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ORIGINAL ARTICLE

# Thin unresponsive endometrium—a possible complication of surgical curettage compromising ART outcome

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## Abstract

*Purpose* Endometrial thickness is important for implantation. Little data addresses the etiology of persistently thin endometrium. We present a patient cohort in order to define common features and draw conclusions.

*Methods* Thirteen out of 1,405 IVF patients repeatedly had thin unresponsive endometrium (<7 mm). Age, history, uterine cavity status, treatment type and outcome were examined.

*Results* Patient age was 35.9±5.7 years. Ten patients had a curettage performed previously. Nine patients had normal cavity and endometrium, and in four adhesions were diagnosed and removed. Out of 99 cycles performed afterwards, endometrial thickness increased in 22. ETs were performed in 49 cycles resulting in 11 pregnancies. Their outcome was eight miscarriages, two terminations due to malformations, and one live birth.

*Conclusions* Thin unresponsive endometrium was associated with curettage, not necessarily with intrauterine adhesions. Even if adequate thickening eventually occurred, the reproductive outcome was still very poor. Therefore other alternatives should be sought for these patients.

**Keywords** ART · Curettage · Thin and unresponsive endometrium

*Capsule* Thin unresponsive endometrium without adhesions is associated with past surgical curettage procedures and results in a very poor reproductive outcome.

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## Introduction

The importance of endometrial thickness, as measured by ultrasonographic examination, to successful *in vitro* fertilization (IVF) outcome is still under debate. While some studies have shown that this parameter is important for predicting the outcome of In Vitro Fertilization (IVF) cycles [1–8], other studies have failed to show such a positive relationship [9–14]. In a third category of studies the endometrial thickness was related to the IVF outcome, but only in correlation with other parameters [15, 16]. Different thresholds of endometrial thickness were suggested as essential for successful implantation and most demonstrated that no pregnancy was established when the thickness of the pre-ovulatory endometrium was <6 mm [17]. Nevertheless, Sundstrom [18] have reported a successful outcome of an IVF cycle in a patient with an endometrial thickness of no more than 4 mm.

This retrospective cohort study examines the clinical characteristics and background of such unique patients treated in our IVF unit, in an attempt to shed some light on the etiology and response of the endometrium to different treatment modalities.

## Methods

One thousand four hundred five patients underwent IVF treatment cycles in our unit between 2004–2007. Of these we identified 13 patients who repeatedly had a thin and unresponsive endometrium during various types of treatment cycles. The ultrasonographic definition was a maximal endometrial thickness of no more than 7 mm, as measured by trans-vaginal ultrasound scans prior to ovulation or to the administration of human chorionic

gonadotropin (hCG) or progesterone, despite adequate ovarian response and serum estradiol ($E_2$) level. None of them had a uterine malformation or was exposed to DES in utero. All patients had a diagnostic hysteroscopy performed and intrauterine adhesions were surgically removed if found. ETs were performed on day 3 under US guidance or according to previous uterine length measurements from the same cycle. The patients' records were studied for general medical and gynecologic history, and for the different protocols which were utilized for ovulation induction and endometrial preparation. The major outcomes that were recorded from the post hysteroscopy cycles were: endometrial responsiveness to the different protocols used, serum estradiol level, the performance or cancellation of embryo transfer (ET), the number and quality of embryos transferred, clinical pregnancies and outcome.

## Results

We identified 13 patients who repeatedly had thin and unresponsive endometrium, as defined by our criteria, in their past and present treatment cycles. Their characteristics are summarized in Table 1.

Four patients had tubal occlusion, four had a male factor problem, four had unexplained infertility and one patient had combined mechanical and male factor infertility. Diagnostic hysteroscopies revealed a normal appearing uterine cavity in nine women, and in four a few thin mild and scarce intra-uterine adhesions were diagnosed and removed. None of these patients had a history acute pelvic inflammatory disease (PID) or of intrauterine device (IUD) insertion. Two patients had a history of prior pelvic surgery (one patient had underwent salpingectomy and the other reconstructive tuboplasty). In one of these patients a later diagnostic laparoscopy was performed and some mild peritoneal adhesions were found. Ten out of the 13 patients had at least one surgical curettage performed in their history, and six of them had more than one. All the curettage procedures were performed in order to terminate past undesired pregnancies or following a diagnosis of missed abortion (IVF and spontaneous pregnancies). These patients were treated with different protocols of hormonal supplements in an attempt to adequately build-up and prepare the endometrium for embryo transfer. The different types of treatment were categorized into six main groups: (i) artificial cycles with exogenous estrogens administered (frozen–thawed embryos only), (ii) induced cycles with exogenous gonadotropins (fresh and frozen–thawed embryos), (iii) induced cycles with exogenous gonadotropins supplemented with exogenous estrogen, (iv) induced cycles with exogenous gonadotropins and low dose (100 mg/d) aspirin (administered during the entire treatment not just after ET), (v) induced cycles combined with sildenafil (Viagra™, Pfizer) and (vi) spontaneous cycles. In the cycles with exogenous estrogens, estradiol was administered mainly orally in incremental doses, and vaginal estradiol was added in some of the cycles. The maximal oral estradiol dose administered was 4 mg qid, and the maximal vaginal dose was 3 mg tid. Transdermal estrogen was added only in two cycles without any benefit. The ETs were performed on day 3 and were not difficult or complicated. The total number of cycles using each protocol, peak serum estradiol level, the number of cycles in which there was an adequate endometrial response, cycles with ET, the number of transferred embryos, embryo quality (according to Rijnders and Jansen [19]) and pregnancies are summarized in Table 2.

Out of 99 additional treatment cycles performed following hysteroscopy, in only 22 cycles an adequate endometrial response was achieved reaching an endometrial thickness of at least 7 mm. Eventually transfer of either of fresh or frozen thawed embryos was performed in only 49 cycles (all 13 patients had one or more ET eventually). Eleven clinical pregnancies were achieved of which eight were in the subgroup patient who had endometrial thickness of 7 mm or more. The overall pregnancy rate per transfer was 22% and much lower when calculated for the initial intent to treat cycles (11%). The pregnancy rate per ET was reasonable in the sub-group in which the endometrial response was adequate (8/22, 36.4%), and low in those who had an ET despite a thin endometrium (3/27, 11.1%). The lowest endometrial thickness in which a successful pregnancy was obtained was 6.8 mm, and this was the only pregnancy that ended in a live birth. The outcome of these pregnancies was poor; they ended in one live birth, two mid-trimester terminations due to malformations, and eight miscarriages.

**Table 1** General characteristics of the 13 women who had thin and unresponsive endometrium

| | Mean±SD (range) |
|---|---|
| Age | 35.9±5.7 (27–42) |
| Gravidity | 2.15±2.8 (0–11) |
| Parity | 0.15±0.37 (0–1) |
| Infertility type (primary/secondary) | 5/8 |
| Infertility duration (years) | 5.3 ±1.7 (3–9) |
| Previous IVF cycles | 2.3±1 (1–4) |
| D&C procedures performed | 1.9±2.5 (0–10) |

## Discussion

Endometrial receptivity is essential for successful implantation and establishment of pregnancies in both natural and

**Table 2** Different treatment protocols, endometrial response, peak blood estradiol, ETs performed and number of achieved pregnancies in 13 patients presenting with thin endometrium

| Treatment protocol | Cycles | Cycles with endometrial thickness ≥7 mm | Peak blood $E_2$ (pmol/L) mean±SD | Cycles with ET | Embryos transferred/ cycle mean±SD | Embryo score[d] mean±SD | Pregnancies (in responsive endometrium cycles) |
|---|---|---|---|---|---|---|---|
| Artificial cycle[a] | 28 | 12 | 4,044±3,363 | 14 | 3.07±0.92 | 1.74±0.54 | 3 (3) |
| Induced cycle[b] | 28 | 6 | 8,093±3,420 | 14 | 3.29±0.73 | 1.89±0.6 | 4 (3) |
| Induced cycle + aspirin[c] | 7 | 3 | 8,577±4,218 | 4 | 3.5±0.58 | 1.93±0.62 | 1(1) |
| Induced cycle + estrogen[c] | 18 | 1 | 8,745±4,336 | 9 | 3.3±1.0 | 1.97±0.61 | 2(1) |
| Induced cycle + Viagra™[c] | 4 | 0 | 5,308±4,555 | 2 | 3.5±0.7 | 1.86±0.69 | 0 |
| Spontaneous cycles[c] | 14 | 0 | 642±274 | 6 | 3.17±1.17 | 2.0±0.58 | 1(0) |
| Total | 99 | 22 | | 49 | | | 11 (8) |

[a] Frozen thawed embryos
[b] 22 fresh embryos+5 frozen–thawed embryos
[c] Fresh embryos
[d] According to Rijnders and Jansen [19], grade 1—no fragmentation; grade 2—<20% fragmentation; grade 3—20–50% fragmentation; grade 4> 50% fragments

ART cycles [20]. There are still no accepted criteria for evaluating endometrial receptivity in IVF patients. However, in an attempt to assess the endometrial receptivity and define uterine predictors of implantation and pregnancy, various ultrasonographic endometrial features like thickness, echogenicity and pattern were studied. Despite the existence of quite a few published studies, the prognostic value of ultrasonographic endometrial thickness measurements (and other parameters) in predicting implantation and pregnancy rates remains controversial. Some investigators have demonstrated a positive correlation between endometrial thickness and pregnancy rates [1–8, 11] while others have not found such an association [9, 10, 12–14], or only in association with other parameters [15, 16]. However, these differences may be in part attributed to different patient populations, stimulation protocols used or measurement timing. The incidence of thin endometrium in natural cycles has been reported to be 5% in women <40 years of age and 25% in 41 to 45 years old women [6]. The etiology of unresponsive endometrium and its impact on ART outcome have not been well characterized.

This retrospective observational cohort study includes 13 women who repeatedly had a thin and unresponsive endometrium in various types of treatment cycles (echogenicity and pattern data are not available). Their age was 35.9±5.7 and had they had a poor outcome of assisted reproduction treatments, despite their quite good embryo quality. One important observation which may shed some light on a possible mechanism is that ten out of 13 patients had a dilatation and curettage performed prior to the onset of their problem, and six of them had more than one curettage performed. All the curettage procedures were performed for the management of induced abortion or miscarriage. Although an association between endometrial curettage and thin unresponsive endometrium seems plausible, post curettage infertility and implantation failure was mainly attributed to the formation of intra-uterine adhesions. This small uncontrolled patient cohort does not allow us to conclude that the curettage procedures without synechiae were the cause of the injury to the endometrium. However, in this group only four out of 13 patients had intra-uterine adhesions and they were quite mild. A possible explanation to this observation might be the existence of a spectrum of post curettage endometrial injuries ranging from a thin and unresponsive (but otherwise normal) endometrium at one end, to Asherman's syndrome on the other. It is impossible to estimate the occurrence rate of such complications based on this small study. However, these post curettage sequelae are devastating to the reproductive future and should be cautiously taken into consideration when intra-uterine procedures are planned. Alternatives to the traditional dilatation and curettage procedure should be considered in women of child bearing age seeking further fertility. Pharmaceutical management of abnormal uterine bleeding, early missed and induced abortions, should be encouraged in young women. Directed hysteroscopic resection of polyps should be preferred upon undirected global curettage. Such measures might prevent the type of endometrial damage reported here.

This unfortunate group of women had undergone various empirical treatments with combinations of steroid hormones

with Silfendanil and Aspirin in an effort to improve the endometrial response as measured by its ultrasonographic thickness. These different modalities, categorized in Table 2, had various success rates in terms of adequate endometrial response (defined as an ultrasonographic thickness ≥7 mm) and pregnancy rates. The treatment plans in all cycles were tailored individually and the data was collected retrospectively. Therefore no treatment was found to be better than the other, adequate endometrial thickening was achieved in only a minority of the patients, and embryo transfers were performed in only half of the cycles. The pregnancy rate was low despite the adequate number of embryos that were transferred. The thinnest endometrium which was associated with a successful pregnancy was 6.8 mm thick, quite close to the established cutoff and in conformity to published data [17]. The outcome of these 11 pregnancies (eight miscarriages, two late terminations due to malformations and one live birth) demonstrated that these patients had a poor reproductive prognosis even if some endometrial thickening or implantation did occur. The failure of the different treatment modalities to improve the poor reproductive outcome in these patients is unfortunately in accordance to published data [20]. The high pregnancy loss rate might be the consequence of an endometrial cellular or molecular defect which is presently beyond our recognition. Further studies involving direct examination of the endometrium are required in order to establish the mechanism of such an endometrial injury. Stimulation of the endometrium by local injury using an endometrial biopsy catheter was reported to be beneficial to patients with normal endometrial measurements who had otherwise unexplained repeated implantation failures [21, 22]. However the patient population in this study differs significantly by having a functionally abnormal endometrium. The effectiveness of endometrial biopsy in patients with thin unresponsive endometrium is yet to be determined.

Once the insult occurred and the endometrium is constantly thin and unresponsive, proper counseling regarding the very low live birth rate achieved by IVF and alternatives such as surrogacy and adoption should be discussed with these patients.

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