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Effect of endometrial receptivity on *in vitro* fertilization/intracytoplasmic sperm injection outcome in HUSM

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Abstract
Study Method: Total of 50 patients *in vitro* fertilization/intracytoplasmic sperm injection(IVF/ICSI) cycles participated in this prospective study. The endometrial thickness, endometrial morphology and the level of serum progesterone were determined on the day hCG was given. Serum beta hCG was measured 14 days after embryos transfer. The association between endometrial thickness, endometrial morphology and level of serum progesterone with pregnancy was analyzed.
Result: Pregnancy was achieved in 10 out of 50 patients (20.0%). The mean endometrial thickness for the pregnant group was 9.86 ±1.68 mm, 7 out of 10 pregnant patients had trilaminar endometrium. The mean progesterone level was 3.717 ± 1.071nmol/L for the pregnant group and 1.408 ± 4.691nmol/L for the non-pregnant group. All differences were not statistically significant.
Conclusion: Endometrial thickness, endometrial morphology and the level of serum progesterone on the hCG day was not significantly associated with the outcome of IVF/ ICSI cycles.

Keywords: Endometrial receptivity, endometrial thickness, progesterone level, IVF/ ICSI cycles

1. Introduction
The advancement of assisted reproductive techniques has led to the improvement of pregnancy rates with *in vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycles. However, despite the advance techniques used, there were lots of failed cycles which have led to disappointment and more stressful condition among the couples who sought the treatment. The stressful condition has virtuously caused an increasing rate of failed cycle. For decades, researchers have tried to look at the factors which may contribute to the failure of IVF/ICSI cycles. Endometrial receptivity has been shown to be one of the factors.
Endometrial thickens during the proliferative phase of the menstrual cycle in response to the oestrogen secretion by the maturing follicles. The thickened endometrium provides a site for embryo implantation during the first few weeks until placenta develops. Although there is little doubt that the physiological thickness of the endometrium is critical in the implantation of a successful pregnancy, there is still a controversy on the variation of thickness contributing to the success of IVF/ ICSI cycles.
Several studies have suggested a correlation between greater endometrial thickness (ET) for pregnant versus non-pregnant of IVF/ ICSI cycles [1-7]. Some studies have reported non-successful pregnancies with ET below 6-9mm, even though the number of transfers to patients below this threshold were small [5-10]. In contrast, many studies reported that there was no correlation between ET with pregnancy rates [9-10].
The current study was designed to determine the correlation between endometrial receptivity, which include ET and endometrial morphology and level of progesterone during hCG injection day with pregnancy in IVF/ ICSI cycles. Should it be significantly correlated, to identify the thickness required for successful implantation.

2. Methodology
This study was conducted over a period of 18 months, from 1st February 2016 until 31st July 2017, in the Hospital USM Fertility Unit. Approval to conduct this study was obtained from the Human Medical Research and Ethics Committee of USM. All patients who were subjected for IVF/ ICSI cycle were recruited using the systematic random sampling method. Patients with

medical illnesses such as uncontrolled diabetes mellitus, antiphospholipid disorders, active pelvic inflammatory disease, tuberculosis, psychiatric illness and recurrent miscarriages were excluded.

Patients were stimulated using the short antagonist protocol. Subcutaneous follitropin beta (Puregon®) at 300iu was administered on daily basis starting from the second day of menstrual cycle. Every other day of transvaginal scan were performed starting from day seventh of the cycle to determine the number and size of growing follicles. When at least three dominant follicles reached 13 to 14mm in diameter, additional 250mg of GnRH antagonist (Orgalutran®) injections were added, to prevent from premature LH surge which may cause premature ovulation, until the growing follicles mature at sizes of 16-18mm in diameter. At this stage, the number of mature follicles, endometrial thickness and morphology, as well as the level of serum progesterone were determined, and 10000iu of hCG injection was administered at 2200hour on the same day.

Ultrasound guided oocyte retrieval was performed 36 hours later with the patient put under general anaesthesia. The number of the oocyte obtained was documented. The oocyte was then inseminated either using the IVF or ICSI as appropriate, using the Vitrolife® culture media. The success of fertilization was determined 17 hours later by looking at the presence of pronuclear body. Subsequently the embryos were cultured until they reached blastocyst stage. The blastocyst –stage embryos were transferred into the uterus five days after fertilization, under ultrasound guidance. Prior to the transfer, the quality of the embryos were determined. Only two embryos were transferred at a time. The remaining embryos were froze in liquid nitrogen. Progesterone supplementation was given to all patients after the transfer.

The serum level of beta hCG was determined three weeks after the transfer. Patients with serum beta hCG more than 2miu/L was labeled as having biochemical pregnancy. Clinical pregnancy was defined by visualization of gestational sac on ultrasound 3 weeks after embryo transfer.

The relationship between patients' age, stimulation length, embryo- quality score, endometrial thickness, morphology and serum progesterone on hCG injection day with success of implantation was determined by t-test. The primary infertility diagnosis was compared by chi-square analysis. Receiver operating characteristic (ROC) analysis was use to evaluate the discriminatory ability of endometrial thickness.

3. Results

Out of 58 patients initially enrolled, only 50 patients completed the cycle until embryo transfer. 2 patients whose age 39 and 42 years had empty oocyte syndrome, 4 patients developed ovarian hyperstimulation syndrome for which the embryo transfer were deferred, and 1 patient had all Grade C embryos and another patient had arrested embryo.

Patients ages ranged from 26-43 years (mean age of 34.74 ±4.34 years). 41 patients (82.0%) were having primary infertility while the remaining 9 patients (18.0%) were secondary infertility. The mean duration of subfertility was 7.70 ±2.95 years. Endometrial thickness on day of hCG administration ranged from 6.1 to 14mm (mean endometrial thickness 9.6 ±2.36mm). The endometrium during the hCG day was noted to be trilaminar in 25 patients (50.0%) and another half was having homogenous morphology of endometrium. The mean level of serum progesterone on hCG day was 6.20 ±11.49nmol/L.

Out of 50 patients who had completed the study, pregnancy was achieved in ten patients (20.0%). Among them, two patients were delivered at term, one patient had preterm prelabour rupture of membranes at 30 weeks, one patient with ongoing pregnancy while the rest aborted during the first trimester. The other 40 patients (80.0%) failed to achieve pregnancy after the IVF/ ICSI procedure.

Table 1: Patient and cycle characteristic between the pregnant and non-pregnant cycles

	Pregnant (n=10)	**Non-pregnant (n=40)**	***p* value**
Patient's age (years)	34.50 (4.22)	34.80 (4.42)	0.296
Types of infertility			
• Primary (n, %)	7	34	0.657
• Secondary (n, %)	9	7	
Duration of subfertility (mean, SD)	7.70 (2.95)	6.60 (3.77)	0.273
Primary diagnosis			
• Male infertility (n, %)	1 (10.0%)	7 (17.5%)	
• Male and female infertility (n, %)	2 (20.0%)	14 (35.0%)	
• Unexplained infertility (n, %)	1 (10.0%)	5 (12.5%)	
Female infertility			
• Ovulation disorder + polycystic ovaries (n, %)	3 (30.0%)	10 (25.0%)	
• Endometriosis (n, %)	1 (10.0%) 2 (20.0%)	2 (5.0%) 1 (2.5%)	
• Tubal factor (n, %)	0 (0.0%)	1 (2.5%)	
• Uterine factor (n, %)	0 (0.0%)	0 (0.0%)	
• Others (n, %)	3 (30.0%)	10 (25.0%)	
Mean stimulation length (days)	10.44 (0.88)	11.59 (1.69)	0.964
Mean endometrial thickness (mm)	9.86 (1.68)	9.77 (2.53)	0.99
Endometrial morphology			
• Trilaminar (n, %)	7(14)	18 (36)	0.157
• Homogenous (n, %)	3 (6)	22 (44)	
Mean progesterone level (nmol/L)	3.717 (1.071)	1.408 (4.691)	0.3843

Table 1 describes the patients' and cycle characteristic between the pregnant and non-pregnant group. There was no difference in the age of the patients in either group. Patients achieving pregnancy seems to have longer duration of subfertility. Female factor remains the leading cause of subfertility in the pregnant group (60.0%) whilst combination of female and male factors is the leading cause for the non-pregnant group (35.0%). Patients who managed to achieve pregnancy have shorter stimulation days (10.44 ± 0.88 days) as compared to the non-pregnant group (11.59 ± 1.69 days).

Table 2: The association between groups of endometrial thickness with success to achieve pregnancy

Variable	Regression coefficient (b)	Crude Odds Ratio (95% CI)	Wald statistic	p-value
Endometrium Thickness (mm)				
< 7	0	1		
7 - 14	19.98	475139773.4 (0.00)	0.00	0.99
> 14	0.00	1 (0.00)	0.00	1

When looking at the ET, most patients have endometrium of more than 8mm thick on the hCG day, regardless of the outcome of pregnancy (9.86 ± 1.68mm and 9.77 ± 2.53mm for pregnant and non-pregnant group respectively). However, patients achieving pregnancy have thicker mean ET. None of the pregnant patients have ET of less than 7mm or more than 14mm. Most of the pregnant patients have trilaminar endometrium on the hCG day (n=7, 70.0%). 55.0% of the non-pregnant group were noted to have homogenous pattern while only 45.0% of them have trilaminar pattern.

Table 3: The association between morphology of endometrium and outcome of IVF/ ICSI

Morphology of Endometrium	Outcome of IVF/ICSI		p-value
	Not Pregnant n (%)	Pregnant n (%)	
Trilaminar	18 (36.0)	7 (14.0)	0.157[a]
Homogenous	22 (44.0)	3 (6.0)	

The mean serum progesterone on the hCG day in the pregnant group was 3.717 ± 1.071nmol/L and 1.408 ± 4.691nmol/L for the non-pregnant group. None of the pregnant patients has serum progesterone more than 6.0nmol/L. The lowest serum progesterone in the pregnant group was 1.29nmol/L and the highest was 5.39nmol/L.

Due to the imbalance number between the pregnant and non-pregnant group, significant comparison could not be made. However, when the number is balanced and compared, none of the variables to test for endometrial receptivity is significant.

4. Discussion

The mean age for this study was 34.74 ± 4.34 years. The age ranged from 26 – 43 years. Age is one of the prognostic factors for IVF/ICSI-ET outcome as fertility declined with advancing age in view of reduction of ovarian reserve. As reported in many studies, advanced age is associated with poorer outcome of IVF treatment compared with younger age (11-39). Pregnancy rate in women more than 37 years old is about 9.4 per cent (37).

The mean duration of subfertility was 7.70 ±2.95 years. Duration of subfertility was has inverse relation with the success of any fertility treatment (34-42). Carrier prioritization was said to be one of the commonest factors for the delay in seeking fertility treatment. On the other hand, it may also indicate lack of fertility knowledge and awareness in the population. This study was performed in Kelantan where the economic status is still considered under average. Although Hospital USM is the only hospital in the state which provides comprehensive fertility treatment, the number of patients who seek early fertility treatment is small, perhaps due to financial constraint as well as the stigma put by the community on those people who seek the treatment.

In this study, the main primary cause of subfertility is combination of male and female factor, contributing to 32.0% of the cases. However, among those who achieved pregnancy, ovulatory disorder including PCOS is the main contributory factor (n=3, 30.0%). Although unexplained infertility carries higher chance to have successful ART treatment, only one out of five patients with unexplained infertility is successful to conceive.

4.1 Endometrial Receptivity

Endometrial receptivity is defined as a temporary unique sequence of factors that make the endometrium receptive to the embryonic implantation. It is the window of time when the uterine environment is conductive to blastocyst acceptance and subsequent implantation. The process of implantation may be separated into a series of developmental phases starting with the blastocyst hatching and attachment to the endometrium and culminating in the formation of the placenta. The steps start with apposition, and progress through adhesion, penetration and invasion. Many measures were used to evaluate endometrial receptivity. In this study, endometrial receptivity is evaluated using endometrial thickness, morphology and the level of serum progesterone during the hCG day.

4.2 Endometrial thickness

Endometrial thickness is traditionally accepted as a non-invasive tool to assess endometrial status. For implantation to occur, adequate proliferative and secretory changes are necessary, but optimum baseline thickness is still debatable. Endometrial thickness can be regarded as a reflection of the degree of endometrial proliferation in absence of endometrial pathology, and it is measured in the midsagittal plane during transvaginal ultrasound scan.

Previous study showed conflicting result as regards to the effect of ET in IVF/ICSI cycles. Bazer *et al* [10] has concluded that ET of less than 7mm on the day of hCG is associated with lower pregnancy rate comparing to the group whose ET more than 14mm. In contrast Dietterich in 2002 and Al Gamdi *et al* in 2008 [20, 28] failed to note such relationship.

In our study, the mean ET in pregnant group is 9.86 $\pm$1.68 mm, while in non-pregnant group is 9.77$\pm$2.53mm. This finding is consistent with previous study by Kovacs *et al* in 2003 who reported the mean ET was 10.1+1.7 mm in pregnant group and 8.9 ±2.0mm in non-pregnant group [3]. Zhoa *et al* in 2014

reported mean endometrial thickness of 11.0 +2.2mm for pregnant group [43].

Most of the study concluded that 7 mm is the cut off ET that described as thin endometrial. Pregnancy rate is higher in thicker endometrial thickness but Weissman *et al*. (1999) reported lower implantation and pregnancy rate among women with ET more than 14 mm on the day of hCG administration [40]. It is not possible to analyse the cut off point for ET in this study due to the very small data for the non-pregnant group. However, all pregnant patients were noted to have ET between 7-14mm, which is consistent with most of previous studies.

When the endometrium is thin, the functional layer is thin or absent, and implanting embryo would be closer to the spiral arteries of the endometrium and higher vascularity and oxygen concentration of basal endometrium. The increase oxygen tension could be detrimental compared with usual low oxygen tension on the surface endometrium.

These variations of all the conflicting studies might be due to the differences in the stimulation protocol or differences in patient characteristics (age, embryo quality and cause of infertility), and differences in time of ET measured.

As this study showed no significant association between pregnancy rate and ET, it is concluded that *Et al*one should not be used as a tool to decide on cycle cancelation, freezing the embryo and refraining from further IVF treatment.

4.3 Endometrial morphology

Endometrial morphology assessment is one of the features describing endometrial receptivity. The assessment of endometrial morphology varies, depending on the echogenicity of the endometrium compared to adjacent myometrium. Endometrial pattern noticed was either trilaminar (triple line), which hypoechoic endometrium with well-defined hyperechoic outer walls and a central echogenic line, echogenic or homogenous endometrium, which is a homogenous hyperechoic endometrium with absent central echogenic line, or intermediate endometrium which appeared as an endometrial pattern that was transitioning into an echogenic one at the myometrial and endometrial interface, but still had some element of well define central echogenic line with hypoechoic area between these line [6].

No triple line endometrial pattern seems to be a less prognostic factor of IVF outcome, while triple line is associated with better outcome. It is noted that the endometrial morphology was equally divided between the trilaminar pattern and the homogenous pattern (n=25, 50.0% each group). Among those who achieve pregnancy, 7 out of 10 patients (70.0%) were noted to have trilaminar endometrium. Even though it seems to be an association between endometrial morphology with successful IVF/ ICSI outcome, when the data was further analyzed using the Pearson Chi Square Test, this association was not statistically significant. This finding supported by Chen *et al*., 2010 in a retrospective cohort study demonstrated no prognostic value of endometrial pattern for pregnancy [24].

A triple line pattern reflects endometrial proliferation. The presence of such pattern on the day of hCG injection has been found to be better prognosis in IVF than absence in this pattern. The absence of triple line pattern may be sign of premature secretory changes and that the time of maximal endometrial receptivity has passed. Jing Zhao *et al*., in 2014 in a huge retrospective study involving 3319 patients found that endometrial pattern had significant pregnancy rate in trilaminar pattern on the day of hCG injection ($p<0.05$). The insignificant finding of this study on endometrium morphology and IVF/ ICSI outcome could be due to the small sample size.

4.4 HCG day progesterone level

Serum progesterone taken during the hCG day is another method used to assess endometrial receptivity. In our study, the mean level of serum progesterone in pregnant patient was 3.717 ± 1.071nmol/L. This level was not proven to be statistically significant to indicate success of IVF/ ICSI cycle. This result is consistent with the report by Makker *et al* in 2006 who concluded that serum progesterone on the day of hCG injection is not significant to assess endometrial receptivity (p value= 0.212). However, it was also concluded that serum progesterone was found to be significantly higher in non-pregnant group (p value= 0.01). The high level of progesterone induced more echogenic endometrium, thus impairing endometrial receptivity. The exact level of serum progesterone to indicate acceptable endometrial receptivity is yet to be concluded. However, several studies have documented that implantation rate is low with progesterone level of more than 6.0mmol/L (43-49). Whether or not to postpone the transfer of embryo when serum progesterone goes beyond this level is yet to be finalized.

5. Conclusion

The results of this study showed that neither endometrial thickness and morphology, nor serum progesterone is associated with higher pregnancy rate. However, the results could be overshadowed by the small number of subjects.

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