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Original article

Estrogen Supplementation to Progesterone as Luteal Phase Support in Patients Undergoing in Vitro Fertilization

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Abstract

Background: Infertility is a complex medical condition affecting a significant portion of the population. Intracytoplasmic sperm injection (ICSI) has become an established technique for addressing infertility. Objective: To evaluate the role of oral oestradiol (E2) supplementation (4mg) with progesterone in the luteal phase versus progesterone alone in the outcome of patients undergoing ICSI cycles (intracytoplasmic sperm injection). Methods: In this study, 160 patients undergoing intracytoplasmic sperm injection (ICSI) at a reproductive medicine centre in Alexandria were randomly assigned to two groups. Group A (n=80) received progesterone I.M. injections (100mg daily) and vaginal pessaries of micronized progesterone 400mg for 14 days from oocyte retrieval, continuing until 10 weeks in case of occurrence of pregnancy. Group B (n=80) received the same progesterone regimen as Group A, with additional oral estradiol valerate (4mg) from oocyte retrieval for 14 days, continuing estrogen until fetal pulsation appeared by ultrasound, and progesterone until 10 weeks in case of pregnancy. Results: There was a significant difference in the number of embryos transferred, it did not influence pregnancy outcomes. Additionally, endometrial thickness was comparable between the two groups. Pregnancy outcomes have insignificant differences between the two groups. Conclusions: To overcome the luteal phase defect in IVF cycles with the use of GnRH antagonist LPS is needed. Progesterone was approved as luteal phase support in IVF/ICSI cycles but the effect of additional estradiol to progesterone, as luteal phase support, on the pregnancy rate in women undergoing IVF/ICSI is debatable.

Keywords: Estrogen; Progesterone; Luteal Phase Support; antagonist.

Introduction

In assisted reproductive technology (ART), stimulation protocols often lead to luteal phase defects, (LPD) with reduced estrogen (E2) and progesterone (P) levels, shorter luteal phases, and suppressed gonadotropin secretion. Granulosa cell curettage during oocyte retrieval can further impair corpus luteum function, reducing progesterone and estrogen production and ultimately affecting implantation and pregnancy rates [1]. Luteal phase support (LPS) is a standard practice in ICSI-ET due to the common occurrence of defective luteal phases in stimulated ICSI cycles [2].

While estrogen plays a crucial role in earlier phases of the menstrual cycle and endometrial preparation, its role during the luteal phase and its impact on embryo implantation remains unclear. Estradiol (E2) has been found to enhance endometrial thickness and receptivity [3].

In IVF cycles, Serum estradiol levels can be decreased during progesterone-only treatment in the mid-luteal phase, potentially affecting pregnancy rates and causing luteal vaginal bleeding. Adding estradiol to progesterone in LPS can enhance the probability of pregnancy [4].

The corpus luteum produces estradiol (E2) and other hormones, suggesting a potential role for estradiol in luteal phase support. Estradiol supplementation may benefit ICSI patients, particularly after using ovarian inhibition protocols with the GnRH antagonist [5].

Despite varying findings, no consensus exists on the specific hormones, dosages, durations, or timing for luteal phase support [6]. Different forms of estradiol didn't seem to significantly impact pregnancy rates, as shown in a study using various estradiol administration routes alongside consistent vaginal progesterone use [3]. There is also no consensus on the optimal estradiol dosage for luteal phase support. While some studies have reported increased pregnancy rates with higher estradiol dosages, others have found no significant differences [7].

More research is needed to confirm the role of E2 supplementation in embryo implantation and improve outcomes in ART cycles [1].

The purpose of this study was to evaluate the role of oral oestradiol (E2) supplementation (4mg) with progesterone in the luteal phase support versus progesterone alone in the pregnancy outcome of patients undergoing ICSI cycles (intracytoplasmic sperm injection).

Patients and Methods:

Type of the study and study population:

This prospective randomized case-control study was carried out in a tertiary private referral centre for IVF and reproductive medicine in Alexandria, Egypt on 160 patients from November 2018 till the required number was fulfilled. during the study patients who lost from follow-up were excluded also patients who didn't meet inclusion criteria were excluded from the start. All patients received ICSI treatment with fresh embryo transfer using the GnRH antagonist protocol and met the inclusion criteria.

Research ethics committee: MD.1.6.2022

The inclusion criteria included women aged 18 to 38 years, with a BMI below 35, and FSH levels not exceeding 12 IU. The eligible participants were subfertile patients with indications for IVF/ICSI, including factors such as tubal issues, anovulation, male factor infertility, or unexplained infertility.

Exclusion criteria were uterine pathologies (sub mucous or intramural fibroids, uterine polyps, adhesions or Mullerian defects), history of more than two implantation failures, medical history of previous deep vein thrombosis (DVT), cardiac or respiratory problems and liver diseases, previous ovarian hyperstimulation syndrome (OHSS), and also smokers.

Methods:

All participants underwent a comprehensive history-taking process, which included collecting personal information such as name, age, duration of marriage, address, and special habits like smoking. Menstrual history was documented, encompassing details like the age of menarche, date of the last menstrual period, dysmenorrhea, menstrual disturbances, and associated symptoms. Information regarding the type of infertility (primary or secondary) and its duration, as well as the etiology of infertility (whether ovarian, tubal, male factor, combined, or unexplained), was recorded. Data on parity and mode of delivery were documented, along with the current history of chronic diseases and medication use. Past history included any previous attempts at IVF and/or ICSI, and any family history of similar conditions was also noted.

Clinical examination for inclusion and exclusion criteria: an examination of the breast for galactorrhea, vaginal examination for infection, bimanual examination for adnexal masses, endometriotic nodules, and large fibroid uterus.

Transvaginal ultrasonography was done for; assessment the antral follicle count on days (2-3) of the cycle and show endometrial thickness for exclusion of polyps, follicullometry from the 6th day of the cycle and followed up every other day till the triggering criteria were achieved (≥3 follicles reached a diameter above18 mm) which is considered mature.

Laboratory evaluation: hormonal profile; basal serum (FSH, LH, and S.E2) on days 2-3 of the cycles. Some cases needed to investigate TSH, prolactin, AMH, and CASA. A transvaginal ultrasound (TVUS), and three-dimensional(3D) ultrasound may be helpful to exclude anomalies of the cavity (septate uterus, SMF, polyps).

Protocol for Ovarian Stimulation:

Participants received a GnRH antagonist protocol for controlled ovarian hyperstimulation (COH) with randomization at the outset, following (ESHRE) guidelines (2020) favoring GnRH antagonist over agonist protocols in IVF/ICSI cycles. Ovarian stimulation began on menstrual cycle day 2 using 75-300 IU of HMG and FSH administered intramuscularly (I.M.) or subcutaneously (S.C.), adjusting the initial dose based on age, ovarian reserve, BMI, and prior COH response. Starting on the 6th day of stimulation, cetrorelix (0.25 mg Cetrotide; Merck Serono, SPA-Italy) was

administered daily via S.C. until trigger day. Follicular growth was monitored with serial transvaginal ultrasound scans, with an ovulation scan using a transvaginal ultrasound probe (TVUS) with a frequency of ≥7 MHz performed daily until criteria for trigger (≥3 follicles ≥18 mm in size) were met. Endometrial thickness was assessed at trigger day, with a thickness <8mm leading to exclusion. Triggering was achieved with HCG (10,000 IU) to induce oocyte maturation.

Oocyte retrieval took place 34-36 hours post-trigger using transvaginal ultrasound-guided follicle aspiration under general anesthesia in the lithotomy position. A needle attached to the ultrasound probe sequentially aspirated follicular contents at 120 mmHg negative aspiration pressure and collected them in test tubes for transport to the IVF lab.

Embryo transfer occurred on day 5 post-oocyte retrieval using fresh embryos loaded into a Wallace catheter. Guided by transabdominal ultrasound, the catheter was positioned 10 mm from the uterine fundus. Microscopic examination confirmed successful embryo transfer, with 1-2 embryos transferred based on quality and patient age. Any remaining viable blastocysts were cryopreserved per patient preference and consent. Before the transfer, the patient assumed a dorsal lithotomy position with a full bladder, and an ultrasound examination guided the catheter's placement into the endometrial cavity via the cervix.

Randomization Procedure for LPS:

A computer-generated random number list was created, and according to the luteal phase support protocol, the studied patients were randomized into two equal groups based on the use of E2 supplementation from the start of the protocol into 2 groups;

In Group A, the patients received progesterone I.M injections of 100mg daily with 2 vaginal pessaries of micronized progesterone 400 mg twice daily starting from the day of oocyte retrieval for 14 days till the pregnancy test is +ve and continued till 10 weeks from pregnancy test.

In Group B, the patients received progesterone I.M. injections of (100 mg daily for 14 days) with 2 vaginal pessaries of micronized progesterone 400 mg twice daily plus oral E2 supplementation (estradiol valerate, 2 mg twice daily for 14 days) started from the day of oocyte retrieval for 14 days till pregnancy test is +ve and continued estradiol till embryo pulsation appeared by ultrasound and progesterone continued till 10 weeks of pregnancy.

The oral form of estradiol was selected as it was most available in our country.

A dose of 4 mg of oral estradiol in addition to progesterone was commonly used as could be considered to reduce the miscarriage rate [8].

Assess the occurrence of pregnancy by serum quantitative B-HCG 14 days after embryo transfer, women considered pregnant if had a quantitative B-HCG test (A value above 50 IU/mL) were considered a positive pregnancy (chemical pregnancy) and considered clinically pregnant with +ve fetal heart rate by ultrasound, which examined by transvaginal ultrasound 4 weeks after

embryo transfer or 2 weeks from +ve B-HCG. It was considered a positive pregnancy (chemical pregnancy) with positive serum βhCG level with no intrauterine or extrauterine gestational sac by ultrasound and considered clinically pregnant with a +ve fetal heart rate which, examined by transvaginal ultrasound 4 weeks after embryo transfer or 2 weeks from +ve B-HCG [4]. Women who were pregnant followed up for the first trimester.

Outcomes:

The primary outcome, "Clinical pregnancy," was defined as the presence of gestational sacs with a fetal heartbeat on ultrasound 14 days after a positive pregnancy test[9]. The secondary outcomes included "Chemical pregnancy," which referred to a positive serum βhCG result without the detection of an intrauterine or extrauterine gestational sac on vaginal ultrasound [4], and "early miscarriage," defined as pregnancy loss occurring spontaneously before 12 weeks of gestation with an initially positive pregnancy test and ultrasound evidence of a gestational sac with a fetal pole [10].

Ethical consideration: This study received ethical approval from the Institutional Review Board, Obstetrics and Gynecology Department, Faculty of Medicine, Benha University. All participants provided written informed consent. The study followed the ethical principles set in the Declaration of Helsinki by the World Medical Association for research involving human beings.

Statistical analysis:

Statistical analysis was conducted using IBM Statistical Package for Social Sciences software (SPSS), 21st edition, IBM, United States. Data, initially collected and coded in Microsoft Excel 2016 for Windows, was subjected to the Kolmogorov-Smirnov test to assess distribution normality. Descriptive statistics were employed, presenting quantitative data as mean and standard deviation (mean ± SD) and qualitative data as numbers and percentages, with results displayed in tabular form. Statistical significance was defined as a p-value less than or equal to 0.05, while p-values less than 0.001 were considered highly statistically significant, and p-values exceeding 0.05 were deemed statistically insignificant. Various statistical tests were utilized, including the Chi-square test for comparing categorical variables across different groups, the Fisher's Exact test as an alternative to the Chi-Square test when cell counts in a 2x2 table were less than 5, the Student T-test for normally distributed quantitative variables when comparing two groups, the Mann Whitney test for abnormally distributed quantitative variables when comparing two groups, and the Z test for comparing proportions between two groups of qualitative data.

Results:

Table (1): Illustrated the age in group A ranged from 21 to 38 years with (mean ±SD) was (30.28± 4.77) years while in group B, the age ranged from (18 to 38) years with (mean ±SD) was (29.66± 4.95) years with no statistically significant difference between the two groups. Illustrated that the most frequent cause of infertility was male factors in group A (42.5%) while unexplained causes were

the most frequent cause in group B (40%). No statistically significant difference between the two groups regarding the cause of infertility. shows that most women in group A (67.5%) had primary infertility V.S. (66.3%) in group B. The duration of infertility in group A ranged from 7 months to 12 years with a mean duration of 4.15± 2.65 years V.S. 3.08± 2.35 in group A Duration of infertility was significantly longer in group A compared to group B while there was a non-significant difference between the two groups regarding type of infertility. Showed that the first trial (no previous ICSI trial) in 77.5% in group A V.S. 58.8% in group B. There was a significant difference while there were no significant differences between the two groups regarding the number of previous trials.

Table (2) showed the mean FSH in group A was 7.44± 2.31 mIU/ml and 7.44± 2.63 mIU/ml in group B. The mean LH in group A was 8.09± 2.31 mIU/ml and 77.76± 2.79 mIU/ml in group B. There was no statistically significant difference between the two groups regarding FSH and LH. The mean E2 in group A and group B was 19.26± 10.22 and 20.50± 8.29 respectively. There was no statistically significant difference between the two groups regarding E2.

Table (3): Illustrated a high statistically significant difference between the two groups regarding the number of embryo transfers in the 5^{th} day ($p<0.001$) while there was no statistically significant difference between the two groups regarding the number of frozen embryos ($p>0.05$).

Table (4): showed that mean endometrial thickness on the day of triggering in group A was 11.11±1.19 mm and 11.20±0.80 mm in group B. There was no statistically significant difference between the two groups regarding endometrial thickness which had been evaluated as noninvasive markers of endometrial receptivity**.**

Table (5): Illustrated the pregnancy test (β-HCG) (chemical pregnancy) was positive in 46.3% of Group A and 51.2% of Group B. There was no statistically significant difference between the two groups regarding pregnancy tests ($p>0.05$).

On the other hand, it was noticed that positive clinical pregnancy was positive in 33.8% of women in group A and 40% of women in group B. There was no statistically significant difference between the two groups regarding clinical pregnancy ($p>0.05$).

Table (6): showed that in group A 6.3% of women showed abortion, 20% of women continued pregnancy with single embryo and 7.5% of women continued pregnancy with twins. Meanwhile, in group B, 2.5% of women showed abortion, 35% of women continued pregnancy with a single embryo and 2.5% of women continued pregnancy with twins. There was no statistically significant difference between the two groups regarding follow-up in 1st trimester ($p>0.05$).

Table (1): Comparison between the two groups regarding age, Comparison between the two groups regarding the cause of infertility, Comparison between the two groups as regard to duration & type of infertility, Comparison between the two groups with regard to the number of previous trials

		Group (A) (No. = 80)		Group (B) (No. = 80)		Test value	P-value
		No.	%	No.	%		
Age groups	<18-25 years	13	16.3%	13	16.3%	X^2= 1.652	0.648
	25- <30 years	19	23.8%	26	32.5%		
	30- 35 years	31	38.8%	26	32.5%		
	> 35-38 years	17	21.3%	15	18.8%		
Age (years)	Mean± SD	30.28± 4.77		29.66± 4.95		^{Z}MWU= 0.761	0.446
	Median	30.50		30.0			
	Range	21.0 – 38.0		18.0 – 38.0			

		Group (A) (No. = 80)		Group (B) (No. = 80)		Chi-Square Test	
		No.	%	No.	%	Test value	P-value
Cause of infertility	Unexplained	27	33.8%	32	40.0%	12.26	0.056
	Male factors	34	42.5%	23	28.7%		
	Tubal Factor	15	18.8%	20	25.0%		
	Male+ tubal obstruction	3	3.8%	0	0.0%		
	PCO	1	1.3%	0	0.0%		
	PGD	0	0.0%	2	2.5%		
	Endometriosis	0	0.0%	3	3.8%		

		Group (A) (No. = 80)		Group (B) (No. = 80)		Test value	P-value
		No.	%	No.	%		
Type of infertility	Primary	54	67.5%	53	66.3%	X^2= 0.028	0.867
	Secondary	26	32.5%	27	33.8%		
Duration of infertility (years)	Mean± SD	4.15± 2.65		3.08± 2.35		Z_{MWU}= 2.53	0.011
	Median	3.0		2.0			
	Range	7 months – 12.0 years		1.0years-10.0 years			

		Group (A) (No. = 80)		Group (B) (No. = 80)		Test value	P-value
		No.	%	No.	%		
Number of previous trials	0	62	77.5%	47	58.8%	X^2= 7.06	0.029
	1	13	16.3%	27	33.8%		
	2	5	6.3%	6	7.5%		
Number of previous trials	Mean± SD	0.29± 0.58		0.49± 0.64		^{Z}MWU= 2.386	0.017
	Median	0.00		0.0			
	Range	0.0 – 2.0		0.0 - 2.0			

Table (2): Comparison between the two groups regarding basal hormonal parameters:

		Group (A) (No. = 80)	Group (B) (No. = 80)	Test value	P-value
FSH (mIU/ml)	Mean± SD	7.44± 2.31	7.44± 2.63	T= 0.001	0.999
	Median	7.65	7.20		
	Range	1.80 – 12.0	2.60 – 13.70		
LH (mIU/ml)	Mean± SD	8.09± 2.31	7.76± 2.79	T= 0.784	0.434
	Median	8.0	7.70		
	Range	2.70 – 15.0	1.0 - 17.0		
E2 (pg/ml)	Mean± SD	19.26± 10.22	20.50± 8.29	Z_{MWU}= 1.797	0.072
	Median	17.0	20.0		
	Range	8.0 – 70.0	6.50 - 45.0		

Table (3): Comparison between the two groups regarding the number of embryos transferred and the number of frozen embryos:

		Group (A) (No. = 80)		Group (B) (No. = 80)		Test value	P-value
		No.	%	No.	%		
Embryo transfer in the 5th day	1ET	25	32.1%	51	68.0%	X^2= 20.16	<0.001
	2ET	52	66.9%	24	32.0%		
Number of frozen embryos	Mean± SD	2.11 ± 2.28		1.77± 1.72		Z_{MWU}= 0.281	0.779
	Median	2.0		2.0			
	Range	0.0 – 9.0		0.0 – 7.0			

Table (4): Comparison between the two groups regarding endometrial thickness on the day of triggering:

		Group (A) (No. = 80)	Group (B) (No. = 80)	Test value	P-value
Endometrial thickness (mm)	Mean± SD	11.11± 1.19	11.20± 0.80	^{Z}MWU= 0.541	0.588
	Median	11.0	11.0		
	Range	7.90 – 14.0	8.90 - 13.20		

No statistically significant difference.

Table (5): Comparison between the two groups with regard to β-HCG (chemical pregnancy) and clinical pregnancy (primary outcomes):

		Group (A) (No. = 80)		Group (B) (No. = 80)		Test value	P-value
		No.	%	No.	%		
β-HCG (chemical pregnancy)	Negative	43	53.8%	39	48.8%	X^2= 0.400	0.527
	Positive	37	46.3%	41	51.2%		
Clinical pregnancy	Negative	53	66.3%	48	60.0%	X^2= 0.430	0.512
	Positive (cardiac pulsation)	27	33.8%	32	40.0%		

No statistically significant difference.

Table (6): Comparison between the two groups as per follow-up in 1st trimester (secondary outcomes):

		Group (A) (No. = 80)		Group (B) (No. = 80)		Test value	P-value
		No.	%	No.	%		
Follow-up at 1st trimester	No pregnancy	53	66.3%	48	60.0%	X^2= 0.430	0.512
	Abortion	5	6.3%	2	2.5%	X^2= 0.598	0.440
	Continue pregnancy with single embryo	16	20.0%	28	35.0%	X^2= 3.793	0.051
	Continue pregnancy with twin	6	7.5%	2	2.5%	X^2= 1.184	0.277

No statistically significant difference

Discussion

This prospective randomized case-control study included 160 patients seeking ICSI and reproductive medicine treatment at a tertiary referral centre in Alexandria for

ICSI, all using a fixed antagonist protocol. The patients were randomly divided into two equal groups: Group A, comprising 80 patients, received daily progesterone I.M. injections of 100mg and two vaginal pessaries of micronized progesterone 400mg twice a day, starting from the day of oocyte retrieval and continuing until 10 weeks after a positive pregnancy test. In contrast, Group B, also consisting of 80 patients, received the same progesterone regimen as Group A, along with oral estradiol (E2) supplementation (2mg twice daily) as luteal support, starting from the day of oocyte retrieval and continuing until the appearance of fetal pulsation. The choice of the antagonist protocol in this study aligned with the (ESHRE) guidelines from 2020, which recommend it over GnRH agonist protocols for the general IVF/ICSI population.

In this study, the addition of oral E2 to luteal progesterone in GnRH antagonist cycles did not yield beneficial effects on pregnancy outcomes, and both groups were comparable. The most frequent causes of infertility were male factors in the control group (42.5%), followed by unexplained infertility (33.8%) and tubal factors. In the studied group, unexplained causes were the most frequent (40%), followed by male factors (28.7%) and tubal factors, with no statistically significant difference between the two groups.

Most women in both groups had primary infertility, and while there was a significant difference in the duration of infertility, there was no significant difference in the type of infertility. The majority of patients in the control group were undergoing their first ICSI trial (77.5%), compared to 58.8% in the studied group, with a significant difference in the number of previous ICSI trials. There was no significant difference in baseline FSH, LH, and E2 levels between the two groups. Regarding ovarian stimulation outcomes, the number of embryos transferred on day five of oocyte retrieval differed significantly between the groups, with single embryo transfer in 31.1% of the progesterone-only group and 68% in the estradiol + progesterone group, while two embryos were transferred in 66.9% of the progesterone-only group and 31% in the estradiol + progesterone group. However, there was no statistically significant difference in the number of frozen embryos between the two groups, in agreement with a study conducted at 2022 [4] while in another study, **(1)** they found no significant difference in the number of embryo transfers between the progesterone and estrogen groups **[1, 4]**.

In the current study, the mean endometrial thickness on the day of oocyte triggering showed no statistically significant difference between group A (progesterone group) at 11.11±1.19 mm and group B (estradiol group) at 11.20±0.80 mm, indicating similar endometrial receptivity. Endometrial thickness, assessed by ultrasound examination, is commonly used as a marker of endometrial receptivity ($p>0.05$). However, this finding contrasts with studies conducted at 2020 and 2022 which reported a significant difference in endometrial thickness between estradiol and control groups **[1,4]**, differences in endometrial thickness between estradiol+progesterone

and progesterone-only groups, potentially may impact pregnancy outcomes[4].

In terms of pregnancy outcomes, there were no statistically significant differences between group A (progesterone group) and group B (estradiol + progesterone group) in this study. Chemical pregnancy rates were 46.3% and 51.2%, while clinical pregnancy rates were 33.8% and 40% for group A and group B, respectively. These findings align with studies conducted at 2020 and 2022, which also observed no significant differences in chemical or clinical pregnancy rates between groups receiving different hormonal regimens for luteal phase support [1,4].

It was found that the addition of oral estradiol to progesterone did not increase pregnancy probability, and Cochrane meta-analysis reported no difference in live birth/ongoing pregnancy rates between progesterone with estradiol supplementation and progesterone alone [7]. While in another study, observing a higher pregnancy rate in the group receiving estradiol with progesterone, also reported that the difference was not statistically significant [12].

Various studies have investigated the effects of adding estradiol (E2) to progesterone for luteal phase support (LPS) in IVF/ICSI cycles. **(5)** and **(13)** found no significant differences in pregnancy rates between E2 + progesterone and progesterone-only groups [5,13] At 2008, in a meta-analysis of 10 randomized controlled trials, also reported no statistically significant differences in ongoing pregnancy and implantation rates when comparing progesterone alone to progesterone plus E2 in LPS [14] A meta-analysis conducted at 2010 included nine randomized controlled trials and found no differences in various IVF outcomes between the two groups [15]. A Cochrane meta-analysis, reported at 2015 no difference in live birth/ongoing pregnancy rate (9 RCT, OR 1.12, 95% CI 0.91-1.38, 1651 women) between progesterone with estradiol supplementation and progesterone alone. [20].

In contrast to these findings, conducted a systematic review indicating that E2 supplementation significantly improved clinical pregnancy and ongoing pregnancy rates compared to progesterone-only LPS [16]. A systematic review and meta-analysis conducted at 2015, showed a higher clinical pregnancy rate with progesterone plus estrogen compared to progesterone alone in IVF cycles [17]. At 2011 and at 2009 it was reported a significantly higher pregnancy rates with E2 supplementation in addition to progesterone. Two RCTs compared different estradiol dosages alongside progesterone and found no significant differences in pregnancy rates between estradiol dosages but significant improvements in pregnancy rates with E2 + progesterone groups [18,19].

In the present study, miscarriage occurred in 6.3% of group A (progesterone only) women, 20% continued pregnancy with a single embryo, and 7.5% continued pregnancy with twins. Meanwhile, in group B, 2.5% of women showed abortion, 35% of women continued pregnancy with a single embryo and 2.5% of women continued pregnancy with twins. There was no statistically

significant difference between the two groups regarding follow-up in the 1st trimester (p>0.05)**.** In line with the study, There was no significant difference between groups in terms of miscarriage rates 2 (3.1%) and 2 (3.1%) in the study group and control group [14].

Potential limitations of this study include the limited sample size (160), and due to randomization of the sample it was noticed a significant difference between the two groups regarding the number of embryos transferred on the 5th day of retrieval with no effect on the results as there was no significant difference in pregnancy rate in both protocol in two group nor difference in miscarriage rate or multiple pregnancies. Also, the study applied to patients with antagonist protocol only.

Conclusions

To overcome the luteal phase defect in IVF cycles with use of GnRh antagonist LPS is needed. Progesterone was approved as luteal phase support in IVF/ICSI cycles but the effect of the addition of estradiol to progesterone, as luteal phase support, on the pregnancy rate in women undergoing IVF/ICSI is debatable. In the present study was found that estradiol supplementation in the luteal phase did not improve pregnancy rates significantly.

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