Reproductive Outcomes after the Treatment of Adenomyosis

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Adenomyosis, also known as endometriosis genitalis interna, is a special form of endometriosis in which endometrial epithelial cells and stromal fibroblasts invade the uterine myometrium.

adenomyosis infertility diagnosis

1. Pharmacological Treatment Options

Nonsteroidal anti-inflammatory drugs (NSAIDs) are most often used as a first-line treatment for women with pain and endometriosis. The mechanism of action is based on blocking the prostaglandin production through the inhibition of cyclooxygenase, an enzyme responsible for the formation of prostaglandins. Common NSAIDs (aspirin®, naproxen, ibuprofen) are very effective in reliving dysmenorrhea [1]. However, researchers have just a few randomized trials on the use of these agents in endometriosis and none of the studies were performed in patients with adenomyosis [2]. NSAIDs are associated with a negative impact on fertility because they may delay ovarian follicle rupture. Nevertheless, there is some evidence that NSAIDs may be used as co-treatment in the ART procedure due to the following theory: adenomyosis may lead to a local hyper-production of uterine prostaglandins, increased uterine tonus, and high-amplitude contractions, thus reducing the possibility of an IVF cycle with successful embryo implantation. It should be noted that NSAIDs have been used to inhibit the negative prostaglandin effect [3].

Combined oral contraceptives (OCs) act by suppressing ovulation and consequently hindering endometrial proliferation. Patients with dysmenorrhea and bleeding disorders, such as hypermenorrhea or meno- or metrorrhagia, benefit especially from this approach. In the extended cycle regimen, OC can be taken for three or six consecutive months before abortion bleeding is induced [4]. In two thirds of women with symptomatic endometriosis or adenomyosis, the use of OCs provides satisfactory pain control in the long term. However, researchers have almost no data concerning the impact of OCs on the subsequent improvement of fertility [5].

Progestogen mono (Progestin-only pill, POP) at the ovulation-inhibiting dose leads to suppression of ovulation and subsequent endometrial atrophy. The benefits of this therapy are good pain and bleeding control in patients with dysmenorrhea or bleeding disorders. The disadvantages of POP are bleeding disorders such as spotting, and depressive moods especially at the beginning of use.

Visanne® (Dienogest (DNG) 2 mg) has been in the market since 2010 and is officially approved for the treatment of endometriosis. DNG is a progestogen with a pronounced effect on the endometrium. It is well-suited for cycle stabilization and has long been used in gynecology for hormonal contraception and hormone replacement therapy. DNG acts in endometriosis by reducing the endogenous production of estradiol, thus suppressing the trophic effects of estradiol in the eutopic as well as ectopic endometrium. With continuous administration, DNG induces a hypoestrogenic, hypergestagenic endocrine state that causes initial decidualization of endometrial tissue, in which glycogen and fat are stored and cells become rounded and tightly packed, followed by atrophy of endometriotic lesions. The antiproliferative effect on the endometrium, combined with potent secretory-transformative and anti-inflammatory activity, make DNG an ideal candidate for the treatment of endometriosis. Visanne® significantly reduces menstrual bleeding, dysmenorrhea, premenstrual pain, dyspareunia, and pelvic pain. In patients with adenomyosis, DNG might cause bleeding disorders, especially menometrorrhagia [6]. Women must be informed that ovulation is suppressed by regular intake of Visanne®, but the agent is not officially approved for contraception [7].

A small number of studies with limited sample sizes have analyzed reproductive outcomes after a Progestogen mono pretreatment for endometriosis [8]. Barra et al. performed a retrospective analysis including 151 women who had failed a previous IVF cycle and all subsequent embryo transfers, and had endometriosis diagnosed by imaging studies. The treatment group comprised 63 women who received 2 m DNG daily for three months, while 88 women underwent the next IVF cycle without any previous hormonal treatment. The rates concerning cumulative implantation, clinical pregnancy, and live birth were significantly higher in the DNG-treated group (39.7%, 33.3% and 28.6%) than in the non-treated group (23.9%, 18.2% and 14.8%; p = 0.049, 0.037 and 0.043, respectively). Additionally, the use of DNG significantly increased the number of retrieved oocytes (p = 0.031), two-pronuclear embryos (p = 0.039) and blastocysts (p = 0.005) in women with endometriomas of a diameter ≥ 4 cm. The authors conclude that pretreatment with DNG leads to better reproductive outcomes [9].

Another group came to similar conclusions in a study comprising 38 patients treated with DNG, 70 patients pretreated with GnRH analogs, and a further 70 control patients who received no hormonal therapy for 6 months preceding IVF. All of the women had undergone laparoscopic surgery for ovarian endometriomas previously. Women who received DNG pretreatment had a 2.5-fold higher clinical pregnancy rate (44.7% versus 16.7%, p = 0.012), and a three-fold higher delivery rate (36.8% versus 11.1%, p = 0.013) than controls [10].

In a third study, also with relatively small sample sizes (n = 33 in the DNG group and n = 35 in the control group), the authors analyzed reproductive outcomes after 12 weeks of pretreatment with DNG vs. no hormonal pretreatment [11]. The numbers of growing follicles, retrieved and fertilized oocytes and blastocysts were significantly lower in the DNG group than in controls. Although there was no significant difference in implantation rates between groups, the cumulative pregnancy rate and live birth rate were lower in the DNG group than in controls [11]. It is important to state, that all the above cited studies address reproductive outcome after progesterone mono in endometriosis. They do not explicitly include patients with adenomyosis or exclude patients with endometriosis genitalis externa. Further studies analyzing the reproductive outcome in patients with adenomyosis are needed.

Levonorgestrel intrauterine system (LNG-IUS) does not cause ovarian suppression, but counteracts dysmenorrhea and bleeding disorders thorugh (a) the impact of progestogen on adenomyosis foci, (b) atrophy of the endometrium, and (c) control of endometrial factors that changed during adenomyosis, such as reduced expression of growth factors and their receptors associated with hypermenorrhea [12][13]. The LNG-IUS is an approved therapy option for women with adenomyosis and completed family planning. Nevertheless, some studies have addressed reproductive outcomes after pretreatment with LNG-IUS following IVF. Liang et al. studied 358 women with adenomyosis undergoing IVF, 134 of whom were enrolled in the LNG-IUS group and 224 in the control group [14]. The authors noted higher rates of implantation (32.1% vs 22.1%, $p = 0.005$), clinical pregnancy (44% versus 33.5%, $p = 0.045$), and ongoing pregnancy (41.8% vs 29.5%, $p = 0.017$) in the LNG-IUS group compared to the control group [14]. One explanation for these positive results might be the influence of LNG-IUS on adenomyosis, especially on the expression levels of steroid receptor coregulators, such as transcriptional intermediary factor 2 or nuclear receptor corepressor. These coregulators were reduced after treatment with LNG-IUS [15].

Gonadotropin-releasing hormone analogs (GnRH-a) are the best studied of all pharmacological treatment options for adenomyosis and subsequent infertility. The effect of GnRH analogs proceeds in two phases: first, there is a so-called flare-up effect. Primarily, the stimulation and release of FSH and LH initially increases estrogen biosynthesis and secretion. Secondarily, persistent binding to the GnRH receptor causes a downregulation of FSH and LH, which leads to the suppression of ovarian estrogen biosynthesis and secretion. Two routes of administration may be used: depot preparations are applied subcutaneously or through the intramuscular route, and regular application consists of a nasal spray. After about 4 weeks, average estradiol levels around 20 pg/ ml are measured after depot administration, which corresponds to the postmenopausal serum estradiol concentration. Nasal application also causes a drop in estrogen after the initial flare-up effect, but not as extensively as a depot preparation. Average estradiol levels of 40 pg/mL are measured after 4–8 weeks, and 30 pg/mL after 24 weeks [16][17]. The use of GnRH analogs for symptomatic adenomyosis has decreased considerably over the past years due to the availability of better tolerated alternatives (see above). Osteoporosis, hot flashes, vaginal atrophy, and depressive moods are among the most common side effects. Due to concomitant osteoporosis, the duration of treatment with GnRH agonists without add-back therapy should not exceed 3 months. In order to enhance reproductive outcomes after ART, GnRH analogs may be used for 3 to 6 months as a means of downregulation. Given that the GnRH receptor is also found in adenomyotic lesions, and GnRH analogs have a direct antiproliferative effect within the myometrium, the treatment reduces the inflammatory response and angiogenesis and also induces apoptosis in the tissue [18]. This might exert a favorable effect on implantation. Long-term treatment with GnRH agonists or an ultra-long protocol may have a therapeutic effect on adenomyosis and improve the outcome of ART [19].

Hou et al. performed an observational cohort study comprising three groups: (a) 362 patients with adenomyosis using the ultra-long GnRH agonist protocol, (b) 127 patients with adenomyosis using the long GnRH agonist protocol, and (c) 3471 patients with tubal infertility using the long GnRH agonist protocol [20]. Long GnRH agonist treatment reduced the clinical pregnancy rate (OR 0.492, 95% CI 0.327 to 0.742, $p < 0.001$), implantation rate (OR 0.527, 95% CI 0.350 to 0.794, $p = 0.002$), and live birth rate (OR 0.442, 95% CI 0.291 to 0.673, $p < 0.001$), and increased the miscarriage rate (OR 3.078, 95% CI 1.593 to 5.948, $p < 0.001$) in adenomyosis patients (Group b)

compared to those with tubal infertility (group c). Ultra-long GnRH agonist treatment in patients with adenomyosis (Group A) increased the clinical pregnancy rate (OR 1.925, 95% CI 1.137 to 3.250, p = 0.015), implantation rate (OR 1.694, 95% CI 1.006 to 2.854, p = 0.047) and live birth rate (OR 1.704, 95% CI 1.012 to 2.859, p = 0.044) compared to long GnRH agonist treatment (Group b) [20]. The authors conclude that adenomyosis has a negative impact on IVF outcomes, and that the ultra-long GnRH agonist protocol provides a better reproductive outcome in those patients [20].

Younes et al. reported similar results in their meta-analysis evaluating the effects of adenomyosis on in vitro fertilization. Whereas adenomyosis has a negative impact on implantation, clinical pregnancy and live birth rate, pretreatment with GnRHa increases pregnancy rates [21].

In contrast to the majority of studies on this subject, a systematic review and meta-analysis performed by Cozzolino et al. yielded different results [22]. The authors analyzed pregnancy outcomes in patients with untreated adenomyosis and surgically or medically treated adenomyosis. After surgery, the authors observed an increased natural conception rate in women with adenomyosis. In contrast, the treatment with GnRHa did not lead to better IVF outcomes. Only three studies concerning this topic were included in the meta-analysis [22]. The authors state that most of the studies did not make a distinction between focal and diffuse adenomyosis; such a distinction might have yielded different results in terms of clinical presentation and treatment options [22].

New findings concerning pathogenic mechanisms have led to new medical approaches for the treatment of adenomyosis, such as selective progesterone receptor modulators, aromatase inhibitors, GnRH-antagonists, danazol, valproic acid, modulation of prolactin and/or oxytocin, and antiplatelet therapy. However, the investigations of these options have been confined to their effect on the symptoms of adenomyosis; studies concerning their impact on reproductive outcomes are still missing [23][24].

Adolescents (aged 12–20 years) diagnosed with adenomyosis but with no current desire for children are in a special situation [25]. The question arises as to whether one could improve or preserve fertility a priori, given the presence of adenomyosis. The treatment recommendation depends on the symptoms. In cases of dysmenorrhea or a bleeding disorder, hormonal treatment with a combined pill, progestogen only or LNG-IUS appears to be advisable. In cases of asymptomatic patients or those with mild symptoms, unequivocal treatment recommendations cannot be made due to the lack of data on subsequent fertility outcomes.

In recent years, several risk factors have been identified for the development of adenomyosis. Estrogen exposure appears to be a primary risk factor [26]. By implication, hormonal treatment that reduces estrogen levels by inhibiting ovulation (such as combined oral contraceptives or progestogen mono) could counteract the progression of adenomyosis and thus increase fertility rates in the future. Nevertheless, clear therapy recommendations can only be issued after further studies have been performed on these patients.

2. Surgical Treatment Options

In surgical treatment, a distinction is made between diffuse adenomyosis and adenomyoma, i.e., localized or focal adenomyosis. An adenomyoma can usually be excised in toto without difficulty, although identification of the layers is usually more difficult than in the case of a myoma. Surgical excision may also be useful in cases of diffuse adenomyosis. The classic technique in case of focal adenomyosis means an open or laparoscopic complete adenomyomectomy and includes the same steps performed in a myomectomy. The classic technique in case of diffuse adenomyosis starts with a vertical or transverse incision in the middle of the uterine wall, recognition and resection of all macroscopic lesions (cytoreductive surgery) and a final wound closure in at least two layers, with care taken not to leave any uterine defect behind [27]. The disadvantage of surgery in diffuse adenomyosis is that the rate of uterine rupture in a future pregnancy appears to be 4–6%, which is higher uterine rupture rates after myomectomy or cesarean section [27][28]. Other pregnancy complications, such as placental disorders, have also been reported. Women undergoing resection should be educated about the need for cesarean section on a labor-free uterus [27].

In a review comprising 64 studies and 1049 patients, Grimbizis et al. noted a reduction of dysmenorrhea and menorrhagia control in 82% and 68.8%, respectively, after complete excision. In addition, the study population achieved a high pregnancy rate of 60.5%. Even after partial excision, a reduction of dysmenorrhea was noted in 81.8%, control of menorrhagia in 50.0%, and pregnancies were achieved in 46.9% of cases [29].

Another systematic review comprising 18 studies and 1396 infertile women with focal and diffuse adenomyosis (AD) analyzed reproductive outcomes after uterine-sparing surgery [30]. Patients with focal AD achieved mean pregnancy and miscarriage rates of 52.7% and 21.1% respectively, whereas patients with diffuse AD had mean pregnancy and miscarriage achieved rates of 34.1% and 21.7%, respectively. Uterine rupture and preterm birth were observed in 6.8% and 4.5% of pregnant patients with diffuse AD versus 0% and 10.9% of patients with focal AD, respectively. No significant differences were noticed between natural conception compared with assisted reproductive technology (ART). Overall, patients with focal AD appear to achieve higher pregnancy rates after conservative surgery compared with diffuse AD, whereas a higher incidence of uterine rupture was reported after surgery for diffuse AD [30]. The indication for surgical resection of adenomyosis must be discussed individually with each patient. Surgery should be recommended especially in cases of younger infertile women who have failed medical management. Sufficient contraception must be discussed with the patient postoperatively for at least 6–12 months before the patient seeks to conceive again. In addition, the patient must have an adequate chance to conceive spontaneously due to the age factor. A demonstration of statistical data from the German IVF Registry (DIR) regarding pregnancy and miscarriage rates may be helpful in this regard.

Surgery can be also recommended in older women with infertility despite ART, and those with a history of recurrent pregnancy loss or implantation failure. There are no rigid age limits that precisely define young and old patients. Rather, the procedure should be discussed individually with the respective patient, taking into account the time of the unfulfilled desire for a child, the age of the patient and the respective egg reserve.

Hysteroscopic resection is indicated in patients with adenomyosis limited to the endo-myometrial junction or adenomoysis foci close to the uterine cavity, and is frequently performed with ultrasound guidance for better

detection. Good results have been reported in cases of abnormal uterine bleeding and dysmenorrhea, but endomyometrial resection is contraindicated in patients who desire pregnancy because it causes destruction of the endometrium together with the JZ. This may lead to higher rates of miscarriage, preterm labor, and placenta-related complications [31][32].

3. Other Methods

High-intensity focused ultrasound (HIFU) or focused ultrasound surgery is a non-invasive local thermal ablation technique. The ultrasound beams penetrate the tissue through the acoustic pathway and are then focused on the target tumor within the body. When the temperature increases to 65 °C, coagulative necrosis occurs in the tumor [33][34]. The treatment is performed under ultrasound or MRI guidance and can be used in cases of focal as well as diffuse adenomyosis. HIFU provides effective and long-term pain and bleeding control, and its application is safe. Patients must be carefully selected to avoid severe complications, such as skin burns (0.2%) or intestinal injuries (0.02%) [34]. The body of data concerning the effect of HIFU in infertile patients is small. Zhou et al. performed a follow-up analysis of 68 HIFU-treated adenomyosis patients who wished to conceive. Of 68 patients, 54 conceived at a median of 10 months (range, 1–31 months) after treatment, and 21 of them delivered [35]. Another study with a similar sample size showed comparable results: 52 adenomyosis patients were treated with HIFU from 2011 to 2016 (Chongqing, China). A total of 20 patients conceived at a median of 8.75 months after HIFU, and 11 delivered at term [34]. Both study groups observed no uterine rupture during pregnancy or delivery. Although the sample sizes were small, the above mentioned results have shown that HIFU treatment does not increase the risk of complications during gestation and delivery. In addition, due to the absence of scar tissue on the uterine wall, patients may attempt to conceive much sooner than they would after surgical treatment. Moreover, the risk of uterine rupture during pregnancy or delivery is lower than after surgery [31].

Hysteroscopic endometrial ablation is frequently performed together with hysteroscopic resection and refers to the coagulation of adenomyosis cysts and crypts [36]. Hysteroscopic ablation can be conducted with yttrium aluminum garnet (YAG) laser, rollerball resection, thermal balloon ablation, cryoablation, circulated hot fluid ablation, microwave ablation, bipolar radiofrequency ablation, or electrocoagulation [37]. Endomyometrial ablation is effective for lesions deeper than the endometrial-myometrial junction, whereas the efficacy of hysteroscopic ablation is limited to foci at a depth of 2–3 mm. Pregnancies have been reported after endometrial ablation, but there is little data about their outcomes. Kohn et al. performed a systematic review of 274 pregnancies from 99 sources, of which 78 were case reports. Women aged 26–50 years (mean 37.5 +/− 5 years) conceived at a median of 1.5 years after hysteroscopic ablation [38]; 85% of pregnancies ended in miscarriage, induced abortion or ectopic pregnancy. Pregnancies that continued had high rates of preterm delivery, caesarean delivery, caesarean hysterectomy, and adherent placenta [38]. Many case reports described a higher risk of preterm premature rupture of membranes, intrauterine growth restriction, intrauterine fetal death, and uterine rupture [38]. Due to the high rate of pregnancy complications as a result of damage to the endometrium, hysteroscopic ablation should not be performed in patients who desire pregnancy.

Uterine artery embolization (UAE) is a means of achieving necrosis of adenomyotic lesions with the aid of transarterial catheters. Vascular access is gained through a femoral or radial artery puncture, and the arteriography is followed under fluoroscopic guidance. Embolization is usually performed using permanent particulate agents of various sizes. The technique used for UAE in adenomyosis is similar to that used for fibroids. Over the last 15 years, UAE has been employed quite extensively for the treatment of symptomatic adenomyosis, and has yielded favorable short- and long-term outcomes [36][39]. Mohan et al. performed a systematic review analyzing the outcome of fertility after UAE. Low-level evidence from these studies suggests that pregnancy rates after UAE are comparable to age-adjusted rates in the general population [40]. Although pregnancy complication rates were comparable to those in patients with untreated fibroid tumors, a few studies have reported higher rates of miscarriage after UAE [40].

In contrast, the current American College of Obstetrics and Gynecology and Society of Interventional Radiology guidelines still mention the desire for future fertility as a relative contraindication to UAE. This recommendation is corroborated by a number of studies concerning reproductive outcomes after UAE in patients with fibroids. Compared to surgical fibroid enucleation, UAE resulted in lower pregnancy rates and higher miscarriage rates [41][42]. Further randomized studies will be needed to make a clear recommendation for these patients [36].

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