veel onduidelijkheid over de exacte relatie tussen endometriose en subfertiliteit. Mogelijk kan een deel verklaard worden door een veranderde anatomie van het bekken. Ook een immunologisch vijandig intraperitoneaal milieu, verminderde receptiviteit van het endometrium, aanwezigheid van ovariële cysten, een potentieel negatief effect op aantal oocyten en de kwaliteit hiervan, spelen mogelijk een rol bij vruchtbaarheidsproblemen bij vrouwen met endometriose.[2]

Een curatieve behandeling voor endometriose bestaat tot op heden niet. Symptomatische behandeling bestaat vooralsnog uit pijnstilling, hormonale behandeling of chirurgische interventie. Uniforme behandelstrategieën ontbreken. In de praktijk wordt de behandeling individueel afgestemd, waarbij een balans moet worden gevonden tussen chirurgische en medicamenteuze behandeling. Het effect van behandeling moet gericht zijn op de reductie van endometriose gerelateerde klachten, waarbij de eventuele wens tot zwangerschap altijd in ogenschouw moet blijven.

Hoofdstuk 1 beschrijft de achtergrond en het doel van de inhoud van dit proefschrift. Uitleg over de pathofysiologie en classificatie van endometriose wordt uiteengezet. Informatie over de huidige stand van zaken met betrekking tot de relatie tussen peritoneale, ovariële en diepe endometriose met pijn en (on)vruchtbaarheid wordt bediscussieerd.

In **hoofdstuk 2** wordt stilgestaan bij de lange termijn effecten van chirurgische behandeling van vrouwen met diepe endometriose met betrokkenheid van de darmen, bij wie een segmentale darmresectie is verricht. Een segmentale darmresectie werd verricht vanwege ernstige pijn en defaecatieklachten, welke gerelateerd zijn aan een partiele of complete darmobstructie. Ook na een lange follow up duur geven patiënten een verbetering aan van hun pijn en ervaren zij een hoge tevredenheid van de behandeling. Na chirurgische behandeling worden veelbelovende zwangerschapsresultaten beschreven, welke via natuurlijke conceptie en middels in vitro fertilisatie (IVF) of intracytoplasmatische sperma injectie (ICSI) tot stand zijn gekomen.[3]

Ondanks deze gunstige resulaten blijft het de vraag of chirurgische behandeling van diepe endometriose met betrokkenheid van de darmen ingezet moet worden als primaire

behandeling ter verbetering van de vruchtbaarheid, aangezien dit tot op heden niet onderzocht is.[4] Zeer belangrijk om in ogenschouw te nemen, is het risico op chirurgische complicaties leidend tot morbiditeit op de lange termijn, zoals het ontwikkelen van een neurogene blaas, rectovaginale fistels, pelviene abcessen en dehiscenties van darmnaden. Derhalve is het advies om terughoudend te zijn in het verrichten van dergelijke ingrepen indien het verbeteren van de vruchtbaarheid de enige reden is van chirurgische interventie. Gerandomiseerde studies van voldoende kwaliteit en omvang zijn nodig om vast te stellen of colorectale endometriose moet worden verwijderd om de vruchtbaarheid te verbeteren, rekening houdend met de voordelen, schade en kosten. In afwachting van deze resultaten, zou chirurgische behandeling van colorectale endometriose niet aangeboden moeten worden in de reguliere klinische zorg indien enkel verbetering van de vruchtbaarheid nagestreefd wordt.

In **hoofdstuk 3** wordt beschreven dat bij vrouwen met matig tot ernstige endometriose er veelbelovende kansen zijn op een levendgeborene na intra-uteriene inseminatie met name als gebruik wordt gemaakt van ovariële hyperstimulatie.[5] Deze resultaten, in combinatie met de uitkomsten van de meta-analyse van observationele studies gepresenteerd in **hoofdstuk 4**, ondersteunen de hypothese dat intra-uteriene inseminatie een potentiele behandelingsoptie zou kunnen zijn bij vrouwen met matig tot ernstige endometriose.[6]

Of een behandelingsstrategie van drie cycli intra-uteriene inseminatie met ovariële hyperstimulatie effectiever is in vergelijking tot IVF/ICSI is tot op heden onbekend. Een gerandomiseerde studie naar effectiviteit van deze twee behandelstrategieen is wenselijk, waarbij tijd tot zwangerschap, kosteneffectiviteit, patiëntvoorkeur en patiënttevredenheid meegewogen moeten worden. Daarnaast zou het potentiele gunstige effect van langdurige hypofysaire onderdrukking met een GnRH (gonadotropine releasing hormone) agonist voorafgaande aan IUI nader onderzocht moeten worden, aangezien bewijs van effectiviteit hiervoor nog niet geleverd is.

In **hoofdstuk 5** wordt stilgestaan bij de effectiviteit en veiligheid van IVF/ICSI bij vrouwen met matig tot ernstige endometriose. Voorafgaand aan IVF/ICSI wordt een gunstig effect van langdurige hypofysaire onderdrukking met een GnRH agonist beschreven in een Cochrane meta-analyse[7] en als zodanig geadviseerd in de huidige ESHRE richtlijn[6]. Er bestaat echter discussie over deze behandelstrategie, aangezien de desbetreffende meta-analyse is gebaseerd op drie studies van kleine omvang met als uitkomst het klinisch zwangerschapspercentage. Deze uitkomstmaat wordt hedendaags niet meer geaccepteerd als primaire uitkomstmaat, aangezien dit niet te extrapoleren is naar de uitkomstmaat welke ertoe doet: het aantal levendgeborenen. Daarnaast werden in de tijd van de drie geïncludeerde studies veel agressievere IVF/ICSI stimulatie en embryo transfer protocollen gebruikt, waardoor de uitkomsten van toen niet zondermeer te extrapoleren zijn naar de huidige tijd. Tegenwoordig wordt het aanbevolen om vanwege verbeterde IVF/ICSI procedures een single embryo transfer

te verrichten en alle overige embryo's van hoge kwaliteit te cryopreserveren, wat resulteert in een lagere kans op een meerlingzwangerschap en een hoger cumulatief geboortecijfer.

Om de effectiviteit van langdurige hypofysaire onderdrukking met een GnRH agonist voorafgaand aan IVF/ICSI te onderzoeken op de huidige behandelingsprotocollen, hebben we een retrospectieve studie uitgevoerd welke is beschreven in **hoofdstuk 5**. Dit liet zien dat de kans op een doorgaande zwangerschap mogelijk lager is na deze voorbehandeling, maar de cumulatieve zwangerschapskans hoger is na plaatsing van gecryopreserveerde embryo's. Op basis hiervan formuleerden wij de hypothese dat langdurige hypofysaire onderdrukking met een GnRH agonist mogelijk een negatieve invloed heeft op de implantatie van een embryo, maar een positieve invloed op eicel kwaliteit.[9] Dit kan onderbouwd worden met in de literatuur beschreven observaties van een slechtere receptiviteit van het endometrium na langdurige hypofysaire onderdrukking met een GnRH agonist als gevolg van een verlaagde expressie van genen, die van belang zijn voor succesvolle implantatie.[10] Een tegengesteld effect van de GnRH agonist behandeling bij adenomyose wordt door anderen beschreven. Langdurige onderdrukking met een GnRH agonist resulteert in een hogere kans op zwangerschap, mogelijk vanwege de onderdrukking van het inflammatoire (intracavitaire) milieu, wat een gunstig effect heeft op de receptiviteit van het endometrium.[11,12,13]

Onze studie laat zien dat meer gedegen onderzoek gedaan moet worden naar de effectiviteit en veiligheid van deze langdurige hypofysaire onderdrukking met een GnRH agonist voorafgaand aan IVF/ICSI. Dit zou bij voorkeur onderzocht moeten worden bij verschillende fenotypen van endometriose, waarbij het effect op levendgeborenen, tijd tot zwangerschap, embryo implantatie, eicelkwaliteit, patiënttevredenheid, recidief klachten en kosteneffectiviteit moeten worden meegewogen.

In **hoofdstuk 6** presenteren we de gegevens van vrouwen die een IUI of IVF behandeling ondergaan, al dan niet voorafgegaan door langdurige hypofysaire onderdrukking middels een GnRH agonist. Deze prospectieve studie toont aan dat de intensiteit van behandeling niet gecorreleerd is aan de mate van tevredenheid. De tevredenheid ten aanzien van de behandelstrategie wordt met name bepaald door het met goed resultaat volbrengen van een behandeling, waaronder zwangerschap, maar ook de verwachting en mogelijkheid om op korte termijn zwanger te worden bepalen de tevredenheid.[14]

Ondanks dat vrouwen een lage tevredenheid hebben ten aanzien van de langdurige hypofysaire onderdrukking met een GnRH agonist, zijn ze gemotiveerd deze behandelingsoptie opnieuw in te zetten, vanwege de besproken positieve invloed op de kans op zwangerschap. Daarnaast toonden we aan dat het directe korte termijn effect van geassisteerde voortplantingstechnieken op recidief endometriose klachten bij vrouwen met matig tot ernstige endometriose gering is.[14]

Deze resultaten onderstrepen nogmaals dat het voor de klinische praktijk zeer van belang is om meer te weten over de daadwerkelijke effectiviteit en veiligheid van verschillende

behandelstrategieën door gerichte gerandomiseerde studies of grote cohort studies uit te voeren, zodat patiënten beter geïnformeerde keuzes kunnen maken.

In **hoofdstuk 7** beschrijven we het onderzoeksprotocol van een gerandomiseerde studie naar de effectiviteit, veiligheid, patiënttevredenheid en kosteneffectiviteit van twee verschillende behandelingen voorafgaand aan een IVF/ICSI behandeling bij vrouwen met matig tot ernstige endometriose: de orale anticonceptiepil in een continu schema vergeleken met de langdurige hypofysaire onderdrukking met een GnRH agonist.[15] Dit onderzoek is inmiddels in meerere centra in Nederland van start gegaan

In **hoofdstuk 8** worden de resultaten van het proefschrift samengevat en bediscussieerd. Tevens wordt een algoritme voor de behandeling van subfertiliteit bij vrouwen met endometriose gepresenteerd. Dit algoritme is gebaseerd op de noodzaak tot het onderdrukken van endometriose gerelateerde klachten met hormonale therapie en de effectiviteit van deze hormonale onderdrukking. Aangezien het gebruik van hormonale onderdrukking het nastreven van een zwangerschap in de weg staat, staat in dit algoritme niet de ernst van ziekte centraal, maar de ernst van endometriose gerelateerde klachten. In de basis vormt dit algoritme een *evidence based* overzicht, dat gebruikt kan worden in bespreken van de potentiële behandelstrategieën met patiënte en partner bespreken wat de potentiele behandelingsstrategieen zijn. Het visualiseert tevens met welke bewijskracht we deze behandelingen aanbieden en waar onze kennis lacunes zich bevinden. Dit onderstreept tevens de noodzaak tot het uitvoeren van nieuwe onderzoeksprojecten.

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Het is af! Wat fijn om dat nu hier zwart op wit te zien.

Vorig jaar werd de **leescommissie** samengesteld en vlak na mijn zwangerschapsverlof hoorde ik dat het manuscript officieel was goedgekeurd. Geachte prof.dr. J.A.F. Huirne, prof. dr. M. Goddijn, prof.dr. T. d'Hooghe, prof.dr. L. Kiesel, prof.dr. D.D.M. Braat en dr. S.J. Tanahatoe, allereerst mijn enorme dank voor uw interesse in mijn proefschrift, uw oordeel en oppositie tijdens mijn verdediging.

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Na die week in de Tjongerschans regelde ik keuzecoschappen bij de gynaecologische oncologie, prenatale diagnostiek en op het IVF centrum van het VUmc. Zo kwam ik in contact met Marchien van Baal, Attie Go en Roel Schats. Een gesprek met Marchien van Baal leidde tot het advies om contact op te nemen met Nils Lambalk, aangezien op dat moment mijn interesse lag bij de voortplantingsendocrinologie.

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CURRICULUM VITAE

Lisette van der Houwen was born on July 10th 1985 in Oegstgeest, The Netherlands. She grew up as the second child of Nico van der Houwen en Caroline van der Houwen-van den Engel with her sisters, Wendy and Jeanine, and little brother, Robbert. She attended secondary school at 'Visser 't Hooft Lyceum' in Leiden, from which she graduated in 2003. In the same year, she started medical school at the VU University in Amsterdam. She obtained her master degree in medicine in 2007 and medical degree in 2009 'cum laude'.

After her graduation she started as a reseach doctor at the IVF clinic of the Amsterdam UMC, location VU medical center. In 2011 she was offered a position as a PhD student to initiate this thesis in collaboration with prof.dr. C.B. Lambalk, prof.dr. V. Mijatovic and dr. P.G.A. Hompes. After three years of fulltime working on her thesis, she worked for a year as a medical doctor at the department of reproductive medicine of the Amsterdam UMC location VU medical center. After the delivery of her first child in 2014, she started her residency in Obstetrics and Gynaecology in 2015 at the Diakonessenhuis Utrecht (dr. Schuitemaker) and continued her residency at the Amsterdam UMC location VU medical center (prof.dr. J.I.P. de Vries).

She lives in Breukelen together with Miguel Segall and their children, Dalí (2003), Kisz (2005), Sèven (2014), Link (2017) and Philein (2018).