Editorial Articles

The importance of sonographic endometrial parameters in influencing success following embryo transfer in the modern era and therapeutic options - Part 1: the importance of late proliferative phase endometrial thickness

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Summary

Purpose: To evaluate the importance in the modern era of either too thin or too thick of an endometrium in the late proliferative phase on success following embryo transfer. *Methods:* Pregnancy rates following fresh embryo transfer in cycles using controlled ovarian hyperstimulation and following donor egg or frozen embryo transfers using artificial estrogen-replaced cycles according to endometrial thickness were determined. *Results:* A thin endometrium has a negative impact on success following embryo transfer but improvement in IVF technology makes this confounding variable much less important than in the early days of IVF. Too thick of an endometrium does not seem to negatively impact success. *Conclusions:* Treatment options, e.g., low-dose aspirin, sildenafil or vaginal estradiol are of marginal value in improving endometrial thickness or outcome. For those with a good frozen embryo program the best option may be to cryopreserve all embryos and transfer in a subsequent graduated estrogen/progesterone replacement cycle.

Key words: Late proliferative active phase; Endometrial thickness; Embryo transfer.

Effect of a thin late proliferative phase endometrium following controlled ovarian hyperstimulation (COH) and IVF-ET

Several publications in the early to mid 1990s reported lower pregnancy rates following in vitro fertilization-embryo transfer (IVF-ET) with a thinner late proliferative phase endometrial thickness. Gonen *et al*. found a significantly thicker endometrium in pregnant vs non-pregnant women using a clomiphene citrate-human menopausal gonadotropin (hMG) controlled ovarian hyperstimulation (COH) protocol [1]. Other studies also found lower pregnancy rates with thinner endometrium using luteal phase leuprolide acetate-gonadotropin COH protocols [2-5].

However some studies published in the late 90s to the early 2000 era challenged the importance of late proliferative endometrial thickness on pregnancy outcome [6-9]. One of the possible reasons for discrepancy in conclusions may have been related to the limited power of smaller case series. A large retrospective study in the modern era was performed on 1,228 IVF intracytoplasmic sperm injection (ICSI) cycles [10]. They found a 28.3% pregnancy rate with < 10 mm endometrial thickness vs 34.3% for ≥ 10 mm ($p < 0.05$). However another large retrospective study of 1,061 cycles found the effect of endometrial thickness to be marginal [6].

Data for Cooper Institute for Reproductive Hormonal Disorders over the last ten years up to June of 2006 evaluated pregnancy rates following controlled ovarian hyperstimulation and pregnancy rates according to endometrial thickness on the day of hCG injection. These data are seen in Table 1 and the pregnancy rates are listed according to endometrial thickness at each mm level starting at 5 mm and ending at 13 mm. If a cut-off at 10 mm is used, as in the studies in the early 90s, there are significantly lower clinical and live delivered pregnancy rates in those with < 10 mm vs those ≥ 10 mm as seen in Table 2.

However, if endometrial thickness between 7-9 mm is evaluated and compared with clinical pregnancy rates in our early publications vs the modern era (with improvement in culture media, transfer catheters and possibly and most importantly performing salpingectomies for hydrosalpinges) there is a vastly improved pregnancy rate in the modern era (3.4% vs 36.3%) as seen in Table 3. Though pregnancy rates have improved in the modern era following embryo transfers with endometrial thickness of ≥ 10 mm as seen in Table 4 the differences are not nearly so dramatic as with thinner endometrium.

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Table 1. — *Pregnancy rates according to specific endometrial thickness levels*.

	Endometrial thickness (mm)								
	5	6	7	8	9	10	11	12	13
# transfers	3	17	78	185	252	346	293	224	208
% clinical pregnancies	0	23.5	30.8	34.6	39.3	44.8	46.8	46.9	46.2
% delivered	0	11.8	24.4	29.7	34.5	34.6	41.0	43.3	42.3
Implantation rate (%)	0	11.8	15.1	17.9	21.1	24	23.5	26.0	25.1

Table 2. — *Pregnancy rates comparing thickness of < 10 mm vs > 10 mm*.

	< 10 mm	≥ 10 mm
# transfers	535	1071
# clinical pregnancies	191	493
% clinical pregnancies	35.7	46.0
# delivered pregnancies	163	442
% delivered	32.1	41.2

$p < 0.05$.

Table 3. — *Comparison of clinical pregnancy rates according to endometrial thickness of 7-9 mm - early 1990s vs the modern era*.

	Early IVF	Modern era
# transfers	29	515
# clinical pregnancies	1	187
% clinical pregnancies/transfer	3.4	36.3

Table 4. — *Comparison of clinical pregnancy rates according to endometrial thickness of ≥ 10 mm - early 1990s vs the modern era*.

	Early IVF	Modern era
# transfers	56	1293
# clinical pregnancies	15	594
% clinical pregnancies/transfer	26.8	45.9

Thus modern technology has provided a 70% increase in clinical pregnancy rates compared to the early 90s with an endometrial thickness of ≥ 10 mm. However there is a 10-fold increase in clinical pregnancy rates in the modern era vs the earlier days of IVF-ET when the maximum endometrial thickness was only 7-9 mm. Table 1 shows only a 10% (2/20) live delivery rate per transfer with an endometrial thickness of 5-6 mm. To date there have only been two case reports of successful live deliveries following embryo transfer with an endometrial thickness of ≤ 4 mm [11, 12]. Another successful pregnancy was reported in a natural conception with a peak endometrial thickness of 4 mm [13]. Thus though pregnancies have been achieved following embryo transfer with a peak endometrial thickness of ≤ 6 mm the marked reduction in pregnancy rates would nevertheless suggest that only attaining this level in a first COH IVF-ET cycle should encourage the strategy of freezing the embryos and not transferring in hopes that a better endometrium could be obtained by artificial estrogen replacement, especially if some of it is given vaginally. In fact at our center we found that 41 of 61 women (67.2%) who deferred fresh embryo transfer because of an endometrial thickness ≤ 7 mm did attain an endometrial thickness ≥ 8 mm in their first frozen embryo transfer cycle [14]. Pregnancy rates in this group will be discussed subsequently.

Effect of thin endometrium on pregnancy rates following embryo transfer in cycles where the endometrium was prepared by artificial estrogen/progesterone

The first study showing that a thin endometrium had a negative impact on pregnancy rates following embryo transfer into an endometrium that was prepared by artificial estrogen progesterone was published in 1993 using embryos derived from donor oocytes [15]. A study in the modern IVF era confirmed that there were lower pregnancy rates in donor oocyte cycles with an endometrial thickness of ≤ 8 mm [16].

We recently presented data at the 2008 meeting of the American Society for Reproductive Medicine concerning pregnancy rates following transfer of frozen-thawed embryos according to late proliferative phase endometrial thickness in artificially prepared endometria [14]. Using the 10 mm thickness cut-off, there were 832 first IVF cycles with < 10 mm thickness vs 1291 with ≥ 10 mm. For all frozen ET cycles there were 977 < 10 mm vs 1432 ≥ 10 mm maximal endometrial thickness.

Thus with artificial estrogen cycles approximately 60% will attain the 10 mm level. Evaluating the 10 mm cut-off in all cycles the live delivered pregnancy rate per transfer of frozen thawed embryos was 29.0% (292/977) with < 10 mm vs 34.8% (498/1432) with thickness ≥ 10 mm ($p = .014$). Interestingly the live delivered pregnancy rates per transfer was not less with the group with thickness ≤ 6 mm (29.2%) or < 8 mm (27%). The results were similar for first cycles only. In this study there were only 4.1% of the 2409 frozen embryo transfers with an endometrial thickness of ≤ 7 mm. The clinical and live delivered pregnancy rate for this group was 29.0% and 27.0%, respectively.

Previously we mentioned a group of women who on their COH IVF cycle had a peak endometrial thickness of 7 mm and were given the option of freezing or transferring fresh. There were 61 who took the freezing option and 98 who proceeded with fresh embryo transfer. The clinical and live delivered pregnancy rates for those deferring to frozen embryo transfer were 34.4% and 29.5% and for those proceeding with fresh embryo transfer they were 27.5% and 21.5% (unpublished data). Thus by cryopreserving and deferring to frozen embryo transfer the pregnancy rates increased by 30% (unpublished data).

Therapies to improve endometrial thickness

There is no magic bullet to improve endometrial thickness. A study by Wada *et al*. found that when taking low-dose aspirin from day 1 of a frozen embryo transfer cycle in women with a previous history of diminished uterine perfusion, there was an improvement in uterine blood flow. In fact they demonstrated a 47% pregnancy rate per transfer in those taking low-dose aspirin from day 1 vs 17% for those starting aspirin on day 13 [17].

There are many publications too numerous to mention evaluating uterine blood flow measurements with success of IVF-ET. I will just state that our own extensive studies of uterine blood flow and perfusion failed to demonstrate any correlation with these measurements and IVF-ET outcome. Nevertheless we did a study to confirm or refute the findings of Wada *et al*. [17]. We did not detect a difference in uterine perfusion studies or endometrial thickness. However shockingly not only did we not confirm an improvement in pregnancy rates but found the opposite – an 11.1% clinical pregnancy rate in those taking aspirin vs 33.3% in the control ($p < 0.05$) [18].

Though some hematologists claim that dosage of aspirin < 100 mg inhibits thrombosis but does not inhibit platelet function so bleeding is not likely; anecdotally, the women who have had the most bleeding at the time of oocyte retrieval were those who took low-dose aspirin (usually against our advise). Also we have observed a higher frequency of subchorionic hematomas in women taking 81 mg aspirin during their first trimester.

Two other therapies have been suggested as methods to improve endometrial thickness. One involves the use of sildenafil taken as vaginal suppositories allegedly to improve uterine blood flow with this vasodilator [19, 20]. Others have suggested that vaginal estrogen could improve endometrial thickness [21-23].

However, our own studies found that if these agents improve endometrial thickness the improvement is only marginal with a slight edge to the vaginal estradiol [24].

Technology has improved in the modern era to allow reduced but reasonably decent pregnancy rates despite thin endometria. The technique that we use for cryopreservation is one that we have developed and it has always provided us with pregnancy rates following frozen embryo transfer comparable to the pregnancy rates following fresh embryo transfer [25]. Our technique is a simplified freezing protocol avoiding the planar programmable freezer (which we believe is the weak link of the classic LaSalle Testard technique used by most IVF centers) with the thawing procedure using a single step addition and removal of cryoprotectants [25, 26]. We are not sure why our technique never became a more frequently used technique for cryopreservation in other IVF centers. Nevertheless vitrification has become more popular and this should also provide comparable pregnancy rates to fresh embryo transfer when these vitrified embryos are thawed and transferred [27]. However, if an IVF center gets much lower pregnancy rates with their present cryopreservation technique the advantage may be to transfer the embryos fresh despite a thinner endometrium.

Increased endometrial thickness in the late proliferative phase

Some studies suggest that too thick of an endometrium in the late proliferative phase is associated with very poor pregnancy rates following embryo transfer. Kupesic *et al*. reported no pregnancies if the endometrial thickness was > 15 mm on the day of embryo transfer in 89 women [28]. Schild *et al*. reported no pregnancies if the endometrial thickness was > 16 mm on the day of oocyte retrieval in 49 women [29]. Weissman *et al*. analyzed 809 IVF cycles in 623 women and found a reduction in pregnancy and implantation rates and an increase in miscarriage rates when an endometrial thickness of > 14 mm was found on the day of hCG administration [30].

Our own study did not confirm the importance of too thick of an endometrium on the day of hCG injection [31]. Comparing ≤ 8-≤ 14 mm endometrial thickness to ≥ 14 mm the clinical pregnancy rates, implantation rates, and miscarriage rates were 43.1%, 20.9%, and 11.8% in the former vs 48.3%, 25.5%, and 13.8% in the increased endometrial thickness group [31]. The conclusions from our study are supported by data from Yakin *et al*. [32]. In fact there was still a 40% clinical pregnancy rate per transfer in those with a 17 or 18 mm thickness [31]. Thus our policy is not to cryopreserve because of an increased endometrial thickness.

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