

# The predictive value of endometrial thickness for assessing neonatal birth weight in ART

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## Abstract

**Background:** Neonatal birth weight is lower after assisted reproductive technology (ART) conception compared with natural conception. The aim of this retrospective study was to evaluate the predictive potential of measuring maternal endometrial thickness (ET) in women undergoing ART for assessing neonatal birth weight. **Methods:** and Results</ST> The patients ( $n = 100$ ) were screened for meeting inclusion criteria with primary or secondary infertility and who underwent In-vitro Fertilization/ Intracytoplasmic sperm injection (IVF/ICSI) or frozen embryo transfer (FET) cycles were enrolled in the study. All women received the antagonist protocol with recombinant gonadotropins/urinary gonadotropins or human menopausal gonadotropin as a stimulation protocol. Only singleton pregnancies were used in neonatal birth weight ( $n = 70$ ) measurements. Retrospective data were collected for age, body mass index (BMI), and ET done by two-dimensional ultrasound that had successful pregnancy. The antenatal details, birth weight/gender of neonates were noted. A univariate regression analysis was performed between ET and neonatal birth weight in patients with live births ( $n = 70$ ) to evaluate association between these parameters. The data were adjusted for variables such as age, BMI, and gestational duration. There was significant association of ET with neonatal birth weight and ET was observed to be a significant independent predictor for neonatal birth weight (slope 0.168,  $P = 0.0052$ ). **Conclusion:** The present study suggests that ET measurement at the time of human chorionic gonadotropin (hCG) trigger in Indian women undergoing ART cycles can be a reliable independent predictor for assessing neonatal birth weight

**Keywords:** Endometrial thickness, infertility, IVF, neonatal birth weight


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## INTRODUCTION

A successful pregnancy has three major stages – fertilization, implantation, and embryo development. It has been observed that any complications in any stages may lead to infertility. Implantation plays a pivotal role in conception of fetus, which got impacted by following two major parameters: endometrial thickness (ET) and endometrial receptivity (ER). Further studies have

shown that inadequate ET is one of the major causes of infertility in females. ER is clinically measured by an ER assay test, while ET can be measured by a simple transvaginal two-dimensional (2D) scan. ET is the most widely used prognostic factor for ER during assisted reproductive techniques (ART). Thus ET, if measured correctly on the day of human chorionic gonadotropin (hCG) triggering, can offer a reliable

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predictive value for live birth rates and neonatal birth weights. In view of recent studies, it has been observed that ET might be an important factor to have effect on placentation that may lead to complications such as placenta previa and low neonatal birth weight. A number of previous studies have shown that neonatal birth weight is lower after assisted reproductive technology (ART) conception compared with natural conception.<sup>[1-4]</sup> Furthermore, in case of ART conception, the risk for obstetrical complications and perinatal mortality is increased even in singleton pregnancies.<sup>[5-7]</sup> Very few studies have reported possible relationship between ET measurement and neonatal birth weights.<sup>[8-10]</sup>

A thin endometrial lining, in both fresh and frozen ET cycles, has been reported to correlate with lower ART success rates.<sup>[11-15]</sup> In another study, it was further reported increased ET was an independent risk factor for placenta previa, suggesting that the potential effect of ET may extend beyond implantation.<sup>[16]</sup> Few recent studies have studied the relationship of the above-mentioned endometrial variables with birth rates and neonatal birth weights. In a recently conducted single cohort ART cycles retrospective study,<sup>[1]</sup> an ET less than 7 mm was associated with a decrease in neonatal birth weight; however, it was not found to have predicted value for clinically defined low birth weight (LBW).

Most of the previous studies have been performed retrospectively and differ in ethnicities and other factors. While the recent studies have reported association of ET with neonatal birth weights, these differ in the degree of association and whether the birth weight is clinical LBW category or not. Also, other factors such as infertility cause, treatment days, paternal body mass index (BMI), frozen embryo transfer (FET) preparation, and year of treatment can impact the birth weights after successful implantation. Clearly, more retrospective and prospective studies are required to ascertain the role of ET measurement on neonatal birth weights and live birth rates, especially in Indian women.

Therefore, we studied the significance of ET measurement in addition to endocrinology before implantation step during ART for assessing neonatal birth weights.

## MATERIALS AND METHODS

### Study design and patients

This retrospective study was conducted at Matritava Advanced IVF & Training Centre between February 2019 and February 2021. The study was approved by

**Table 1: The exclusion criteria for patient enrollment**

| S. No. | Exclusion criteria characteristic                   |
|--------|---|
| 1.     | Endometrial disease                                 |
| 2.     | Uterine disease                                     |
| 3.     | Ovarian cysts or masses                             |
| 4.     | Endometriosis, history                              |
| 5.     | Abnormal uterine cavity (evaluated by hysteroscopy) |
| 6.     | Active pelvic infections                            |
| 7.     | With more than one myoma larger than 3 cm           |
| 8.     | Multiple births                                     |

Independent Ethics Committee of Indian Fertility Society as per the letter (Ref F.I./IEC/IFS/2020 NO. 60) dated December 31, 2020. All patients ( $n = 100$ ) aged 24 to 42 years with BMI less than  $30 \text{ kg/m}^2$  were screened for exclusion criteria [Table 1]. The patients with primary or secondary infertility recruited for In-vitro Fertilization/ Intracytoplasmic sperm injection (IVF/ICSI) or FET cycles were enrolled in the study. Only singleton pregnancies were used in neonatal birth weight ( $n = 70$ ) measurements.

### Clinical protocol

Retrospective data was recruited for IVF/ICSI and FET cycles and data were collected for age, BMI, and ET done by 2D ultrasound that had successful pregnancy after IVF/ICSI or FET cycles. The antenatal details of the patients, birth weight of neonates, and obstetrics complications were noted.

All women received the antagonist protocol with recombinant gonadotropins/urinary gonadotropins or human menopausal gonadotropin as a stimulation protocol. Transvaginal ultrasound was done using Voluson S8 machine (GE Healthcare Austria) equipped with a 5 to 7.5 MHz transvaginal probe for folliculometry and ET was done every other day starting from the sixth day of the gonadotropin stimulation till achievement of hCG trigger criteria as our standard protocol.

At the day of hCG triggering, transvaginal ultrasound ET was measured in the longitudinal plane at the widest anteroposterior diameter with a transvaginal 2D ultrasound. All measurements were done three times by the same examiner and the mean of these measures was calculated.

Similarly, endometrium was prepared by oral estrogen (tab estradiol valerate 8–6 mg/day) therapy maximum of 12 to 14 days and ET was measured before starting progesterone in the same manner in FET cycles. Embryos were transferred at cleavage (D3) or blastocyst (D5) stage with partially filled bladder under guidance of transabdominal

ultrasound. Luteal phase support was given in all women as per the standard protocol.

### Parameters

The primary outcome variables measured in the study cohort are as follows:

- (1) Endometrial thickness: We consider the ET as the maximal anterior–posterior distance between both endometrial layers about 1 cm from the uterine fundus by ultrasonographic visualization.
- (2) Neonatal birth weight: Weight (in grams) of live born neonate beyond 28 weeks of gestational age measured at the time of birth.

Along with these, there are other variables to be considered for their potential to be confounders such as female age, BMI, and fresh or frozen embryo transfer.

### Statistical analysis

A univariate regression analysis was performed between ET and neonatal birth weight in patients with live births ( $n = 70$ ) to evaluate association between these parameters. The patient characteristics will be compared between fresh embryo transfer and frozen embryo transfer cycles by *t*-test or chi-square test as appropriate. A multiple regression analysis was also performed to provide the effect of all secondary variables (age, BMI,

etc.) on predictive value of ET for neonatal birth weight. The primary goal of the statistical analysis was to determine whether ET or associated factors significantly and independently can predict the neonatal birth weight. Results are presented as regression slopes with corresponding standard errors and *P* values. All statistical analyses were performed by using GraphPad Prism software.

### RESULTS

The overall demographic characteristics of the patients who met inclusion criteria ( $n = 70$ ) such as age, BMI, cause of infertility are given in Table 2. The mean values or percentage of patients are shown for all cycles [Table 2].

The patients were grouped into frozen or fresh embryo transfer cycles with comparable demographic characteristics. There were no significant differences in means of age, BMI, infertility type or causes between frozen or fresh embryo transfer cycles when analyzed with *t*-test or chi-square test as applicable [Table 2].

We observed no significant differences in ET [Table 3] or neonatal birth weights [Table 4] between fresh and frozen type cycles ( $P = 0.85$ ). We also analyzed data for the predictive value of measuring ET for assessing the neonatal birth weight in all live births from our fresh

**Table 2: Demographic and maternal characteristics of all women**

|                                | All cycles ( $n = 70$ ) | Fresh ( $n = 25$ ) | Frozen ( $n = 45$ ) | <i>P</i> |
|--------------------------------|-------------------------|--------------------|---------------------|----------|
|                                | Mean (range) or %       | Mean (range) or %  | Mean (range) or %   |          |
| Age (years)                    | 31.98<br>(24–42)        | 32.44<br>(25–42)   | 31.72<br>(24–40)    | 0.82     |
| BMI ( $\text{kg}/\text{m}^2$ ) | 26.6<br>(20.2–29.5)     | 25.9<br>(20.2–29)  | 27.2<br>(20.6–29.5) | 0.37     |
| Primary infertility (%)        | 68.6                    | 72                 | 66.6                | 0.43     |
| Secondary infertility (%)      | 31.4                    | 27                 | 33                  | 0.77     |
| Cause of infertility           |                         |                    |                     |          |
| Male infertility (%)           | 7.1                     | 4                  | 8.8                 | 0.32     |
| Tubal infertility (%)          | 40                      | 54                 | 32                  | 0.21     |
| Ovarian (%)                    | 25.9                    | 20                 | 28.2                | 0.36     |
| Unexplained (%)                | 27                      | 22                 | 31                  | 0.53     |

BMI, body mass index.

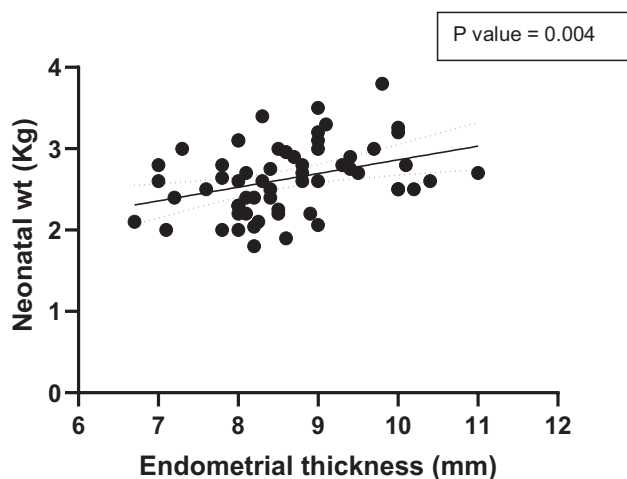
**Table 3: Endometrial thickness data as measured on day of hCG trigger of all women**

|                            | All cycles ( $n = 70$ ) | Fresh ( $n = 25$ ) | Frozen ( $n = 45$ ) | <i>P</i> |
|----------------------------|-------------------------|--------------------|---------------------|----------|
|                            | Mean or %               | Mean or %          | Mean or %           |          |
| Endometrial thickness (mm) | 8.49 (6.5–11.2)         | 8.38 (6.5–11)      | 8.55 (7–11.2)       | 0.85     |
| <8 mm                      | 22%                     | 26%                | 20%                 | 0.32     |
| 8.1–10 mm                  | 60%                     | 64%                | 57%                 | 0.21     |
| >10.1 mm                   | 18%                     | 10%                | 23%                 | 0.53     |

HCG, human chorionic gonadotropin.

**Table 4: Neonatal characteristics of all cycles with live births**

| Neonatal characteristics  | All cycles (n = 70) | Fresh (n = 25)  | Frozen (n = 45) | P    |
|---------------------------|---------------------|-----------------|-----------------|------|
|                           | Mean or %           | Mean or %       | (Mean or %)     |      |
| Male (%)                  | 42                  | 45              | 37.7            | 0.64 |
| Female (%)                | 58                  | 55              | 62.3            | 0.57 |
| Birth weight (kg)         | 2.64 (2.05–3.9)     | 2.57 (2.05–3.7) | 2.70 (2.2–3.9)  | 0.82 |
| Birth weight (kg), male   | 2.73 (2.1–3.9)      | 2.65 (2.1–3.7)  | 2.78 (2.1–3.9)  | 0.43 |
| Birth weight (kg), female | 2.55 (2.05–3.5)     | 2.5 (2.05–3.4)  | 2.58 (2.05–3.4) | 0.74 |



**Figure 1:** The univariate regression curve showing association of neonatal birth weight with endometrial thickness for both genders of neonates ( $n = 70$ ). The endometrial thickness was found to be a significant independent predictor ( $P = 0.004$ ) for neonate birth weight (unadjusted) in all singleton pregnancies included in the study

and frozen cycles. The univariate linear regression test was applied, and we observed a significant association (slope 0.162,  $P = 0.004$ , unadjusted) of neonatal birth weight with ET [Figure 1, Table 5].

We also performed the multiple regression test for predictive value of ET for assessing neonate birth weight where other variables such as age, BMI, infertility diagnosis, embryo transfer cycle type, and gestational duration [Table 6] were also included in regression analysis as all these variables can affect birth weight. All variables passed the normality testing during analysis. After adjusting for these variables, the ET value still remained to be a significant independent predictor for neonatal birth weight (slope 0.168,  $P = 0.0052$ ). The only other factor that was observed to be a significant predictor of birth weight was found to be gestational duration (slope 0.027,  $P = 0.0001$ ) as expected [Table 3].

## DISCUSSION

Some of the previous studies have reported an association between ET and neonatal birth weight in women

**Table 5: Univariate regression analysis predicting neonatal weight (unadjusted)**

|                            | Estimate | S.E.  | P     |
|----------------------------|----------|-------|-------|
| Endometrial thickness (mm) | 0.162    | 0.034 | 0.004 |

**Table 6: Univariate regression analysis predicting neonatal weight adjusted for maternal age, BMI, diagnosis, embryo transfer, pregnancy duration, and neonatal gender**

|   | Estimate | S.E.    | P             |
|---|----------|---------|---------------|
| Endometrial thickness (mm)              | 0.1681   | 0.0578  | <b>0.0052</b> |
| Age (years)                             | -0.0008  | 0.01066 | 0.9426        |
| BMI ( $\text{kg}/\text{m}^2$ )          | 0.00349  | 0.02233 | 0.8765        |
| Infertility (primary or secondary)      | 0.031    | 0.026   | 0.43          |
| Embryo transfer cycle (fresh or frozen) | 0.002    | 0.0015  | 0.48          |
| Gestational duration                    | 0.027    | 0.001   | <b>0.0001</b> |

BMI, body mass index.

undergoing ART.<sup>[8-10]</sup> While there appears to be a relation between these two factors, the degree of association varies.<sup>[11,12]</sup> Thus, the present study attempted to explore the predictive potential of ET for assessing neonatal birth weight in our cohort of Indian women undergoing ART cycles. We observed a strong association of ET values, measured at the day of hCG trigger during standard ART protocol, with the neonatal birth weight from singleton pregnancies ( $n = 70$ ). The statistical analysis also revealed that there is a significant predictive value of ET as an independent predictor for assessing birth weight.

The contributing factors of LBW after ART procedure can be diverse, with little understanding on the main underlying causes. These causes that are thought to affect birth weight after ART can range from age, BMI, gestational duration to genetics or environmental factors.

The adjustment of regression with age, BMI, gestational duration, and neonatal gender also led to the predictive value of ET to be significant for assessing neonatal birth weight in our study cohort [Table 6]. Our study consisted of fresh cycle or frozen cycle embryo transfer, which may also be affecting fetal growth and thus birth weight; therefore, we adjusted the data for this variable also.

However, there was no significant effect of this variable on birth weight assessment by ET. The gestational duration however was another independent predictor of neonate birth weight, which was expected as the shorter than normal gestational period is a well-known factor that leads to reduced neonatal birth weight. Previous studies have also clearly shown that assisted reproduction techniques are also associated with preterm birth that is associated with reduced birth weight.<sup>[10-13]</sup> The lower birth weight has long-term consequences for health of future adults.<sup>[14]</sup> Recently, a study found that ET was an independent predictor of neonatal birth weight in women undergoing ART with obstetric complications.<sup>[17]</sup> However, our study group was a diverse one that included women with and without obstetric complications, which make these observations even more important. The limitations of this study are the retrospective nature and the relatively small sample size ( $n = 70$ ), which limited our ability to categorize patients into subgroups based on several variables including obstetric complications. Another limitation remains the unaccounted variables such as diet and other environmental factors. Even with these limitations, we were successfully able to test our hypothesis, the results of which are in line with previous reports.

In conclusion, our study suggests that ET measurement at the time of hCG trigger in Indian women undergoing ART cycles can be a reliable independent predictor for assessing neonatal birth weight and this aspect should be taken into consideration for making clinical decisions wherever required.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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