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ARTICLE

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.

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

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Introduction

Fecundity is commonly impaired in patients with endometriosis (Collins et al., 1995). Since its cause is still not unravelled, management of infertility in endometriosis patients is widely debated in literature (de Ziegler et al., 2010).

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 (Kennedy et al., 2005). 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 (Kennedy et al., 2005) and American Society for Reproductive Medicine (ASRM; Practice Committee of the American Society for Reproductive Medicine, 2012), 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 (Macer and Taylor, 2012; Ozkan et al., 2008). Observational, noncomparative studies showed pregnancy rates of 4–32% per cycle (Dickey et al., 1991, 1992; Dodson and Haney, 1991; Göker et al., 2002; Lodhi et al., 2004; Tay et al., 2007; Vollenhoven et al., 1996; Yovich and Matson, 1988). 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 (Kim et al., 1996; Rickes et al., 2002).

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 (D'Hooghe et al., 2006), 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. (2006) 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 favourable 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 analysed 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 $\geq$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, Mölndal, Sweden) HEPES-human tubal fluid (HTF; Lonza, Basel, Switserland) medium supplemented with human serum albumin (HSA; Albuman, Sanquin, Amsterdam, The Netherlands) at 710***g*** for 15 min. The pellet was washed with HTF/HSA medium at 270***g*** for 7 min. After removal of the supernatant, a maximum of 50×10^6 spermatozoa were resuspended with 0.5–5 ml HTF/HSA medium and incubated at room temperature (5% CO_2). Prior to insemination, one last wash step was performed (200***g*** for 7 min). The pellet was concentrated to a volume of 250 μl. Insemination was performed with a total motile sperm count of 0.5×10^6 up to a maximum of 50×10^6 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

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