Successful pregnancy and delivery of a healthy baby after endometrial biopsy treatment in an in vitro fertilization patient with severe Asherman syndrome

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Objective: To implement the procedure of endometrial biopsy in a case of severe Asherman syndrome as a possible treatment to increase uterine receptivity.

Design: Case report.

Setting: IVF Unit, Kaplan Medical Center, Rehovot, Israel.

Patient(s): A 29-year-old patient with severe Asherman syndrome, who underwent six operative hysteroscopies combined with hormonal treatment, and no functional receptive endometrium was achieved.

Intervention(s): We performed three endometrial biopsies on days 8, 12, and 21 of a progyluton-induced menstrual cycle, and a fourth biopsy on day 21 of the next induced menstrual cycle. After that cycle the patient underwent an IVF treatment.

Main Outcome Measure(s): Ultrasound measurement of endometrial thickness, serum $\beta-$hCG, sonography test for the presence of a gestational sac with heartbeat, and pregnancy follow-up until birth.

Result(s): Biopsy treatment increased the thickness of the endometrium from unobservable by sonography to 7 mm on the day of hCG administration. The next IVF cycle resulted in implantation of an embryo and the birth of a healthy baby boy.

Conclusion(s): Repeated endometrial biopsies may be used in patients with Asherman syndrome immediately after forming a uterine cavity by hysteroscopy to improve its receptivity. (Fertil Steril® 2009;91:1956.e1–e3. ©2009 by American Society for Reproductive Medicine.)

Key Words: Asherman syndrome, biopsy, endometrium, in vitro fertilization

Intrauterine adhesions were first reported in 1894 by Heinrich Fritsch (1) and were further characterized by Joseph Asherman in 1948 and 1950 (2, 3). Asherman syndrome occurs mainly as a result of trauma to the endometrium after abortion or a birth with complications that leads to partial or complete obliteration of the uterine cavity by adhesions. The clinical manifestation of Asherman syndrome includes hypomenorrhea or amenorrhea, infertility, and recurrent pregnancy loss. The prevalence of Asherman syndrome varies with the populations and depends on the diagnostic methods used by the clinicians (4). Among patients who undergo hysterosalpingography (HSG) for a fertility survey, 1.5% are diagnosed to have the syndrome with different degrees of severity (5). Although hysteroscopy is widely used to diagnose and treat Asherman syndrome, the success in achieving pregnancy and a live birth remains challenging.

Many fertility disorders have been overcome by a variety of assisted reproductive techniques (ART). Nevertheless, implantation remains the rate-limiting step for the success of IVF treatment, with approximately two-thirds of implantation failures resulting from inadequate uterine receptivity (6, 7). In 2003 we demonstrated that local injury of the endometrium in patients undergoing IVF substantially increased uterine receptivity. Specifically, endometrial biopsies taken during the spontaneous cycle that preceded IVF treatment more than doubled the rates of implantation, clinical pregnancies, and live birth (8). A similar beneficial effect of endometrial biopsy was reported by Raziel et al. in 2007 (9) and Zohu et al. in 2008 (10).

In this article we describe a case in which a successful pregnancy was achieved after the use of local injury to the endometrium in a patient with severe Asherman syndrome.

CASE REPORT

A 29-year-old patient was admitted to our IVF unit in Kaplan Medical Center, Rehovot, Israel, in June 2007. She had been married for 5 years and had given birth 1.5 years earlier. Her

medical history recorded only a tracheostomy due to meconium aspiration syndrome at birth. Her first menstrual period appeared at the age of 11 years and the cycles were regular until her first pregnancy. In 2005 she conceived spontaneously. During the third trimester, premature contractions and preeclampsia developed. She delivered a healthy baby girl in the 34th week of gestation in a normal vaginal delivery. Examination of the placenta revealed a possible partial retention. Therefore, a manual survey of the uterine cavity was performed. Two days after delivery, a postpartum hemorrhage occurred and oxytocin was administered. Two weeks later the patient underwent hysteroscopy accompanied by curettage, which revealed decidua with no sign of infection.

Due to secondary amenorrhea the patient underwent a fertility survey in which the hormonal profile and spermogram were normal. An attempt to perform HSG failed due to inability to inject iodine solution into the uterine cavity. Therefore, in April 2006, a second hysteroscopy was performed during which total occlusion of the uterine cavity due to severe adhesions was observed. A severe degree Asherman syndrome was diagnosed. After these findings, an operative hysteroscopy was performed. An artificial triangular uterine cavity was established but without any functional endometrium. Another operative hysteroscopy with adhesiolysis was performed in August 2006. After this procedure, a normal uterine cavity was obtained. In April 2007 a fifth hysteroscopy with adhesiolysis was performed. During this procedure, as well as in previous hysteroscopies, it was impossible to visualize both tubal osteumes.

To obtain a functional endometrium and cyclic menstruation, the patient was treated with estrogen (E) and progestins. However, after several consecutive cycles of this treatment, no endometrium could be visualized by sonography. Before attempting an IVF treatment, a sixth hysteroscopy was performed. A tubular uterine cavity, occlusion of left uterine horn, larger right uterine horn, and occlusion of both tubal osteumes were diagnosed.

Since six hysteroscopies combined with hormonal treatment failed to induce the development of a functional endometrium, we decided to use the endometrial biopsy treatment that was shown to improve uterine receptivity in IVF patients with repeated implantation failures (8–10). We performed three endometrial biopsies using a Pipelle catheter (Pipelle de Cornier, Prodimed, Neuilly-en-Thelle, France) on days 8, 12, and 21 of a menstrual cycle that was induced with progyluton (Schering AG, Berlin-Wedding, Germany). The endometrium that could not be observed by sonography on day 8 of the cycle, developed and thickened to 6 mm on day 21. A fourth biopsy was performed on day 21 of the next induced menstrual cycle in an attempt to further increase endometrial thickness. After that cycle, the patient underwent IVF treatment. Pituitary down-regulation was obtained by daily SC injections of triptorelin acetate (Decapeptyl; Ferring Pharmaceuticals, Caesarea, Israel) starting on the second day of the menstrual cycle. After 14 days, when down-regulation was achieved, daily injections of 150 U of follitropin alfa (go-

nal-F; Serono, Herzlia Pituach, Israel) were administered for ovarian stimulation. On the 12th day of stimulation, 250 μg of choriogonadotropin alfa (ovitrelle; Serono S.A.) was administered to induce oocyte maturation. Endometrial thickness on that day was 7 mm. Ovum pick-up was performed 34 hours later under general anesthesia. Four eggs were retrieved and were fertilized by conventional insemination. Three days later an eight-cell embryo was transferred to the uterus and an additional seven-cell embryo was cryopreserved. Progesterone (Utrogestan; Besins International Labs, Paris, France) was administered for luteal support.

Fourteen days after ovum pick-up, a blood test for serum β−hCG levels showed a positive result of 107 U. Ultrasound examination performed 3 weeks later revealed a gestational sac with a heartbeat-positive embryo.

Prenatal survey included sonography of nuchal translucency, which was 1.8 mm, and an early biochemical blood test. Statistical analysis of the results revealed the risk of Down syndrome to be 1:320. An early anatomical survey detected cervical cysts. A triple test revealed α-fetoprotein (AFP) levels of 2.88 multiple of medians (MOM). Subsequent to these results, the patient was advised to undergo genetic amniocentesis, which was performed in the 21st week of gestation. A normal male karyotype was diagnosed.

The patient was hospitalized in the 24th week of gestation due to premature contractions and vaginal bleeding. Placenta previa was ruled out but vasa previa was suspected. She was treated with nifedipine (presolat; Perrigo, Bnei Brak, Israel) and a course of betamethasone (Celestone chronodose; Schering Plough) was administered. During hospitalization, gestational diabetes was diagnosed and treated with insulin.

In the 30th gestational week a preterm premature rupture of the membrane occurred. The patient was treated conservatively for 5 days and received another course of betamethasone. Five days later in the 31st week of gestation a sonographic examination revealed vasa previa. An emergency cesarean section was performed. A healthy normal baby boy was delivered, weighing 1,776 g and with an Apgar score of 9/10. During the surgery the placenta was suspected to be adherent. Placental site bleeding was diagnosed and treated with sutures until full hemostasis was achieved. The postoperative course was normal and the patient was discharged 5 days after the cesarean section.

DISCUSSION
We herein present a case of secondary infertility due to severe Asherman syndrome. Although the patient underwent six operative hysteroscopy treatments to form a normal uterine cavity, no functional endometrium was observed. Hormonal treatment also failed to induce the development of a functional receptive endometrium. Therefore, we decided to use the endometrial biopsy treatment that was shown to improve receptivity of the endometrium in IVF patients who had repeated implantation failures (8–10). Four biopsies were performed resulting in an increase in the thickness of the

endometrium from unobservable by sonography to 7 mm on the day of hCG (ovitrelle) administration. The next IVF cycle resulted in implantation of an embryo and the birth of a healthy baby boy.

The preferred treatment of Asherman syndrome is operative hysteroscopy with adhesiolysis to form a suitable uterine cavity (11). According to the literature, postoperative adhesions occur in almost 50% of the severe cases and in 21.6% of the moderate cases of Asherman syndrome (12). To prevent reformation of adhesions three mechanical methods are described: the use of an intrauterine device (IUD), a pediatric Foley catheter, or an intrauterine balloon (4, 13). It is important to perform a second-look hysteroscopy to evaluate the effectiveness of the treatments and to perform more operative procedures if needed. It may be necessary to repeat the hysteroscopy several times in a patient who has severe Asherman syndrome (4, 13).

The hysteroscopy procedure is followed by hormonal treatment to restore a functional endometrium. Two hormonal protocols have been previously described: sequential treatment with E and progestin for a few cycles or E treatment alone (4, 13). It has been suggested to combine the hormonal treatment with drugs, such as low dose aspirin, nitroglycerine, or sildenafil citrate, to improve the postoperative vascular perfusion to the endometrium, facilitating the development of a functional endometrium (13). The protocol used in our case was sequential treatment with E and progestin alone.

Decidualization and formation of a receptive endometrium involves morphological and functional changes that are induced by the sex steroids E and P. In parallel, modulations in the expression of different cytokines, growth factors, transcription factors, and prostaglandins take place (14, 15). Decidualization could also be provoked by injury as was initially reported in animal models (16, 17). Local injury was later shown by our group and other investigators to increase endometrial receptivity in humans (8–10). We have further demonstrated that local injury performed during a spontaneous menstrual cycle modulates a variety of genes, the effect of which is sustained in the next cycle that represents the cycle of IVF treatment (18).

We postulate that the hormonal treatment administered to the patient, as described in this case report, was insufficient to induce decidualization, and that endometrial receptivity was improved by the contribution of the biopsy procedure.

Our case is the first example in which the alternative approach of endometrial biopsy was used to produce a functional endometrium in a case of severe Asherman syndrome, following the failure of conventional treatments. We therefore suggest that repeated endometrial biopsies be used immediately after forming a uterine cavity by hysteroscopy in patients with Asherman syndrome.

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