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Case Report

Pregnancy complicated by adenomyosis resulted in miscarriage in three cases of *in vitro* fertilization–embryo transfer

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Three women with adenomyosis conceived by *in vitro* fertilization–embryo transfer (IVF–ET), but miscarried in the second trimester. The uterus in each case was inflamed post-partum and one patient underwent total abdominal hysterectomy as treatment for the severe inflammation. Although the mechanism of the miscarriages is unclear, these cases strongly suggest that it is related to the inflammation of the myometrium associated with adenomyosis, and that such pregnancies have a high risk of not continuing to term. Preventing inflammation could result in a live birth. (Reprod Med Biol 2004; 3: 95–98)

Key words: adenomyosis, inflammation, *in vitro* fertilization–embryo transfer, miscarriage.

INTRODUCTION

ALTHOUGH UTERINE ADENOMYOSIS is considered to be closely related to infertility, there is no agreement on the most appropriate therapy. The options are hormonal treatment, surgery and *in vitro* fertilization–embryo transfer (IVF–ET), but information regarding the outcome of these treatments is not extensive.[1] There are case reports of successful pregnancies following treatment with a gonadotropin releasing hormone agonist (GnRH-a)[2,3] or danazol-loaded intrauterine device,[4] and complete microsurgical resection of the visible adenomyotic area followed by GnRH-a therapy has resulted in live births.[5,6] The clinical pregnancy rate after IVF–ET in women with adenomyosis is equivalent to that in women with endometriosis, a condition that has a high rate of spontaneous abortion.[7] We present three cases of patients with adenomyosis who conceived by IVF–ET and then miscarried in the second trimester.

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CASE REPORTS

THE CLINICAL CHARACTERISTICS of the three patients are shown in Table 1. All had been diagnosed by transvaginal ultrasonography, which showed typical adenomyosis of the uterus.[8] The posterior myometrium was thicker than the anterior and had a heterogeneous, poorly circumscribed area in all cases. Patients 2 and 3 underwent laparoscopy and the stage of endometriosis was defined as IV according to the revised American Fertility Society classification.[9] Therefore, the cause of infertility was assumed to be endometriosis and tubal factors. Patient 1 was treated with GnRH-a for 6 months, but although the size of her uterus decreased dramatically after the treatment, she did not conceive and subsequently underwent treatment with assisted reproductive technology (ART). The initial treatment for infertility for patients 2 and 3 was ART.

All three patients failed to conceive after several conventional IVF trials, so they then underwent 3–4 months of treatment with a GnRH-a prior to further IVF. This 'ultra long' pretreatment has been reported as more effective than conventional regimens for women with endometriosis[10] and in the present cases each subsequent IVF treatment succeeded. All fetuses were singletons.

Table 1 Characteristics of three patients with adenomyosis who conceived by *in vitro* fertilization–embryo transfer and then had a miscarriage

Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	34	37	39
Infertility	Primary	Primary	Primary
Dysmenorrhea	Severe	Severe	Severe
Duration of infertility (years)	3	3	3
Uterine size (by internal exanimation)	Fist size	Under goose size	Under fist size
Uterine appearance (by transvaginal ultrasound)			
Asymmetric thickness of anterior and posterior myometrium	Yes	Yes	Yes
Heterogeneous, poorly circumscribed area	Yes	Yes	Yes
Increased echotexture of the myometrium	Yes	Yes	Yes
Examination for infertility			
Semen analysis	Normal	Normal	Normal
Ovulation disorder†	No	No	No
Tubal factor (Hysterosalpingography)	Normal	Obstruction	Obstruction
Peritoneal factor	Unknown	Peritubal adhesion	Peritubal adhesion
Cervical factor‡	Normal	Normal	Normal
Endocrinology§	Normal	Normal	Normal
CA125 (U/mL)	95	113	112
Laparoscopic surgery	No	Yes	Yes
r-American Fertility Society classification¶	Unknown	IV	IV
GnRH-a therapy (months)	6	No	No
History of assisted reproductive technology			
Number of trial *in vitro* fertilization	4	3	9
Number of fertilized oocytes	1	1	6
Number of transferred embryos	1	1	3
Number of fetus	1	1	1
Week of termination	22	18	14

GnRH-a, gonadotrophin releasing hormone agonist. †Documentation of ovulation included basal body temperature, luteinizing hormone (LH) surge, ultrasound monitoring; ‡Hühner test; §endocrinology survey included serum LH, follicle-stimulating hormone, prolactin, dehydroepiandrosterone sulfate and testosterone; ¶revised American Fertility Society.

Patient 1

At 10 weeks' gestation she was hospitalized for 5 days because of vaginal bleeding and after discharge from hospital, she was followed up weekly at the outpatient clinic where she reported occasional episodes of slight bleeding. At 22 weeks' gestation, intrauterine fetal death (IUFD) occurred. The dead fetus was normal in appearance and chromosomal analysis showed a normal male karyotype. Post-partum, the patient had a high fever and severe lower abdominal pain, with increased levels of white blood cells and C-reactive protein (CRP). The focus of the inflammation was the myometrium and because antibiotic therapy was not effective, she underwent a total abdominal hysterectomy. Pus was discharging through a fistula of the myometrium into the pelvic cavity. Pathological examination of the resected uterus showed that the extensive and highly degraded area of the posterior myometrium was part of the adenomyosis lesion.

Patient 2

In this case, a slight, brown vaginal discharge continued throughout the first trimester. At 18 weeks' gestation, she was admitted as an emergency with preterm rupture of membranes. The dead fetus was a normal male in appearance, but chromosomal analysis was not carried out. Pathological examination of the placenta showed mild chorioaminionitis. Post-partum, the patient was strongly CRP positive and had lower abdominal pain. Antibiotics were effective.

Patient 3

The course of the pregnancy in this case was almost normal except for occasional brown discharge, but at 14 weeks' gestation, IUFD occurred. The dead fetus was normal in appearance. Pathological examination of the placenta showed moderate perivillous fibrin deposition

and no chorioaminionitis. Post-partum, the patient had a slight fever and lower abdominal pain. Antibiotics were effective.

DISCUSSION

IT IS UNCLEAR why these pregnancies complicated by adenomyosis resulted in miscarriage. All three patients had inflammation of the uterus post-partum and the pathological findings of the resected uterus in case 1 are very suggestive of the possible mechanism. The myometrium was highly inflamed, despite the short time that elapsed after the IUFD, so the inflammation of the myometrium may have gradually progressed during pregnancy. Patients with endometriosis have an increased number of macrophages in the peritoneal fluid.[11] These cells secrete several cytokines, including interleukin-1 and tumor necrosis factor, that are involved in inflammation.[12,13] Therefore inflammatory cytokines could be present in ectopic endometrial tissue, not only in the peritoneum, but also in the myometrium. Inflammatory cytokines are considered a key substance in the mechanism of preterm delivery,[14,15] so we hypothesize that the endometrial glands in the myometrium lose function histologically and physiologically during pregnancy and then become simple cavities containing abundant macrophages, which secrete the inflammatory cytokines that cause miscarriage.

Endometriosis may be an autoimmune disease, because it is often associated with the presence of autoantibodies, other autoimmune diseases and recurrent immune-mediated abortion,[16,17] and that etiology has also been suggested for adenomyosis.[18] Patients with antiphospholipid antibodies often experience unexplained IUFD, regardless of the conception method, and thus, an alternative mechanism of the miscarriage could be an autoimmune response. Unfortunately, autoimmune antibodies, including anticaldiolipin antibody, anticaldiolipin beta-2 glycoprotein 1 antibody, antidouble strand DNA antibody and antinuclear antibody, were analyzed in patient 2 only and none were positive.

These cases imply that pregnancies complicated by adenomyosis have a high risk of miscarriage and anti-inflammatory therapy could result in a live birth. Alternatively, there is cytoreductive surgery prior to IVF treatment to remove the adenomiotic tissue that contains the inflammatory cytokines.

In conclusion, there is no agreement on the most appropriate therapeutic management of infertility caused by uterine adenomyosis, and even with therapy there is still a high risk of miscarriage after conception. Prevention of inflammation during pregnancy, as well as strict obstetrical management, may achieve a live birth.

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