Endometrial compaction and serum progesterone measurements at the day of embryo transfer cannot predict pregnancy outcomes in frozen-thaw embryo transfer cycles

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ABSTRACT

Endometrial receptivity plays a basic role in successful embryo implantation and pregnancy outcomes and can be assessed by many of non-invasive markers. Our study evaluated the impact of two of these markers specifically serum progesterone and endometrial thickness at embryo transfer day in prediction pregnancy outcomes on (60) patients attempting medicated frozen embryo transfer (FET) cycles. All patients were received sequential estrogen & progesterone medications for endometrial preparation then submitted to measurements of endometrial thickness (EMT) by transvaginal-ultrasound (TV-US) & serums progesterone (P) analysis at the embryo transfer day, thereafter day 3 verified-thawed embryos grades (A±B) were transfereed. Compacted (decreased) EMT was seen in 48.3% of patients with higher pregnancy rate (PR) of 58.6% than non-compacted EMT (no change or increased) which was seen in 51.7% of patients with (PR) of 29.0%, (P value=0.021). However ongoing pregnancy rate (Ong PR) not differed significantly between both groups (44.8% in compacted vs 25.8% in non-compacted, P value=0.053), also the means of serum P not differed between pregnant and non-pregnant patients (P value=0.374). ROC curves for Ong PR prediction in relations to endometrial compaction & serum progesterone at embryo transfer day were poor (AUC= 0.630, & AUC=0.576, respectively). This study suggested that endometrial compaction or serum P levels measurements at embryo transfer day were poor predictors for ongoing pregnancy where any kind of EMT changes (decreased or not) seen after P administration not significantly affect pregnancy outcomes in frozen-thaw cycles of cleavage stage embryos transfer.

INTRODUCTION

In our time frozen-thaw embryo transfer considers as a fundamental part of IVF cycles owing to the availability of advance cryopreservation techniques, its safety & increment of cumulative life birth rates (LBR) (Bosch et al., 2020). However, its implantation and pregnancy rates are not always superior compared to fresh cycles (Basirat et al., 2016). Recent attention has been paid more toward the endometrium since both euploid embryo & receptive endometrium sharing as equal as a role in determining embryo implantation and pregnancy out-
EMT measurement by the US is one of the non-invasive markers of endometrial receptivity that had been suggested to predict pregnancy outcomes in IVF cycles. It’s widely accepted since the US is a simple, cost-effective & more convenient tool (Zhao et al., 2012). A lot of studies evaluated EMT measurement before embryo transfer day as a predictive sign for pregnancy outcomes in medicated-FET cycles (El-Toukhy et al., 2008). While limited studies concentrated on measuring EMT at embryo transfer day, recent data are shedding the light on dynamic changes of EMT after P administration in frozen cycles as a predictors for pregnancy outcomes albeit with controversial conclusions (Forman, 2019).

In medicated-FET cycle, endometrial receptivity are induced artificially. Hence, every effort are seem necessary to mimic normal physiology by optimizing steroid hormones concentration specifically P around a window of implantation (WOI) as endometrial receptivity acquired by the action of P on estrogen primed endometrium via its interaction with steroid receptors which are induced by estrogen itself (Lessey and Young, 2019). Progestosterone down-regulates estrogen and epithelial progestosterone receptors (ERs, PRs), while stromal PRs remains constant leading to antagonize the proliferative effect of estrogen ultimate in endometrial decidualization with structural, molecular changes resulting in a synthesis of many growth factors & cytokines facilitating embryo implantation (Punyadeera et al., 2003). There are robust agreements that serum P threshold must exceeding 5 ng/ml during WOI for acquiring endometrial secretory changes & receptivity. However, debates still persist about the adequacy of this level in expression all necessary genes for implantation and to tolerate pregnancy in artificial cycles (Haas et al., 2019; Smith and Paulson, 2019).

Anyway, measurement of serum P at the end of estrogen phase in medicated-FET is logical as level exceeding 1.5 ng/ml indicating premature luteinization perhaps due to escape ovulation in ~ 1.9–7.4% of cycles that’s required cycles cancellation (Mackens et al., 2017). However, controversial opinions regarding ideal serum P around the implantation period, especially at embryo transfer day in FET cycles utilizing different progestosterone routes still persist (Coroleu and Gaggiotti-Marre, 2019). Given this controversial backgrounds, we performed a prospective study to observe serum P levels association with dynamic EMT changes on the embryo transfer day especially endometrial compaction and to see if both parameters can predict Ong PR in frozen-thaw cycles of cleavage-stage embryo transfer.

**MATERIALS AND METHODS**

This was a prospective observational study of (60) FET cycles from October 2019 to April 2020 in the IVF department at AL Hayatt private Hospital in Najaf Ashraf-Iraq. The study was approved by the Institutional Review of Arab Board of Medical Specializations & from Iraqi Fellowship of Reproductive Medicine. Counselling & writing agreements were taken from all patients.

**Inclusions criteria** were: Age (20-40) yrs., BMI (19-35) kg/m2, normal uterine cavity & fallopiantubes after US &hysterosalpingography imaging, Day 3 grade (A± B) embryos transfer. **Exclusions criteria** were: recurrent implantation failure, pelvic pathology (fibroid, Mullerian duct anomalies, polyp, hydrosalpinx, ovarian cyst), EMT <7mm or serum P ≥1.5 ng/ml at the end of estrogen phase, estrogen phase exceeding 21 days.

On cycle day 1-2 oral estradiol (as hemihydrate) (Estrace, Estrofem; Novo Nordisk) was started in (2mg/ bid) for the first 4-5 days then increased in step-up protocol until adequate EMT was reached, in the meantime serial US via ACUSON NX3 Elite ultrasound system with linear endocavity transducer of TFI=7.6 MHz (©Siemens Medical Solutions USA, Inc.) was used for EMT tracking. At the end of estrogen phase (usually ranged from 10-14 days in all patients) serum P was measured using compact automated immunoassay system (MINIVIDAS® BIOMÉRIEUX, France) by VIDUS PRG Kit & when it is ≥1.5 ng/ml, FET cycle was cancelled. In addition to US measurement of EMT which is recorded as initial EMT, If it reached ≥ 7 mm with triple-line appearance micronized progesterone was given in the form of vaginal Cyclogest (400 mg bid; Actavis Uk Ltd) to all patients ± oil injection (Progesterone Injection USP 50 mg/ml intramuscular once daily; Watson). The last dose of vaginal P was taken rectally the night before the day of embryo transfer.

At the morning of FET day (one hour before transfer), serum P & EMT measurements were taken again. EMT was measured by expert Ultrasonographic practitioner independently assessed the images without known pregnancy outcomes. Day3 (grade A & B) embryos resulted from ICSI cycles were thawed after vitrification using Vitrifreeze Es™-Vitrithaw Es™ universal media (Technical Support Assistance Technique, Ferti Pro N.V. Belgium) and by an open device techniques. Thereafter thawed embryos were transferred to an equilibrated culture dish for 2-3 hours where viability...
& grading of embryos have been assessed again by expert embryologist depending on grading system proposed by the Istanbul Consensus Workshop on Embryo assessment (Balaban et al., 2011). Only (grades A± B) embryos with viability 100-75% based on the percentage of intact blastomeres post thawing were chosen for transfer on 4th day of P administration via Soft Catheter (Gynétics Medical Products N.V. Belgium) under abdominal US guidance.

According to our center policy, 2-3 embryos were replaced for each patient by one experienced IVF specialist. Serum (β-HCG) test was measured 14 days after embryos transfer, where the level >10 mIU/ml were considered positive for pregnancy. TV-US was performed to confirm clinical PR (intrauterine gestational sac with viable foetus <12weeks), Ong PR (viable pregnancy ≥12 weeks of gestation & miscarriage (loss of clinical pregnancy before 12week of gestation). Hormonal replacement therapy (HRT) was continued until 10-12th weeks if pregnancy occurred.

Data collection & statistical analysis
Patients were grouped at embryo transfer day into; compacted endometrium group, that’s EMT was decreased & non-compacted endometrium group; that’s had either an increase or no changes in their EMT in response to serum P at that day. The main outcome was the impact of both serum P levels & dynamic EMT changes, especially endometrial compaction on the embryo transfer day in prediction ongoing pregnancy. Data analysis was carried out using SPSS-25 and presented in simple measures of frequency, percentage, means, standard deviation, and range (minimum-maximum values). For Quantitative data, Students-t-test or ANOVA test was used while the qualitative data Pearson Chi-square test was used. P-value was ≤ 0.05 indicated statistical significance. "ROC" curve technique was used to determine the predictive accuracy of serum P & compaction percentage for Ong PR.

RESULTS AND DISCUSSION
In this study, a total of sixty patients were grouped according to EMT changes at FET day into compacted & non-compacted groups. Table 1 Shaw compacted endometrium was seen in (29/60) 48.3 % & non-compacted in (31/60) 51.7 % of patients & there were no statistical differences in patient’s baseline & frozen cycles characters between both groups.

Table 2 illustrated frozen cycles measurements which were performed for all patients; there were no significant differences in the mean of initial EMT (9.9 ±1.7 (7.5-15) mm, P-value = 0.129) or the mean EMT at FET day (8.5±1.5 (6.7-13) vs 9.9±1.5 (7.3-13) mm, P-value = 0.217) also in the means of serum P at FET day (29.9±16.8 ng/ml vs 25.3±13.8 ng/ml, P-value=0.252) in both compacted & non-compacted groups respectively. However, most of the compacted endometrial thickness was occurred in serum P levels (≥20ng/ml) than non-compacted (P-value = 0.049) which was significant.

Table 3 revealed Biochemical pregnancy rate (β-HCG test positive) was seen significantly higher in compacted than non-compacted groups (17/29) 58.6% vs (9/31) 29.0% respectively, (P-value = 0.021), however, clinical PR not differed between both groups as P value = 0.445. Final pregnancy outcomes where Ong PR was seen in (13/29) 44.8% vs (8/31) 25.8%, miscarriage rates was seen in (4/29) 13.8% vs (1/ 31) 3.2% and no pregnancy occurred in (12/29) 41.4% vs (22/31) 71.0% in both compacted & non-compacted groups respectively, P-value = 0.053 indicating weak statistical differences between both groups. We further analyzed the distribution percentage of Ong PR across EMT change ratio as seen in Figure 1, we observed Ong PR was seen in (66.7%) at -5% endometrial compaction compared to (25%) in +5% endometrial expansion. However, an approximate
Table 1: Baseline patients and frozen cycle characteristics according to endometrial thickness changes at FET day

| variables                  | Endometrium thickness at FET day | p-value |
|----------------------------|---------------------------------|---------|
|                            | Compacted (No=29)               | Non-compacte (No=31) |
| Age (years)                | Mean±SD (Range) 28.2±4.6 (18-37)| 29.0±5.8 (19-40) | 0.547 |
| BMI (Kg/m2)                | Mean±SD (Range) 27.1±3.7(19.2-34.3) | 27.3±4.3(20.7-35.3) | 0.783 |
| Gravidity                  | 0                               | 1       | 2       |
|                            | 4                               | 13.8    | 13.8    |
|                            | 4                               | 6       | 2       |
| Parity                     | 0                               | 27      | 93.1    |
|                            | 2                               | 4       | 13.8    |
|                            | 2                               | 4       | 6.5     |
| Type of infertility        | Primary                         | 21      | 72.4    | 0.876 |
|                            | Secondary                       | 8       | 27.6    | 25.8   |
| Cause of infertility       | Male factor Yes                 | 19      | 65.5    | 0.464 |
|                            | No                              | 10      | 34.5    | 25.8   |
|                            | PCOS Yes                        | 13      | 44.8    | 0.979 |
|                            | No                              | 16      | 55.2    | 54.8   |
|                            | Tubal factor Yes                | 3       | 10.3    | 0.269 |
|                            | No                              | 26      | 89.7    | 96.8   |
|                            | Unexplained Yes                 | 5       | 17.2    | 0.193 |
|                            | No                              | 24      | 82.8    | 93.5   |
| Years of infertility       | Mean±SD (Range) 5.9±3.2 (2-12)  | 7.7±4.0 (2-16) | 0.063 |
| Trial of embryo transfer   | First                           | 13      | 44.8    | 0.801 |
|                            | Second                          | 15      | 51.7    | 45.2   |
|                            | Third                           | 1       | 3.4     | 6.5    |

*pSignificant difference between proportions using Pearson Chi-square test at ≤ 0.05 levels.

SD: standard deviation, BMI: body mass index, PCOS: polycystic ovarian syndrome

equal distributions for Ong PR were found on either compacted & non-compacted groups.

According to Table 4; the means of serum P no differed significantly in compacted & non-compacted groups (29.9±16.8ng/ml vs 25.3±13.8 ng/ml respectively, P-value = 0.252) or with endometrial compaction % (P values =0.363) as in Figure 2, neither with final pregnancy outcomes, (P-value = 0.374) in our study.

The ROC curve was performed for the prediction of pregnancy outcomes in relation to endometrial compaction % & serum P as seen in Figure 3, compacted endometrium% was a weak predictor as Area under curve (AUC) = 0.646 (95% CI= 0.504-0.789) with (P-value =0.053) while the mean of serum P was poor predictor as (AUC) = 0.597 (95% CI= 0.453-0.742) with (P-value =0.200) for biochemical pregnancy.

However, ROC curves for Ong PR was seen in Figure 4 show AUC for P was 0.576 (95% CI= 0.425-0.727) with (P-value =0.337) while AUC for endometrial compaction% was 0.630 (95% CI=0.478-0.782) with (P-value =0.099) indicating both measurements were poor predictors for Ong PR in our set data. Thus, no further analysis was done. Of interest, Ong PR was 52.4% when endometrium compacted at -5% however, increasing percentage of endometrial compaction ≥-5% had a negative effect on Ong PR as seen in Figure 5.

Our findings might be agreed with (Bu et al., 2019; Riestenberg et al., 2020) results who found no benefit from endometrial compaction on increasing pregnancy rates in FET cycles. In contrast (Haas et al., 2019; Zilberberg et al., 2020) confirmed a significant link between EMT compaction and Ong PR, where an increasing percentage of compaction could improve Ong PR. In addition (Gill et al., 2020; Kaye et al., 2020) stated that failure of compaction resulted in implantation failure of some euploid embryos. Hence, they were considering it as a promising non-invasive marker of endometrial receptivity to pre-
Table 2: Frozen cycles measurements of endometrial thickness and serum progesterone in relation to endometrial thickness changes at FET day

| variables                        | Endometrium thickness at FET day | Serum progesterone at FET day |
|----------------------------------|----------------------------------|------------------------------|
|                                  | Compacted                        | Non-compacted                | P-value |
| initial EMT (at the end of estrogen phase) mm | No=29 | No=31 |                               |
| Mean±SD (Range)                  | 9.9 ± 1.7 (7.5-15)                | 9.0 ± 1.4 (7-12.5)           | 0.129 |
| EMT at FET day mm                | Mean±SD (Range)                  |                               |
| <10.0 ng/ml                      | 8.5±1.5 (6.7-13)                  | 9.9±1.5 (7.3-13)             | 0.217 |
| 10.0—                            | 3                                | 3                             | 9.7    |
| 20.0—                            | 17                               | 10.3                          | 32.3   |
| 30.0—                            | 4                                | 13.8                          | 19.4   |
| 40.0—                            | 1                                | 3.4                           | 9.7    |
| 50.0—                            | 1                                | 3.4                           | 6.5    |
| =>60.0 ng/ml                     | 2                                | 6.9                           | -      |
| Mean±SD (Range)                  | 29.9±16.8 (8.6-80)               | 25.3±13.8 (1.14-57.24)       | 0.252 |

*Significant difference between proportions using Pearson Chi-square 0.05 test at ≤ levels.

SD: standard deviation, EMT: endometrial thickness, FET: frozen embryo transfer

Table 3: Pregnancy outcomes according to endometrial thickness changes at FET day

| Frozen cycle outcomes | Endometrium thickness at FET day | P-value |
|-----------------------|----------------------------------|---------|
|                       | Compacted                        | Non-compacted |
| Biochemical pregnancy rate (ß-HCG test) | Positive | 17 | 58.6 | 9 | 29.0 | 0.021*|
|                       | Negative                         | 12 | 41.4 | 22 | 71.0 |
| Clinical pregnancy rate | Viable | 13 | 76.5 | 8 | 88.9 | 0.445 |
|                       | Not viable                       | 4  | 23.5 | 1 | 11.1 |
| Final pregnancy outcomes | Ongoing pregnancy | 13 | 44.8 | 8 | 25.8 | 0.053 |
|                       | Miscarriage                      | 4  | 13.8 | 1 | 3.2 |
|                       | Not pregnant                     | 12 | 41.4 | 22 | 71.0 |

*Significant difference between proportions using Pearson Chi-square test at ≤ 0.05 levels.

dict pregnancy in FET cycles. Thought these studies were differed in the type of US used (TA vs TV), but all were retrospective & utilized blastocyst embryos where the decreased EMT still suitable for a good clinical outcome as blastocyst implant shortly after transfer. However, this was not ideal for cleavage embryo as stated by (Shaodi et al., 2020) who performed a large retrospective analysis of 10,165 HRT-FET cycles of cleavage stage embryos using TV-US for EMT measurement, they found that endometrial compaction on embryo transfer day has a negative consequence on pregnancy outcomes whereas the EMT cut-off value of 8.7 mm & interval of (8.7–14.5 mm) were correlated better with clinical outcomes than the delta of EMT before & after P administration, that’s thin <7mm or thick >14.5mm EMT might lowered Live birth rate (LBR).

Measurement of EMT at embryo transfer day is equivalent to the early luteal phase, Meanwhile, P causes gradual decline ERs until their absence in
Table 4: Frozen cycles characteristics and outcomes in relation to means serum progesterone at FET day

| Variables                        | Progesterone (ng/ml) at FET day | P-value |
|----------------------------------|---------------------------------|---------|
|                                  | Mean±SD                          | Range   |
| Age (years)                      |                                 |         |
| <20 years                        | 19.3±10.2                        | (12.10-26.48) | 0.361 |
| 20—29                            | 25.7±12.2                        | (1.14-57.24) |
| 30—39                            | 31.7±19.1                        | (10.37-80.00) |
| =>40 years                       | 19.6±14.8                        | (9.17-30.08) |
| BMI (Kg/m2)                      |                                 |         |
| Normal (18.5-24.9)               | 25.7±15.4                        | (1.14-57.24) | 0.551 |
| Overweight (25-29.9)             | 29.9±17.6                        | (10.37-80.00) |
| Obese (=>30)                     | 25.3±9.8                         | (8.64-43.95) |
| No                               | 21.4±8.6                         | (10.37-40) |
| EMT at FET day                   |                                 |         |
| Compacted                        | 29.9±16.8                        | (8.60-80) | 0.252 |
| Non-compacted                    | 25.3±13.8                        | (1.14-57.24) |
| Endometrial compaction %         |                                 |         |
| <-10%                            | 25.4±9.9                         | (8.60-43.95) | 0.363 |
| -10—19%                          | 28.0±17.6                        | (11.06-77.7) |
| =>-20%                           | 36.4±19.9                        | (20.25-80) |
| Endometrial non compaction %     |                                 |         |
| <+10%                            | 25.0±15.0                        | (1.14-50.5) | 0.768 |
| +10—19%                          | 27.5±14.6                        | (13.46-57.24) |
| =>+20%                           | 21.5±6.5                         | (12.1-27.17) |
| Biochemical pregnancy rate (β HCG) test |                   |         |
| Negative                         | 30.7±16.0                        | (11.06-77.7) | 0.166 |
| Viable                           | 25.1±14.6                        | (1.14-80) |
| Not viable                       | 31.1±17.2                        | (11.06-77.7) | 0.807 |
| Surgical pregnancy rate          |                                 |         |
| Ongoing pregnancy                | 31.1±17.2                        | (11.06-77.7) | 0.374 |
| Miscarriage                      | 29.1±11.2                        | (14.62-43.95) |
| Not pregnant                     | 25.1±14.6                        | (1.14-80) |

*Significant difference between two independent means using Students-t-test at ≤ 0.05 levels.

#Significant difference among more than two independent means using ANOVA-test at ≤ 0.05 levels.

the endometrium during the mid-luteal phase (Jabbour et al., 2006). As such endometrial proliferation persists for first 2-3 days after ovulation where EMT becomes plateau during early luteal phase but the glandular and vascular stromal growth continues under the peak of P during mid-luteal phase then EMT growth ceases prior to menstrual shedding at the late luteal phase, these morphological endometrial changes parallel with dynamic genes expression necessary for implantation (Malhotra et al., 2014; Diedrich et al., 2007). Thus, a decrease or increased EMT after P administration in FET cycles looks comparable to normal endometrial changes & explains pregnancy occurrence in both compacted & non-compacted endometrium as seen in multiple studies.

Furthermore, we observed no significant association between serum P levels & endometrial changes at embryo transfer day. Also, serum P was poor predictors for Ong PR. Our findings might be different from some studies (Kofinas et al., 2015; Labarta et al., 2017) where they could determine the cut-off level of P that’s diminished pregnancy outcomes despite their differences in serum threshold, doses & routes of progesterone medications, While (Boynukalin et al., 2019) could determine serum P threshold for improving pregnancy outcomes in FET cycles. Nerveless our results might be closer to (Volovsky et al., 2020) study who performed a large retrospective study of 2010 blastocyst-FET cycles utilized vaginal P stated that neither serum P ≥10 ng/mL nor ≥ 20 ng/ml on embryo transfer day significantly improved pregnancy outcomes while level ≥5 ng/ml might improve LBR considering it as the lowest threshold to salvage FET cycles.

Evidences from many studies recognized unreliable associations between actual serum P with histological & molecular endometrial maturation, on the other hand, they stated that serum P exceed-
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Figure 3: ROC curve for endometrial compaction % and serum progesterone at FET day in relation to biochemical pregnancy rate. AUC is 0.646, 0.597 respectively.

Figure 4: ROC curve for endometrial compaction % and serum progesterone at FET day in relation to ongoing pregnancy rate. AUC is 0.630, 0.576 respectively.

Figure 5: Ongoing pregnancy rate (positive) in relation to endometrial compaction ratios

Strengths of our study are prospective in nature, TV-US was done for EMT measurements, using same HRT protocol & EMT cut-off was ≥ 7mm at the end of the estrogen phase for all patients, at least two top-qualities of D3 embryos were transferred by one professional IVF specialist beside good endometrial compaction rate was seen in our study. However, limitation of this study was a small sample size, US endometrial assessment is a subjective test with some imprecision regardless operator’s expert, utilized Day3 not blastocyst embryos, included only medicated FET cycles & it was only observational study with no medical interventions.
est threshold at embryo transfer day which are indicating a favourable response to progesterone medications ultimate in optimizing pregnancy outcomes, certainly further studies are essential to validate these topics.

CONCLUSIONS

Measurements of endometrial compaction or serum P levels at embryo transfer day in frozen-thaw cycles were poor predictors for Ong PR since pregnancy can occurred at a flexible range of endometrial thickness & serum P levels, that’s any kind of EMT changes (decreased or not) seen after P administration not significantly affect pregnancy outcomes in frozen-thaw cycles of cleavage stage embryos transfer.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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