Thin endometrium in patient undergoing Assisted Reproductive Technology: pathogenesis and treatment

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Summary
Since the “elective single blastocyst transfer” policy has led to an unquestionable improvement in success rates of Assisted Reproductive Technology, it is now becoming clear that the endometrium plays a more active role than previously thought in determining whether the embryo will implant or not. The aim of this paper is to review the currently available strategies to improve the endometrial lining in women with thin endometrium (<7mm), unresponsive to conventional treatments. Each technique is thoroughly described, lastly focusing on a novel approach that implies Platelet-Rich Plasma (PRP) as a direct promoter of endometrial proliferation. Being active only on the vascular side of the uterine functional network, indeed, most of the techniques available (Tochopherol, Sildenafil citrate, Aspirin, Electroacupuncture extended use of E2) often fail, since they require a healthy endometrium to work. A direct proliferative effect on endometrium of Granulocyte-colony stimulating factor has been recently presumed, given its ability in establishing endometriotic lesions in mice, but no studies on human endometrium are available yet. Autologous PRP is safe, simple to obtain and to administrate. If the ongoing studies will confirm its efficacy in improving pregnancy rates of treated patients, PRP will be included as an innovative proposal to treat women with thin endometrium.

KEY WORDS: thin endometrium, Assisted Reproductive Technology, platelet-rich plasma, estradiol valerate.

Introduction
Good embryo development and receptive endometrium are essential conditions for achieving implantation success and pregnancy after embryo-transfer (1). Although the extension of the blastocysts culture and the ability to perform Preimplantation Genetic diagnosis for aneuploidy testing (PGD-A) have resulted in significant improvements in Assisted Reproductive Technology (ART) (2, 3), the life birth rate per
euploid embryo transfer still do not exceed 50%. Failure of implantation is a major factor which negatively influences ART outcomes. Recently, thanks to the scientific progress in molecular biology, genetics and metabolomics, the implantation process is becoming increasingly clear and these new research tools could soon provide innovative solutions to improve outcomes. By the way, at the moment, we do not know why euploid embryos fail to implant. Among the causes of interference on the correct implantation of a developing embryo indeed there are female factors, primarily the age of the woman (which is accompanied with reduced ovarian reserve, poor egg quality and increased incidence of aneuploidy) together with male factors, such as azoospermia and increased sperm DNA fragmentation. About the uterus, thin endometrium is one, but not the only cause of implantation failure after a good-quality embryo transfer, so that the presence of intracavitary pathologies, a not suitable uterine environment and procedural errors must be always ruled out in these cases (4). Ultrasound examination is a commonly used non-invasive method to assess endometrial thickness and blood supply (5, 6). Adequate endometrial growth is considered essential for successful implantation and its evaluation is performed using grey-scale ultrasound (7). The minimal endometrial thickness required for embryo transfer is now considered about 7 mm at the end of natural or medically endometrial preparation cycle (1). Some investigators demonstrated that an endometrial thickness less than 8 mm resulted in significantly lower implantation and pregnancy rates (8, 9) while others reported different cut-off values, ranging between 7 and 10 mm (10). Currently, there are no evidence-based data showing the predictive positive value of endometrial thickness on pregnancy rate after embryo-transfer (11) and the only statistically significant evidence is that pregnancy is very unlikely when endometrial thickness is below 7 mm (12). In clinical practice, when we have a thin endometrium despite the use of conventional therapy, cancel the cycle and embryo cryopreservation is recommended to avoid embryo wastage (13).

Etiopathogenesis of thin endometrium

Thin endometrium can be caused by various factors, but the most common reasons are inflammatory and iatrogenic; these can be responsible for a unresponsive endometrium after conventional therapy. This event is relatively frequent in women with previous trauma of the uterus (cesarean sections, repetitive curettage), patients affected by Asherman’s syndrome, chronic infections (endometritis, Pelvic Inflammatory Disease) and inadequate blood flow (stress, malposition of uterus, fibrosis) (16). Low estradiol values and excessive use of Clomiphene Citrate are other causes of thin endometrium, given the antiestrogenic effect of the latter (17). Antitumoral treatments, such as radical surgery, chemotherapy and radiotherapy (RT) can permanently affect present or future reproductive function both in males and females (18). Knowledge on the effects of radiation on uterine function is derived from patients treated in childhood for abdominal malignancies (Hodgkin’s disease, Wilms tumors, unilateral ovarian dysgerminoma, etc.) (19-21). The clinical incidence of uterine radiation injury varies according to various factors: patients are asymptomatic with a low RT dose (20Gy) (22), while a prepubescent uterus or “microuterus”, with an atrophic endometrium, may be observed as a consequence of higher doses (40Gy) (23). Fibrosis, which takes place also during acute or chronic infections, is at the base of tissue healing and causes the destruction of the basal layer of the endometrium, also narrowing the uterine cavity. When the basal layer is damaged by fibrosis, regeneration of endometrium is very difficult. Surgeries, such as reiterated curettage intracavitary myomectomy and polypectomy may lead to intrauterine adhesions and damage the endometrium via the same mechanism (23).

Treatment options for thin endometrium

Various strategies have been studied over the years to try to increase the endometrial thickness.
in poor endometrial responders (Figure 1); among the others, those currently considered in the clinical practice are the extended use of exogenous estrogens (24), the administration of low-dose Aspirin (25), Tocopherol (in association with Pentoxifylline) (26, 27), vaginal Sildenafil Citrate (28), Electroacupuncture (29) and application of Granulocyte Colony Stimulation Factor (G-CSF) (30). Recently, an innovative therapeutic proposal, which involves the use of autologous Platelet-Rich-Plasma (PRP) has been introduced by different groups (31-33). The following, thereafter, is a description of the strategies available to date to improve endometrial thickness, focusing on PRP as a novel and promising approach.

**Extended use of exogenous estrogens**

Physiologically, the endometrium responds to hormonal influence according to the Noyes criteria (transition from proliferative to secretory and menstrual phases) (34). In clinical practice, advances in embryo culture technology and cryopreservation programs have determined an increase frozen-thawed blastocyst stage transfer. Reports from observational studies and RCT suggest some advantages: a) better endometrium in natural cycles for implantation, b) pregnancy rates are increased following FET, c) lower maternal and infant morbidity and mortality after FET. However, this approach required upskilling of IVF units and favorable government regulation. Frozen/thawed embryos may be transferred into the uterus in a natural cycle, a hormone replacement cycle or a stimulated cycle. Although there is insufficient evidence, in term of pregnancy rates, to recommend any one protocol for endometrial preparation over the others, transfer in natural cycle is usually recommended in young women with regular menstrual cycles and ovulation or when the gynecologist or the IVF center do not need to schedule patients conveniently. On the contrary, hormone replacement cycle with exogenous estradiol (E2) administration is recommended for older women, those without ovaries or with irregular menstrual cycles. This protocol is also preferred when we want to synchronize the time of ET for the needs of the patient or of the IVF center (35).

In women in which the endometrium does not

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**Figure 1 - Schematic reproduction of the targets of action of the proposed treatments.**
grow under the standard E2 regimen (10-12 days of daily administration), the extended use of exogenous estrogens consists in the administration of estradiol at a higher dose and for a period of time longer than the one sufficient for conventional therapy. In a study by Chen et al. (24), among 36 women enrolled, 23 were subjected to a fresh embryo transfer (control group), while 13 were suggested to cancel it, because of poor response, and become part of the study group. These women were then subjected to a frozen-thawed embryo transfer in the next cycle after extended exogenous estrogen replacement. The therapy started on day 3 of the cycle and the duration of the estrogens administration ranged from 14 to 82 days, with a mean value of 30 days. In the study group, the mean endometrial lining increased significantly from 6.7 mm to 8.6 mm (P=0.031). Pregnancy rate was also significantly higher in the study group than that in the control group (38.5 vs 4.3%, P=0.016) (24).

Vaginal E2 could be particularly indicated for women who do not obtain sufficient endometrial thickness by other means. Tourgemann et al. (36) demonstrates that the extended use of vaginal E2 (from 4 to 6 weeks) was successful in achieving adequate endometrial lining. In his study, 10 patients who had previously failed under conventional oral regimen, obtained positive effect after prolonged E2 administration per vaginal route and 7 of them get an ongoing pregnancy after embryo transfer (36). Fanchin et al. (37) demonstrated that vaginal E2 administration improves endometrial thickening and uterine blood supply, acting on systemic and local level simultaneously: first, vaginal estrogen reach the systemic circulation such as those taken orally; moreover, the hormone concentration in the uterus is higher whether estrogens are administered per vaginal route, so their effect on endometrial proliferation in presumably greater (37).

By the way, the presence of a healthy endometrium is required for the success of this therapy: indeed, all the available studies reporting positive outcome after extended E2 administration have been performed on healthy women, excluding patients with possible endometrial damage. In support of this assumption, Pierro et al. (38), in an in vitro study, demonstrated that 17β-Estradiol, added to Epithelial Endometrial Cells (EEC) cultured alone, produces no proliferative outcome. In the mentioned study, EEC grew only when cultured together with an adequate stroma. Actually, Endometrial Stromal Cells (ESC), secreting IGF-1, play the main role in mediating the effect of 17β-Estradiol on human EEC proliferation. Endometrial receptivity to estrogens requires stromal-epithelial interactions together with adequate paracrine growth factors production. Therefore, what probably makes the difference is the environment and the simultaneous presence of growth factors (38).

### Tocopherol (associated with pentoxifylline)

Tocopherol (Vitamin E), well known for its antioxidant properties, is proposed as favoring the growth in endometrial thickness for its action on the vascular side, as it is for treatments with Aspirin and Sildenafil. Thin endometrium, after all, is often the result of the onset of a vicious cycle: high blood flow impedance of uterine radial arteries results in a decrease in Vascular Endothelial Growth Factor (VEGF) expression; low VEGF levels cause poor vascular development, which in turn decreases blood flow in the endometrium that compromises the glandular epithelial proliferation (39). Tocopherol acts by avoiding the lipids hydrolysis of red blood cell membrane, that results in the improving of the development of blood vessels and the consequent growth of glandular parenchyma (40).

In a prospective observational pilot study, Takasaki et al. (41) demonstrated that Vitamin E improves the uterine vascularization and then the endometrial thickening through the increase in VEGF expression: the study showed an improvement of uterine radial artery-resistance index (RA-RI) in 72% of patients and of endometrial thickness in 52% of patients (41). In a prospective, single-center, randomized controlled clinical trial (42), conducted on 103 patients, Cicek et al. found that infertile women treated with Tocopherol had significantly thicker endometrium (mean of 9.6 vs 8.2 mm) but no significantly different implantation or pregnancy rates (42).

Pentoxifylline (PTX), a methylxanthine derivative, has vasodilating, antiaggregant and anticoagulant properties. It also plays an anti-inflammatory and antifibrotic role, antagonizing TNF-α production. Given the hypothesis that any thin endometrium, even from unexplained causes, can be considered as a consequence of iatrogenic...
TNF-α mediated induced fibrosis, the association of Tocopherol with Pentoxifylline (PTX) has been proposed. In a study by Ledée-Bataille et al. (43), patients have been treated with a combination of 400 mg PTX and 500UI Vitamin E, twice a day, for 6 months: combined PTX-Vitamin E significantly promoted endometrial thickening from 4.9 to 6.2 mm, with 72% of treated patients defined good responders (P<0.001) (43). Actually, higher TNF-α expression has been associated with implantation failure as a consequence of an inflammation-like reaction (44); in this context, implantation failure may be due to a not suitable environment, with reduced endometrial thickness only as a secondary effect. Therefore, combined PTX-Vitamin E administration can represent an adequate treatment in some cases of implantation failure but not in all patients with thin endometrium (45, 46).

**Sildenafil citrate**

As previously mentioned, the effectiveness of Sildenafil Citrate (Viagra) in increasing endometrial thickness is assumed because of its vasodilating effect. Some years ago, also Nitroglycerine has been used to improve endometrial thickness via the same mechanism, but this treatment was abandoned because of the side effects on treated patients (headaches and hypotension) (47). The rationale of the use of Viagra is linked to its effect in term of Nitric Oxide (NO) release, that can lead to relaxation of vascular smooth muscle through a cGMP-mediated pathway (48). The vascular endothelium of human endometrium and myometrium presents inducible NO synthase isoforms (49); phosphodiesterase (PDE) is an isoenzyme that hydrolyzes cyclic nucleotides, such as cGMP. Sildenafil (Viagra) is a type 5-specific PDE inhibitor that augments the vasodilatory effects of NO on vascular smooth muscle by preventing the degradation of cGMP. In an observational study by Sher et al. (50) vaginal administration of Sildenafil markedly enhanced endometrial development by the improvement of endometrial artery blood flow (decrease in Pulsatility Index, PI, of uterine arteries). On the contrary, in a prospective randomized trial conducted by Check et al. (51) no significant differences in endometrial thickness between patients treated with vaginal Sildenafil Citrate and controls have been found. According to these spare evidence, the use of Sildenafil cannot be expected to help all patients with a thin endometrial lining and women with intractable damage to the basal endometrium may be less likely to respond to the enhancement of uterine blood flow (28).

**Aspirin**

Due to its antithrombotic and vasodilatory effects, Aspirin has been one of the most studied agents in several clinical trials, aimed to evaluate its potential role in increasing IVF success rate through improving uterine and ovary vascularization (52). The exact role of Aspirin in the improvement of endometrial thickness is still controversial. In a prospective randomized study, Hsieh et al. (53) found higher pregnancy rate and better endometrial lining in patients with thin endometrium treated with Aspirin. One hundred fourteen and 122 women were included in the Aspirin and non-Aspirin groups, respectively: significantly higher percentages of trilaminar endometrium (46.5 vs 26.2%) and pregnancy rates (18.4 vs 9.0%) were registered in the study group, despite Aspirin did not significantly increase the endometrial lining and the resistance of uterine arteries in the same population (53). No favorable effect of low-dose Aspirin administration on pregnancy rates following frozen embryo transfer was seen in a matched controlled trial conducted by Check et al. (54). In this study 36 women were included, 18 in the Aspirin group, 18 in the non-Aspirin group: in midcycle evaluation, the mean endometrial thickness and the mean Resistance Index (RI) were similar in both groups. In the luteal phase the endometrial lining was 2 mm higher in the Aspirin group compare to controls, but a no homogeneous hyperechogenic pattern was found in 58% of the Aspirin group, compared with the 28.6% of non-Aspirin group (54). According to a recent meta-analysis on the effect of Aspirin in women undergoing IVF (25), although an improvement in PI was observed in treated women, this effect did not result in better clinical outcomes. Considering these results, Authors concluded that the outcome of IVF does not depend significantly on PI of uterine artery, and the blood flow enhancement due to Aspirin is not necessarily related to an enhancement of the endometrial pattern (25).
Electroacupuncture

As previously mentioned, the endometrial circulation or blood flow impedance in the uterine arteries, measured through PI, is one of the useful indirect tools adopted in the clinical practice to assess endometrial receptivity. Steer et al. (55) found that a PI value ≥ 3.0 at the time of Embryo-Transfer leads to a lower pregnancy rate. Stener- Victorin et al. (56) demonstrated a reduction in PI in the uterine arteries following a series of electroacupuncture (EA) applications in 10 infertile women with a PI ≥ 3.0 in the uterine arteries enrolled in a prospective, non-randomized study. Compared to the main baseline, PI was significantly reduced (P < 0.0001) after EA, regardless of the duration of the treatment. Moreover, skin temperature on the forehead increased significantly during the EA application; both of these effects being probably related to the inhibition of the sympathetic activity.

Low frequency electrical stimulation induces hypothalamus to release β-endorphin, whose concentration increases in the cerebrospinal fluid (CSF) and involves the reduction of the sympathetic tone (57). The reduction of the sympathetic activity implies the decrease in the tone of the vasoconstrictor fibers in the uterine arteries (56). The acupuncture points were selected following the innervation of the uterus and ovary and, according to traditional Chinese medicine theory, are associated with relaxation of the myometrium (29). In a prospective, randomized trial conducted by Ho et al., among 44 patients enrolled, 30 were subjected to EA, and 14 were not. The EA treatment consisted in four applications, for a duration of 30 minutes, twice a week for 2 weeks. Despite the mean PI of both uterine arteries was significantly reduced after EA, however, no significant differences in endometrial thickness and pregnancy rate have been found between groups (29).

Granulocyte-Colony Stimulating Factor (G-CSF)

Granulocyte-Colony Stimulating Factor (G-CSF) is a glycoprotein that carries out both growth factor and cytokine activities. It is currently used for the treatment of neutropenia in immunocompromised patients (as those affected by cancer and AIDS). An additional potential growth-expanding effect of G-CSF on endometrium may be presumed from its role in establishing early endometriotic implants (58). Mettler et al. (59), in an in vitro study aimed to evaluate whether the ectopic proliferation of endometriotic cells is related to the stimulation of peritoneal macrophages, demonstrated that the expression of G-CSF receptor (c-fms) is higher in endometriotic lesions compared to the ectopic endometrium. Moreover, in this study, mice homozygous for a G-CSF mutation or treated with Imatinib, a c-fms kinase inhibitor, developed endometriosis significantly less frequently than controls (59). Up to now, however, a direct growth-promoting effect on endometrial thickness has never been reported (no in vitro tests are available in literature).

In a case report published by Gleicher et al. intrauterine instillation of G-CSF produced successful endometrial thickening in patients previously resistant to conventional and alternative treatments (30). The few studies available on the topic, however, failed in demonstrating any improvement in pregnancy and implantation rates following G-CSF administration (60-62). In a study by Kunicki et al. (60), for example, all the 37 recruited women with thin endometrium showed, after G-CSF instillation, a significant increase in endometrial lining to 8.42 ± 1.73 mm. However, when the Authors divided the group into two subgroups, based on the conception occurrence, no significant differences between the two subgroups in term of endometrial thickness respecting to the G-CSF infusion were found (60). Barad et al. (61), in a study conducted on 141 patients, reported no statistically significantly increase in pregnancy rate in the G-CSF group compared to controls, treated by placebo (61). In a study by Li et al. (62), 34 infertile patients with thin endometrium received intrauterine instillation of G-CSF for 40 cycles, defined as G-CSF group, while the 49 previous cycles of the same population were considered as self-controlled group; moreover, 25 patients refused the therapy and their 80 cycles were included in the control group. The percentage of cycle cancellation was 69.39%, 48.75% and 17.50% in the self-controlled group, in the control group and in the G-CSF group respectively, (P < .05) although no significant differences in implantation and pregnancy rates were found among the three groups (P > .05) (62).
Novel approach

**Autologous Platelet-Rich-Plasma (PRP)**

First results from an *in vitro* study ongoing on the evaluation of Platelet-Rich Plasma (PRP) effect on endometrial cell proliferation have been presented in October 2016 at the American Society for Reproductive Medicine (ASRM) conference (63). In their interesting talk, Authors demonstrated that PRP increased proliferation not only on cultured fibroblasts, as currently known, but also on mesenchymal cells, which are progenitors of different types of cells, including endometrial cells. This evidence supports the hypothesis that PRP stimulates some of the cellular processes involved in endometrial regeneration, that can be relevant to the management of a thin lining (63).

Only two studies have been yet conducted to assess whether inadequate, thin endometrium (<7 mm), after standard treatment options failed, could be responsive to PRP treatment, and another one is ongoing. In the first one, Chang et al. (31), for the first time in literature, reported positive results of intruterine infusion of autologous PRP in improving the endometrial thickness in 5 women with thin endometrium undergoing IVF with Hormone Replace Therapy (HRT). Successful endometrial thickening and pregnancy were observed in all the patients after PRP infusion (31). According to the results presented by Nazari et al. (32), moreover, PRP seems to be effective in improving pregnancy outcome in Repeated Implantation Failure (RIF) patients. In its experience, twenty women with a history of RIF who were candidates for frozen-thawed embryo transfer were enrolled; intruterine infusion of 0.5 ml of Platelet-Rich Plasma was performed 48 hours before blastocyst transfer. Eighteen (90%) participants were pregnant, one had an early miscarriage and one a molar pregnancy; sixteen clinical pregnancies were therefore ongoing at the time of the study publication (32).

A prospective randomized trial named “Platelet-Rich Plasma (PRP) for endometrial regeneration and repair”, conducted by the team of the University of San Francisco, California (33), has been registered on July 2016 on www.clinicaltrial.gov and is still ongoing. The study proposal is to assess if intruterine infusion of PRP promotes endometrial thickening in IVF patients affected by Asherman’s Syndrome, particularly those unresponsive to conventional therapies (33).

**Procedure**

Autologous Platelet-Rich Plasma is prepared from fresh whole blood which is collected from a peripheral vein and processed to separate platelets from the other blood components (64). PRP has been widely used to promote the tissue healing in different clinical areas (65-69). PRP contains activating platelets that stimulate action of cytokines and growth factors. They can regulate cell migration, attachment, proliferation and differentiation, and promote extracellular matrix accumulation. According to this hypothesis, local infusion of PRP (that contains several growth factors and cytokines) may improve endometrial receptivity and implantation (31).

Patients considered to be candidates for a PRP application must undergo a minor hematological evaluation to exclude blood disorders or platelet dysfunction. The following are relative contraindications for PRP application: platelet count less than 105/μL, hemoglobin level less than 10 g/dL, presence of a blood tumor or metastatic disease, and other concomitant infections (64). Each study involving the use of PRP must be approved by Ethical Committee and all participants have to sign an informed written consent.

Intruterine infusion of PRP must be done 48 hours before ET. PRP is obtained from autologous blood after chemistry checks and virologic tests; on the 10th day of ART cycle, 8 ml of venous blood is drawn from the pre-filled syringe, and centrifuged immediately at 1500g (RCF) for 10 min. The repeated reversal of the tube allows to obtain the quantitative of PRP at the concentration required. PRP must be infused into the uterus cavity immediately with Tomcat catheter (0.5-1 ml) (Figure 2). Endometrial thickness is re-assessed 48-72 h later. If the endometrial thickness is not satisfying, infusion of PRP can be performed 1-2 times more.

Any concerns of immunogenic reactions or disease transmission, that exist with homologous blood products, are eliminated because PRP is produced from autologous blood. Preparation of PRP, however, demands many processing steps, thus there is theoretic possibility of contamination. For these reasons, all samples are subjected to quality and sterility controls within a closed mechanism. No wound infections after PRP applications have been reported (64). Despite PGF has mitogenic properties, there is no evidence that the growth factors included in PRP promote
tumor growth or that they are involved in carcinogenesis. Furthermore, Authors showed that growth factors act on cell membranes and not on the cell nucleus, therefore PGF stimulates already certain genes (70).

Conclusions

Transfer of single euploid blastocyst greatly reduces the embryonic causes of implantation failure, so that studies and researches in IVF are now focusing on the endometrial side. In ART, treatment of patients with thin endometrium, unresponsive to conventional therapies, remains a challenge. Alternative treatments, such as extended use of exogenous estrogens, Tochopherol (with or without Pentoxifylline), vaginal Sildenafl Citrate, Aspirin and Electroacupuncture, cannot be considered the answer in many cases: some of them, indeed, require a not damaged endometrium, other act on endometrial blood flow and have no direct proliferative effect on endometrium. A direct G-CSF proliferative effect on endometrium was only presumed but not demonstrated by in vitro studies; the poor literature available do not show a statistically significant improvement following such treatment neither in terms of endometrial thickness nor of implantation rate. Finally, early results obtained about autologous PRP are encouraging and, once confirmed, should lead clinicians to consider it as a new therapeutic proposal for the treatment of patients with thin endometrium.

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