

## Original Article

# Does the endometrial thickness really matter in Assisted Reproductive Technology Cycles - A Retrospective analysis

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### Abstract

**Aim:** The objective of the study was to observe the thickness of endometrium on HCG trigger day during Assisted Reproductive Technology (ART) cycles and correlating it with pregnancy outcome. **Materials and Methods:** From September 2008 to December 2014, 57 patients undergoing assisted reproduction cycles were retrospectively analyzed for the pregnancy outcome in relation to endometrial thickness. The study was done in the Reproductive Medicine department, Chettinad Hospital and Research Institute, Kelambakkam. All fresh Intra Cytoplasmic Sperm Injection treatment cycles using short flare protocol were included and categorised into two groups based on the pregnancy results: 1. Group A (pregnant), 2. Group B (non-pregnant) **Results:** The mean endometrial thickness in the groups A and B were  $10.02 \pm 1.46$  (7.1 to 13.4mm) and  $10.40 \pm 2.19$  (7.8 to 19 mm) [P < 0.447, Not significant]. The clinical pregnancy rate was 42.10% and the implantation rate was 22.81%. Pregnancy rate was good probably because of the selection of grade 1 embryos and limiting the age of patients to <35yrs. **Conclusion:** From our study, the endometrial thickness is not the deciding factor for the successful implantation of human embryo. We also infer that thin endometrium of < 7 mm is an unlikely occurrence in ART cycles unless there is pathology in the uterus.

**Key Words:** Endometrial thickness, Embryo, Implantation, Pregnancy outcome.

### Background

Despite numerous papers analyzing the influence of endometrial thickness in influencing pregnancy outcome, the issue remains unclear. Compared to the escalating cost, the outcome of pregnancy is low in ART/ICSI cycles which mandates the reevaluation of the predictive factors for success in ART.

### Introduction

Implantation of embryos is the final and most critical step in assisted reproduction. Both embryo quality and endometrial receptivity play a vital role in implantation of embryo<sup>1</sup>. The assessment of endometrial receptivity is by simple 2D ultrasonographic (USG) examination during stimulation. Since USG is a simple, non-invasive, patient friendly and reliable technique for the evaluation of endometrium, it is commonly employed.

For the implantation to take place, priming of endometrium occurs in each and every menstrual cycle. The communication between the blastocyst and the endometrium is expected to be closer if the implantation is to be successful. If these cyclic changes are prevented by abnormalities of endometrium, there are less implantation and more miscarriages<sup>2</sup>.

The relationship between thickness or pattern of endometrium and the receptiveness of the uterus has been analyzed by many authors<sup>3-11</sup>. Some studies reported with increased endometrial thickness pregnancy rates are less<sup>7,12,13</sup>. Some other studies reported that with increase in endometrial thickness, the pregnancy rates also increases<sup>5,14</sup>. Both the endometrial thickness and pattern are analysed in few other studies to prognosticate the pregnancy outcome of ART<sup>12</sup>. Recent studies analyzed the endometrial blood flow by doppler studies to predict the pregnancy outcome in ART<sup>15</sup>. But some others concluded that there is absence of influence over pregnancy outcome by the endometrial thickness and pattern<sup>16-20</sup>.

In the first systematic meta-analysis, the predictiveness of the role of endometrial thickness over ART outcome was investigated. The chances of clinical pregnancy was significantly less in patients when the endometrium was < 7mm compared to > 7mm (23.3% vs 48.1%) and OR was 0.42 (95% CI 0.27 - 0.67)<sup>21</sup>.

### Endometrium:

Distance between endometrial-myometrial junction of one side to the other is measured as the endometrial thickness. The measurement is taken in the longitudinal axis on the day of hCG trigger by using two dimensional transvaginal ultrasound.

The thickness of the endometrium at early follicular phase in the antero- posterior(AP) view is approximately 5-7mm. It becomes triple line around ovulation and is about 8-12mm. Echo pattern becomes homogeneously hyper-echoic in luteal phase. Remarkable changes take place in the endometrium after ovulation. By 13 days post ovulation, the endometrium clearly differentiates into 3 zones:

1. Stratum basalis
2. Stratum spongiosum
3. Stratum compactum

The cardinal morphologic change around implantation is the formation of edema of the endometrial stroma which is on days 21 - 22 of the menstrual cycle. More production of prostaglandin by the endometrium occurs due to sex steroids. Ultimately the permeability of the capillaries are increased with rise in prostaglandins. There are receptors available for the sex steroids in the vasculature of the endometrium.

## Implantation

Implantation is defined as the adhesiveness of the blastocyst with the epithelial lining of uterus and subsequently invading the epithelium, occurring approximately 18-19th day of menstrual cycle<sup>22, 23, 24</sup>.

The objective of our analysis was to observe only the endometrial thickness on the day of hCG trigger during ART cycles and to study the influence of endometrial thickness over ART outcomes.

## Materials and Methods

**Study population:** From September 2008 to December 2014, 57 patients who underwent ART cycles were retrospectively analyzed for the pregnancy outcome in relation to endometrial thickness after excluding the factors discussed later. The study was done in the department of Reproductive Medicine, Chettinad hospital and research institute, Kelambakkam.

## Methodology

All fresh ICSI cycles using short flare protocol who underwent oocyte retrieval and also transfer of embryos were included.

### Inclusion criteria:

1. Age < 35yrs
2. First cycle ART
3. Only short agonist protocol
4. Normozoospermia
5. Transfer of three, grade 1 embryos

### Exclusion criteria:

1. Cycles using donor oocytes /embryos
2. Cycles using cryopreserved embryos
3. Presence of known uterine anomalies
4. Presence of hydrosalpinx
5. Ovarian stimulation method other than the short agonist protocol.
6. Male factor infertility

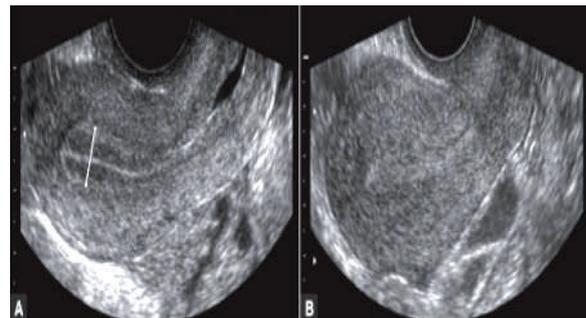
## Procedure:

The pituitary was down regulated with short GnRH agonist (flare) protocol from D2 of menstrual cycle to HCG trigger and stimulation of ovaries was achieved with urinary gonadotrophins. When at least three follicles reached  $\geq 18$  mm by 2D USG, oocyte retrieval was planned. The clinician measured the thickness of the endometrium and recorded in the patient's case sheet. Inj.HCG trigger was given and the oocytes were retrieved 35-36 hours later. ICSI was carried out to achieve fertilization. Embryo transfer was planned post oocyte retrieval (D2/D3/D5). Luteal phase was supplemented with progesterone vaginal pessaries from the day of OPU and continued till day 14 post embryo transfer. Two weeks after positive  $\beta$ HCG, USG was planned. When fetal cardiac activity was present, clinical pregnancy was confirmed.

## Ultrasound examination

The maximum thickness of the endometrium in the longitudinal plane was measured on the day of HCG trigger. Based on pregnancy results, all cycles were categorised into :

1. Group A (pregnant)
2. Group B (non- pregnant)



**Fig 1 -** Ultrasonography picture of endometrium. (A) Multi layered endometrium or triple line pattern and (B) Non-multi layered pattern

## Statistical Analysis

Continuous data are measured as Mean + SD and analysed. To test the equality of mean values of two groups, independent samples t-tests are used and  $P < 0.05$  was considered as statistical significance. To compare the differences between two groups when the characteristic of interest is qualitative in nature, Mann Whitney tests are applied. IBM SPSS (Version 21.0) software was used for statistical analysis.

## Results

All the 57 women who met the inclusion criteria were analyzed in our study. The patients were between 25 and 34 years of age with the mean of 30.86 yrs. The baseline characteristics of the two groups, with pregnancy (group A) and without pregnancy (group B) are shown in table 1. Comparison of baseline characteristics revealed no statistical difference in parameters such as age, BMI and period of infertility in the pregnant and non-pregnant groups. There was also no significant difference seen in the basal FSH and total AFC (Antral Follicle Count).

Baseline Characteristics	Pregnancy outcome						Independent Samples t-test	
	Group A (n = 28)			Group B (n = 29)				
	Mean	SD	SE	Mean	SD	SE	t-Value	P value
Age (yrs.)	31.39	2.59	0.49	30.34	2.44	0.45	1.574	0.121
Period of infertility(yrs.)	6.27	4.26	0.81	6.38	3.42	0.63	-0.112	0.911
BMI (weight in kg/height m <sup>2</sup> )	25.83	3.62	0.68	25.55	3.11	0.58	0.314	0.755
AFC Total	11.52	5.69	1.09	11.86	4.82	0.90	-0.244	0.808
D <sub>2</sub> FSH (m IU/ml)	7.42	2.47	0.47	7.54	2.04	0.38	-0.188	0.852

**Table 1 - Baseline Characteristics**

Both groups have comparable baseline features.

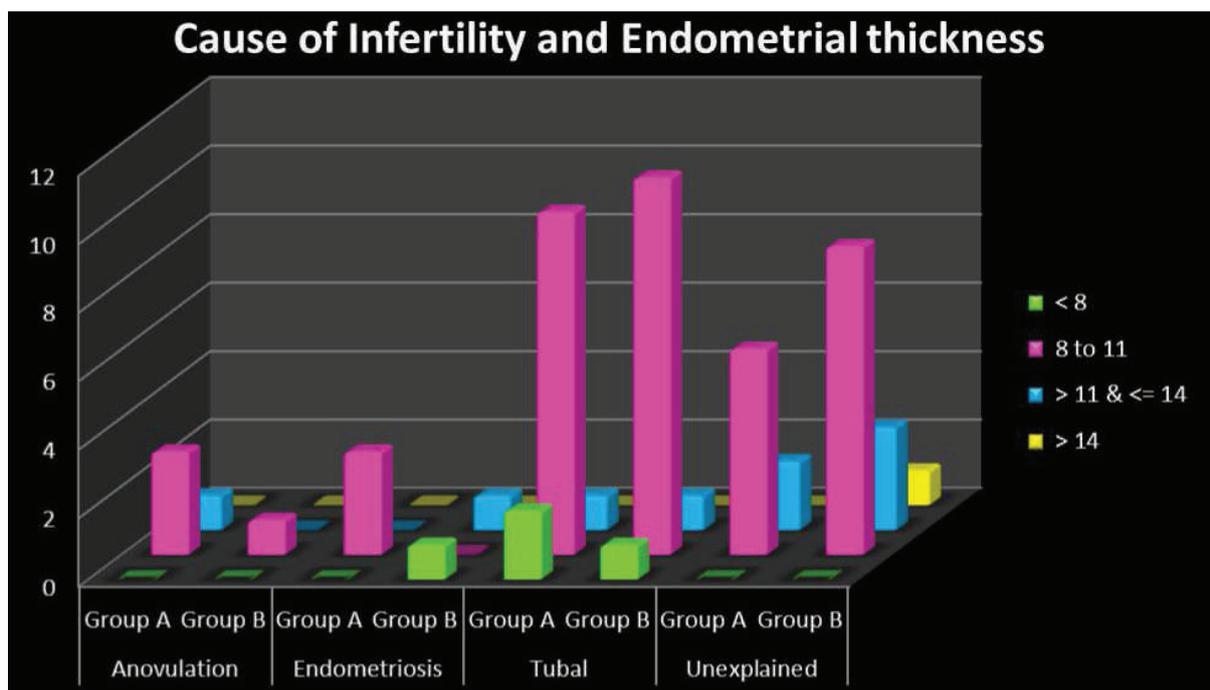
Group A patients had mostly secondary infertility (46.43%) and group B had predominantly primary infertility(72.41%).The predominance of primary infertility in group B and secondary infertility in group

A is not significant (NS) statistically (P<0.144) and the patients were selected based on random allocation. In table 2 and fig 2, the cause of infertility in the two groups was given. The major cause of infertility in both the groups were tubal factor (46.43 and 44.83%).

S.No	Endometrial Thickness (mm)	Anovulation		Endometriosis		Tubal		Unexplained	
		Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
1	< 8	0	0	0	1 (3.45%)	2 (7.14%)	1 (3.45%)	0	0
2	8 to 11	3 (10.71%)	1 (3.45%)	3 (10.71%)	0	10 (35.71%)	11 (37.93%)	6 (21.43%)	9 (31.03%)
3	> 11 & ≤ 14	1 (3.57%)	0	0	1 (3.45%)	1 (3.57%)	1 (3.45%)	2 (7.14%)	3 (10.34%)
4	> 14	0	0	0	0	0	0	0	1 (3.45%)

**Table 2 - Cause of infertility and Endometrial thickness**

Cause of infertility did not influence the endometrial thickness.(P<0.672,NS)



**Fig 2 - Major cause of infertility in both the groups was tubal factor.**

Table 3 shows the clinical findings of the two groups. No significant difference was observed in the duration of stimulation, amount of gonadotrophins utilized for stimulation and the number of dominant follicles. Though the number of oocytes retrieved and mature oocytes (MII) were more in group B, it is not significant statistically.

The endometrial thickness on the day of HCG trigger was between 7.1mm and 19 mm with the mean of 10.21mm .The mean endometrial thickness in the groups A and B were 10.02 + 1.46 ( 7.1 to 13.4 mm) and

10.40 + 2.19 (7.8 to 19 mm) and it was not significant statistically(P < 0.447). In our study, no patient had endometrial thickness < 7 mm. Both the groups had almost similar duration of ovarian stimulation (11.18 + 2.23 vs 10.72 + 2.07). The total dose of gonadotrophins used was comparable between both the groups (3334.82 + 1074.22 vs 3300 + 1091.46). The total number of embryos transferred was 3, grade 1 embryos which is similar in both the groups. It is evident that the cause of infertility has no influence on endometrial thickness.

Clinical Characteristics	Pregnancy outcome						Independent Samples t-test	
	Group A ( n = 28)			Group B ( n = 29)			t-Value	P value
	Mean	SD	SE	Mean	SD	SE		
Endometrial thickness (mm)	10.02	1.46	0.28	10.40	2.19	0.41	-0.766	0.447
Duration of Stimulation (days)	11.18	2.23	0.42	10.72	2.07	0.38	0.798	0.428
Total dose of gonadotrophins (IU)	3334.82	1074.22	203.01	3300.00	1091.46	202.68	0.121	0.904
No. of dominant follicles (DF)	8.32	4.88	0.92	9.66	3.76	0.70	-1.158	0.252
No. of Oocytes retrieved	8.43	3.70	0.70	9.86	4.10	0.76	-1.384	0.172
Total MII oocytes	6.68	3.03	0.57	8.31	2.61	0.48	-2.182	0.033
Fertilised	5.29	2.14	.40	5.83	2.14	0.40	-0.956	0.343
Cleaved	5.11	2.10	.40	5.55	2.21	0.41	-0.778	0.440

**Table 3 - Clinical Characteristics**

Pregnant and non-pregnant groups show no significant difference in the clinical characteristics.

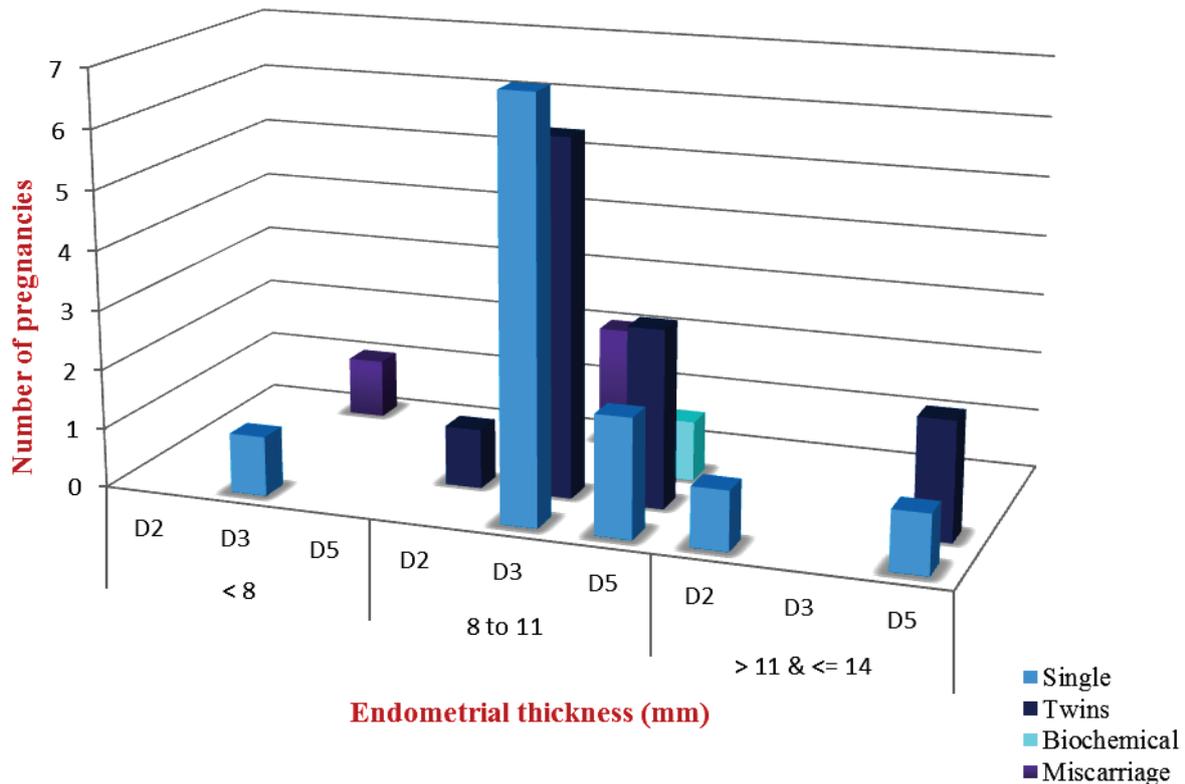
S.No	Endometrial Thickness (mm)	Day of Transfer	Pregnancy Outcome			
			Single	Twins	Biochemical	Miscarriage
1	< 8	D2				
		D3	1			1
		D5				
2	8 to 11	D2		1		
		D3	7	6		2
		D5	2	3	1	
3	> 11 & <= 14	D2	1			
		D3				
		D5	1	2		

**Table 4 - Day of embryo transfer with positive outcome and Endometrial thickness**

Endometrial thickness has no influence over pregnancy outcome

Table 4 and fig 3 shows the day of transfer with positive outcome and endometrial thickness. The mean day of embryo transfer for group A was 3.57 and group B was 3.66 which were similar between both the groups and not significant statistically. The pregnancy rate and clinical pregnancy rate of the study group were 49.12% and 42.10% respectively. The implantation rate was 22.81%. Pregnancy rate is good probably because of the selection of grade 1 embryos and limiting age of patients to < 35yrs.

Single and twin pregnancies were 12 (42.86 %) and 12 (42.86 %). The number of miscarriages was 3 (10.71 %) and we had one (3.57%) biochemical pregnancy with D5 transfer. The single/twin pregnancies were in the range of 8 to 11 mm endometrium mostly. Also we had miscarriages and biochemical pregnancy in that range of endometrium. Hence we could not arrive at a conclusion regarding influence of endometrial thickness and the outcome of pregnancy.



**Fig 3** - The above diagram shows the different pregnancy outcomes with different range of endometrium and the day of transfer.

## Discussion

Since the introduction of ART by Prof. Edwards and Mr. Steptoe in 1978, the success rate hovers around 40 to 45 %. Hence, to improve the success rate, various factors are analyzed from time to time. The pioneering work on human implantation was done by Hertig and colleagues 50 years ago<sup>25</sup>. Since then different opinions have emerged regarding implantation and now recently the focus is shifted to endometrial receptivity to identify the receptors. The present day receptor mediated model which estimates the window of implantation of the endometrium was described by Yoshinga and Wilcox<sup>26,27</sup>. Different ART cycle parameters and the outcome have been analysed and endometrial thickness is one such parameter which has been evaluated by several authors<sup>13,14,18,22,23,24,28,29,30</sup>. Adequate preparation of the endometrium is essential for a successful implantation to take place. Endometrial thickness reflects the enlargement of endometrium in the absence of uterine pathology.

In a study by Noyes et al (1995), analysis of 516 IVF cycles showed more pregnancies with the endometrial thickness of  $> 9$  mm<sup>23</sup>. Weissman et al (1999), found in a study that with thickness of  $> 14$  mm the implantation rate was less. Also they found that the miscarriage rate was more when it was  $> 14$  mm on the day of trigger injection<sup>31</sup>. Likewise, in a study by Dickey et al., more biochemical pregnancies were found with endometrial thickness of  $> 14$  mm<sup>32</sup>. No pregnancy with endometrial thickness  $> 12$  mm was reported by Rashidi et al<sup>12</sup>. However, there are case series which reported successful pregnancies when endometrial thickness was  $\geq 20$  mm. Quintero reported a single case of successful

pregnancy when endometrial thickness was  $\geq 20$  mm. However, later studies found absent influence of endometrial thickness on outcome of pregnancy<sup>13,18,34</sup>. Also in the latest study by Fang et al (2016), no unfavourable pregnancy outcome when endometrial thickness  $> 14$  mm was observed<sup>35</sup>.

In our study, one patient with endometrial thickness  $> 14$  mm was negative for pregnancy. Hence it is difficult to comment on influence of increased thickness over pregnancy outcome. When there is an endometrial pathology as in Asherman's syndrome, the usual endometrial changes do not occur. Hence there is less implantation and more miscarriages. Though there are many studies showing successful pregnancies in cycles where the endometrial thickness of  $< 4$  mm was observed<sup>20</sup>, we have not seen a patient with  $< 7$  mm endometrial thickness in 830 ART/ICSI cycles since 2008 in our centre. Hence endometrial thickness  $< 7$  mm is an unusual occurrence in ART patients unless there is presence of uterine anomalies/pathology.

In our study majority of women had endometrial thickness  $> 8$  mm with the mean of 10.21 mm. Our study does not conclude any adverse effect of endometrial thickness  $> 14$  mm over pregnancy. No conclusive evidence from our study with regard to pregnancy mishaps like miscarriages. Nor does an ideal endometrium (8 to 11 mm) guarantee a pregnancy. Though implantation of the embryo happens in the endometrium, we are not able to conclude that the thickness of the endometrium really has an influence on the favorable outcome of ART.

On the contrary, we feel the quality of embryos has a vital role in deciding the implantation of the embryos. Hence it seems obvious that the process of implantation is much more complex than what can be determined by a single and simple USG measurement of the endometrium<sup>36</sup>.

## Conclusion

We have limited the confounding factors which may have effect over implantation and then assessed the influence of endometrium on implantation of embryo. From our study, the endometrial thickness is not the deciding factor for the successful implantation of human embryo. We feel that a good quality embryo has more potential to implant in any reasonable environment and grow further. We also infer that thin endometrium of < 7 mm is an unlikely occurrence in ART cycles unless there is pathology in the uterus. Limitations of our study are it is a retrospective study and small number of patients analyzed.

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