

## How Close we have Reached in Overcoming the Limiting Factor in IVF-ET Success Namely the Endometrium

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With the advances in getting novel stimulation protocols, reproductive immunology, having facilities of embryo culture along with testing technologies, implantation continues to be the step which basically prevents the success in artificial reproductive technology (ART). Earlier we reviewed on how chronic endometritis has become a major factor in limiting implantation and how lot of advances have been achieved in diagnosis and treatment of chronic endometritis (CE) and steps that are being taken to optimize diagnosis and treatment of CE which is one step that might help in improving implantation [1]. Here we discuss another factor creating controversy regarding implantation concerning the role of endometrium thickness at the time of transfer of embryos. There has been no doubt that having the most thick endometrium has >relation with success in implantation at the time of *in vitro* fertilization (IVF) [2-5]. Almost all of us have had in mind that if the endometrium is thin it is not suitable for moving on to embryo transfer (ET). We presume at that stage that once ET has crossed 7 or 8mm that further results are on the basis of the embryo. Of these the latest study by Liu., *et al.* [2] documented a reduction in both clinical pregnancy along with live birth rates at a significant level for every mm decrease below 8mm in preovulatory phase in 24,000 fresh IVF-ET cycles. Similarly, in frozen thawed embryo transfer (FET) cycles with every mm decrease in Endometrial Thickness < 7 mm in > 20,000 FET cycles.

Haas., *et al.* [6] published a retrospective study from which it could be interpreted that compacted endometrium, or as the term is used endometrium is thin, following progesterone (P) initiation might result in the best pregnancy rates. 274n frozen ET's of single blastocysts was examined and observation was that ongoing pregnancy rates were lower in the cycles where no compaction of the endometrium occurred at the junction of end of proliferative phase and the time of ET.

Most prominent separation was observed in the cycles where peak ET attained was 8 mm or 11 mm. In the cycles where 8 mm was the ET achieved, the ongoing pregnancy rates was 54.1%. If a minimum of 10% compaction was there in contrast to 21.8% in case no compaction was found in the endometrium. Among the cycles in which ET reached 11 mm, this separation was most obvious, i.e. 62.5% vis a vis 18.5%.

The secretory phase in the normal natural cycle is indicated by an increase in circulating P released by the corpus luteum (CL), that is behind these endometrial differences seen. There is a halt on proliferation and hence the tissue appears denser, as visualized by echogenicity as seen on ultrasonography (USG). Normally endometrium compacts at the time of implantation, although this has never been checked in the form of a typical biomarker, a positive one when conducting IVF.

Prior to thawing at the time of ET certain people routinely check the endometrium. With this they can be sure regarding doing the ET and that patient has been actually using the P as advised. In case for any reasons patient could not initiate P, then the thaw could be

prevented. Other than confirmation of use of P, it is debatable if the actual P amounts might have an association with success rates in recipients in an egg donation cycle when vaginal P was utilized [7]. But contrary to that a different retrospective study demonstrated that P amounts might have an association with reduced success rate on replacing euploid embryos in frozen embryo transfer (FET) cycles with the utilization of intramuscular P [8].

Further one might observe abnormal patterns or fluid within the lining when trying to test the endometrium prior to ET. In another centre where they thought that if endometrium thinned highly it might cause poor success. Ultimately, they observed that > 5 mm reduction in ET had no effect on pregnancy results [5].

Thus, this is an innovative idea that compaction might work as a positive biomarker and requires future detailed study. With this study designs certain limitations are seen. Hence prospective studies could be carried with proper designing. Subjects having thinner ET's < 7 mm were not taken up in this study, hence the knowledge of what point ET might be too thin. Moreover, this study was done only in subjects receiving medicine prior to FET for a single blastocyst transfer, thus clarification is not there if one can use these observations even for fresh ET or natural cycle ET. If a study is designed where preimplantation genotyping testing (PGT) is utilized particularly might aid in trying to observe the effect of compacted endometrium as then controlling for embryo quality is in hand. In this study ultrasonography (USG) was performed transabdominally, that we know is not equivalent to transvaginal sonography (TVS) in efficacy, mainly in women presenting with high body mass index (BMI) or with uterine fibroids. Haas, *et al.* [6] themselves want to conduct all these in a prospective study.

Although now further query arises if one does not get the compaction what needs to be done further. Although earlier a correlation of ET and IVF results have been well documented, there has never been shown if in a particular patients cancel of ET and repeating IVF thinking ET might get thicker might help. Although lot of discussions, no prospective data that doing intervention helps in increasing the outcome in women presenting with thin lining, echogenic finding on USG or endometrium that has increased contractility. Although now platelet rich plasma (PRP) can be offered and have been found to improve success [9] no prospective trials done in a large group of patients.

Here further Haas, *et al.* [6] advise to cancel if no complications occur, but > 10% compaction was not observed in most. A probable action in next cycle suggested is increase the dose/time of P, reduce E2 dose, shift to more natural FET, although not proved to be of help. One query arises can this endometrium that does not get compacted turn out to be 'prereceptive'. Instead of cancel of ET does one need to postpone the ET and re check the endometrium following 24h. Over 7 yrs of time Robert Casper the elder author of this article said that time had arrived that we start concentrating on the endometrium, this area remains mysterious although emphasis getting laid on this with us getting more insight regarding how implantation can get maximized [10]. Thus, step by step we are getting closer to overcoming the limiting factor of implantation that is the role played by endometrium in IVF-ET success rate getting optimized.

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