10.5005/jp-journals-10016-1039
RESEARCH ARTICLE

Is Endometrial Thickness on the Day of ET Really Predictive of IVF Outcome?

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ABSTRACT

Background: The effect of endometrial thickness on pregnancy rates in assisted reproductive technology (ART) patients has been evaluated by many authors, with controversial results. Endometrial thickness has been utilized as an indirect indicator for endometrial receptivity.

Objective: To evaluate relationship between endometrial thickness on day of embryo transfer and pregnancy outcome in *in vitro* fertilization and embryo transfer (IVF-ET) cycles. Should we cancel cycles based on endometrial thickness only?

Material and methods: A prospective analysis was conducted at Dr Kamini Rao Hospital, Bangaluru, of 239 patients. Various parameters were compared between pregnant and non-pregnant patients to see whether there is any cut-off for endometrial thickness on day of embryo transfer by which we can predict good prognosis in form of pregnancy and what effect other variables on endometrial thickness and pregnancy respectively and should we cancel embryo transfer, if endometrial thickness is not within certain range?

Results: In the study population, 174 (73%) had primary and 65 (27%) had secondary infertility, Ovarian stimulation was performed with long protocol in 37% cases, antagonist protocol in 47% and other protocols like microflare, short, ultralong, ultrashort in 15%. Mean age of patients was 31.04 ± 3.79 years. Among causes of infertility male factor was present in 39%, tubal factor was seen in 18%, unexplained were 13%, polycystic ovarian syndrome in 11%, poor ovarian reserve in 4.1% and mixed causes in 13%. Majority of our patients were in normal and overweight as per body mass index (BMI). ET were easy in 90% of cases and 14 (5.8%) ETs were cancelled. The reason for cancellation was ovarian hyperstimulation syndrome (OHSS) in 9 cases, fluid in cavity in 2 cases, one patient had hyperpyrexia on day of ET and 2 cases of failed fertilization. Endometrial thickness was >10 mm in 35% cases. Overall clinical pregnancy rate was 39% with implantation rate of 21%, fertilization rate of 92% and cleavage rate of 95% and live birth rate of 26%. There were more follicles, oocytes and embryos, the endometrium was >10 mm and embryo quality was higher among women who became pregnant when compared with nonpregnant women after assisted reproduction though not statistically significant ($p > 0.05$). The pregnancy rate improved as endometrial thickness increased showing a linear association.

Conclusion: Increased endometrial thickness is associated with higher pregnancy rates, but as such a cut off cannot be decided. In our study we have seen pregnancies at both thin and thick endometrium so we should not cancel ET merely on the basis of endometrial thickness as pregnancy is affected by multiple variables and not by endometrial thickness alone.

Date of Received: 18-07-12
Date of Acceptance: 14-08-12
Date of Publication: May 2012

Keywords: Endometrial thickness, Gonadotropin, *In vitro* fertilization, Pregnancy.

How to cite this article: Sharma R, Rao K, Srinivas MS, Jones T. Is Endometrial Thickness on the Day of ET Really Predictive of IVF Outcome? Int J Infertility Fetal Med 2012;3(2): 40-47.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Assisted reproductive technology (ART) has been commonly used in infertility treatment over the last two decades. The high cost and relatively low implantation and pregnancy rates (PRs) in *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment cycles has led to a need to evaluate the predictors of success in these patients.

During the menstrual cycle the endometrium undergoes cyclic changes in preparation for implantation. In the follicular phase, the growing follicles produce increasing amounts of estradiol that will induce proliferative endometrial changes.[10] Following ovulation, the corpus luteum produces progesterone that will initiate secretory changes. If implantation does not occur during the window of implantation, the endometrium will shed once the corpus luteum regresses. An association of various cycle characteristics and treatment outcome has been evaluated since the introduction of ARTs. According to its appearance in the longitudinal section, the endometrial morphologic characteristics can be classified as 'triple layer' or 'nontriple layer.'[20]

One of the important factors is the endometrial receptivity. Endometrial thickness has been utilized as an indirect indicator for endometrial receptivity and is measured in the mid-saggital plane during transvaginal ultrasound, which is considered as both atraumatic and simple.[1]

The effect of endometrial thickness on pregnancy rates in ART patients has been evaluated by many authors.[2-11] Some authors demonstrated a higher pregnancy rate at certain endometrial thickness,[12-15] while others did not show a significant correlation between endometrial thickness and PRs in IVF/ICSI patients.[5,7,8] Other authors reported a threshold of <7 mm and/or >14 mm with a significant

reduction in implantation rate and PR.[16,17] With these controversies, no conclusive cutoff value of endometrial thickness has been established in order to help clinicians in counseling the couple about the outcome. The reason for such controversy could be probably due to a relatively low number of cycles for patients with both extremes of endometrial thickness.

MATERIALS AND METHODS

It is a prospective clinical study of 239 patients performed at Jayanagar center, which is a unit of BACC (Bangalore Assisted Conception Centre), Bengaluru, Karnataka.

Inclusion criteria were fresh nondonor IVF cycles in age group of 25 to 35 years and patients with variable indications for IVF were enrolled.

Exclusion criteria were those with frozen embryo transfer (FET), donor oocyte or embryos, gestational surrogacy, having history of prior uterine surgery or Ashermann´s syndrome, genital tuberculosis, congenital uterine or endometrial or myometrial anomalies and failed fertilization.

During the study period various stimulation protocols were used—long, antagonist and other protocols (ultralong/short/ultrashort/microflare) depending on patient characteristics.

Various patient variables were taken in form of age, indication of IVF, baseline follicle stimulating hormone (FSH) level, type-fresh and number of cycle, body weight, height, body mass index (BMI), treatment protocol used, number of days of stimulation, number of ampules of gonadotropins used, type of gonadotropins, oocyte retrieval rate, fertilization rate, cleavage rate, endometrial thickness on day of embryo transfer which was performed on day 5 after human choronic gonadotropin (hCG) injection.

Various parameters were compared between pregnant and nonpregnant patients.

The pregnancy was accepted to be positive when beta-hCG level was over 50 IU on day 14 of ET. Clinical pregnancy was accepted when the embryo cardiac activity was observed by ultrasonography.

Their mean age was 32 years (range: 27 to 35 years). Infertility causes were male factor infertility in 93 cases, tubal factor infertility in 44 cases, unexplained in 33 cases, diminished ovarian reserve in 10 cases, ovulation disorders as PCOS in 27 cases, 8 case of endometriosis and other causes in 24 patients. About 229 (96%) patients showed a normal basal FSH level (<10 mUI/ml), had regular menstrual cycles. Approval for the study was obtained from the local institutional review board (IRB). Oral informed consent from the patients was required for this study, and was approved by the local ethics committee. In short, we performed ovarian stimulation with gonadotropins after pituitary suppression according to a long gonadotropin-releasing hormone (GnRH) protocol or antagonist protocol depending upon the patient parameters. Beginning with 150-225 IU of recombinant FSH–GonalF (Serono, Italy) or Recagon (Organon) on a daily basis, the dose was adjusted according to follicular response and serum estradiol levels. In most cycles, purified human menopausal gonadotropin (hMG) was added (Menopur or hMG) to improve follicular growth. When a minimum of three dominant follicles greater than 18 mm were confirmed, 5,000 IU of hCG (Ovutrig HP, VHB Life Sciences, Mumbai, India) were administered.

The oocyte retrieval was performed 36 hours after the hCG injection. Oocytes were fertilized by IVF or ICSI, and the embryos were classified by grades (grade 1 for the best embryo) and given points through a cumulative embryo score. One to three embryos were transferred under ultrasound guidance. After the follicular puncture, all patients received 400 mg of progesterone vaginally and luteal support was in form of estrogen and progesterone along with low dose Ecosprin and low molecular weight heparin (LMWH) in selected cases.

A pregnancy was confirmed by quantification of the serum hCG level 14 days after the ET. Values above 50 IU were considered positive. Ongoing gestation was defined as fetal heart activity at 12 weeks of gestation. A clinical pregnancy was defined by the presence of one or more gestational sacs with living embryos or alternatively by histologic confirmation of products of miscarriage.

RESULTS

Total number of patients—239, pregnant—87, nonpregnant—138, number of cancelled cycles—14.

DISCUSSION

An association of various cycle characteristics and treatment outcome has been evaluated since, the introduction of ARTs. One such parameter, which has been evaluated by several groups, is that of endometrial thickness.[3,18-21] Adequate proliferative and secretory changes are necessary for successful implantation to occur.

A triple-layer endometrial pattern and an endometrial thickness greater than 7 mm have been proposed as markers of endometrial receptivity but have yielded a high percentage of false-positive results. Uterine receptivity improves when blood flow increases under hormonal replacement therapy. The absence of a triple-layer pattern may be a sign of premature secretary changes indicating that the period of maximal receptivity may be over. Nonetheless, a pregnancy with a nontriple layer

pattern is still possible so it cannot be sole indicator to cancel ET.[12]

The results of the present study identified a positive correlation in endometrial thickness between cycles that resulted in pregnancy and those that did not.

In our study, long protocol was used in 37% patients, antagonist protocol in 47% cases and other protocols in 15% of patients. Mean age of 31.04 ± 3.79 years (Table 1 and Fig. 1). Among causes male factor in 36.4%, tubal in 18%, unexplained in 13%, PCOS in 11% and mixed causes in 20% (Table 2). Majority (87%) of patients fall in normal and overweight as per BMI (Table 3 and Fig. 2). Seventy-three percent had primary and 27% had secondary infertility. Ninety percent ETs done were easy (Table 4) and 14 ETs cancelled in view of ovarian hyperstimulation syndrome (OHSS) in 9 cases and fluid in cavity in 2 cases, one patient had hyperpyrexia on day of ET and 2 cases of failed fertilization. Thirty-five percent had ET >10 mm and overall clinical pregnancy rate was 39% with implantation rate of 21%, fertilization rate of 92% and cleavage rate of 95% and live birth rate of 26%. There were more follicles, oocytes and embryos, the endometrium was >10 mm and embryo quality was higher among women who became pregnant when compared with nonpregnant women after assisted reproduction though not statistically significant ($p \geq 0.05$). The pregnancy rate improved as endometrial thickness increased showing a linear correlation.

In cycles that resulted in pregnancies, patients were younger, had more number of oocytes, more embryos transferred and the embryo quality was good. Also mean endometrial thickness on day of ET was higher in cases which got pregnant.

Adequate endometrial development is required for pregnancy to occur, and pregnancy rates were found to be higher when the endometrium reached at least 10 mm thickness. Consequently, clinicians providing IVF for infertile couples must pay close attention to endometrial development as well as to follicle growth.

In our study, we actually made analysis by dividing patients into two main groups:

- Group A with endometrial thickness <10 mm
- Group B with endometrial thickness >10 mm.

Results were analyzed in comparison between pregnant and nonpregnant patients.

In group A, pregnancy rate was 37% and in group B, pregnancy rate was 41% but outcome is statistically similar between two groups with p = 0.514 (Table 5).

We further subdivided these patients into eight subgroups depending on the endometrial thickness on the day of embryo transfer. Highest pregnancy of 34.5% was found in 9 to 10 mm group, 18.3% between 10 to 11 mm, 16.1% in 11 to 12 mm, up to 9.5% in 8 to 9 mm, 5.9% in 7 to 8 mm and 2.3% in those with endometrial thickness >13 mm. This linear correlation has been shown in figures. Thus, inference drawn was that higher endometrial thickness is positively associated with positive outcome with p = 0.0.166 (Tables 6 and Fig. 2).

One pregnancy reported at 15 mm but turned to be missed abortion.

We had one pregnancy at <7 mm (6.8 mm) but unfortunately it turned out to be a missed abortion at 6 weeks gestation.

Besides we tried to see the affect of other variables (Tables 7, 8 and Figs 3 to 14) on pregnancy in comparison

Table 1: Age distribution of patients studied

Age (years)	*Number of subjects*	*%*
21-25	11	4.6
26-30	123	51.5
31-35	103	43.1
36-40	2	0.8
Total	239	100.0

Mean ± SD: 31.04 ± 3.79

Table 2: Indication of infertility

Indication	*Number of subjects*	*%*
Severe oligoasthenoterato-zoospermia	70	29.2
Tubal	44	18.4
Unexplained	33	13.8
Poor ovarian reserve	10	4.1
PCOS	27	11.3
Azoospermia	23	9.6
Mixed causes	32	13.3
Total	239	100.0

Table 3: BMI distribution of subjects studied

BMI (kg/m^2)	*Number of subjects*	*%*
<18.5	3	1.3
18.5-25.0	84	35.1
25.0-30.0	125	52.3
>30.0	27	11.3
Total	239	100.0

Mean ± SD: 25.68 ± 3.81

Table 4: Embryo transfer

ET	*Number of subjects*	*%*
Easy	214	89.5
Difficult	11	4.6
ET cancelled	14	5.8
Total	239	100.0

to the their effect on endometrial thickness. We found a nonsignificant correlation.

One group found that fecundity was increased when the endometrium was at least 9 mm thick, and had a triple-line appearance during IVF cycles. However, biochemical pregnancies were more frequent with a thinner endometrium. Others demonstrated an improved pregnancy rate with a thicker endometrium.[10]

Another group[10] subsequently evaluated 516 IVF cycles and found pregnancy and ongoing pregnancy rates to be higher when the endometrial thickness was >9 mm. Likewise, a minimum thickness of 10 mm during IVF was found to produce a higher pregnancy rate.

The day of measurement might also influence the association between endometrial thickness and cycle outcome.

In the present study, an increased endometrial thickness was not related to improved pregnancy rates, although the measurements were made on the day of transfer-that is, at 4 or 5 days after the hCG injection. Endometrial thickness

Table 5: Comparison of outcome according to endometrial thickness (mm)

Outcome	*Endometrial thickness (mm)*		*Total*
	<10.0	*>10.0*	
Negative	90 (62.9%)	48 (58.5%)	138 (61.3%)
Positive	53 (37.1%)	34 (41.5%)	87 (38.7%)
Total	143 (100.0%)	82 (100.0%)	225 (100.0%)

Inference: Outcome is statistically similar between two groups with p = 0.514

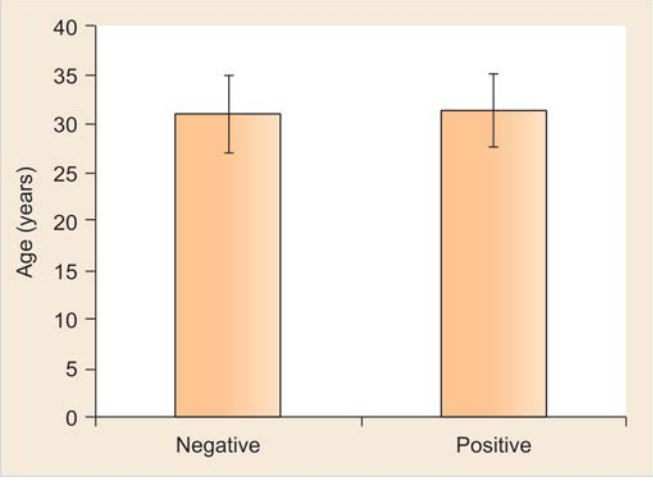

Fig. 1: Correlation between age and IVF outcome

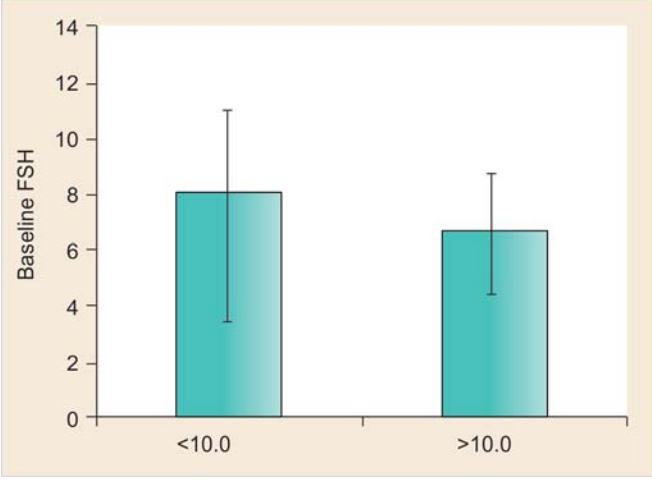

Fig. 3: Correlation between baseline FSH and endometrial thickness in two groups (A and B)

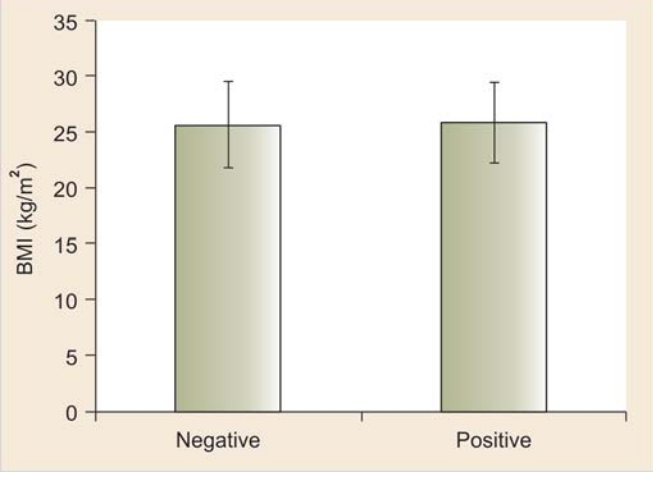

Fig. 2: Correlation between BMI and IVF outcome

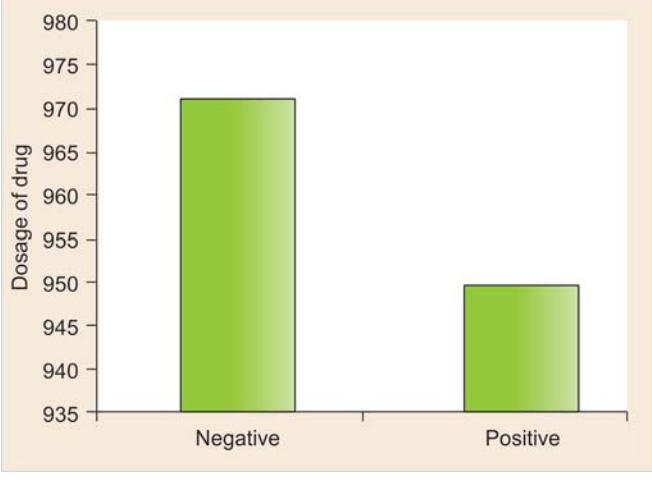

Fig. 4: Correlation between dosage of gonadotropins and IVF outcome

evaluated on the day of embryo transfer might be influenced by an increased luteal phase progesterone secretion, and various measurement methods (including outer edge to outer edge, or outer edge to inner edge) could further affect outcome. Differences in the analysis might also provide a further explanation for the conflicting results.

Table 6: Comparison of endometrial thickness (mm) with cycle outcome

Endometrial thickness (mm)	*Cycle outcome*	
	Negative (n = 140)	*Positive (n = 87)*
<7	0	1 (1.1%)
7-8	14 (10.0%)	5 (5.7%)
8-9	31 (22.1%)	17 (9.5%)
9-10	46 (32.9%)	30 (34.5%)
10-11	30 (21.4%)	16 (18.3%)
11-12	16 (11.4%)	14 (16.1%)
12-13	2 (1.4%)	2 (2.3%)
13 and above	1 (0.7%)	2 (2.3%)
Mean ± SD	10.07 ± 1.31	10.32 ± 1.39

Inference: Higher endometrial thickness is positively associated with positive outcome with p = 0.166

The effect of 'increased' endometrial thickness has also been evaluated. For example, one group[4] reported lower implantation and pregnancy rates among women with an endometrial thickness >14 mm on the day of hCG administration. However, no adverse effect of thickened (>14 mm) endometrium on implantation, pregnancy or abortion rates was identified by others.[21] In our study, we found a direct relation between the endometrial thickness and the IVF outcome as we got pregnancies in 34% cases with endometrial thickness between 9 and 10 mm on the day of ET.

Table 8: Comparison of BMI with cycle outcome

BMI (kg/m^2)	*Cycle outcome*	
	Negative (n = 140)	*Positive (n = 87)*
<18.5	2 (1.4%)	0
18.5-25.0	47 (33.6%)	32 (36.8%)
25.0-30.0	76 (54.3%)	46 (52.9%)
>30.0	15 (10.7%)	9 (10.3%)

Inference: BMI is not statistically associated with cycle outcome with p = 0.699

Table 7: Comparison of study variables according to outcome

Study variables	*Cycle outcome*		*p-value*
	Negative (n = 140)	*Positive (n = 87)*	
Age in years	30.92 ± 3.89	31.21 ± 3.72	0.586
BMI (kg/m^2)	25.67 ± 3.88	25.84 ± 3.62	0.755
Baseline FSH	7.29 ± 3.41	7.74 ± 4.77	0.410
Dosage of drug	975.89 ± 987.36	949.62 ± 892.58	0.859
Number of follicles >14 mm	10.50 ± 6.18	11.48 ± 7.73	0.297
Mean no. of oocytes	9.81 ± 6.44	11.05 ± 7.84	0.201
Mean no. of M2 oocytes	7.01 ± 4.93	7.87 ± 5.78	0.232
Mean number of fertilized oocytes	6.36 ± 4.41	7.10 ± 5.26	0.252
Mean oocyte retrieval rate	91.74 ± 16.62	93.92 ± 11.85	0.293
Mean no. of embryos transferred	2.45 ± 0.82	2.58 ± 0.67	0.194
Number of embryos frozen	3.98 ± 2.99	4.58 ± 4.18	0.210
Endometrial thickness (mm)	10.07 ± 1.31	10.33 ± 1.39	0.166
Fertilization rate	92.26 ± 14.47	92.57 ± 11.76	0.871
Cleavage rate	95.24 ± 11.78	97.32 ± 7.59	0.161

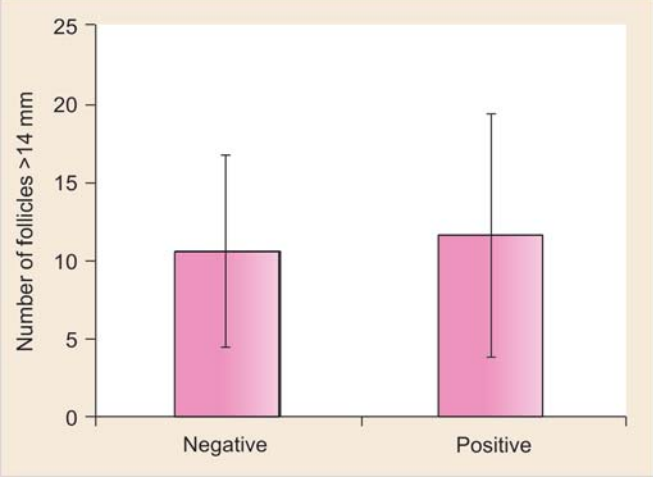

Fig. 5: Correlation between number of dominant follicles and IVF outcome

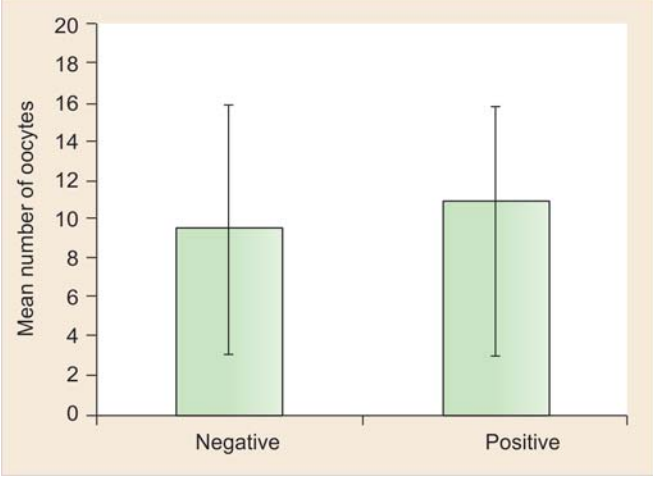

Fig. 6: Correlation between total number of oocytes and IVF outcome

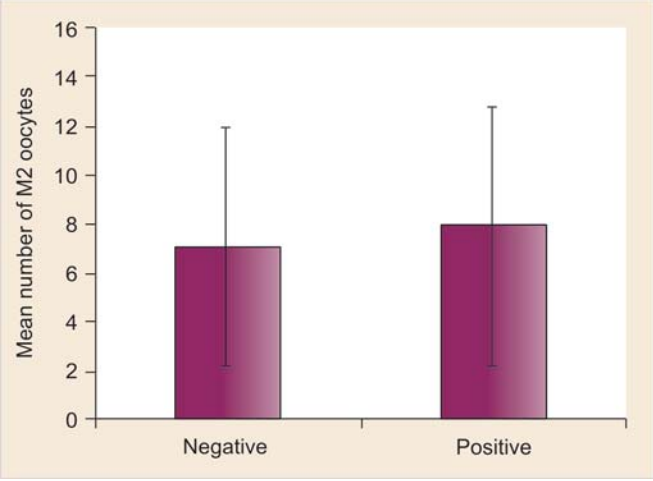

Fig. 7: Correlation between number of M2 oocytes and IVF outcome

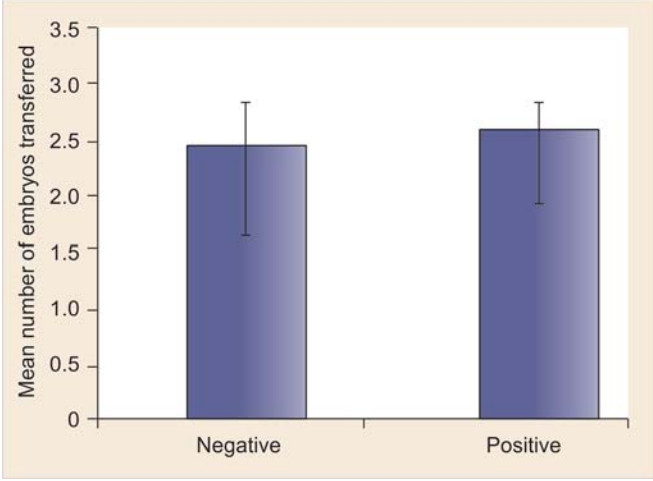

Fig. 10: Correlation between mean number of embryos transferred and IVF outcome

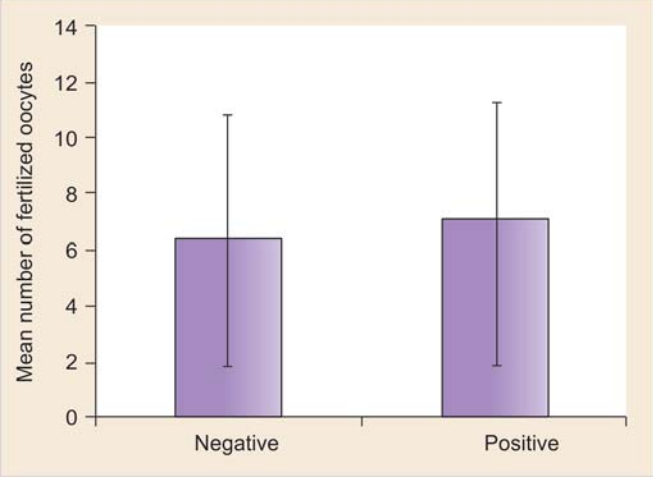

Fig. 8: Correlation between mean number of fertilized oocytes and IVF outcome

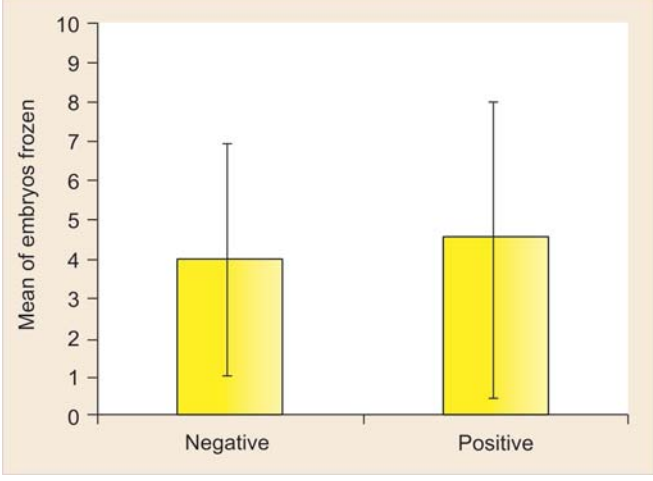

Fig. 11: Correlation between number of embryos frozen and IVF outcome

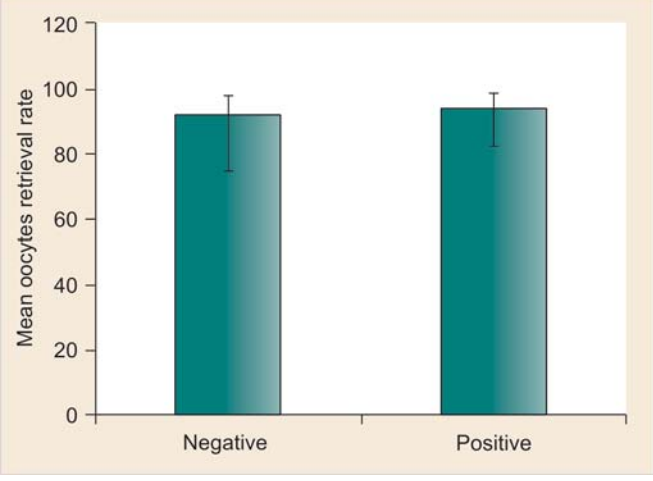

Fig. 9: Correlation between oocyte retrieval rate and IVF outcome

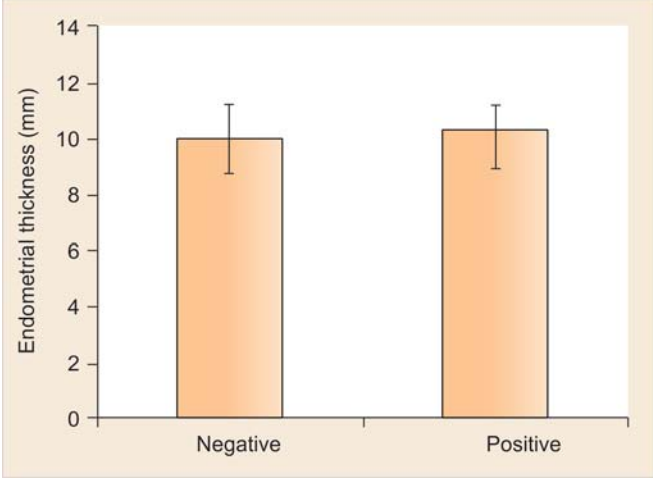

Fig. 12: Correlation between endometrial thickness and IVF outcome

Adequate endometrial development is one of the factors that play a significant role in IVF outcome. Other variables, such as age, embryo quality, number of embryos transferred and stimulation protocol were also shown to have an impact on treatment outcome though not statistically significant.

From our study, we can conclude that pregnancy rate shows a linear correlation with increasing endometrial

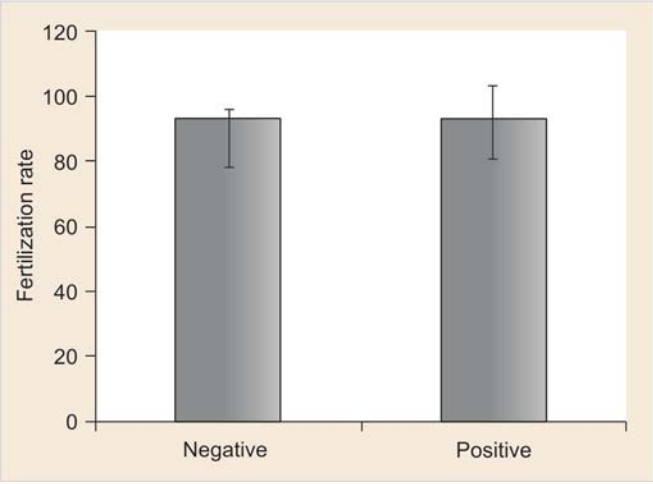

Fig. 13: Correlation between fertilization rate and IVF outcome

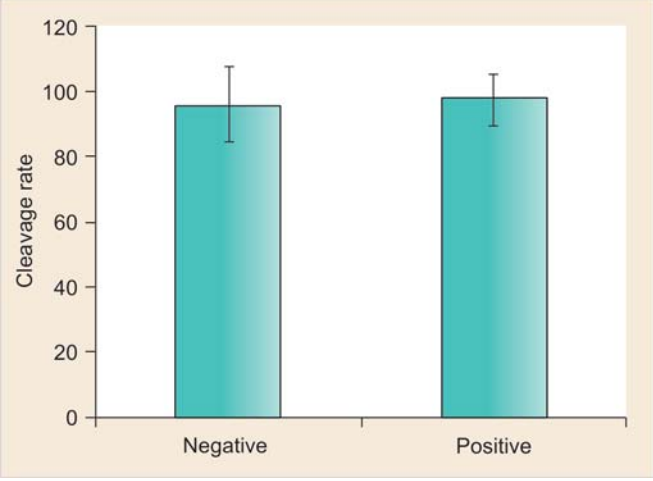

Fig. 14: Correlation between cleavage rate and IVF outcome

thickness but, as such cutoff for endometrial thickness cannot be decided. Thus, we are not justified in cancelling ET merely by keeping a cutoff in mind.

This is a prospective study and we are still continuing to analyse our results with a higher number.

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