Thin endometrium in donor oocyte recipients: enigma or obstacle for implantation?

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Objective: To evaluate the combined effect of endometrial thickness and anatomic uterine factors on clinical outcome in oocyte donation recipients.
Design: Retrospective analysis of oocyte donation cycles conducted between 2005 and 2010.
Setting: Two private IVF centers.
Patient(s): A total of 737 donor oocyte cycles.
Intervention(s): None.
Main Outcome Measure(s): Clinical pregnancy and live birth rates.
Result(s): No statistically significant difference was found in clinical pregnancy rates and live birth rates in cycles with endometrial thickness <6 mm compared with those with endometrial thickness >10 mm. However, a relatively high rate of live births was found within a medium range of endometrial thickness (8.2–10 mm). All intrauterine adhesion cases occurred in cycles with thinner endometrium.
Conclusion(s): No statistically significant difference was found in clinical pregnancy rates and live birth rates in cycles with endometrial thickness <6 mm compared with those with thickness >6 mm. A relatively high rate of live births was found within a medium range of endometrial thickness (9.1–10 mm). (Fertil Steril® 2013;100:1289–95. ©2013 by American Society for Reproductive Medicine.)
Key Words: Endometrial thickness, oocyte donation, uterine factors, estrogen replacement therapy

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The success of IVF depends primarily on embryo quality and uterine receptivity. Precise and specific endometrial maturational development is critical for embryo implantation and subsequent growth. Adequate proliferation and differentiation during the proliferative phase are followed by timely secretory changes during the luteal phase with stromal decidualization (1).

Because of its noninvasiveness and reasonable accuracy, sonographic assessment of the endometrium has become the gold standard for diagnostic workup and follow-up of patients undergoing fertility evaluation and treatment. Several parameters have been used in the evaluation of uterine endometrium by ultrasound: endometrial thickness (Eth), endometrial pattern assessment (2), Doppler sonography of uterine and subendometrial blood flow (3), and endometrial volume computation (4). Because Eth is an easily measured factor, several studies have tried to determine its influence on pregnancy success. The conclusions are conflicting. Some studies have reported significantly lower rates of clinical pregnancy in patients with decreased Eth (5–8), whereas others have shown pregnancy rates not to be influenced by the degree of endometrial proliferation assessed by ultrasound (9–13). Moreover, clinicians have not been able to establish an ideal uterine lining growth measurement for conception. Although several studies reported that the thickness of the endometrium for a successful implantation may be as low

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as 4 mm (14–16), a minimum of 6 mm is classically considered adequate for achieving pregnancy (17–21).

A thin endometrium, which is defined as between 6 and 9 mm in different studies, is a relatively frequent finding. Sher et al. (22) reported a 5% incidence of Eth <9 mm in natural cycles among women aged <40 years, and up to 25% in women aged 41–45 years. Despite the inconclusive evidence, the currently prevailing practice is to treat women with inadequate Eth with extended administration of estrogen (E) (23), to switch the oral preparation to a transdermal or intramuscular one, or to treat with low-dose aspirin (24), vaginal sildenafil citrate (25, 26), pentoxifylline, or vitamin E (27). According to a survey conducted among Israeli gynecologists, only 13% preferred IVF without any additional treatment in cases of thin endometrial measurements (28). Another option is to offer patients with a nonsatisfactory Eth to freeze all embryos and postpone ET (29). In fact, assessment among medical professionals showed that 30% tend to defer ET at Eth of ≤6 mm (28).

In oocyte donation, the low variability of age and embryo quality affords an opportunity for examination of the independent effect of uterine receptivity parameters, such as Eth (18, 30–32). Treatment with donated oocytes is indicated for a wide spectrum of infertility conditions, including advanced female age, premature ovarian failure, repetitive failure of IVF, and genetic disorders. Studies examining the effect of Eth on successful pregnancy rates in donor oocyte recipients have also reported conflicting conclusions (33–36).

Limited information is available regarding the possible factors responsible for impaired endometrial growth. Failure to develop a normal uterine lining may reflect any of several factors, such as infection, leiomyomas, scarring from dilatation and curettage (37), low E levels, poor uterine blood supply or, possibly, endometrial antibodies. However, in most cases the causative agent remains unknown. It is possible that only some of the causes associated with a sonographic finding of poor endometrial growth are related to impaired embryo implantation rates, whereas thin endometrium in many other cases may be a normal finding with no adverse effects on implantation rates. Determination of the factors accompanying thin endometrium that are related to decreased pregnancy rates may help to identify the patients requiring a more specific and tailored medical treatment to build an adequate Eth.

In this study we examined correlations between Eth measurement, diagnostic procedures, uterine findings, and IVF outcome. This is the largest patient cohort reported to date of donor oocytes with a maximal Eth of 6 mm. Our objective was to investigate whether integrated analysis of Eth, combined with uterine factor parameters, may improve the prediction of donor oocyte cycle outcomes: clinical pregnancy, biochemical pregnancy, miscarriage, and live birth rates.

MATERIALS AND METHODS

Data from all oocyte donation cycles performed at two private IVF centers between June 2005 and October 2010 were obtained from a computerized database and reviewed retrospectively.

Oocyte Donors

Oocyte donors were aged 23–30 years, all women with proven fertility. All donors underwent counseling and filled in a health questionnaire. They underwent routine screening tests for human immunodeficiency virus, cytomegalovirus, syphilis, and hepatitis, and genetic tests for Fragile X and cystic fibrosis, and signed an informed consent form before starting a treatment cycle. The protocol for ovarian stimulation, ovum retrieval, IVF–intracytoplasmic sperm infection, and embryo handing in the laboratory was performed as previously described (38). The best-graded (morphology and cleavage) fresh embryos were selected for ET, and the rest were frozen using the slow-freezing technique. Embryo transfer was performed on day 2 to 6 after egg collection. The cycles were shared-recipient, but each recipient received six to seven mature eggs, and if this was not available no sharing was performed.

Recipients

All recipients underwent general health assessments, implications counseling, and genetic counseling and provided the welfare of the child form from their general practitioners as per the Human Fertilization and Embryology Authority code of practice. All recipients underwent routine screening tests and assessment of uterine cavity by three-dimensional transvaginal ultrasound, saline sonohysterography, and/or diagnostic hysteroscopy. When present, intrauterine adhesions and submucous myomas were removed by operative hysteroscopy.

The protocol for hormonal treatment for recipients was maintained as previously described (39). Recipients received hormonal treatment with estradiol valerate (EV), starting with the standard dose of 6 mg daily and increased according to response. Women with a menstrual cycle were synchronized by a low-dose oral contraceptive pill or GnRH agonist (IM decapeptyl, 3.75 mg), and started EV on day 5, after stopping oral contraception, or on the desired day after down-regulation. Serial vaginal scans were performed during the treatment cycle.

On the day of recovery of donated oocytes, recipients received intravaginal P (Uterogestan 800 mg/d [micronized progesterone]; Besin International Laboratories). Ultrasound-guided ET was performed 2–6 days after oocyte recovery. In recipients with Eth <6 mm, 12–14 days after starting EV treatment the dose was increased to 8–12 mg. In some women 50–100-μg E patches were added on alternate dates.

Ultrasound examinations were performed 4 to 5 weeks after positive β-hCG test results. Clinical pregnancy was defined by visualization of a gestational sac with a positive fetal heartbeat. Biochemical pregnancy was determined by an initial rise and subsequent decrease in serum β-hCG concentrations, without any sonographic findings. A miscarriage was defined as a pregnancy loss before gestational week 12, after sonographic visualization of an intrauterine gestational sac at 5 to 6 weeks' gestation. Live birth was defined as a pregnancy that ended with delivery of live infant(s).

Endometrial thickness was measured as the maximal distance between the echogenic interfaces of the myometrium