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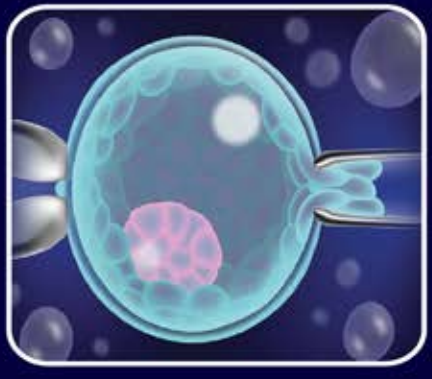
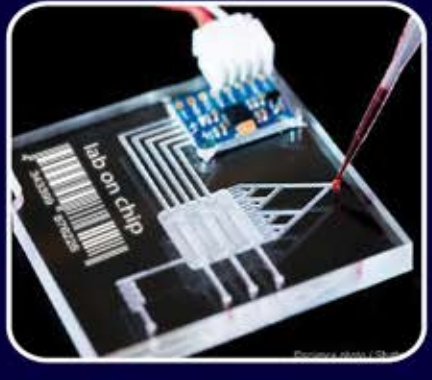
Advances Breakthroughs Controversies & Dilemmas in ART









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Chapter

Thin Endometrium: How Thin is Actually Thin?

Manish Banker, Jwal Banker, Parul Arora

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INTRODUCTION

Implantation, a complex process involving interactions between the endometrium and the blastocyst, is necessary for establishing a viable pregnancy. To define the endometrium as a biosensor of embryo quality, the notions of endometrial receptivity and selectivity were introduced by Macklon and Brosens in 2014.[1] Endometrial receptivity is an indispensable part of implantation; however, a reliable and ideal marker of receptivity is not yet defined. Histological, biochemical, and genetic marker of receptivity lack validation have low predictive values and need invasive testing. Sonological assessment of endometrial thickness (EMT) remains to be the reliable, reproducible, cost-effective, and universally available noninvasive marker of endometrial receptivity.[2]

Endometrial thickness is easily quantified by transvaginal ultrasound (TVS). Studies that looked into the connection between EMT and in vitro fertilization (IVF) outcomes have yielded inconsistent results. According to some theories, thinner endometrium is linked to poorer IVF success rates. The fact that there is no precise definition of thin endometrium as determined by ultrasound may help to explain this lack of agreement.[3] As a result, it is impossible to draw a firm conclusion about the clinical importance of EMT for the likelihood of conceiving following IVF.

Despite all this, EMT evaluation has evolved into a useful tool of monitoring throughout IVF process. Clinicians and infertile couples may thus be forced to make the difficult decision of whether to move forward with a fresh IVF cycle or opt to cryopreserve the embryos for conceivably improved chances to conceive with an endometrium grown under natural circumstances in subsequent cycles.

IMPLANTATION PHYSIOLOGY AND IMPORTANCE OF ENDOMETRIUM

Human embryos are implanted through a series of stages that include apposition, adhesion, and invasion of an endometrium that has been hormonally prepped for receptivity. The EMT is supposed to be "surrogate marker for endometrial receptivity". The endometrial luminal epithelium develops pinopode-like projections that help the blastocyst adhere to the uterine lining and its invasion into the deeper endometrial stroma. The endometrium becomes decidualized and triggers the release of vascular factors which stimulate fetal vessels and remodeling of maternal uterine spiral arterioles to form fetomaternal circulatory connections.[4,5] Human implantation thus requires complicated molecular and physical interactions between the host endometrium and the embryo in a complex, well-coordinated, ongoing process.

With the successful endometrial preparation with exogenous hormones in a woman with premature ovarian failure and consequent live birth reported in 1984, importance has been given to optimal endometrial preparation in IVF leading to an optimal thickness.[6]

ASSESSMENT OF ENDOMETRIUM

Transvaginal sonography is an ideal noninvasive modality to evaluate the EMT. Endometrium is measured on an empty bladder with a transvaginal probe. This transducer is physically closer to the endometrium and uses a higher frequency (5–8 MHz) as compared to transabdominal assessment. This results in better visualization of the endometrium due to better resolution. Following are the markers used routinely for the endometrial assessment.[7]

- *Endometrial thickness:* It is measured from outside to outside in an anteroposterior view at the widest point.

It should be measured in the sagittal plane or the long axis. Measurement is of "thickest echogenic area from one stratum basalis endometrial interface to other". The definition and cutoff for "thin endometrium" differ but most of the studies use EMT <7–8 mm on the day of human chorionic gonadotropin (hCG) administration.

- *Endometrial pattern:* Apart from the EMT, another marker of an optimal endometrial preparation is the pattern of the endometrial stripe. An ideal endometrial pattern is trilaminar on the day of trigger (grade or type A).
  - *Type A:* Triple-line pattern consisting of central hyperechoic line surrounded by two hypoechoic layers.
  - *Type B:* An "intermediate isoechogenic pattern with the same reflectivity as surrounding myometrium and poorly defined central echogenic line".
  - *Type C:* "Homogeneous hyperechogenic endometrium"; likely nonreceptive
- Endometrial vascularity (measured by 3D color Doppler ultrasound). Vascularity in
  - *Zone 1:* 2 mm thick area surrounding the hyperechoic outer layer of endometrium
  - *Zone 2:* Hyperechoic outer layer of endometrium
  - *Zone 3:* Hypoechoic inner layer of endometrium
  - *Zone 4:* Endometrial cavity
- *Endometrial volume assessment using 3D ultrasonography:* Volume of <2.5 mL is predictive of low pregnancy rate or pregnancy loss, but it has low sensitivity.

THIN ENDOMETRIUM IN ASSISTED REPRODUCTIVE TECHNOLOGY

Over the last four decades, studies have noted the route of estrogen administration and the duration of estrogen to achieve the optimal thickness. The mode and dose of estrogen administration and duration of estrogen priming do not really matter as long as the EMT and the trilaminar pattern are adequately achieved.[8] A big proportion of embryo transfers are canceled because the endometrium is not optimal. However, what remains to be deciphered is what is the cutoff below which pregnancies are not possible or does architecture equally matter as the thickness in the endometrium.

Thin endometrium is often defined as EMT <7 mm or <8 mm. The incidence of thin endometrium in ovarian stimulated cycles can be as high as 38–66% while in IVF it is between 1 and 2.5%.[2,9] The true incidence of thin endometrium in assisted reproductive technology (ART) especially in frozen embryo transfer (FET) cycles cannot be reported as such cycles are canceled before reporting. The incidence of thin endometrium is higher in ovarian stimulation cycles and is also heterogeneous; depending upon the drug used in the cycle: clomiphene, letrozole, or gonadotropins.

FACTORS AFFECTING ENDOMETRIUM

The following are four crucial elements that have an impact on endometrial growth:

1. Levels of serum estradiol
2. Uterine blood flow
3. The condition of the endometrial tissue (any infections or prior injuries)
4. Age of the woman also influences the endometrium indirectly possibly due to reduced vascularity.

CAUSES OF THIN ENDOMETRIUM

- *Iatrogenic:* It can happen during D&C (dilation and curettage), myomectomy in which endometrial cavity is opened or, cesarean section in which uterine cavity has been curetted to remove placental bits, overzealous or repeated curettage, postabortal adhesions, polypectomy, etc.
- *Inflammatory:* In India, endometrial tuberculosis is a significant and frequent cause of thin and irreparably damaged endometrium. In addition, other conditions that can cause endometrial scarring permanently include chronic bacterial infections, sexually transmitted diseases (STDs), and pelvic inflammatory disease. Any infective trigger can lead to destruction of the basal layer and healing by fibrosis, adhesions, and shrinkage of the cavity.
- *Other causes:*
  - *Low estrogen levels:* Because the endometrium is an estrogen-dependent tissue, it will remain thin if estrogen stimulation is insufficient for any reason, as is the case in prepubertal girls, postmenopausal women, and hypogonadotropic hypogonadism instances.
  - *Excessive clomiphene use:* Clomiphene has an antiestrogenic impact on the endometrium and repeated use can result in the endometrial estrogen receptors being downregulated, which can cause the endometrium to remain thin for an extended period of time.

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- *Prolonged usage of progesterone and combination contraceptive pills:* Endometrial lining becomes thin when oral contraceptive (OC) pills and progestins are used for an extended length of time.
- *Improper blood flow:* Blood flow to the uterus indirectly controls endometrial growth by improving vascular development of the endometrium. In 2010, Takasaki et al. demonstrated that a "thin endometrium was characterized by poor epithelial growth, decreased vascular endothelial growth factor (VEGF) expression, and poor vascular development. It is likely that endometrial growth partly depends on angiogenesis and uterine blood flow.[10]
- *Systemic causes:* Thin lining is thought to be more common in those who have certain illnesses, such as hypertension, diabetes mellitus, asthma, depression, and substance addiction like smoking.
- *Idiopathic:* Intrinsic properties of the endometrial architecture may cause it to be thin; unrelated to any pathology.

NATURAL VERSUS MEDICATED FROZEN EMBRYO TRANSFER

In natural cycle FET, endogenous estradiol secreted by dominant follicle is responsible for endometrial proliferation while in medicated FET, estrogen and progesterone are administered in sequential fashion to mimic the natural window of implantation.

Investigators have reported similar pregnancy rates and live birth rates (LBRs) between natural and medicated cycles.[11,12] Another systematic review also reported no advantage of any particular method of endometrial preparation in frozen transfer cycles with similar outcomes noted among modified natural and medicated FET.[13] A prospective cohort study of patients undergoing modified natural cycle FETs revealed no association between EMT and pregnancy outcomes and they reported that there is no minimal EMT below which pregnancy rates would be compromised.[14] A study conducted by Pan Y et al. 2020 showed that natural cycle protocol yielded thicker endometrium and higher implantation rate as compared to hormone replacement.[15]

EVIDENCE ON ENDOMETRIAL THICKNESS AND PREGNANCY RATES

Numerous studies have linked decreasing EMT at the time of both fresh embryo transfer and FET to a decreased likelihood of implantation and continued pregnancy. There is no EMT at which the chance of pregnancy and a subsequent live birth has been reported to be zero, despite the fact that the results appear to get worse as EMT drops to <7 mm or 8 mm.[16,17]

Perhaps the most important factor for positive perinatal outcomes is also the placenta, and placentation is likely to be affected by the underlying endometrium. According to several researches, thin endometrium (<8 mm) had low levels of VEGF, which caused poor endometrial vascularization and poor placentation. The risk of pregnancy loss, preeclampsia, preterm delivery, and placenta previa is also elevated in pregnancies conceived with thin endometrium, according to several studies.[18,19] Studies on obstetric and neonatal outcomes in intrauterine insemination (IUI) cycles with thin endometrium failed to identify a negative correlation between the two, hence the source of these findings is multifactorial.[20]

A systematic review by Kasius et al. did not find any difference in LBR and ongoing pregnancy rates for thin endometrium (≤7 mm), though the sample size was small. However, the clinical pregnancy rate (CPR) was significantly reduced with EMT ≤7 mm, with an odds ratio (OR) of 0.42 and a narrow confidence interval. They suggested that EMT alone cannot be used as a parameter for cycle cancelation, freezing embryos, or discontinuation of treatment. The review had studies with a mix of prospective and retrospective studies and selection bias.[18]

In a recent study, Liu et al. 2018 found that EMT of 8 mm at the end of the estrogen phase in >20,000 frozen-thawed embryo transfer (FET) cycles resulted in the best clinical and ongoing pregnancy rates following IVF. It was observed in the study that if EMT ≥8 mm, CPR was 43% while if endometrium is 7–7.9 mm, CPR was 34%. Thus, for every millimeter decrease in thickness below 8 mm for fresh embryo transfers and below 7 mm for FETs, the pregnancy rates decreased significantly. Numerous other studies on EMT have found results that are in agreement with the above. Therefore, it seems that the EMT of at least 8 mm and a trilaminar appearance on ultrasound would be the best for embryo implantation.[21]

As per Canadian guidelines 2019, in fresh IVF embryo transfer cycles, patient should be counseled that ET <8 mm may have deleterious impact on pregnancy and LBR while the cutoff for the same in frozen IVF embryo transfer cycles is <7 mm.[22]

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In a similar study conducted by Banker et al. in 2021 on effect of EMT and IVF-ICSI (intracytoplasmic sperm injection) outcome, it was shown that a progressive improvement in LBR was noted with each millimeter increase in EMT starting from 6 mm after transfer of either single or double blastocyst.[23] A recent study on 96,000 autologous fresh and FET concluded that in cycles with a fresh embryo transfer, LBR increases significantly until an EMT of 10–12 mm, while in FET cycles LBR plateaus after 7–10 mm. However, an EMT <6 mm was associated clearly with a significant reduction in LBR in fresh and FET cycles.[24] Değer et al. recently concluded that each 1 mm increase in EMT resulted in a significant increase in CPR and LBR. The lowest CPR was detected at EMT <6 mm, while the EMT value with the highest CPR was 11–12 mm in both groups. Clinical pregnancy and LBRs are optimal if the EMT is between 11 and 12 mm in both fresh and frozen-thawed cycles.[25]

HOW THIN IS DELETERIOUS?

Despite the evidence positively correlating EMT thickness and pregnancy, EMTs as low as 4 mm have also led to pregnancies.[26-28] Mahutte et al. have reported a LBR of 22% in EMT of 6–7.9 mm in their study of 5,000 transfers below 8 mm. In EMT of 4–5.9 mm, the LBR was 15.8%. These results are only from those cases of thin endometrium where transfers were proceeded and appear reassuring.[24]

Women with thickness of below 8 mm in a fresh cycle can be counseled to choose between preceding with a fresh transfer or attempt a frozen cycle in a subsequent medicated cycle aiming for a higher EMT. In cases where the endometrium is <8 mm across repeated cycles despite different preparation methods, women should be counseled about the reduced but acceptable pregnancy rates and can proceed with transfer.

In contrast to IVF, thin endometrium has a less pronounced effect on pregnancy rates in controlled ovarian stimulation (COS) or IUI cycles.[20,29]

OBSTETRIC AND NEONATAL OUTCOMES

Despite the lower pregnancy and LBRs at thin EMTs, there is no EMT below which a pregnancy is not feasible. However, in any pregnancy, the placenta plays a pivotal role for obstetric and perinatal outcome by acting as a temporary organ. Placentation in pregnancy if influenced by the underlying endometrium as reported by Miwa et al. who found that VEGF was underexpressed in an endometrium <4 mm[30] causing impaired placentation. Several authors have reported increased risks of hypertensive disorders, pregnancy losses, preterm delivery, placenta previa, placenta accreta, etc., in cases with thin endometrium at conception. In addition, infants born to such mothers have additional risks of growth restriction, small for gestational age, and consequent neonatal risks. Such risks could be additional complicated by the medicated FET which itself has an additional risk due to absence of corpus luteum.

MANAGEMENT OF THIN ENDOMETRIUM

Identification of the optimal EMT for implantation and livebirth remains a challenge. For women with thin endometrium, both natural and medicated protocols have been proposed for better endometrial development. The choice of estradiol formulation in medicated FET cycles has been evaluated; but no differences have been found.

Estradiol adjustment: In majority of the cases, the thin EMT responds to simplest interventions. Sometimes, extended estrogen administration or increasing the estrogen dosage or changing the route of estrogen administration (oral, vaginal, and transdermal) helps in achieving the EMT in a different cycle. Vaginal administration of estradiol helps in achieving a higher blood level; however, implantation rates are not increased.[31,32] Another simple option is to extend the duration of estrogen exposure (14–82 days) to achieve the optimal EMT. Many authors opt for an extended oral estrogen regime with added vaginal estrogen. Some clinicians stop the endometrial preparation after 3 weeks if not optimal and start all over again in the next cycle with a different protocol or route after inducing menses. Sometimes, multiple hormone replacement therapy (HRT) cycles for endometrial preparation stimulate the regeneration of the endometrium.

In ovulatory women, natural cycle is another option for FET in cases with refractory thin EMT or the usage of low dose gonadotropins for a modified natural cycle.

Various adjuvants have been tried in the management of thin endometrium not responding to estrogen. Although few have shown promising results in small sample-sized observational studies, randomized controlled trials to validate their usage are lacking at present. The additional cost of such therapies and their experimental nature and nonvalidated results should always be discussed with the patient before they are tried in cases with thin EMT.

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Adjuvants commonly used for management of thin endometrium:

- *Surgical intervention:* Hysteroscopy
- *Vascular approach to increase blood flow:* Aspirin, heparin, and vasodilators such as sildenafil and L-arginine
- Endometrial scratching/endometrial injury
- Endometrial receptivity analysis (ERA)
- *Reproductive immunology testing and potential therapies:*
  - Corticosteroids, intravenous immunoglobulin (IVIG), intralipid infusion, growth factor (GF) and granulocyte colony-stimulating factor (G-CSF)
  - Autologous platelet-rich plasma (PRP) therapy
  - Lymphocyte immune therapy and leukemia inhibitory factor
- Stem cell therapy
- *Uterine relaxants:* Piroxicam, atosiban, etc.

Some of the abovementioned adjuvants are explained in detail:

- *Hysteroscopy:* Routine use of diagnostic hysteroscopy before IVF to optimize the uterine thickness and receptivity is controversial; still it is practiced by some clinics. Routine use of hysteroscopy in asymptomatic women before the first IVF cycle is generally not recommended.[33] Role of hysteroscopy in refractory endometrium (failure to achieve EMT despite various attempts of endometrial preparation protocols) is justified to diagnose and correct undetected pathologies like adhesions or those with an abnormal sonological result pointing toward uterine pathology.[34]
- *Role of aspirin:*
  - *Mechanism:* By inhibition of *cyclooxygenase enzyme* in platelets and reduction of prostaglandin synthesis.
  - Causes shift from thromboxane A2 to prostacyclin
  - Inhibits platelet aggregation
  - Leads to vasodilatation and improves blood flow to implantation site.

  In 2017, Wang et al. conducted a meta-analysis that comprised 13 RCTs. The implantation rate, LBR, miscarriage rate, fertilization rate, and EMT did not differ significantly from each other, but it did show that aspirin treatment may marginally improve the CPR [risk ratio (RR): 1.16; 95% confidence interval (CI): 1.04–1.28] when compared to placebo or no treatment. Therefore, more high-quality studies are necessary to justify its empirical usage.[35]
- *Role of heparin:* It is postulated to act by
  - Improved blood flow at the implantation site by its antithrombotic effect
  - Promotes trophoblastic invasion
  - Modulation of inflammatory responses.

  Present evidence is weak such that its routine use in all women undergoing IVF treatment is not warranted.
- *Role of ERA:* Endometrial receptivity analysis is a molecular test to define the window of implantation by the analysis of receptivity genes. In a study by Mahajan et al. in women with EMT<6 mm, the ERA revealed a receptive ERA in 77% with a PR of 33.3%; suggesting that the proportion of receptive endometrium was not different from women with EMT >6 mm. ERA may be employed to personalize the timing in women with thin EMT after checking for receptivity.[2]
- *Endometrial scratching:* It is performed with a Pipelle during luteal phase prior to IVF cycle.
  - *Mechanism:*
    - Induction of endometrial decidualization
    - Wound-healing response, associated with a beneficial inflammatory response
    - Modulation of gene expression
    - An improved synchronicity

  Various studies have showed no significant increase in pregnancy rate or LBR with the use of scratching.[36,37]
- *Role of PRP:* It is a concentrate of autologous platelets in plasma collected from a peripheral vein.
  - *Mechanism:* Releases cytokines and growth factors [VEGF, transforming growth factor (TGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF)] and exerts a regenerative effect on tissues and cells including the endometrial lining damaged secondary to a disease or procedure.
  - PRP is collected from autologous blood sample, so it is more accessible and cost-effective with minimal risks of transmission of infection and immunological reactions since it is made from autologous blood samples.
  - Few studies have shown promising results with the use of PRP in women with thin EMT with improvements in EMT and pregnancy rates;[38,39] however, its role in improvement of live births is still debatable in the absence of well-designed multicentric trials. There is still very limited evidence of its use,[38] so further larger well-designed multicentric RCTs are awaited before

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recommending generalized usage of PRP for thin endometrium. Considering limited evidence, the additional cost, lack of standardized preparation protocols, the experimental nature of this intervention must be discussed with patients before offering it as a therapeutic modality.

- *Role of G-CSF:* It is a hematopoietic lineage-specific cytokine synthesized by stromal cells, bone marrow cells, endothelial cells, fibroblasts, lymphocytes, macrophages, endometrium, and human ovary.
  - *Mechanism:*
    - Suppresses immune response
    - Vascular modeling of the endometrium
    - Enhance cellular adhesion pathways
    - Improves endometrial receptivity
    - Embryonic development, implantation, and trophoblastic growth
      - *Dose:* Subcutaneous—300 µg G-CSF; Intrauterine—30 mIU/mL
      - *Route:* Subcutaneous—for recurrent implantation with normal EMT; Intrauterine—for thin endometrium (<7 mm).

  Few studies have shown improvement in EMT and endometrial regeneration after G-CSF instillation; however, these were poorly designed and had a small sample size. The Cochrane meta-analysis in 2020 for the usage of G-CSF in women with thin endometrium showed insufficient evidence for its use (Cochrane meta-analysis 2020; RR: 1.58, 95% CI: 0.95–2.63; 4 RCTs; low-quality evidence). These trials also did not address the safety of the procedure.[40]
- *Role of sildenafil:* Another adjuvant routinely used to improve the EMT in women with thin endometrium is sildenafil. It is a vasodilator which is theoretically beneficial to increase the endometrial prefusion and consequently improve EMT. Results from studies using sildenafil for endometrial improvement are mixed.[41] The Cochrane meta-analysis in 2018 found that although sildenafil did improve the EMT (0.80–3.57 mean difference higher) at the cost of adverse effects such as tachycardia and headache.[42]

CONCLUSION

Endometrial thickness is considered the indirect surrogate marker for endometrial receptivity. A rare but problematic occurrence in assisted reproduction is thin endometrium. Clinicians often try different protocols and wait across various menstrual cycles to achieve an optimal EMT before transfer as studies have consistently reported lower pregnancy outcomes with decreasing EMT. An endometrium >7 mm is acceptable by most authors as the cutoff for the optimal EMT. Studies have also shown that pregnancies have been reported below 6 mm when the pattern is trilaminar. Etiology of thin EMT also helps in prognosticating; endometrial damage secondary to inflammatory fibrosis may be more extensive than that due to idiopathic or architectural causes.

If a patient chooses to continue therapy despite having a thin endometrium or opts for alternative therapies, doctors must weigh the prognosis for that patient. Unfortunately, there is no agreement on what constitutes a thin endometrial lining; although studies have consistently indicated that decreased EMT is associated with a lower rate of implantation and pregnancy, yet successful pregnancies have been reported at so-called "thin endometrium" also. Therefore, a thin endometrial stripe is not always detrimental and pregnancies can be achieved. For patients with thin endometrium, there is currently little data to support any specific regimens or adjuvants that would significantly improve pregnancy outcomes. A change in dosage or route of estrogen or performing a diagnostic hysteroscopy may be simplest and the most rewarding intervention in majority of the cases. Adjuvants for increasing EMT should be individualized with the patients being counseled on their experimental nature, additional costs, and unproven results so far. Despite all interventions, if all measures fail to improve the EMT, patients should be counseled to proceed with transfer knowing the low results versus gestational surrogacy if feasible.

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The book *Advances, Breakthroughs, Controversies & Dilemmas in ART* compiles the major advancements and breakthroughs in this ever-growing field of assisted reproductive technology (ART). The book is divided into three sections. *Section 1* covers the recent advances and breakthroughs in the field of in vitro fertilization (IVF) and assisted reproduction. *Section 2* deals with all the difficult and challenging and controversial situations encountered in day-to-day practice, while *Section 3* deals with the various debates and dilemmas in the field of ART. The book will serve as a ready reckoner not only for the novice consultants but also for seasoned experts. It will also be a guide for the students appearing for infertility superspecialty examinations and for the gynecologists aspiring to learn infertility.



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