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Endometriosis: From Diagnosis to Implantation and Pregnancy

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SUMMARY

This thesis focused on the pathophysiological aspect of endometriosis. This was presented in two parts; part I focused on the enhancement of surgical diagnosis and (fertility) treatment in endometriosis patients, part II focused on the consequences of endometriosis in pregnancy.

ENHANCEMENT OF SURGICAL DIAGNOSIS AND TREATMENT

Laparoscopic identification, including histological verification, remains the gold standard for diagnosing endometriosis [1]. However, due to the polymorphic appearance of endometriotic tissue, laparoscopic visualization could be impaired. Especially non-pigmented lesions may be hard to distinguish from healthy peritoneum [2-4]. In [Chapter 2](#) we evaluated the available literature reporting on the use of enhanced laparoscopic imaging techniques in endometriosis surgery. Based on the results of nine studies (mainly cohort studies), including 432 patients, we concluded that enhanced laparoscopic imaging techniques have the potential to detect endometriosis with a better sensitivity and equal specificity when compared to conventional 2D white-light laparoscopy. In [Chapter 3](#) we investigated the use of enhanced laparoscopic imaging techniques in a clinical trial and showed that with the combined use of 3D white-light imaging and narrow-band imaging (NBI), the sensitivity rates for the laparoscopic detection of endometriosis significantly improved (91.2% vs 75.8%, $p < 0.001$) when compared to 2D white-light imaging. The single use of NBI or near-infrared imaging with indocyanine green (NIR-ICG) showed no additional value. By improving the laparoscopic detection of endometriosis, diagnosing endometriosis as well as surgical treatment of endometriosis can be improved with the potential of reducing recurrences. However randomized controlled trials are needed to establish whether an improved laparoscopic detection of endometriosis results in a more complete resection affecting long-term clinical outcomes in a favorable way.

ENHANCEMENT OF FERTILITY TREATMENT

Endometriosis is in up to 50% of patients associated with subfertility [5]. IVF/ICSI-treatment is therefore frequently applied to women with endometriosis in order to overcome the endometriosis associated fertility problems. However, lower success rates of IVF/ICSI are reported, especially in patients with moderate to severe endometriosis (ASRM stage III-IV) and in patients with ovarian endometriomas [6-9]. Therefore it is recommended by the ESHRE guideline to pre-treat these women with a GnRH agonist prior to IVF/ICSI in order to increase the chances of pregnancy [1]. However this recommendation is debated since it is based on only three small studies, executed in a different IVF/ICSI-treatment era including different study-populations with varying degrees of endometriosis (ASRM stage II – IV). Recently, a revised version of the Cochrane systematic review reporting on the use of long-term GnRH agonist therapy prior to IVF/ICSI in endometriosis patients, was published [10]. In comparison



to the previous version of the Cochrane systematic review [11], the conclusion was downgraded towards uncertainty whether GnRH agonist treatment prior to IVF/ICSI may positively affect reproductive outcomes in patients with endometriosis [10]. In [Chapter 4](#) we therefore described a protocol of a non-inferiority randomized controlled trial (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; Dutch Trial Register ref. no. NTR6357), which will investigate the use of continuously administered oral contraceptives as an alternative pre-treatment strategy compared to long-term pituitary desensitization with a GnRH-agonist in endometriosis patients undergoing IVF/ICSI treatment. Observational data show that treatment with oral contraceptives is favorable in patients with severe endometriosis undergoing IVF/ICSI treatment, as clinical pregnancy rates are reported higher in comparison to endometriosis patients treated without oral contraceptives and comparable to that of control patients without endometriosis [12]. However, a randomized comparison between continuous use of oral contraceptives and GnRH agonist treatment prior to IVF/ICSI in patients with endometriosis has not yet been made. The COPIE study is currently recruiting participants in six Dutch centers and will investigate treatment efficacy, as well as treatment safety, patient preferences and cost-effectiveness of both interventions. Alongside this randomized trial a prospective cohort study is running in which patients who do not wish to be randomized will be included. In 2015 the Dutch Society for Obstetrics and Gynaecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie) prioritized the objective of this study as an important knowledge gap in reproductive medicine. Besides, the trial is supported by the Dutch patient association for women with endometriosis (Dutch Endometriosis Society) as well as Freya.

As mentioned previously, endometriosis related subfertility might as well be based on an impaired endometrial receptivity. In order to investigate whether uterine bathing with a pharmacologically neutral gel (ExEm gel) prior to IVF/ICSI treatment improves live birth rate after fresh embryo transfer, the TUBIE trial (Trial on Uterine Bathing before IVF/ICSI treatment in patients with Endometriosis) was conducted and described in [Chapter 5](#). A multicenter randomized, placebo-controlled clinical trial, which was performed in four endometriosis referral centers in the Netherlands and Belgium. A formal interim analysis was performed when 50% of the patients completed the trial and revealed no significant difference in primary outcome. The live birth rate after fresh embryo transfer was 16/60 (26.7%) after GIS versus 8/52 (15.4%) after sham procedures (relative risk (RR) 1.73, 95% confidence interval (CI) 0.81-3.72; p value 0.147). Besides, uterine bathing resulted in a higher pain score compared with a sham procedure (VAS score 2.7 [1.3-3.5] versus 1.0 [0.0-2.0], $p < 0.001$). Therefore, we concluded that uterine bathing with ExEm gel is not advised as routine add-on to IVF/ICSI-treatment in women with endometriosis.

ENDOMETRIOSIS IN PREGNANCY

In part II of this thesis we discuss the pathophysiological aspects of endometriosis in pregnancy, especially the occurrence of Spontaneous Hemoperitoneum in Pregnancy (SHiP). SHiP is defined as a “spontaneous (nontraumatic) intraperitoneal hemorrhage during pregnancy and up to 42 days postpartum, requiring surgical intervention or embolization, excluding ectopic pregnancy, uterine rupture and caesarean section associated bleeding” [13]. To gain more insight in this assumed rare, but potentially life-threatening complication of pregnancy, we collected Dutch cases of SHiP in collaboration with the Dutch Working Group on Endometriosis. Eventually 15 cases of SHiP were identified and published in the largest original case series addressing this topic. In this case series, described in [Chapter 6](#), we offer important practical take-home messages for the management of this phenomenon. To further improve the outcome of pregnancies complicated by SHiP, gaining and growing knowledge was advocated. Therefore a systematic review of the international literature was conducted ([Chapter 7](#)) evaluating the clinical course and pregnancy outcomes of SHiP. Endometriosis was present in 56% of the cases (33/59 cases), an association between the severity of SHiP and the stage of endometriosis could however not be established, consistent with the outcome of an earlier review [14]. SHiP seemed to occur predominantly in the third trimester of pregnancy (51%) and the main presenting symptom was (sub)acute abdominal pain (95%). For the first time recurrence of SHiP was reported in 8.5% of the cases. Since the exact etiology of SHiP is unknown and preventive measures are lacking, identifying risk factors is of importance in order to detect patients which may develop SHiP. In [Chapter 8](#) we described that, besides endometriosis, the use of controlled ovarian stimulation for artificial reproductive techniques (ART) contributes to the occurrence and severity of SHiP. This seems of importance since subfertility and the concomitant use of ART are more common in women diagnosed with moderate to severe endometriosis [15]. In [Chapter 9](#) the types of lesions that lead to SHiP were identified. After collecting information on the pathological and histological findings of SHiP lesions, we showed that a link exists between decidualization in ectopic endometrium and the occurrence of SHiP.