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Original Research Article

Evaluation of Serum progesterone Level and progesterone/estradiol ratio on day of triggering by hCG as predictors of pregnancy in ICSI cycles

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Abstract

The premature rise of progesterone and increase in progesterone/estradiol ratio on the late follicular phase, negatively affect the clinical outcome of fresh embryo transfers in ICSI cycles, a progesterone level above 1.5 ng/ml and P_4/E_2 ratio above 1 on the day of trigger have different endometrial gene expression profiles, lead to asynchrony between the endometrium and the fresh embryo transfer. The aim is to analyze the relationship between pre ovulatory progesterone rise and increase in progesterone/estradiol ratio on the late follicular phase with clinical pregnancy outcomes of fresh embryo transfers in Intracytoplasmic sperm injection (ICSI). This study done on 120 infertile women selected according to the type of programs used in intra cytoplasmic sperm injection (ICSI) cycles, divided into 60 infertile women stimulated by long agonist protocol and 60 infertile women stimulated by antagonist protocol. Parameters which measured included basal blood sampling and hormones assays in preceding cycles and clinical characteristic of ICSI cycle, on cycle day 2-3, stimulation parameters and on triggering day measured serum progesterone, serum E_2, LH by VIDAES and ratio of P_4/E_2, ultrasound for endometrium thickness (ET) and finally calculated number of oocytes pickup, the maturation rate, fertilization rate, cleavage rate, implantation rate and biochemical and clinical pregnancy rate. (120) infertile women, 35(29.16%) women had positive pregnancy while 85(70.83%) with negative pregnancy. All parameters that measured and clinical characteristics that examined showed no significant difference in the current study except serum progesterone level at trigger day was significantly lower (P=0.010) and the ratio P_4/E_2 was highly significantly lower (P<0.001) in women who succeed to get pregnant in comparison to women who failed to get pregnant. Total number of embryos was significantly higher (P=0.033) and there was significant increase in mean number of fresh embryo transfer grade 1 (P=0.037) in pregnant women in comparison with women with negative pregnancy. Conclusion: Serum progesterone level and P_4/E_2 ratio can be used as accurate and sensitive predictors of pregnancy outcome in fresh embryo transferred in ICSI.

Keywords: ICSI, progesterone, premature progesterone rise, control ovarian stimulation

INTRODUCTION

During the menstrual cycle, ovarian hormones control gene expression of different endometrial cell types (Ruiz-Alonso, Blesa and Simón 2012). Proliferative phase of endometrium is controlled by estrogen allowing stromal cells and uterine glands proliferation and marked elongation of the spiral arteries. The postovulatory progesterone (P_4) rise leads to reduces proliferation of epithelial cells while inducing their differentiation, it promotes stromal cells proliferation and stimulating the glandular secretory activity and the endometrium acquires a receptive phenotype permitting blastocyst implantation. This period of endometrium receptivity is known as the "window of implantation" (WOI).Women with 28 days cycle this window of implantation opens on

day 19 or 20 and remains open for just 4–5 days at the time when P_4 reaches peak serum concentrations (Lessey, 2011). Progesterone (P_4): is a steroid hormone have major rule in the implantation in an estrogen-primed endometrium in normal as well as in induced cycles; it's concentrations is low, during the first half of the normal ovulatory cycles then its concentration start to increase gradually (12–24) h before the onset of luteinizing hormone (LH) surge (Jawa, Swarankar and Garg 2017). The adrenal glands is the source of progesterone in the early follicular phase, while in the late follicular phase, progesterone source is mainly from the growing follicles (Jawa, Swarankar and Garg, 2017). Premature progesterone rise (PPR) occur on day of hCG trigger when it's level above a threshold concentration which is usually (1.5 ng/ml) has negative effect on clinical pregnancy outcomes of in vitro fertilization (IVF) (Gunderson, Anderson and Riley 2018). Progesterone rise (>1.5 ng/ml) causing acceleration of the endometrial maturation process that have negative effect on endometrial receptivity by narrowing the window of implantation which decreases the pregnancy outcome when fresh embryo transfer is performed due to failure of implantation (Kasum et al., 2013). In contrast, in frozen/thawed cycles, no decrease in pregnancy rates were detected when embryos originated from women with elevated progesterone during control ovarian hyper stimulation cycle, were transferred to an endometrium not exposed to elevated progesterone level (Venetis et.al., 2015).The suitable explanation for occurrences of PPR, is use high FSH-dose only in control ovarian stimulation cycles leads to recruits a large number of growing follicles causing an increased steroidogenic activity of ovary results in increase in progesterone production without an LH drive to theca cells so progesterone will not be more metabolized and change to androgen and it will finally takes its way to the blood circulation (Fleming and Jenkins 2010). Prolongation period of stimulation and induction to ovarian tissue causes an increase in serum progesterone levels significantly on day of final oocyte maturation (Kyrou et al., 2011). Other observed that lack of hCG/LH activity which has a protective effect and could prevent the premature progesterone rise (Smitz et.al., 2007). Progesterone rise during the late follicular phase has been considered a negative predictive factor for clinical outcome in both GnRH long agonists (Elnashar, 2010). And antagonist protocols (Papanikolaou et al., 2009)

MATERIAL AND METHODS

This study is conducted at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, AL-Nahrain University and Kamal AL-Samarai Hospital, center of fertility and in vitro fertilization – Ministry of Health at Baghdad-Iraq, during the period from the 1st of December 2017 to the 31st of August 2018.

The study was designed to be prospective intervention study. The sample size was 120 Iraqi infertile women divided into 60 infertile women stimulated by long GnRH agonist protocol of down regulation of pituitary-ovarian axis and control ovarian hyper stimulation (COH) and second group include 60 infertile women ovarian stimulated by antagonist protocol. All infertile females were subjected to a full history, general and gynecological examination with approved consent.

Inclusion Criteria

First trial of Intracytoplasmic sperm injection, patient's age between (19-40 years), endometriosis grad 1 and 2, both ovaries are present, normal responders, documented normal uterine cavity by Hysterosalpingography.

Exclusion Criteria

Endocrine abnormalities such as hyper prolactinemia, thyroid diseases and diabetes mellitus, endometriosis grade 3and 4, previous ICSI trials, azoospermia partner, congenital anomalies of the uterus, patients age more than 40 years, E_2 level on the trigger day more than 4000pg/ml. The age of infertile women in this study ranged from (19-40years), (89) had primary infertility and (31) had secondary infertility for period of one to twenty three years.

Treatment protocols with GnRH long agonist (GnRH-a)

The GnRH agonist was started on day 21 of the preceding cycle, daily administration of subcutaneous injection of GnRH-a, triptorelin (Decapeptyl®; 0.1 mg Ferring Co, Kiel, Germany) ® for pituitary down-regulation and continue till the day of hCG administration. Ovarian stimulation is initiated on cycle day 2-3of menstruation when (serum E_2 level reaching <50 pg /ml and endometrial thickness was ≤ 3-5 mm) (Hass *et.al.* 2014). By (recombinant human follicle stimulating hormone) (rFSH) (Gonal F, Merck ® 75 IU of FSH activity per ampoules) or HMG (Inj. Menogon, Ferring), by daily subcutaneous injection in a dose of 150-225 IU. The follicle growth and the doses of Gonal-F® were monitored by trans-vaginal ultrasound and by serum E_2 level and till the day of hCG administration. (Elder and Dale 2011).

Treatment protocol with GnRH antagonist

In this antagonist protocol (60) infertile women were enrolled; ovarian stimulation is initiated by (rFSH) or

Table 1. Pregnancy outcome according to type of protocol and demographic characteristics

Characteristic	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P*
Long agonist	42 (70 %)	18 (30 %)	0.841 ¥ NS
Antagonist	43 (31.7)	17 (28.3)	
Age (years), Mean ± SD	30.33 ±5.11	30.63 ±5.01	0.770 † NS
BMI (kg/m^2), Mean ± SD	28.46 ±4.13	28.04 ±4.29	0.619 † NS
Duration of infertility (years), Mean ± SD	7.34 ±3.64	6.97 ±4.51	0.644 † NS
Primary infertility	67 (75.3 %)	22 (24.7 %)	0.069 ¥ NS
Secondary infertility	18 (58.1)	13 (41.9 %)	

(HMG) by daily subcutaneous injection in a dose of 150-225 IU were administrated from the second day of cycle, GnRH antagonist (Cetrorelix) is usually given daily in a dose of 0.25 mg if the leading follicle reaches (12-14mm) by ultrasound. The antagonist is given together with the (Gonal-F®) stimulation till a good response is obtained (Pu, Wu and Liu 2011) and Ovulation induction was induced by the administration of recombinant hCG (rhCG 6500IU,Ovitrelle®; Merck, Italy) subcutaneously (Zegers-Hochchild *et.al.* 2009), The serum (progesterone, E_2 and LH) level on trigger day was measured by VIDAS.

Oocyte Retrieval

After 34-36 hours of hCG injection, under general anesthesia with Trans vaginal ultrasound-guided aspirations of oocyte were done and sperm from her partner was collected on day of oocyte retrieval and subjected to ICSI. Fertilization was checked on day 1 of insemination and embryos cultured in sequential medium embryos were graded, about two to three embryos grade 1 or 11 transferred under transvaginal US guidance. Serum β-hCG levels were recorded 15 days after embryo transfer. Positive β-hCG, that is ≥50 mIu/ml, was considered as biochemical pregnancy rate. Clinical pregnancy rate was calculated by the presence of intrauterine gestational sac with fetal cardiac pulsation at 6 weeks of gestation. Statistical analysis was performed with the Statistical Package for the Social Sciences trial version 23.0 software for Windows (SPSS Inc., Chicago, IL, USA) and Primer software. Using Chi-square test, Student's *t*-test and ANOVA test. (*P*) Value <0.05 was considered statistically significant.

RESULTS

In table (1) there was no significant difference in mean age, mean body mass index, mean duration of infertility and proportions of primary and secondary infertility between the two groups (*P*>0.05). In table (2) there was insignificant difference in mean baseline serum hormonal levels on cycle day (CD) 2-3 and endometrial thickness.

Table (3), there was no significant difference in mean of CD2-3 clinical Characteristic of ICSI cycles between the two groups (P>0.05). Moreover, table (4) shows (stimulation characteristics) disclosed no significant difference between both groups (P>0.05). while clinical characteristics and parameters at trigger day shows that Serum progesterone level at trigger day was significantly lower in women who succeed to get pregnant than women who failed to get pregnant, 1.25 ±0.45 ng/ml versus 1.83 ±1.27 ng/ml (*P*=0.010) as explained in figure (1) and in table (5).

The ratio P_4/E_2 was highly significantly lower in pregnant women when compared to non-pregnant women, 0.56 ±0.27 versus 1.14 ±0.91 (*P*< 0.001) as explained in table (5) and figure (2).For that reason, it was suggested that a cutoff value may exist for both serum progesterone at trigger day and P_4/E_2 ratio that can predict positive pregnancy outcome with acceptable level of accuracy, therefore receiver operator characteristic (ROC) curve analysis was conducted and results are shown in figures (3) and (4).

The best cutoff values according to Youden index were ≤ 1.69 ng /ml for serum progesterone and ≤ 0.744 for $P4/E_2$ ratio, table (6). However, the P_4/E_2 ratio was more accurate significantly, 78.1 % versus 65.4 %, respectively (*P* = 0.002).

In table (7), there was no significant correlation between pregnancy outcome and oocytes characteristics and fertilization parameters (P>0.05). In table (8), total number of embryos was significantly higher in women who got pregnant in comparison with women with negative pregnancy, 5.09 ±2.77 versus 4.02 ±2.32, respectively (*P* = 0.033). In table (9), mean number of fresh embryo transferred grad 1 was significantly higher in pregnant women than non-pregnant women with significant difference (2.40 ±1.22 versus 1.87 ±1.26) (P=0.037).

In table (10), there was no significant different in number of women use different types of progesterone

Table 2. Pregnancy outcome according to baseline Characteristic cycle day 2-3 of preceding cycles in all sub-fertile women

Characteristics	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P*
FSH (IU/L)	6.52 ±2.66	6.34 ±2.24	0.726 † NS
LH (IU/L)	4.89 ±2.90	5.57 ±4.00	0.306 † NS
Prolactin (ng/ml)	17.32 ±16.21	15.55 ±13.70	0.572 † NS
Testosterone (IU/L)	0.95 ±0.37	0.88 ±0.47	0.396 † NS
TSH (mIU/L)	2.17 ±1.14	2.22 ±0.82	0.818 † NS
T3 (IU/L)	2.90 ±13.97	1.36 ±0.20	0.515 † NS
T4 (nmol/L)	119.13 ±23.98	115.72 ±22.26	0.471 † NS
E_2 (pg/ml)	49.85 ±21.23	55.74 ±34.35	0.257 † NS
AMH (ng/ml)	3.80 ±1.73	3.85 ±2.40	0.896 † NS
Endometrial thickness (mm) in CD12- CD13	9.81 ±1.35	9.97 ±1.33	0.534 † NS

Table 3. Pregnancy outcome according to CD2-3 Characteristic of ICSI cycles in all sub-fertile women

Characteristics	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P* †
E_2 (pg/ml)	35.99 ±11.62	37.51 ±10.17	0.503 NS
LH (mIu /ml)	2.80 ±1.40	2.88 ±1.16	0.781 NS
Number of antral follicle	17.62 ±5.07	17.66 ±6.29	0.976 NS
Endometrial thickness (mm)	4.60 ±0.57	4.66 ±0.44	0.618 NS

Table 4. Pregnancy outcome in all sub fertile women according to stimulation characteristic

Characteristics	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P* †
Duration of stimulation (days)	9.76 ±1.09	10.03 ±1.01	0.221 NS
Dose of FSH (IU)	1501.80 ±516.64	1429.30 ±572.90	0.500 NS
Dose of LH (IU)	707.65 ±483.77	872.14 ±696.97	0.142 NS
Days of agonist (42/18)	19.76 ±1.32	19.89 ±1.78	0.760 NS
Days of antagonist (43/17)	4.33 ±2.53	4.18 ±0.53	0.812 NS

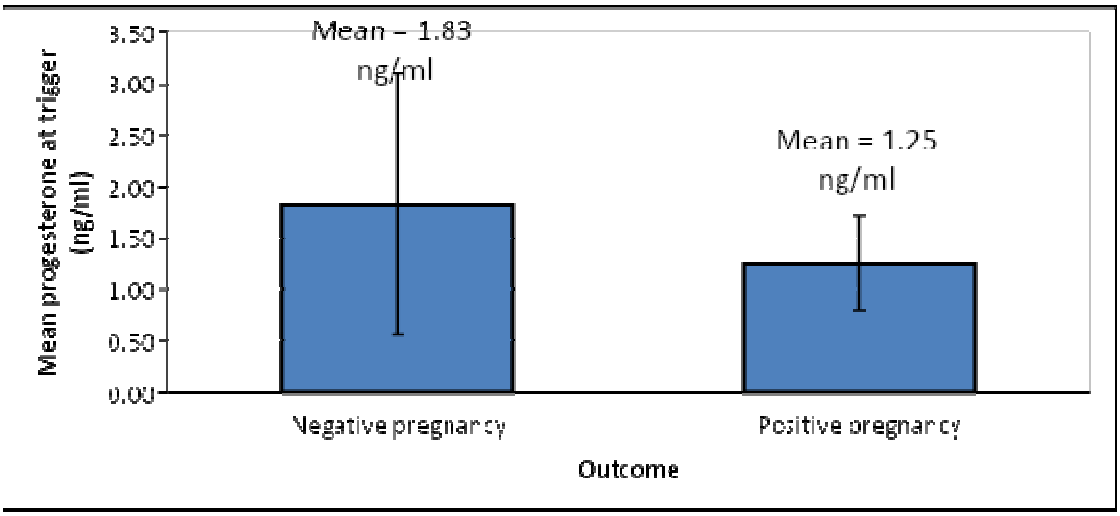

Figure 1. Mean serum progesterone at trigger in pregnant and non-pregnant women

Table 5. Pregnancy outcome in all sub fertile women according to outcome characteristic at trigger day

Characteristics	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P* †
Number of follicles ≥15mm - ≥18mm	13.00 ±3.84	13.69 ±4.64	0.405 NS
E_2 (pg/ml)	1904.70 ±1440.30	2318.50 ±703.73	0.108 NS
Progesterone(ng/ml)	1.83 ±1.27	1.25 ±0.45	0.010 S
LH (mIu/ml)	3.36 ±1.33	3.34 ±1.28	0.939 NS
$P4/E_2$	1.14 ±0.91	0.56 ±0.27	<0.001 HS
Endometrial thickness (mm) in CD12-CD13	10.47 ±1.48	10.79 ±1.15	0.256 NS

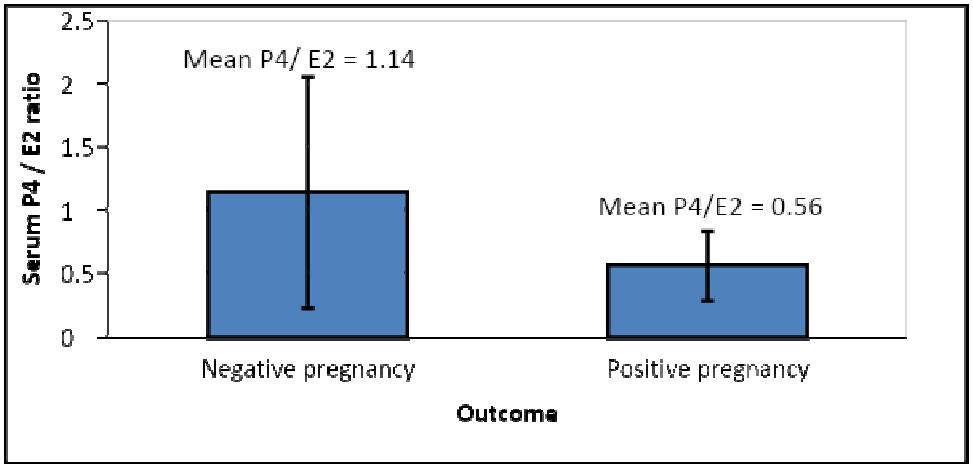

Figure 2. Mean serum P4 /E2 ratio in pregnant and non-pregnant women.

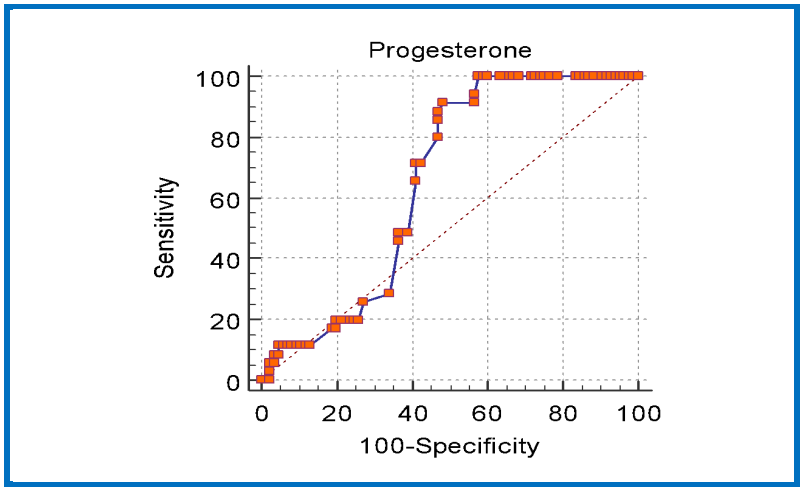

Figure 3. Receiver operator characteristic (ROC) curve analysis to find the best serum progesterone cutoff value at trigger that predicts positive pregnancy outcome

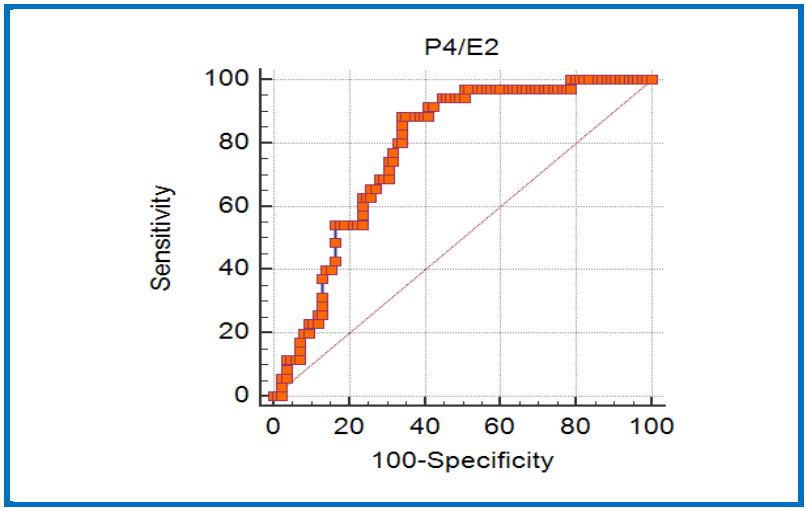

Figure 4. Receiver operator characteristic (ROC) curve analysis to find the best P4/E2 cutoff value that predicts positive pregnancy outcome.

Table 6. Comparison of validity of serum progesterone at trigger and P4/E_2 ratio at trigger in predicting positive pregnancy outcome

Characteristics	Serum progesterone at trigger	P4/E_2 ratio
Cutoff value	≤ 1.69	≤ 0.744
Sensitivity	91.4 %	88.6 %
Specificity	51.8 %	65.9 %
AUC	0.654	0.781
95 % CI	0.561 to 0.738	0.696 to 0.851
Accuracy	65.4 %	78.1 %
P-value	0.002 HS	< 0.001 HS
Difference in AUC	0.127	
Difference in accuracy	12.7 %	
P-value for comparison	0.002 HS	

Table 7. Pregnancy outcome according to oocytes characteristics and fertilization parameters

Characteristic	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P* †
Number of oocytes pickup	8.84 ±3.91	9.14 ±4.21	0.702 NS
MI	1.22 ±1.39	1.34 ±1.19	0.657 NS
MII	6.08 ±3.00	6.49 ±3.16	0.511 NS
GV	1.00 ±1.52	0.86 ±0.91	0.605 NS
Atretic	0.59 ±0.97	0.46 ±1.29	0.543 NS
Maturation rate	70.35 ±18.97	73.00 ±17.45	0.477 NS
Fertilization percent	83.00 ±21.91	90.91 ±15.28	0.054 NS
Two-pro-number	4.99 ±2.75	5.91 ±2.96	0.104 NS
Cleavage rate	84.23 ±21.03	87.41 ±18.82	0.439 NS

Table 8. Pregnancy outcome according to embryo characteristics

Characteristic	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P*
Total number of embryos, Mean ± SD	4.02 ±2.32	5.09 ±2.77	0.033 S
Embryo transfer Day			
Day2, *n* (%)	15 (68.2 %)	7 (31.8 %)	0.904 NS
Day3, *n* (%)	66 (71.7 %)	26 (28.3 %)	
Day4, *n* (%)	3 (75.0 %)	1 (25.0 %)	
Day5, *n* (%)	1 (50.0 %)	1 (50.0 %)	
Grade I, Mean ± SD	2.28 ±2.02	3.00 ±2.13	0.084 NS
Grade II, Mean ± SD	1.65 ±1.86	1.71 ±1.60	0.852 NS
Grade III, Mean ± SD	0.14 ±0.64	0.34 ±1.03	0.195 NS

Table 9. Clinical characteristics of fresh and frozen embryos in association with pregnancy outcome in all sub-fertile women

Characteristic	Negative pregnancy *n* = 85	Positive pregnancy *n* = 35	*P* †
Total number of fresh embryos	2.91 ±1.01	3.26 ±0.89	0.075 NS
Fresh embryo Grade I	1.87 ±1.26	2.40 ±1.22	0.037 S
Fresh embryo Grade II	0.95 ±1.15	0.80 ±1.13	0.508 NS
Fresh embryo Grade III	0.13 ±0.63	0.11 ±0.40	0.896 NS
Total Frozen embryo	0.65 ±1.68	0.89 ±1.49	0.467 NS
Frozen embryo Grade1	0.34 ±1.15	0.46 ±1.15	0.616 NS
Frozen embryo Grade2	0.32 ±1.26	0.26 ±0.70	0.789 NS
Frozen embryo Grade3	----	0.09 ±0.51	----

Table 10. Pregnancy outcome in association with luteal phase supportive medications in all sub-fertile women

Characteristic	Negative pregnancy *n* = 85		Positive pregnancy *n* = 35		*P*
Luteal phase progesterone, *n* (%)	83	97.6	35	100.0	1.000 € NS
Luteal phase Estrogen, *n* (%)	1	1.2	0	0.0	1.000 € NS
Cyclogest suppositories 400mg, *n* (%)	67	78.8	23	65.7	0.132 ¥ NS
Duphaston 10mg tab, *n* (%)	85	100.0	35	100.0	---
Primolut depot injection, *n* (%) 250mg / 1ml ampoule	70	82.4	32	91.4	0.206 ¥ NS
Crinone gel 8%, *n* (%) 90mg	18	21.2	12	34.3	0.132 ¥ NS

drugs as luteal phase support between women success to get pregnancy and women failed to get pregnancy.

DISCUSSION

The relationship between serum progesterone level and P_4/E_2 ratio on day of hCG trigger and positive pregnancy outcome in ICSI cycles of both long agonist and antagonist programs with fresh embryo transferred considers as a good and sensitive predictors with high accuracy. There were no significant difference (P >0.05) in mean of (age, body mass index, duration of infertility and proportional distribution of primary and secondary infertility) between the two group, these observation was incomparable to the study by (Al-Obaidi, Mahdi and Alwasiti, 2018). Show that there are negative effect of age and BMI on oocytes number and quality. also no significant difference in mean baseline serum hormonal levels as well as endometrial thickness in cycle day 12-13 of preceding cycles between both groups (*P* >0.05), the result of this study eliminated any variations that may affect the results of the measured biochemical parameters, similar conclusion by few studies for example, about the effect of the endogenous LH environment that pre-ovulatory progesterone level increase in ICSI cycles is not correlated to serum LH levels (Al-Azemi *et.al*. 2012). Also there was no significant difference in CD2-3 Characteristics of ICSI cycles between the two groups (*P*>0.05), moreover, stimulation characteristics and characteristics of trigger day outcome disclosed no significant difference between both groups (P>0.05), with exception of serum progesterone level on day of hCG trigger was significantly lower (*P*=0.010) in pregnant women than in non-pregnant women and this was comparable to the studies by (Al-Zemi *et.al.* 2012), clinical pregnancy rate decrease when serum progesterone levels are elevated. On the other hand, the ratio P_4/E_2 was lower with highly significance (P<0.001) in pregnant women when compared to women who failed to get pregnancy and this results is in agreement with studies by (Abuelghar et al., 2013) there explanation was, that the endometrial advancement is not controlled by progesterone levels alone but by corresponding levels of both estrogen and progesterone in circulation, so both serum progesterone levels and P_4/E_2 ratio were considered as a novel marker to pregnancy outcome, for that reason, it was suggested that a cut off value may exist for both serum progesterone level and P_4/E_2 ratio on day of hCG trigger which can predict positive pregnancy outcome with acceptable level of accuracy, The recent published studies by (Van, Fatemi and Blockeel, 2011). Founded this cut-off value is determine and set at 1.5 ng/ml. This cut-off is hold up by the presence of an obvious difference in the endometrial genetic expression contour, endometrial genetic expression transfer the endometrium from perceptive to acceptant and Susabitable stage and this normal physiological changes was alter in women with elevated serum progesterone level more than 1.5ng/ml on trigger day, suggesting advance endometrial maturation during the pre-ovulation period and, as a result, premature opening of receptivity window that lead to a synchronization of the crosstalk between the fresh embryo transfers and uterine endometrium which end in failure of implantation and clinical pregnancy. These differentiations seen clearly between patients with a progesterone serum concentration above and below the threshold of 1.5ng/ml (Labarta *et.al.* 2011). Some studies could not find any association between progesterone levels on hCG trigger day and pregnancy rates (Andersen *et. al.* 2011). Whereas other studies have same observation that a negative impact on cycle outcome when serum progesterone levels are increased. (Al-Zemi *et.al.* 2012) and this was comparable with results of this current study which showed negative impact on implantation percentage and biochemical and clinical pregnancy rate in long agonist and antagonist groups. Therefore receiver operator characteristic (ROC) curve analysis was conducted in this study, that the best cutoff values on day of hCG trigger according to Youden index were ≤ 1.69 ng /ml for serum progesterone and ≤

0.744 for P_4/E_2 ratio however, the P_4/E_2 ratio was more accurate significantly than serum progesterone, 78.1 % versus 65.4 %, respectively (P=0.002) .Furthermore, there was no significant correlation between pregnancy outcome and oocytes characteristics and fertilization parameters (P>0.05), but, increase in mean number of total embryos with significant difference (P=0.037) and increase in mean number of fresh embryo transfer grade1 with significant difference (P=0.033) in women who got pregnant in comparison with women with negative pregnancy and this was conflicted to results of studies by (Swati, Surbhi and Deepa 2016) that conducted no deleterious effect of elevation progesterone on embryo quality but it was comparable to results observed by (Racca *et.al.* 2018). Pre ovulatory progesterone rise will not only cause an endometrial advancement but also to affects embryo quality resulting in implantation failure and decreased pregnancy rates. The supportive medication proved to play no significant role in pregnancy outcome, this observation was comparable with publish data of (Van der Linden *et.al.* 2011) suggested no significant difference in pregnancy outcome between different progesterone regimes use as luteal phase support in ICSI cycles.

CONCLUSION

In ICSI cycles with fresh embryo transferred, serum progesterone level and P_4/E_2 ratio can be used as predictors for pregnancy outcome. Progesterone was significantly lower in pregnant women than non-pregnant one while P_4/E_2 ratio is highly significant lower in women with positive pregnancy than women failed to get pregnancy. There is also significant increase in mean total number of embryos and in mean of (grad1) fresh embryo transfer in women with positive pregnancy than women with negative pregnancy.

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