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Relationship Between Endometriosis and Pregnancy

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Contents

1.The Effect of Pregnancy on Endometriosis

Endometriosis is a chronic disease that affects women of reproductive age and can cause estrogen-dependent pelvic pain and infertility. The relationship between endometriosis and pregnancy is very important in this group where pregnancy demand is important. [1] The effects of pregnancy on endometriosis and endometriosis on pregnancy have been investigated for a long time. However, the studies conducted show differences according to the variety of treatment modalities such as the differences in diagnostic methods and assisted reproductive techniques used for endometriosis. [1]

There are studies showing that pregnancy has effects on endometriosis. Those who claim that endometriosis regresses during pregnancy state that decidualization caused by increased progesterone in endometrial tissue is the main mechanism for regression, while those who argue that endometriosis progresses during pregnancy suggest that increased angiogenesis causes progression in endometriosis foci. [1]

It has been thought for many years that pregnancy has a positive effect on endometriosis and its symptoms by prevention of bleeding of endometriotic foci due to anovulation and amenorrhea, and different metabolic, hormonal, immunological and angiogenic changes. However, there is not enough study to prove this theory. Experimental endometriosis models have been created in mice and it has been reported in studies that shrinkage in lesions occur during pregnancy. [1]

Estrogen stimulates the development of the endometriotic focus, while progesterone has an antiproliferative and pro-apoptotic effect on both the eutopic and ectopic endometrium. Menopause and pregnancy are natural conditions that affect the formation of endometriosis.

Since 1958, especially by two researchers named Kistner and Andrews, imitation of pregnancy (false pregnancy) has been widely used in the treatment of endometriosis. [1,2] On the observed benefits, Enovid (norethynodrel and mestranol), the first produced oral contraceptive, was prescribed to 23 patients with endometriosis. [3] After these initial trials, synthetic progesterone is still used in the treatment of endometriosis today. According to studies, the use of progestin reduces endometriosis-related pain in 90% of the patients. [3]

Apart from corpus luteum cysts, 11% of adnexal masses detected during pregnancy have been reported as endometrioma and 1% as endometrioid cancer. [4] Epithelial ovarian cancers account for more than half of these cancers. [5] It has been reported that there may be changes in the appearance and size of endometriotic cysts during pregnancy. [6,7] Ueda et al. [8] reported that cysts were reduced in size by 52% in their studies, while Benaglia et al. [9] stated that this rate was 13%. Benaglia et al. reported that 46% of these cysts were not seen later on, 33% did not change in cyst size and 8% increased in size. Ueda et al. reported that the dimensions did not change in 28% of the cysts and increased in 20%. It is thought that the failure of the endometriomas to behave in the same way in each pregnancy depends on the characteristic histology of the endometrioma. It has been suggested that those surrounded by the endometrium are more prone to decidualization, contraction or even extinction. [9]

Increase in endometriosis foci in glandular epithelial secretion, stromal vascularity and edema is due to decidualization under the effect of progesterone during pregnancy. [10,11] Similar to the ectopic endometrium, atrophy resulting in fibrosis in the endometriotic lesions, necrosis of the decidual cells and lymphocyte infiltration can be seen in pregnancy. [12] There are typical ultrasound images, histological and molecular patterns of decidualized endometriosis. [10]

Generally, there are vascularized papillary projections in a properly limited uni or multilocular cystic structure as ultrasound finding. Depending on the vacuole rupture, a myxoid structure can be seen in the stroma. Apart from this, there is no clear information about the frequency of decidualization. In the study in which Benaglia et al. examined the number and size of endometrioma before and after IVF in 24 patients, none of the 40 endometriomas evaluated were found to be decidualized. [9] In another study, 12% (in 3 cases) of decidualization was detected in 24 patients who followed for 25 endometriomas. [11] Decidualized endometriomas are very difficult to classify as borderline tumors, as they have characteristic features of both malignant and benign adnexal masses. In addition, this diagnosis can be skipped due to the routine examination of the ovaries in obstetric ultrasonography. Unlike malignant tumors, there is no septation in decidualized endometriomas and it may be reassuring that there is no increase in size in serial ultrasound follow-ups.

Although there are studies suggesting that endometriosis lesions regress due to increased progesterone in pregnancy, there are also studies that advocate progression of the disease due to increased angiogenesis.

CA 125 levels increase both in endometriosis and pregnancy. Therefore, it cannot be used in differential diagnosis of adnexal mass during pregnancy. [13] However, compared to premenopausal women, human epididymis protein 4 (HE4) values are significantly lower in pregnant women and rarely increase in ovarian endometriotic cysts. [13] Therefore, it is believed that the combined use of CA125 and HE4 can help differentiate adnexal masses from malignant or benign.

It is considered safe to use magnetic resonance (MR) imaging without gadolinium for adnexal mass assessment during pregnancy. [14-16] Although a negative result in the fetus after exposure to gadolinium has not been reported in the literature, there are no well-designed human studies investigating the teratogenic effect of gadolinium in pregnant women. In different studies, it has been shown that gadolinium persists in amniotic fluid, and the fetus swallows, evacuates and reabsorbs this fluid through the gastrointestinal tract. [15] Management of adnexal cysts presenting during pregnancy is controversial. If a surgical decision is made by a multidisciplinary team, it should be taken into consideration that the risks associated with surgery increase after the 23 rd week. [16] If surgery is decided in the late 3rd trimester, the operation should be postponed until after delivery. [17]

Complications of endometriosis that exist during pregnancy are also described. Although these complications are rarely seen, they may cause life-threatening risks for the mother and fetus. For this reason, it is recommended that physicians following the patient with endometriosis should have information about these complications. Adhesions caused by endometriosis or endometriosis surgery may attract more surrounding structures as the uterus grows. [18] In addition, tissues and vessels may become more fragile due to chronic inflammation caused by endometriosis. [19] Tissue rupture may be seen by intrusion of decidualized endometriotic tissues into the vascular wall and structures. [20] As a result, the decidualized endometrium becomes a tissue with increased permeability, edema, vascular remodeling, angiogenesis and increased luminal diameter and showing good vascularity. [21] Due to the progesterone dependence of decidualization, in case of progesterone withdrawal, the decidual vessels may become invasive and bleed. [22,23] In endometriosis disease, which is characterized as a progesterone resistant disease, rupture of these vessels and unpredictable bleeding due to

necrosis of a decidualized ectopic endometrium tissue localized on the utero-ovarian or parametric vessels is possible. [24] In addition, complications such as intestinal perforation, appendicitis, spontaneous hemoperitoneum, spontaneous pneumothorax, aortic aneurysm, uroperitoneum, uterine rupture, infected endometrioma, and endometrioma rupture have been reported in the literature. [25]

In summary, although the foci of endometriosis seem to be receding during pregnancy, there is insufficient data on the subject. It should be kept in mind that pregnancy complications can be observed especially due to abnormal bleeding caused by decidualized endometrial tissue.

Tissues and vessels may be more fragile due to chronic inflammation caused by endometriosis. Accordingly, intestinal perforation, appendicitis, spontaneous hemoperitonium, spontaneous pneumothorax, aortic aneurysm, uroperitonium, uterine rupture, infected endometrioma and Complications such as endometrioma rupture may occur.

2.Pregnancy Follow-Up and Obstetric Complications of Endometriosis

The causes of obstetric complications due to endometriosis are anatomic and ovulatory changes induced by ectopic endometrium, increased inflammatory cell responses in peritoneal fluid, endometrial progesterone resistance and abnormal uterine contractility, disturbance of embryonic development programming, disorders in implantation and decidualization

mechanisms [26,27]. In studies it has been shown that disorders in the preimplantation period have an impact on the pathogenesis of progressing gestational weeks [25]. Endometriosis-related obstetric undesirable conditions such as gestational hypertension, preeclampsia, placenta previa, placental abruption, postpartum hemorrhage, preterm labor, small gestational age (SGA) and neonatal intensive care unit admission according to gestational age were investigated in the literature. [25-27]

Some rare obstetric complications occur during surveillance of pregnant women with endometriosis disease. The first one is Spontaneous Hemoperitonium in Pregnancy (SHiP) and its overall prevalence was detected as 0.4%. [28] The factors of SHiP were determined by Glavind et al. [29] including chronic inflammation of tissues affected by endometriosis, organ involvement of endometriotic lesions, and the presence of pre-existing endometriotic lesions secondary to progesterone levels in pregnancy. It has been reported that more than 50% of SHiP cases likely have previous history of endometriosis stage III-IV disease specially conceived artificial reproductive techniques (ART) treatment which presented severe acute abdominal pain, hypovolemia, collapse without vaginal bleeding between in the third trimester of pregnancy. In these cases, it is difficult to identify the source of severe bleeding that is most often situated in posterior wall of uterus, broad ligaments and in some cases retroperitoneum.[30] Also, these severe bleedings accompanied by adverse maternal morbidities and 31% neonatal death have been reported [31]. And some adverse perinatal outcomes are comprised stillbirth, cerebral palsy, miscarriage and prematurity. Furthermore, the most important causes of maternal morbidity are delayed transportation, hysterectomy, adnexectomy and the need for reoperation. [32] In most cases, delivery was performed by cesarean section, and thereby it may be related with significant blood loss that necessitate extensive transfusion blood and blood products.[30]

Spontaneous hemoperitoneum in pregnancy (SHiP) can be seen in more than 50% of endometriosis cases, especially in patients with stage III-IV endometriosis who were conceived with IVF treatment, clinical features may be associated with severe acute abdominal pain, hypovolemia, collapse without vaginal bleeding during the second half of pregnancy.

In addition, expansion can be observed in approximately 5 to 20% of endometriomas during pregnancy [28] and a rapidly grown endometrioma is associated with the risk of ovarian abscess and rupture formation.[31] Also, distant endometriotic lesions such as bladder, umbilicus, cesarean scar and vulva confused on malignancy lesions [33]. Furthermore, acute appendicitis, ureteral rupture, spontaneous pneumothorax and pseudoaneurysm of the thoracic aorta cases have also been reported depending on the distant location of endometriosis in pregnancy [33]. Moreover, in various case reports, terminal ileum [34] and rectosigmoid colon perforation due to endometriosis have been observed in some patients who complained acute abdominal pain.[35] Maggiore et al. reviewed, 63 cases of uterine pregnancy rupture pregnant women with endometriosis were identified during pregnancy one of this rupture took place in postpartum 6 weeks.

When the studies related with obstetric and neonatal complications with endometriosis are examined, Horton et al. systemic review and meta-analysis demonstrated that risk of abortion due to both adenomyosis and endometriosis (OR: 3.40, 95% CI: 1.41–8.65 and OR: 1.30, 95% CI: 1.25, respectively) –1.35), risk of preterm delivery (OR: 1.38, 95% CI: 1.01-1.89), cesarean delivery (OR: 1.98% CI: 1.64–2.38) and admission rate to the neonatal unit after delivery (OR: 1.29, 95% CI: 1.07–1.55) was increased and this increment could

likelihood be linked with obstetric and neonatal complications. [27] Zullo et al. reported their meta-analysis of 1,924,114 cases that, high rate of preterm delivery (OR: 1.63; 95% CI, 1.32-2.31), abortion (OR 1.75; 95% CI, 1.29-2.37), placenta previa (OR 3.03; 95% CI, 1.50) –6.13), SGA (OR 1.27 95% CI, 1.03-1.57) and cesarean delivery (O R 1.57; 95% CI, 1.39–1.78) were detected with endometriosis compared to the healthy control group. However; no difference was found incidence of gestational hypertension and preeclampsia in the same study.[36] According to the recent observational study of Chen et al, baseline demographic features of 469 pregnant with surgically diagnosed endometriosis among 52,202 pregnant compared with women without endometriosis, found that the average age of conception of patients with endometriosis having a history spontaneous abortion and conceive with assisted reproductive technology was higher than those without endometriosis [26]. It was found that women with endometriosis demonstrated an increased risk of placenta previa (relative risk [RR], 3.30; 95% confidence interval [CI], 1.65–5.40) and cesarean delivery (RR, 1.24; 95% CI, 1.10–1.40). [26]

Increased preterm delivery, abortion, placenta previa, placental abruption, SGA and cesarean delivery rates were found in pregnancies with endometriosis.

The limitations of studies are summarized that some of the patients become conceived with ART in which these pregnancies have specific increased negative maternal and neonatal outcomes. In addition, most of studies are retrospective, limited sample size, inappropriate comparison groups, insufficient maternal surgical care and neonatal care by the same center occurring differences in treatment protocol and quality of care can be named among the other

causes of limitations. On the other hand, another limitation is that the presence of endometriosis in most of the patients could not be confirmed by diagnostic laparoscopy.

To conclude, various adverse effects such as insufficient uterine contractility due to progesterone resistance during implantation period and pregnancy as well as endometrial and systemic inflammatory processes and free radicals leading to endometrial over activity may occur on women with endometriosis. All these changes in the local endometrial environment can cause preterm labor, placental detachment, placenta previa, fetal retardation, increased cesarean delivery and neonatal intensive care unit admission. These findings suggest that women with endometriosis should receive prenatal counseling and until the counterproof is found, they must be considered as high risk pregnancy during pregnancy period.

3.Endometriosis and Miscarriage

Approximately 30-50 % of clinical pregnancies end in spontaneous abortion which is the most common complication of pregnancy. [37] To date, available evidence from epidemiological studies between endometriosis and spontaneous abortion is scanty and conflicting. [38] In these studies, it was mentioned that adenomyosis may be a factor that alter the outcomes due to frequent coexistence of adenomyosis and endometriosis. [28]

The changes in humoral and cellular immunity in endometriosis may have negative effects on fertility through various mechanisms such as ovarian reserve and quality, sperm-oocyte interaction and implantation. [38,39] Uterine environment before pregnancy may be a risk factor for placental bed disorders. The eutopic endometrium in patients with endometriosis may show abnormal immune, morphological and biochemical changes compared to the

endometrium in normal patients. In obstetric studies, this endometrium has been shown to cause preterm birth, intrauterine growth retardation and small for gestational age newborns. [40]

There are many theories as to why endometriosis contributes to poor obstetric outcomes. These may include endometrial resistance to progesterone activation, an inflammatory process at the endometrial and systemic level, inadequate uterine contractions, and excessive activation in endometrial free radical metabolism. [25,26,41-44] Increased macrophage, cytokine and other immunological mediator concentrations in the abdominal cavity are also thought to have an embryotoxic effect. [45] It has been reported that cultured endometriotic cells may adversely affect implantation by producing IL-6. [46] Aromatase, an enzyme locally increased in endometriotic foci, is overexpressed, leading to abnormal biosynthesis of estradiol (E2). This condition leads to a positive feedback between estrogens and prostaglandins, increasing the production of inflammatory and proliferative products such as COX-2 and PGE2. [47] Therefore, endometriosis-related abortions are thought to be due to highly complex immunological processes. [48]

In addition to estrogen dependence, genetic, environmental and inflammatory processes may play an important role in the development of endometriosis. [49] Macrophages play a key role in regulating the body's immune response in a variety of conditions. In current studies, it has been shown that macrophages play an important role in the feto-maternal junction during pregnancy, especially in the inflammatory process. In particular, decidual macrophages that can communicate and interact with trophoblast cells are likely to contribute significantly to balancing and regulating trophoblast function. [50,51]

Laminin-1 membrane protein is emerging as the key molecule in embryogenesis, embryonic implantation and placentation. [49] The presence of IgG anti-laminin-1 antibodies in endometriosis-associated infertility has been demonstrated. These antibodies are thought to play a role in autoimmune-associated reproductive failure and spontaneous abortions. [51] Spontaneous abortion may be linked to changes in cholesterol and lipopretin metabolism, which are regulated and transported with apolipoprotein E levels throughout pregnancy. In the study of Collaza et al., it was investigated whether there is a relationship between apolipoprotein E genotype (ε2, ε3, ε4) and endometriosis and/or endometriosis-associated infertility. [52] At the end of the study, although there is no relationship between apoliprotein E genotype and endometriosis, ε2-carrier is 3 times and ε4-carrier is 2 times higher in patients with endometriosis with at least one abortus.

In addition to studies indicating that the risk of abortion increases [26, 53-58] in endometriosis, there are also studies indicating the opposite side. [36,37, 39, 47, 59-62] 31,068 pregnant patients were followed in the 12-year cohort study of Aris et al., of which 30,284 as patients without endometriosis and 784 as patients with endometriosis were registered. [54] In this study, spontaneous abortion was reported as 2.8% (22/784) in patients with endometriosis and 1.5% (454 / 30.284) in the control group, and it was stated to be statistically significant. This paper is the first study to show the effect of endometriosis on spontaneous abortion. [54] In the retrospective study of Chen et al., the spontaneous abortion rate was 30.1% (141/469) in the group with endometriosis and 24.7% (12.811 / 51.733) in the group without endometriosis. [26] In the study, no information was given about the relationship between endometriosis stage and abortion. Kohl Schwartzve et al. reported that patients with ASRM stage 1/2 and superficial

lesions had a higher risk of abortion compared to patients with ASRM stage ¾, endometrioma and deep infiltrating endometriosis (DIE). [56] The authors claimed that early stage lesions had more inflammatory diseases, which could lead to possible defective folliculogenesis, fertilization and/or implantation.

Studies investigating the effects of endometriosis on IVF success due to increased risk of miscarriage could not reach a clear conclusion. [37,39,63] Pallacks et al. found significantly higher risk of spontaneous abortion in patients with surgically diagnosed endometriosis compared to the control group in 588 fresh embryo-transferred IVF cycles. [63] In contrast, in the study of Yang et al., the risk of abortion was found similar in the study and control groups (OR 1.143 95% Cl (0.951–1.374), the rates were reported as 225/1006 (with endometriosis) for the study group and as 405/2012 (without endometriosis) for the control group. [39] In the subgroup analysis, when the spontaneous abortion risk factors were corrected, it was observed that endometrioma size or presence did not cause a significant increase in the risk of abortion. In the study by Benaglia et al., examining IVF patients with 239 endometriosis and 239 without endometriosis after 12 weeks of gestation, spontaneous abortions were 2 in the study group and 1 in the control group and the results were not statistically significant. [37]

There are few studies to report the effect of DIE on pregnancy outcomes. [57,64,65] Exacoustas et al. reported that pregnancies resulted in abortion in 21.2% of 52 pregnant women with rectovaginal DIE (≥ 2 cm in size). [64] There was no difference in terms of miscarriage between IVF-treated women or patients who conceived spontaneously. In a study of 419 women with endometriosis in which spontaneous abortions were examined according to the location of endometriosis, the total spontaneous abortion was found to be 87 (20.8%) in patients with

rectovaginal, endometrioma + peritoneal, peritoneal only and endometrioma only. [32] No significant difference was found between the groups in terms of abortion. In another study, no significant difference was found between the endometriosis stage and spontaneous abortion. [65] On the contrary, Santulli et al., found higher risk of spontaneous abortion in both endometrioma and DIE groups compared to the control group. [57]

There are several studies on how surgical treatment of endometriosis affects spontaneous abortion rates. [49, 55, 66-69] There was no significant difference in the risk of abortion between patients with treated moderate to mild endometriosis and the control group (16.2% and 23.1% respectively). [66] In another prospective randomized study investigated abortus rates after endometriosis surgery, post-treatment abortion rates did not decrease significantly. [67] In a meta-analysis, there was no difference in terms of the risk of fetal loss between laparoscopic endometriosis surgery and only diagnostic laparoscopy. [68] Similarly, Gergolet et al. did not show a significant difference in spontaneous abortion rates before or after metroplasty in patients with endometriosis. [49] On the contrary, Metzger et al. stated that the rates of abortion decreased from 63% to 0% after laparoscopic treatment of endometriosis. [69] Interestingly, another result in this study was to decline in abortion rates in the expectant management arm. In other similar studies, it has been reported that abortion rates decrease after surgical treatment of endometriosis. [55, 70]

As a result, the data in studies on endometriosis and spontaneous abortion are not sufficient. Nevertheless, pathophysiological mechanisms that play a role on the basis of endometriosis are considered to be a common risk factor for spontaneous abortion.

Although it is thought that pregnancy outcome may be negatively affected in women with endometriosis, the data obtained from epidemiological studies do not provide sufficient evidence.

4. Endometriosis and Infertility

Endometriosis is diagnosed in 25-40% of patients presenting infertility. Endometriosis distrupts tuba-ovarian anatomy and reduces follicular reserve by follicular atresia as a result of inflammatory reaction triggering oxidative stres and it is known to affect negatively the quality of oocytes especially in infertile patients.[71] Fecundability rate for healthy couples is 15-20% monthly, but this rate varies as 2-10% in endometriosis. Endometriosis related infertility varies depending on peritoneal, ovarian or deep infiltrative. When compared to other reasons of infertility, fertilization, implantation and pregnancy rates during IVF treatment were found to be lower, especially in stage III/ IV endometriosis cases.[72, 73]

There are two different treatment approaches of endometriosis, medical or surgical. It has not been proven that simply ovarian suppression with medical treatment increases spontaneous pregnancy rates. However, there are also data about the rising preganancy rates by the application of IVF after ovarian suppression with oral contraceptives, dienogest 2 mg or GnRH agonist for 3-6 months. [74] Accordingly, in infertility group associated with endometriosis, surgery or IVF approaches forms the current treatment options; but there is controversial data about the superiority to each other. [75]

Although lower oocyte yield and higher cycle cancellation rate per cycle are observed in patients with endometrioma, live birth rate does not differ from patient without endometrioma.[76] Therefore, the decision of endometrioma surgery previous to IVF must be evaluated according to the degree of pain symptom and the availability of follicle aspiration.[77] In patients without surgery before IVF, progression of endometriosis, increased inflammatory and oxidative stress, rupture or infection during oocyte pick up procedure, misdiagnosed of occult malignancy and complications related to pregnancy may be seen. [77] On the other hand, in patient undergoing endometrioma surgery before IVF, surgical complications at the opposite rate with experience of the surgeon, diminished ovarian reserve, premature ovarian failure and delay in IVF procedure may increase. [77] Similarly, when ICSI outcomes of infertile patients undergo to the surgery of endometrioma are compared to endometrioma group without surgery and endometriosis free group; in patients who underwent endometrioma cystectomy, basal FSH level was high, the number of antral follicles was low and the total amount of gonadotropin administered was higher. [78] Withal, total oocyte yield, numbers of MII oocyte and fertilization rate are lower. So it is obvious that in patients who underwent endometrioma cystectomy, ovarian reserve loss may be higher than the compared groups. [78]

Both researches about the decline of follicular reserve after endometrioma surgery and researches about the complications of pain and infection which may occur during IVF in patients with endometrioma who are not scheduled for surgery are just a few and evidence level is not enough. [74,77] Antibiotic prophylaxis is a rational approach during oocyte pick up procedure in patients with endometrioma.

Thus, the decision of endometrioma surgery before IVF should be individualized according to the patient. Conservative approach should be preferred in asymptomatic patients

with advanced maternal age and low ovarian reserve. Similarly, bilateral endometrioma, accompanied by male factor and history of previous endometriosis surgery are factors to recommend initially IVF. [75]

In the light of current evidencen, the decision of endometrioma surgery before IVF should be individualized and conservative approach should be preferred in asymptomatic patients with advanced age, low ovarian reserve or bilateral endometrioma.

Deep infiltrative endometriosis (DIE) is an advanced form that includes 12% of patients with endometriosis.[72] In DIE cases, highly impaired anatomy due to widespread adhesions effects gamet transportation negatively. Although there are retrospective and prospective observational studies comparing spontaneous pregnancy rates and IVF pregnancy rates in groups with and without surgery, there are no prospective randomized controlled studies. [72] There is no sufficient evidence about the positive effect of DIE surgery to IVF success. The complications of DIE surgery has been reported 9% in retrospective studies and 13% in prospective observational studies. The most important complications are bowel leakage as 5% and the second most common intestinal atony. [72] Current data shows that long term clinical results are satisfactory regardless of complications, but the risks of major complications should always be considered in DIE surgery which would be performed to increase spontaneous pregnancy rates and IVF success. [72,79] There is no prominent difference between the resection techniques 'local excision' or 'segmental resection' to increase IVF success in DIE patients with colon involvement. Minimizing the complication should be the goal when making a decision what technique to use. [72] Roman et al. reported that ovarian hyperstimulation during

IVF may trigger the intestinal occlusion in DIE patients.[80] However, four further clinical studies do not find any relation between IVF / ICSI procedure and endometriosis recurrence.[81,82]

Supporting data for potential benefit of deep infiltrative endometriosis surgery infiltrating intestinal wall to increase spontaneous pregnancy rate and IVF success is inadequate and also these type of surgeries will be associated with the risk of major complications.

As a result, although the data regarding DIE surgery success before IVF is weak and inadequate, the surgical option may be recommended if there is concomitant severe pain and /or recurrent IVF failure, provided that it is performed in an advanced endometriosis surgery center after careful evaluation.

5. The Effect of Adenomyosis on Pregnancy

Adenomyosis is defined as the ectopic proliferation of endometrial glands and stroma in myometrium.[83] This disease affects about 10-20% of women of reproductive age and often occurs with severe dysmenorrhea and / or hypermenorrhea.[84] Studies in the literature reported that adenomyosis affects fertility and increases spontaneous and second trimester abortions.[85,86]

In recent studies, it has been reported that adenomyosis may have an effect on obstetric and neonatal outcomes.[87] In a meta-analysis about this topic in 2018, Bruun et al.[88] included a total of about two and a half million women with adenomyosis and there was a relationship between adenomyosis and preterm labor (OR: 3.09, 95% CI; 1.88-5.09) and SGA (OR: 3.23, 95% CI; 1.71-6.09), and as a result, the authors reported that women with adenomyosis should

be closely monitored. Mochimaru et al.[89] reported that women with adenomyosis had higher rates of preterm delivery, fetal growth restriction and fetal malpresentation in their pregnancies. Hashimoto et al.[86], as previously reported, showed that adenomyosis is associated not only with an increased incidence of preterm labor, but also with second trimester abortion, preeclampsia and placental invasion anomaly. Yamaguchi et al.[87] showed that adenomyosis is a risk factor for preterm delivery, low birth weight and SGA in their study using data from the Japanese national birth cohort study. In 2019, Scala et al.[90] showed that the presence of diffuse adenomyosis may be related to SGA and placental dysfunction in their retrospective study which included 148 endometriosis, 38 focal adenomyosis and 20 diffuse adenomyosis patients.

It has been reported that adenomyosis can be associated with preterm delivery, SGA, preeclampsia and placental dysfunction.

Studies investigating the effect of adenomyosis on pregnancy outcomes have given conflicting results. The problem underlying these contradictory results is that some of the adenomyosis patients become pregnant with assisted reproductive technologies (ART) and this ART pregnancies have specific increased negative maternal and neonatal outcomes. To eliminate this situation, Harada et al.[91], after adjustment the possible effects of the ART results of the presence of adenomyosis, showed that obstetric complications significantly increased the prevalence in a prospective cohort study in 2019. In a meta-analysis involving 6 studies on this subject, only spontaneously conceived adenomyosis patients were included and the authors stated that adenomyosis had a negative effect on pregnancy outcomes by increasing the incidence of preterm labor, preeclampsia and SGA.[92]

In conclusion, pregnancies of women with adenomyosis are at risk for preterm delivery, fetal growth restriction, fetal malpresentation, SGA and placental dysfunction. Prenatal follow-up of pregnant women suffering from adenomyosis is recommended more frequently in order to prevent negative pregnancy outcomes.

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