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Endometrial Compaction and its Impact on IVF Outcomes

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Abstract: ***Purpose: To study the IVF outcomes in women having endometrial compaction undergoing frozen embryo transfer cycles. Methods : It is a prospective observational study involving eighty women undergoing frozen embryo transfer(FER) at the Institute of Reproductive Medicine and Women's health, Madras Medical Mission, Chennai, a single academically affliated fertility centre. Endometrial preparation for these cycles started on Day 2 after a baseline transvaginal scan. Endometrial thickness is measured on the day of starting progesterone and endometrial compaction is checked on the day of embryo transfer by transvaginal scan. Once frozen embryo transfer is done, patients are started on full luteal support and advised to confirm pregnancy by a serum beta hCG after 2 weeks. If positive, a transvaginal scan is done 2 weeks later to confirm a pregnancy. Results: Only 30 % (24/80) of the cycles demonstrated compaction whereas 70 % (56/80) either expanded or remained unchanged. Overall clinical pregnancy rate was 38.75 %. There were no differences in the patient's age, body mass index, cause and duration of infertility, parity, baseline Follicle stimulating hormone, Anti-Mullerian hormone, or day of transfer between the groups. When comparing cycles with and without compaction, no significant difference was seen in pregnancy rate. Conclusion: This study investigates the relationship between endometrial compaction and the success rates of IVF treatments. Despite the observed variations in endometrial compaction, our findings indicate no significant correlation with pregnancy outcomes. These results contribute to the understanding of factors influencing IVF success and suggest the need for further research in this area.***

Keywords: Endometrial compaction; Progesterone; Frozen embryo transfer; Pregnancy rate

1. Introduction

Globally, infertility is now a significant public health problem. According to available data, 15.5% of couples experience infertility, and 55.2% of those couples seek medical intervention[1]. Worldwide, assisted reproduction is now a feasible option for infertile couples due to medical advancements. Invitro fertilisation (IVF) offers hope and solutions to those who are experiencing infertility. IVF success depends not only on the quality of the gametes but also on the complex interactions between the quality of the embryo and the endometrium's receptive environment[2]. An essential component of implantation, the endometrial lining acts as a dynamic interface to promote embryo attachment and eventual pregnancy. Factors like embryo quality, endometrial receptivity and embryo-endometrial communication significantly influence these outcomes[3]. Creating an optimal environment for embryo development and placenta formation hinges on achieving optimal endometrial receptivity.

Statistics show that the success rates per cycle after in vitro fertilisation range from 8.6% to 46.2% every cycle[4], contingent on the quality of the embryo, endometrial receptivity, and embryo-endometrial communication[5]. Preimplantation genetic testing or PGT has been more widely used recently, which has helped to lessen the impact of aneuploid embryos on IVF and in some cases, enhanced the quality of implanted embryos. Its positive predictive value, however, is only between 50-60%[6]. Therefore, prior to embryo transfer, endometrial assessment is crucial.

Despite the prevalent use of endometrial thickness as a marker for assessing endometrial receptivity, there remains controversy surrounding its predictive value for pregnancy outcomes[7]. Many cycles experience delays in embryo transfer due to inadequate endometrial thickness. Recent research has examined the potential predictive value of endometrial compaction, which is characterised as the variation in endometrial thickness from the end of the estrogen-only phase and the day of embryo transfer. The endometrial compaction upon starting progesterone suggests that it is receptive to the hormone, suggesting that it may serve as a surrogate for endometrial receptivity. Contradictory findings have been reported in three cohort studies on the connection between endometrial compaction and clinical outcomes after embryo transfer[8-10]. Pregnancy rates and endometrial compaction were shown to have a positive correlation in two studies conducted by the same group[8,9].

The purpose of this study is to examine the impact of endometrial compaction on the outcomes of IVF treatments, particularly focusing on the clinical pregnancy rates following frozen embryo transfer. This research is significant as it provides insights into the role of endometrial compaction in IVF outcomes, offering valuable information for reproductive medicine practitioners and contributing to the optimization of IVF protocols.

2. Materials and Methods

This is a prospective observational study conducted at a single private academically affliated fertility centre between March and October 2023 for a period of 8 months.

- **Inclusion criteria:** All subfertile women who underwent FER with endometrial thickness ≥ 8 mm.
- **Exclusion criteria:** Those women with endometrium < 8 mm before starting progesterone.

All women were subjected to antagonistprotocol for controlled ovarian stimulation. Oocyte retrieval was performed 35 hours after final oocyte maturation with trigger (HCG, GnRH agonist or dual trigger).

Intracytoplasmic sperm injection was done to fertilize all metaphase II oocytes and the embryos were cryo preserved. Endometrial preparation for FER involved administration of estradiol valerate from day 2 after taking a baseline transvaginal scan (TVS). Once the endometrial lining was ≥ 8 mm, progesterone was started. Endometrial compaction was checked on the day of embryo transfer by TVS.Once frozen embryo transfer was done, patients were started on full luteal support and advised to confirm pregnancy by a serum beta hCG after 2 weeks. If positive, a transvaginal USG was done 2 weeks later to confirm a pregnancy. Clinical pregnancy was defined as the presence of fetal cardiac activity on ultrasound.

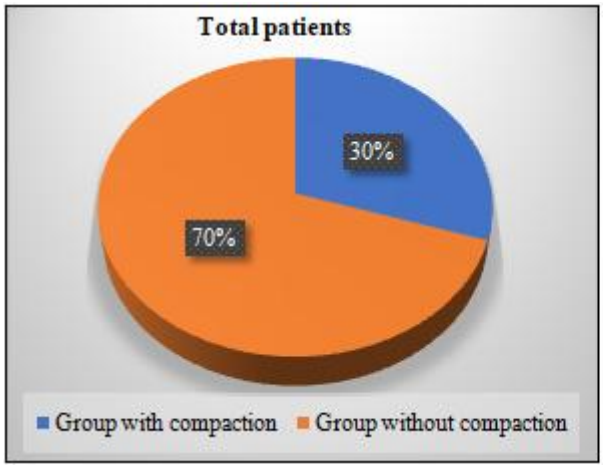
Endometrial compaction is defined as a decrease of ≥ 5%in endometrial thickness and expansion was defined as a ≥ 5% increase in endometrial thickness. Cycles in which the compaction was ≤5% were considered unchanged.

Statistical analysis:
Data was analysed using SPSS version 22. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Non-normally distributed quantitative variables were summarized by median and interquartile range (IQR). All quantitative variables were checked for normal distribution within each category of explanatory variable by using visual inspection of histograms and normality Q-Q plots. Shapiro- wilk test was also conducted to assess normal distribution. Shapiro wilk test p value of >0.05 was considered as normal distribution.

For normally distributed quantitative parameters the mean values were compared between study groups using independent sample t-test (2 groups). For skewed distributed quantitative parameters, medians and interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). Categorical outcomes were compared between study groups using Chi square test /Fisher's Exact test (If the overall sample size was < 20 or if the expected number in any one of the cells is < 5, Fisher's exact test was used.). P value < 0.05 was considered statistically significant.

3. Results

In this prospective observational study, a total of eighty frozen embryo transfer cycles were included. We compared the endometrial thickness on the day of starting progesterone and on the day of frozen embryo transfer in all the participants. Among the 80 women, endometrial compaction was noted in 24 (30%) women and the remaining 56 (70 %) exhibited either no change or increase in endometrial thickness.



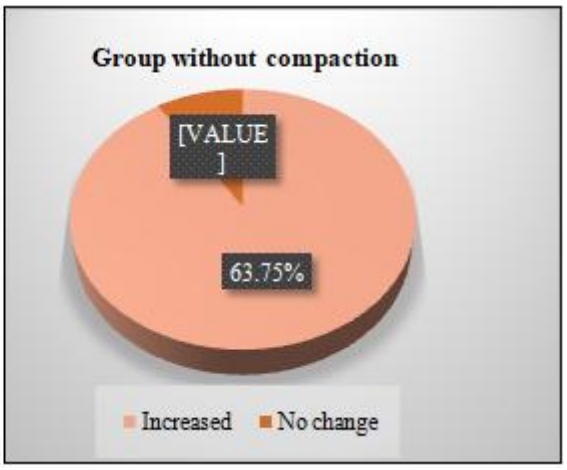


Table 1: Baseline characteristics and endometrial compaction

Parameter	Compaction (Mean± SD)		p value
	Yes (n=24)	No (n=56)	
Age	33.67 ± 5.84	34.38 ± 5.75	0.617
BMI	24.69 ± 2.69	25.3 ± 2.81	0.371
Duration of infertility (years)	5.79 ± 3.47	6.79 ± 3.98	0.292
AMH	3.17 ± 2.34	2.84 ± 2.41	0.567
Day 2 FSH	6.22 ± 1.55	8.75 ± 11.68	0.296

The baseline characteristics like age, BMI, duration of infertility, AMH (Anti-Mullerian hormone), day 2 FSH (Follicle stimulating hormone) were compared and there was no statistical significance.

Table 2: Causes of infertility between the groups

Cause of infertility	Compaction		Chi square	P value
	Yes (N=24)	No (N=56)		
Both	10 (41.67%)	22 (39.29%)	1.287	0.972
Female – endometriosis	1 (4.17%)	1 (1.79%)		
Female – PCOS	2 (8.33%)	5 (8.93%)		
Female – POI	1 (4.17%)	3 (5.36%)		
Female – Tubal	1 (4.17%)	1 (1.79%)		
Male	5 (20.83%)	16 (28.57%)		
UI	4 (16.67%)	8 (14.29%)		

Among the women with compaction (n=24), the distribution of the causes were unexplained infertility (UI) accounting for 16.67% (4 cases), male factors (Oligoasthenoteratozoospermia - OATS) at 20.83% (5 cases) and a mix of both male and female factors (both) contributing to 41.67% (10 cases). Female causes were tubal factors (4.17%), premature ovarian insufficiency (POI - 4.17%), polycystic ovary syndrome (PCOS - 8.33%), and

endometriosis (4.17%). In the group without compaction (N=56), similar patterns were observed without statistically significance. The comparison of causes of infertility between the groups with and without compaction revealed no significant differences.

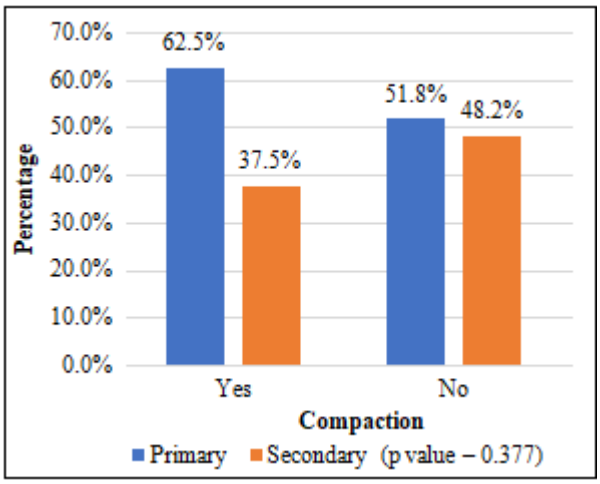


Figure 2: Comparison of type of infertility between compaction (n=80)

There was no statistically significant difference between the two groups with regard to the type of fertility (p value – 0.377)

Table 3: Comparison of day of embryo transfer and endometrial compaction

Day of embryo transfer	Compaction		Chi square	p value
	Yes (n=24)	No (n=56)		
P+3	7 (29.17%)	18 (32.14%)	0.164	0.921
P+4	10 (41.67%)	24 (42.86%)		
P+5	7 (29.17%)	14 (25%)		

The analysis comparing the day of embryo transfer between groups with and without endometrial compaction didn't reveal any statistically significant differences. In the group with compaction (n=24), the distribution of day of embryo transfer showed 29.17% (7 cases) for transfers on P+3, 41.67% (10 cases) on P+4, and the remaining 29.17% (7 cases) on P+5. Similarly, in the group without compaction (n=56), the proportions were 32.14% (18 cases) for P+3, 42.86% (24 cases) for P+4, and 25% (14 cases) for P+5. There was no statistically significant distinction in the distribution of day of embryo transfer between these groups, implying a similar pattern of transfer timing regardless of endometrial compaction status (p value - 0.921).

Table 4: Comparison of mean of S. Progesterone and endometrial compaction (n=80)

Parameter	Compaction (Mean± SD)		p value
	Yes (n=24)	No (n=56)	
S. Progesterone	22.83 ± 15.23	26.46 ± 10.74	0.228

The comparison of progesterone levels between the groups with and without endometrial compaction revealed no statistically significant difference. In the group with endometrial compaction (n=24), the mean progesterone level was 22.83 ± 15.23 ng/ml, while in the group without compaction (N=56), it measured 26.46 ± 10.74 ng/ml. Therefore, based on this analysis, the presence or absence of endometrial compaction did not appear to correlate significantly with differences in progesterone levels within this study population (p value - 0.228).

Table 5: Endometrial thickness in both groups

Parameter	Compaction (Mean± SD)		p value
	Yes (n=24)	No (n=56)	
Endometrial thickness on the day of starting progesterone	8.71 ± 0.51	8.21 ± 0.28	<0.001
Endometrial thickness on the day of embryo transfer	8.04 ± 0.24	9.49 ± 0.99	<0.001

We noted that the women who demonstrated endometrial compaction had significantly thicker endometriumon the day of starting progesterone compared with those that did not (8.7 mm vs 8.2 mm, $p < 0.001$).Additionally, endometrial thickness 48 hours after starting progesterone was noted, it showed that the mean value for the group with compaction (n=24) was 8.27 ± 0.88 mm, whereas for the group without compaction (n=56), it was 8.89 ± 1.14 mm and showed no significance in either groups with regard to pregnancy rate.

The group without compaction (n=56) was further analysed into those whose endometrial thickness increased and those unchanged from the day of starting progesterone to the day of embryo transfer. There was no significant difference with regard to pregnancy rate among the 3 groups.

Table 6: Comparison of pregnancy rate across 3 groups (n=80)

Pregnancy rate	Total no. of women			Chi square	p value
	Endometrial compaction (n=24)	Endometrial thickness increased (n=51)	Endometrial thickness unchanged (n=5)		
Non-pregnant	13 (54.17%)	35 (68.63%)	1 (20%)	5.261	0.072
Pregnant	11 (45.83%)	16 (31.37%)	4 (80%)		

The comparison between the presence of endometrial compaction and pregnancy outcomes exhibited no significant difference. In the group with compaction (n=24) 45.83% (11 cases) showed a positive pregnancy, while 54.17% (13 cases) had a negative result. On the other hand, in the group without compaction (n=56) 35.71% (20 cases) were positive and 64.29% (36 cases) were negative for pregnancy. The comparison showed no statistically significant association between endometrial compaction status and pregnancy results (p value - 0.395). This implies that the presence or absence of compaction did not appear to influence the pregnancy outcomes in this study population.

4. Discussion

Infertility is still a complicated issue that affects many couples worldwide, which has led to a greater dependence on assisted reproductive technologies such as in vitro fertilisation[10]. The purpose of this study was to investigate the possible impact of endometrial compaction on pregnancy outcomes in frozen embryo transfer cycles, taking into account the endometrium's crucial role in a successful implantation.

In our study, there was no statistically significant differences between the two groups concerning age (p = 0.617), BMI (p = 0.371), duration of infertility (p = 0.292), AMH (p = 0.567) and day 2 FSH (p = 0.296). While comparing with a study by Erdogan K et al[11], AMH (p = 0.567 in our study, p = 0.290 in the Erdogan K et al study) and baseline FSH (p = 0.296 in our study, p = 0.918 in the Erdogan K et al study)did not demonstrate statistical significance.

There were no discernible differences between the groups with and without endometrial compaction when the causes of infertility were examined(p value– 0.972). This implies that certain underlying reproductive problems may not be directly associated with the presence or lack of compaction. These results support earlier research suggesting that infertility is a complex condition and emphasise the need for a more comprehensive understanding that goes beyond endometrial changes. Also there was not a significant difference in progesterone levels between the groups with and without compaction (p value – 0.228). This indicates that additional mechanisms may influence endometrial receptivity independent of progesterone levels, given the critical function of progesterone in endometrial receptivity as described in a study by Labarta et al[12].

When compared to the group without compaction, the group with endometrial compaction had a delayed embryo transfer. This finding raises the possibility of a relationship between the implantation window and endometrial compaction[13]. There may be a way to predict endometrial receptivity in those individuals with endometrial compaction, which might lead to new insights into the best time to transfer depending on endometrial characteristics as seen in a study by Gao G et al[14] and Chen XT et al[15].

The comparison of pregnancy rate with the day of embryo transfer across between the groups with and without compaction, as shown in Table3, did not reveal any statistically significant differences. This lack of statistically significant distinctions in pregnancy outcomes concerning the varied days of embryo transfer, regardless of endometrial compaction status, suggests that the timing of embryo transfer in relation to endometrial characteristics may not exert a substantial influence on pregnancy outcome. The absence of a pronounced association between embryo transfer timing and pregnancy outcomes in different compaction groups underscores the complexity of factors influencing IVF success beyond the isolated consideration of embryo transfer days[16].

Moreover, several research studies have echoed this lack of significant differences between endometrial compaction groups concerning IVF success rates. Chen XT et al.'s research[15] indicated that the clinical pregnancy rate between the endometrial compaction and non-compaction groups exhibited no significant disparity (RR [95% CI=0.98 [0.90, 1.08]; I2 = 69.76%). Similarly, Riesentenberg C et al's study[17] highlighted that live birth rates did not differ significantly among cycles demonstrating different levels of compaction (≥ 5%, < 5%, or expansion), emphasizing a lack of association between compaction status and IVF success. Similarly, Shah JS et al.'s[18]findings suggested that various thresholds of endometrial compaction (>0%, ≥5%, ≥10%, ≥15%, and ≥20%) did not serve as predictive factors for live birth outcomes.

Collectively, these studies corroborate the outcomes observed in our study, reinforcing the notion that different levels of endometrial compaction do not significantly impact IVF success rates. Despite variations in endometrial conditions during embryo transfer, the pregnancy rates demonstrated consistent results across various levels of endometrial compaction, highlighting the complexity of factors influencing IVF success beyond solely endometrial characteristics[19].

5. Limitations

However, this research had limitations, including a relatively small sample size and being conducted at a single centre, potentially limiting the broader applicability of the results. The study's design might not have been sensitive enough to capture subtle variations, urging caution in making definitive conclusions based on these findings.

6. Conclusion

In conclusion, our study indicates that endometrial compaction is insufficient to predict the success of a pregnancy. The lack of pregnancy and the resulting childlessness are often highly stigmatizing, leading to profound social suffering for infertile couples and infertile women in particular[20]. Future research efforts should involve larger and more diverse participant groups to validate these results more robustly. This might include comprehensive evaluations of both endometrial characteristics and biomarkers of receptivity to better understand the intricate connections between endometrial compaction, hormonal factors, and the outcomes of IVF. Long-term studies that track the window of implantation and subsequent pregnancy rates could reveal more precise associations between endometrial conditions and reproductive success.

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