Endometrial Thickness in Infertility Treatment: Thick or Thin or Something More?

Endometrial thickness is a routine ultrasound measurement taken in the late follicular phase in patients who are receiving infertility treatment to become pregnant [1-4]. Generally, the endometrial thickness measurement taken on the day of the hCG medication administration used to trigger ovulation of the dominant follicles is the measurement that is used for clinical assessment.

The endometrial thickness has been measured for intrauterine insemination (IUI) cycles in a number of studies. Weiss et al. published a systematic review and meta-analysis of IUI cycles [1]. The evidence they analyzed showed no difference in endometrial thickness between women who conceived and those who did not. The use of medication type was found to be associated with endometrial thickness. No difference in endometrial thickness was found in their analysis between clomiphene citrate and letrozole cycles. Liu et al. studied the relationship between gonadotropin and IUI cycles [5,6]. They found that endometrial thickness was a poor predictor of outcomes in these treatment cycles. Recently, Quass et al. [7] showed in a large and well-designed study that in ovarian stimulation-IUI cycles, the endometrial thickness is not associated with live birth rate when there is the adjustment of outcomes of the thickness based on the treatment type (clomiphene, letrozole or gonadotropins). This study examined a key end point, which is the live birth rate, and was able to assess in sufficient detail the relationship between the thickness of the endometrium and live birth rates.

In patients undergoing IVF treatment, “thin” endometrium of less than 7 mm has been associated with first trimester loss. Kasius performed a systematic review and determined that in IVF, endometrial thickness of less than 7 mm reduces the chance of conception [8-10]. However, the liveborn rates are not statistically different in the patients with an endometrium that is less than 7 mm. The embryo is hypothesized to be closer to the uterine spiral arteries when the endometrium is thin. Thus, thin endometrium may be associated with elevated oxygen levels (greater than 5% oxygen) for the embryo. However, it should be noted that endometrial thickness of less than 7 mm is only reported for 2.4% of IVF cycles. In addition, for frozen embryo transfers, the endometrial thickness appears to have a relationship to the pregnancy outcomes [11,12].

The endometrial thickness is one measurement that is used, but the pattern type of the endometrial stripe has also been studied as potentially useful in predicting outcomes of the fertility treatment cycles. Gingold et al. studied the pattern of the endometrium in IVF patients [13]. They used the Grunfeld et al. [14] method of categorizing the endometrium: (1) late proliferative pattern with hyperechoic basalis and hypoechoic functionalis that is <50% of the endometrium; (2) early secretory pattern with hyperechoic basalis and functionalis extending to >50% of the endometrium and (3) mid-late secretory pattern with homogenous hyperechoic functionalis in the entire layer. Gringold et al. found that endometrial thickness was not associated with clinical outcomes, but the category 3 pattern (mid-late secretory pattern) on the day of the hCG trigger was associated with a lower implantation rate.

The areas of uncertainty at this moment include the following: endometrial thickness in relationship to live birth rates, treatments to enhance endometrial thickness, and pattern of the endometrium during the luteal phase in relation to pregnancy outcome for ovarian stimulation-IUI cycles.

GAPS THAT NEED TO BE ADDRESSED

The gaps in the understanding of the endometrium in infertility treatment include the following: what is the normal thickness in fertile (normal implantation) cycles, what is the rate of change of the endometrium that is optimal, what is the optimal thickness in frozen embryo transfer (FET) cycles, what is the endometrial thickness in IUI cycles? In addition, the key pieces of information of the luteal phase during the period leading to the window of implantation, in the window of implantation, and in the period after the window of implantation are needed.

The first area is understanding the endometrium in normal cycles. Studies are needed to be done to provide baseline information on the endometrium during cycles that include real pregnancy and live birth. Two important characteristics that need to be defined are the thickness of the endometrium and the rate of change in the endometrium in which normal pregnancy occurs. Does thinner endometrium have less blood flow? Or is it that the thinner endometrium puts the embryo closer to the uterine spiral arteries so that the oxygen tension is too high for optimal embryo development? What is the histology of the endometrial stripe?

A second area that needs more investigation is the endometrial thickness during different infertility treatment cycles and the live birth rates. This includes IUI cycles, IVF cycles, FET cycles, and donor egg cycles. Only a few studies have focused on the relationship between the endometrial thickness and the live birth rates, which should be the gold standard endpoint of fertility studies. Thus, the relationship between the endometrial thickness and live birth rates should be investigated more thoroughly and definitely.

A third area of investigation is to further understand the luteal phase. What is the relationship between the pattern of the endometrial stripe and the endometrium in the luteal phase “window of implantation”? This includes the period of time after
ovulation, during the period of “window of implantation”, and in the luteal phase after this window of implantation. The information needed includes proteomics, mRNA expression, vascular flow, oxygen tension levels and additional information about tests such as the endometrial receptor assay, the “ERA”.

CONCLUSION

The measurement of the endometrial thickness during infertility treatment is taken every day, but the optimal use and evidenced based understanding of this measurement has not yet been achieved. The measurement of the thickness of the endometrium in infertility treatment cycles appears to suggest that the measurement of the endometrial thickness during the follicular phase may be prognostic of the prospect of pregnancy in that cycle. Until then, what do we tell the patients? It appears that for ovulation induction-IUI cycles, the thicker endometrial thickness measurement is reassuring but should not dictate management of that cycle. For fresh IVF embryo transfers, the endometrial thickness of less than 7 mm is associated with lower clinical and live birth rates, but the clinical and live birth rates are still reasonable. For the frozen-thaw embryo transfers, the clinical and live birth rates appear to be higher with endometrium that is thicker, but the evidence showing that there really is a clinical difference has not yet been obtained. Thus, overall, it appears that the management of a patient undergoing treatment should not solely be dependent on the thickness of the endometrium in the late follicular phase. Scientific advances still need to be made to improve the gathering of endometrial information in the infertility treatment cycles to optimize the chances of pregnancy and, ultimately, the chances of live birth of term pregnancy.

REFERENCES