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## Endometriosis associated subfertility

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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.<sup>1</sup>

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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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)<sup>5</sup>) 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<sup>6</sup> and advised as such in the current ESHRE

guideline<sup>7</sup>. 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.<sup>8</sup> 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.<sup>9</sup> Contrary to these findings, pituitary desensitization with a GnRH agonist in adenomyosis results in improved pregnancy rates<sup>10,11</sup>, which is probably related to a reduced inflammatory reaction at the endometrium<sup>12</sup>. 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<sup>13</sup>, 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.<sup>14</sup> 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.