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Pregnancy Success Prediction Using Uterine and Sub-Endometrial Arteries Doppler Indices Comparison Between the Trigger Day and the Mid Luteal Phase Day When Using Oral Ovarian Induction Medication in Sub Fertile Patients

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ABSTRACT

Background: Doppler of uterine and sub-endometrial arteries might be beneficial for the prediction of pregnancy success. None or few studies evaluated them when using oral ovulation induction.

Methods: This study is a randomized prospective study. We recruited infertile couples with PCOS or unexplained subfertility from the infertility unit at Al-Moosa Specialist Hospital in eastern province in the Kingdom of Saudi Arabia. We randomize cycles to use clomiphene or letrozole. We study the uterine arteries doppler indices difference between the hCG trigger day and the mid-luteal phase day with positive and negative pregnancy test groups.

Results: In the negative pregnancy test group, there was no sufficient evidence suggesting a difference for sub endometrial artery PI and RI between the trigger day and mid-luteal phase day with a p-value of 0.95 and 0.765, respectively. For the uterine artery PI and RI, there was evidence suggesting a difference between the trigger day and the mid-luteal phase day with a p-value of .003 for both of them. In the positive pregnancy test group, there was evidence to suggest a difference between the trigger day and the mid-luteal phase day for the sub endometrial artery RI with a p-value of 0.035. However, there was no sufficient evidence to suggest that there was a difference for PI of the sub endometrial artery and the uterine artery PI and RI between the day of the trigger and mid-luteal phase day with a p-value of 0.137, 0.533 and 0.687 respectively.

Conclusions: When uterine artery PI and RI decrease, we can predict failed ovulation treatment. In comparison, we can predict a successful pregnancy with increasing sub-endometrial artery RI.

Key words: Pregnancy, Arteries, Ovulation inducers, Oestrogen, Sonography

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INTRODUCTION

It is a common practice to use clomiphene citrate and letrozole as ovulation inducers. We thought that letrozole is better than clomiphene due to the weight of the studies that suggest that letrozole should be the first oral ovulation-inducing treatment [1].

We thought that doppler would change our view to subfertility when we have sufficient studies to justify its vital role in infertility management [2]. Doppler of uterine arteries [3,4] and sub-endometrial arteries [5] can predict successful pregnancy. We also think that changes in doppler indices over cycle could help to predict pregnancy outcome.

Clomiphene bind to oestrogen receptors, causing mainly antagonizing effects [6]. So it will cause pseudo oestrogen deficiency by occupying the oestrogen receptors [7]. Side effects of clomiphene are thinning of the endometrium [8] and decreased quality and quantity of cervical mucus [9] due to pseudo deficiency of oestrogen. On the other hand, letrozole causes a real decrease in oestrogen due to its suppression of androgen transformation to oestrogen. Both oestrogen receptors antagonization and decreased oestrogen deficiency will cause an increase in FSH and LH by positive hypothalamus feedback. Increased FSH and LH are responsible for the growth and maturation of follicles.

Objective

To assess doppler indices changes over the cycle during infertility management in patients from the eastern province of Saudi Arabia.

Hypothesis

There is a change in doppler indices between mid-cycle day and mid-luteal phase day with oral ovulation medications.

MATERIALS AND METHODS

Selection of study subjects

Our study is a randomized comparative prospective study. All couples gave informed consent with detailed study information, and if they agree they will sign for that to guarantee study participation permission. Also, we applied and took an ethical committee approval at Al Moosa Specialist Hospital. The IVF unit outpatient department was the source of the couples.

Inclusion criteria were patients in reproductive age, healthy pelvis organs and acceptance to participate. In contrast, exclusion criteria were: distorted pelvic organs, big leiomyomas (> 4 cm), sub endometrial leiomyomas, primary or secondary ovarian failure (hypogonadism), male subfertility, Unmanaged Thyroid diseases or hyperprolactinemia, Non-responsive cases, cases with early ovulation (before triggering) and obesity.

We used the 2003 Modified Rotterdam consensus to diagnose PCOS using [9,10]. To avoid the inter-observer variability, we did all doppler sonography studies by the same doctor. We used a GE Voluson P80 ultrasound machine with a transvaginal probe of 5-9 MHz.

Randomized groups are

Group A: clomiphene induced group.

Group B: letrozole induced group.

We gave 100 mg of clomiphene once daily from the third day of the cycle for five days. Letrozole was given with an amount of 5 mg once daily for five days starting from the third day of the cycle.

Evaluation of study subjects

Trigger criteria were when the follicular size is 18 mm or more. We measure follicular size using the mean of perpendicular diameters [11]. We used ten thousand units of Choriomon or Pregnyl to trigger ovulation in the morning of the same day. We timed intercourse at 1 and 1.5 days from triggering.

If we found no follicle more than 12 mm after 15 days from induction, we would cancel the cycle. We did a doppler study on the trigger day and the mid-luteal day.

Sub endometrial arteries studied at 1-2 mm distal from the endometrial outer edges. Uterine arteries studied on the lateral edges of the cervix. The minimum filter PRF was used (usually 1.3 for the uterine arteries and 0.3 for the sub endometrial arteries). We used the mean of both sides of the uterine arteries doppler indices.

We used 10 mg of Dydrogesterone (Duphaston) twice daily orally for 14 days, starting from day three after the trigger day. We did test for pregnancy 16 days after hCG triggering. To confirm embryo viability, we did a pelvic scan after four weeks. We repeated the same steps (up to 2 successive cycles) in unsuccessful cycles if the couple agrees.

Data analysis

We used Excel and SPSS for data analysis and the G Power software for calculating the required sample size and power.

RESULTS

Using G Power software, we calculated Fisher's exact test sample size with control group proportion of .05, experimental group proportion of .4, two-sided α error of .05, the power value of 80% and an allocation ratio of 1. The calculated sample size was 48 cycles. The calculated sample size for the point biserial correlation test was 52 cycles. We also used G Power software with an α error of .05, moderate effect size of .37 and an 80% power.

In our study, we used 54 cycles of ovulation induction; in each group, there were 27 cycles. There were differences in the mean BMI (p= .153), and the mean age (p= .109) but they were not significant in both groups (Table 1).

With the negative serum pregnancy test group, the sub endometrial artery PI was almost the same between the day of the trigger (mean=1.23, SD =0.32) and the mid-luteal phase day (mean=1.24, SD=0.35). So, there was no evidence suggesting a difference between them with a p-value of 0.95. Also, the mean of sub endometrial artery RI on both days was the same (mean=0.66, SD =0.09) with no sufficient evidence to suggest a difference, p=0.765. The mean of uterine artery PI was lower on the trigger day (2.91 ± 0.49) than the mid-luteal phase day (2.64 ± 0.45). The evidence was enough to suggest a higher uterine artery PI on the trigger day than the mid-luteal phase day. The correlation was moderate, rs=0.432, p=0.003. Also, the mean of uterine artery RI was higher on the trigger day 0.89 with SD of 0.04 than the mid-luteal phase day (mean=0.86, SD=0.04). Also, there was sufficient evidence to suggest that the uterine artery RI was higher on the trigger day than the mid-luteal day with a moderate correlation, rs=0.436, p=0.003. When the uterine artery PI was higher on the trigger day than on the mid-luteal phase day, the pregnancy failure rate was 91.4%. While, when the uterine artery PI was lower on the trigger day than on the mid-luteal phase day, the pregnancy failure rate was 63.2%. When the uterine artery RI was higher on the trigger day than on the mid-luteal phase day, the pregnancy failure rate was 88.8%. While, when the uterine artery PI was lower on the trigger day than on the mid-luteal phase day, the pregnancy failure rate was 66.7% (Table 2).

On the other hand, the positive serum pregnancy test group caused lower sub endometrial artery PI on the trigger day (mean=1.14, SD =0.54) when compared with the mid-luteal phase day (mean=1.38, SD=0.32). However, the evidence was not sufficient to suggest a difference between them, rs=0.505, p=0.137. On the other hand, the mean of sub endometrial artery RI was lower on the trigger day (0.62, SD=0.1) than on the mid-luteal phase day (0.71, SD=0.08) with sufficient evidence p=0.035 and a strong correlation, rs=0.667. The mean of uterine artery PI on the day of the trigger was 2.29 (SD=0.41) whereas, on the mid-luteal phase day, the mean was 2.41 (SD=0.42). However, there was no sufficient evidence to suggest a difference between them, rs=-0.224, p=0.533. Also, the mean of uterine artery RI on the day of the trigger was .838 (SD =.04) whereas the mean on the mid-luteal phase day was 0.845 (SD=0.04). Nevertheless, there was no sufficient evidence to suggest a difference between them, rs=-0.146, p=0.687. When the sub endometrial artery RI was lower on the trigger day than on the mid-luteal phase day, the pregnancy rate was 39.1%. While, when the sub endometrial artery RI was higher on the trigger day than on the mid-luteal phase day, the pregnancy rate was 3.2% (Table 3).

Finally, the total pregnancy rate was 18.52%. The pregnancy rate in the clomiphene group was 14.8% while it was 22.2% for letrozole group. However, the evidence was not sufficient to suggest a difference with a p-value of 0.728 (Figure 1).

Table 1: Age and BMI with letrozole and clomiphene citrate groups.

	Protocol					
	Clomiphene citrate group			Letrozole group		
	Mean	N	Std Deviation	Mean	N	Std Deviation
Age	26.4	27	4.9	28.3	27	4.5
BMI	256	27	51	27.9	27	6.2

Table 2: Comparison in the negative pregnancy test group.

Doppler indices comparison between the day of the trigger and the mid-luteal phase day									
	Negative Pregnancy Test Group								
	Day of Trigger			Mid-Luteal Phase day					
	Mean	N	Std. Deviation	Mean	N	Std. Deviation	Statistical Test	P	RS/Phi
H EPI VS PH EPI	1.23	44	0.32	1.24	44	0.35	Spearman's correlation	0.95	-0.01
H ERI VS PH ERI	0.66	44	0.09	0.66	44	0.08	Spearman's correlation	0.765	-0.046
H MUPI VS PH MUPI	2.91	44	0.49	2.64	44	0.45	Pearson's Correlation	0.003	0.432
H MURI VS PH MURI	0.89	44	0.04	0.86	44	0.04	Spearman's correlation	0.003	0.436

Table 3: Comparison in the positive pregnancy test group.

Doppler indices comparison between the day of the trigger and the mid-luteal phase day									
	Positive Pregnancy Test Group								
	Day of Trigger			Mid-Luteal Phase day					
	Mean	N	Std. Deviation	Mean	N	Std. Deviation	Statistical Test	P	RS/Phi
H EPI VS PH EPI	1.14	10	0.54	1.38	10	0.32	Spearman's correlation	0.137	0.505
H ERI VS PH ERI	0.62	10	0.1	0.71	10	0.08	Spearman's correlation	0.035	0.667
H MUPI VS PH MUPI	2.29	10	0.41	2.41	10	0.42	Pearson's Correlation	0.533	-0.224
H MURI VS PH MURI	0.838	10	0.04	0.845	10	0.04	Spearman's correlation	0.687	-0.146

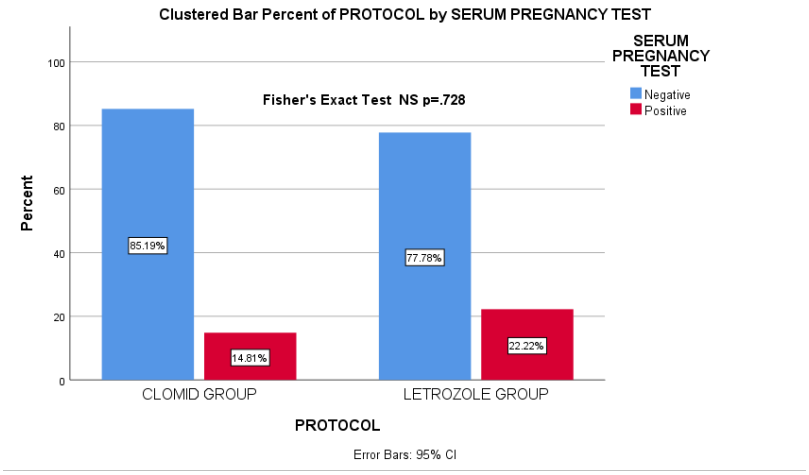

Figure 1: Pregnancy rate.

DISCUSSION

In the negative pregnancy test group, the mean of sub endometrial artery PI and RI was almost the same between the trigger day and the mid-luteal phase day with no sufficient evidence suggesting any difference between them.

Interestingly, the mean of uterine artery PI and RI decreased significantly from the day of the trigger to the mid-luteal phase day with a moderate correlation.

While in the positive pregnancy test group, the mean of sub endometrial artery PI on the trigger day was lower than the mid-luteal phase day, but the evidence was not sufficient to suggest that there was a difference between them.

On the other hand, the mean of sub endometrial artery RI on the day of the trigger was lower than the mid-luteal phase day with enough evidence suggesting the difference with a strong correlation.

While the mean of uterine artery PI and RI was lower on the day of the trigger when compared with the mid-luteal phase day. However, this difference has no sufficient evidence.

CONCLUSIONS

Predictors for negative pregnancy test are higher uterine artery PI and RI on the day of the trigger when compared with the mid-luteal day.

Predictor for positive pregnancy test is when sub endometrial artery RI is lower on the trigger day than when compared with the mid-luteal phase day.

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ETHICAL CONSIDERATIONS

We took consent of involvement in the research from every participating couple. Moreover, we also obtained approval from the ethical and research Committee in Almoosa specialist hospital.

FUNDING

The authors bore the entire cost of the research and did not obtain any economic assistance from any organization.

CONFLICT OF INTEREST

The authors state no conflicts of interest.

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