Comparison of Reproductive Outcomes on addition of GnRH agonist for Luteal phase Support in Antagonist IVF cycle

Omokanye LO[1], Durowade KA[2], Olatinwo AWO[3], Panti AA[4], Salaudeen AG[5], Balogun OR[6]

1.Associate Professor, department of Obstetrics and Gynaecology, College of Health Sciences, University of Ilorin, Nigeria
2.Associate Professor, department of Community Medicine, Afebabalola University. Ado-Ekiti, Nigeria.
3.Professor, department of Obstetrics and Gynaecology, College of Health Sciences, University of Ilorin, Nigeria
4.Professor, department of Obstetrics and Gynaecology, College of Health Sciences, UsmanuDanfodiyo University, Sokoto,Nigeria
5.Professor, department of Epidemiology and Community Health, College of Health Sciences, University of Ilorin, Nigeria
6. Professor, department of Obstetrics and Gynaecology, College of Health Sciences, University of Ilorin, Nigeria

Corresponding author:
Omokanye LO, department of Obstetrics and Gynaecology, College of Health Sciences, University of Ilorin, Nigeria
Email address: lukmanomokanye@gmail.com
Phone no: +2348033630497

Abstract

Background: The luteal phase supplementation was reported to be necessary in Controlled Ovarian Hyperstimulation cycles for IVF or ICSI, independently when agonists or antagonist were used for pituitary desensitization. The effectiveness of GnRH agonist in luteal phase supplementation remains controversial.

Aims and Objectives: This study aimed at comparing the clinical outcomes of addition of GnRH agonist for luteal phase support in antagonist IVF cycle.

Materials and Methods: A cross-sectional study of 150 eligible clients who underwent assisted reproduction program in two autonomous IVF centers between 1st January, 2017 and 31st December, 2020. Clients were divided into two groups; (I) Antagonist stimulation protocol with progesterone and oestradiol valerate and (II) Antagonist Protocol with a single bolus of buserelin in addition to progesterone and oestradiol valerate for luteal phase support. The primary outcome was live birth rates while the secondary outcomes were clinical pregnancy, miscarriage rates and the safety for OHSS.

Results: There were no statistically significant differences between the number of oocyte received, fertilized, embryos availability for transfer, duration of infertility, duration of FSH usage, endometrial thickness and OHSS risk between the groups ($p>0.05$). The clinical pregnancy and live birth rates were more in group II while the miscarriage rate was lower compared to group I. The differences were statistically significant ($p<0.005$).

Conclusion: From this study, buserelin addition to the luteal phase of antagonist cycles appears to improve pregnancy outcomes with no associated increase in OHSS risk. Further multi- centered studies with larger sample sizes are required to validate these findings.

Keywords: Comparison, Antagonist protocol, GnRH- agonist, luteal phase.

Introduction

Luteal phase support (LPS) is an integral part of assisted reproduction treatment (ART). Defective luteal phase in assisted reproduction cycles has been attributed to adverse effects of controlled ovarian stimulation, suppression of the pituitary luteinizing hormone (LH) release by gonadotropin releasing hormone (GnRH) analogs, and to depletion of granulosa cells due to follicle aspiration. [1] Controlled ovarian stimulation has been shown to advance endometrial maturation thus disrupting the delicate mechanism of embryo-endometrium interaction. [2]

It has been long recognized that supporting the luteal phase with progesterone or human chorionic gonadotrophin (hCG) is associated with higher pregnancy and delivery rates. [3] The initial agent of choice to support the luteal phase has been hCG, however, due to an increased risk of Ovarian Hyperstimulation Syndrome, it has been largely replaced by progesterone. Luteal phase support exclusively with progesterone might not always be sufficient to promote implantation, and other approaches can be attempted. [4, 5, 6]

Recently, the co-administration of a single dose GnRH agonist in the mid-luteal phase was reported to significantly increase implantation and live birth rates in women undergoing intracytoplasmic sperm injection (ICSI) and embryo transfer (ET). [5] It has been suggested that GnRH agonist may act both through an indirect stimulus to corpora lutea by gonadotropin discharge from pituitary gland, leading to a stimulus to corpora lutea, and via a direct effect on endometrium and embryo. [7] The data on donor cycles, obtained when agonist was added in the luteal phase in the absence of corpora lutea, suggested that the effect might be due to a direct effect, on the endometrium or the embryo. [4, 6]

The effects of GnRH agonist administration in the luteal phase has been the focus of different studies. Lemay et al. [8] suggested that GnRH agonist can act as a luteolytic agent due to desensitization of GnRH receptors. Furthermore, Dubourdieu et al. [9] and Herman et al. [10] reported deterioration of corpus luteum function with the administration of GnRH agonist. However, attempts to interrupt pregnancy or even prevent implantation have not been impressive. [11] On the other hand, a series of studies show that the inadvertent administration of GnRH-a in the luteal phase does not compromise the continuity of pregnancy, and suggested, to the contrary, a possible favorable effect on implantation. [12, 13, 14] Recently, different studies analyzing single [15, 16] or multiple administrations [17, 18] of medication have, in fact, suggested a beneficial effect in supporting the luteal phase.

We therefore seek to assess the impact of addition of GnRH agonist for luteal phase support on pregnancy outcomes in antagonist protocol IVF cycle in two independent IVF centers as compared to the conventional Progesterol and oestradiol valerate.

Materials and Methods

This study is a cross-sectional study of 150 eligible clients that underwent assisted conception program (IVF/ICSI) at two independent IVF centers between January 1, 2017 and December 31, 2020. Clients were recruited using a purposive sampling method and informed consent was obtained from selected clients. The case records and the theatre records of the clients were retrieved from IVF centers using a prepared proforma. Data extracted from the case notes are; biosocial variables, types of stimulation protocols, dose of FSH needed, duration of stimulation, risk for OHSS, and pregnancy outcomes.

All clients had a body mass index (calculated as weight in kilograms divided by the square of height in meters) [19] ranging between 18 and 30 with a mean of 24 ± 4 Kg/m^2. All had antagonist protocol for Controlled Ovarian Hyperstimulation. Their infertility evaluation results were normal. Furthermore, all had oral contraceptive pills for menstrual cycle

synchronization and pre-cervical assessment (trial/dummy transfer) on day 2/3 of menses prior to commencement of stimulation.[20]

Stimulation protocol

All patients were treated with the gonadotropin-releasing hormone (GnRH) antagonist protocol. They were commenced on 150 IU (2 vials) of recombinant follicle-stimulating hormone (FSH) Gonal F (Gonal F[R]; Merck Serono, Germany) and 75 IU (1 vial) highly purified FSH (Folliculin ®; Barrat pharmaceutical, India) on day 3 of menstrual cycle for 11–14 days. Transvaginal ultrasonographic scan was done at interval from day 5/6 of stimulation to determine the numbers, size of follicles, and endometrial thickness. Subcutaneous 2.5 mg daily GnRH antagonist (Cetrotide ®; Merck Serono, Germany) was administered whenever the follicles have grown to 14 mm size usually around day 6/7 of stimulation and was continued till the day of trigger to prevent premature luteinizing hormone surge. Eighty-three microgram (2000 IU) of recombinant human Chorionic gonadotrophin (hCG: Ovitrelle; Merck Serono, Germany) and 0.25 mg of buserelin (Supricur ®; Aventis Pharm, West Malling, UK) were administered subcutaneously for trigger whenever two or more follicles have grown to 18 mm or more. [20]

Oocyte retrieval

Oocyte retrieval was done at 35.5 h of hCG injection by transvaginal needle aspiration under ultrasound guidance using general anaesthesia (Propofol and Midazolam). [21] The aspirate in conical test tubes each containing 1 ml of Global Collect ® was then transferred immediately to the laboratory for oocyte screening and pickup. Oocytes were rinsed in oocyte handling medium (Global collect ®; LifeGlobal, Europe) and also rinsed and cultured in a center well dish (Oosafe, Denmark) of 1 ml fertilization media (Global total for fertilization, LifeGlobal, Europe) overlaid with 1 ml paraffin oil (LifeGlobal, Europe) which is then incubated for 4–6 h prior insemination.[20]

Sperm preparation

All semen samples were allowed to liquefy at room temperature for 30 min. Semen analysis was performed according to the World Health Organization (WHO) guidelines (WHO, 2010).[22] The density gradient centrifugation method of semen preparation was used. All Grad 90% and 45% (LifeGlobal, Europe) were overlayed with a maximum of 2 ml raw semen and centrifuged at 300 g for 20 min. The pellets were resuspended into Falcon tube containing 5 ml All Grad wash (LifeGlobal, Europe) and centrifuged again at 300 g for 10 min.

Insemination procedure

Postwash spermatozoa at a final concentration of $150{,}000 \times 10^6$/ml were added to the oocytes and incubated for 16–18 h. A maximum of eight oocytes were inseminated in a center well dish (Oosafe, Denmark) of global total for fertilization (LifeGlobal, Europe) overlaid with paraffin oil (LifeGlobal, Europe). Intracytoplasmic sperm injection was performed on metaphase II oocyte if indicated

Assessment of fertilization

Denudation of cumulus cells was performed by the use of glass denuding pipettes (Vitromed GmbH, Germany). The oocytes were then rinsed four times in a single-step medium (Global total, Life Global, Europe) and assessed for fertilization before further culture in global total (Life Global, Europe). The oocytes were considered fertilized when two distinct pronuclei and two polar bodies were visible.

Embryo culture

A maximum of six fertilized oocytes were cultured in a center well dish with 1 ml single-step media (Global total, Life Global, Europe) under oil (Paraffin oil; Life Global, Europe) at 37°C in a humidified atmosphere of 5% O_2 in air for day 3 or day 5.

Embryo grading

Assessment of cleavage stage embryos and grading was done on postretrieval day 3, based on the number of blastomeres, symmetry (evenness of blastomere size), and the degree of fragmentation using the Society for Assisted Reproductive Technology grading system.[23] Assessment of blastocyst and grading was also done postretrieval day 5, based on the expansion, inner cell mass, and Trophectoderm according to Gardner et al. [24]

Embryo transfer

The best quality blastocyst and expanded blastocyst were transferred on day 5 for all the groups. ET was done under transabdominal ultrasound guidance, and the transfer catheters were checked to ensure that all the embryos were transferred. In case of retained embryo (s), the embryo (s) were reloaded in a new transfer catheter and transferred immediately. The number of embryo transferred was individualized, 2 or 3 in most cases. All ET were performed with a soft catheter (Kitazato, Spain). [9]

Luteal phase support

Luteal phase support was conducted with progesterone (400 mg twice daily [cyclogest pessaries®; Cox, Brarnstaple, UK] and Intramuscular 100 mg twice weekly [Gestone®; Ferring, pharmaceutical, Mumbai, Maharashtra, India]) [9] and Oestradiol valerate 4mg daily [oestrafert ®; Mark Pharmaceutical; Gujarat, India] for group (I) while addition of a single bolus of subcutaneous 0.25 mg of buserelin (Supricure®; Aventis Pharm, West Malling, UK) was administered one week oocyte retrieval in Group (II)

Pregnancy test

Serum pregnancy test was carried out 2 weeks after ET and subsequently transvaginal ultrasound at 6th week for detection of gestational sac and/or viability of the fetus.

Statistical analysis

Statistical analysis was done using IBM SPSS (Statistical Package for Social Sciences) Version 20. Categorical data were expressed as numbers and percentages, while numerical data were expressed as a mean and standard deviation. Associations of categorical variables were tested using Chi-square test, while statistical significance was set at $P \leq 0.05$. Results were presented in table

Results

A total of one hundred and fifty (150) normoresponder clients were enrolled for the study. Clients' mean age and their spouses were 32.8 ± 4.0 and 37 ± 4.3 years respectively. Majority (98%) were Para 3 and below. Most (60.7%) had primary infertility. Their mean duration of infertility was 4.7 ± 2.9 years with the majority (95.3%) having experienced more than a year duration of infertility [Table 1]. All had antagonist protocol for Controlled Ovarian Hyperstimulation. The mean number of oocytes retrieved, fertilized, embryos available for transfer, duration of FSH use, ampoules of FSH and endometrial thickness were 11.2 ± 5.1, 7.3 ± 3.2, 4.9 ± 2.3, 13.6 ± 1.9 and 8.8 ± 2.0 respectively. The overall clinical pregnancy, miscarriage, OHSS and live birth rate were 45.3%, 13.3%, 12% and 32% respectively. Among whom were 8 triplets and 22 twins' births. [Table 2].

Table 3 shows the association between luteal phase support and pregnancy outcomes. The

clinical pregnancy rate in group II (60.3%) was higher than 39.7% in group I, live birth rate in group II (48%) was also higher than group I (16%), while the miscarriage rate was more in group I (20%) compared with group II (6.6%), the differences were statistically significant ($P < 0.05$). Conversely, the risk for OHSS was found not to be statistically significant between the two groups. There were no statistically significant differences between the number of oocytes received, fertilized, embryos availability for transfer, duration of infertility, duration of FSH usage, number of FSH ampoules, endometrial thickness and OHSS risk between the groups ($p>0.05$)

Discussion

The use of GnRH agonists to enhance embryo implantation has a relatively long history. As in many other cases of important scientific innovation, the concept of luteal phase support with a GnRH agonist was born of fortuitous observational findings rather than a clearly defined scientific project. [25] This study aimed at comparing the effectiveness of addition of GnRH agonist for luteal phase supplementation in antagonist IVF cycles. The primary outcome was live birth rates while the secondary outcomes were clinical pregnancy and miscarriage rates and the safety for OHSS respectively.

In this study, there were no statistically significant differences in the of number oocyte retrieved, fertilized and available embryos for transfer between the groups. This is in keeping with the findings of Isik et al [26] in a similar study which reported significantly higher rates of implantation and pregnancy rates in favor of GnRH agonist luteal phase support group. The clinical pregnancy and live birth rates were significantly higher in the GnRH agonist luteal phase group while the miscarriage rate is significantly lower. This is in consonance with the reports from previous studies [5 12-14, 16, 26] which documented a significant improvement in implantation, clinical pregnancy rates and live birth rates in GnRH agonist luteal support group. The beneficial effects of the GnRH agonist may be attributed to a direct effect on the embryo or to an effect on endometrium mediated by luteinizing hormone (LH), in accordance with previous observations on the effects of LH activity on endometrial receptivity, independent of ovarian function. [4] However,further studies also have shown a beneficial effect ofGnRH agonists on embryo implantation in ovarian stimulation cycles, particularly in those using a GnRH antagonist protocol. [5, 27] This informed the basis of adoption of antagonist protocol for Controlled Ovarian Hyperstimulation in this study.

On the contrary, other studies reported a significant reduction in implantation and ongoing pregnancy rates in luteal GnRH agonist group as compared with placebo. [8-10] However, clinical pregnancy rates were similar in the GnRH agonist and placebo groups. This may be related to the luteolytic effects of GnRH agonist due to desensitization of GnRH receptors resulting in deterioration of corpus lutea functions. [8-10, 28]

Although the safety of GnRH agonist in luteal phase is still at experimental phase, however there was no reported increase in embryonic or fetal malformations related to this treatment since its routine use after embryo transfer, which supports the safety of using GnRH agonists. [6,12-18] This is similar to the findings from our series.

Ovarian Hyperstimulation Syndrome (OHSS) which a potentially life-threatening iatrogenic complication of Controlled Ovarian Hyperstimulation during assisted reproductive therapy (ART). This study reported no significant increase in OHSS risk between the two groups despite addition of GnRH agonist for luteal phase supplementation in group II, thus affirming its safety.

Conclusion

Findings from this study demonstrate that the luteal-phase single-dose GnRH-a administration is effective in increasing pregnancy outcome in antagonist IVF cycle devoid of increase in OHSS risk. Further multi- centered studies with larger sample sizes are required before evidence-based recommendation can be provided.

Conflict of interest: Nil

Financial support: None

References

1. B. Ata, K. Yakin, B. Balaban, B. Urman, GnRH agonist protocol administration in the luteal phase in ICSI–ET cycles stimulated with the long GnRH agonist-protocol: a randomized, controlled double blind study. Hum Reprod. 2008; 23: 668–673
2. Fauser BC, Devroey P. Reproductive biology and IVF: ovarian stimulation and luteal phase consequences. Trends Endocrinol Metab. 2003; 14: 236-242.
3. Daya S, Gunby J. Luteal phase support in assisted reproduction cycles, Cochrane Database Syst Rev, 2004 CD004830
4. Tesarik J, Hazout A, Mendoza C. Enhancement of embryo developmental potential by a single administration of GnRH agonist at the time of implantation. Hum Reprod. 2004;19:1176–80.
5. Tesarik J, Hazout A, Mendoza C. Beneficial effect of luteal-phase GnRH agonist administration on embryo implantation after ICSI in both GnRH agonist- and antagonist-treated ovarian stimulation cycles. Hum Reprod. 2006; 21:2572–9.
6. Oliveira JB, Baruffi R, Petersen CG, Mauri AL, Cavagna M, Franco JG Jr. Administration of single dose GnRH agonist in the luteal phase in ICSI cycles: a meta-analysis. Reprod Biol Endocrinol. 2010; 8:107–12.
7. Humaidan P, Van Vaerenbergh I, Bourgain C, Alsbjerg B, Blockeel C, Shuit F et al. Endometrial gene expression in the early luteal phase is impacted by mode of triggering final oocyte maturation in recFSH stimulated and GnRH antagonist co-treated IVF cycles. Hum Reprod. 2012; 27:3259–72.
8. Lemay A, Faure N, Labrie F, Fazekas AT. Gonadotroph and corpus luteum responses to two successive intranasal doses of a luteinizing hormone-releasing hormone agonist at different days after the mid-cycle luteinizing hormone surge. Fertil Steril. 1983;39:661–667.
9. Dubourdieu S, Charbonnel B, Massai MR, Marraoui J, Spitz I, Bouchard P. Suppression of corpus luteum function by the gonadotropin-releasing hormone antagonist Nal-Glu: effect of the dose and timing of human chorionic gonadotropin administration. Fertil Steril. 1991;56:440–445.
10. Herman A, Ron-El R, Golan A, Nachum H, Soffer Y, Caspi E. Impaired corpus luteum function and other undesired results of pregnancies associated with inadvertent administration of a long-acting agonist of gonadotrophin-releasing hormone. Hum Reprod. 1992;7:465–468.
11. Oliveira JB, Baruffi R, Petersen CG, Mauri AL, Cavagna M, Franco JG Jr. Administration of single-dose GnRH agonist in the luteal phase in ICSI cycles: a meta-analysis. Reprod Biol Endocrinol. 2010;8:107.
12. Papanikolaou EG, Platteau P, Albano C, Kolibianakis E, Devroey P. Achievement of pregnancy three times in the same patient during luteal GnRH agonist administration. Reprod Biomed Online. 2005;10:347–349.
13. Platteau P, Gabbe M, Talbot M, Healy D. Two consecutive pregnancies during inadvertent gonadotropin-releasing hormone agonist desensitization. Fertil Steril. 2000;73:1244–1246.

14. Tan HH, Yeong CT, Loh KE. Perinatal outcome of pregnancies after inadvertent exposure to gonadotrophin-releasing hormone analogue. Aust N Z J ObstetGynaecol. 2006;46:336–340.

15. Isik AZ, Caglar GS, Sozen E, Akarsu C, Tuncay G, Ozbicer T, Vicdan K. Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: a prospective randomized study. Reprod Biomed Online. 2009;19:472–477.

16. Razieh DF, Maryam AR, Nasim T. Beneficial effect of luteal-phase gonadotropin-releasing hormone agonist administration on implantation rate after intracytoplasmic sperm injection. Taiwan J Obstet Gynecol. 2009;48:245–248.

17. Qublan H, Amarin Z, Al-Qudah M, Diab F, Nawasreh M, Malkawi S, Balawneh M. Luteal phase support with GnRH-a improves implantation and pregnancy rates in IVF cycles with endometrium of <or = 7 mm on day of egg retrieval. Hum Fertil (Camb) 2008;11:43–47. doi: 10.1080/14647270701704768.

18. Pirard C, Donnez J, Loumaye E. GnRH agonist as luteal phase support in assisted reproduction technique cycles: results of a pilot study. Hum Reprod. 2006;21:1894–1900.

19. El Salam MAA. Obesity, an enemy of male fertility: A mini review. Oman Med J 2018; 33:3-6.

20. Omokanye LO, Olatinwo AW, Saadu LO, Biliaminu SA, Durowade KA, Panti AA. Assisted reproductive technology: Experience from a public tertiary institution in north-central Nigeria. Afr J Infertil Assist Concept 2016 ;1:23-6.

21. Omokanye, L.O., Olatinwo, A.W.O., Saadu, L.O., Biliaminu, S.A., Durowade, K.A., Panti, A.A. & Salaudeen, A.G. Assisted Reproduction Technology: Comparison of Anesthetic Techniques for Oocyte Retrieval in a Tertiary Health Facility in Ilorin, Nigeria.Afr J Infertil Assist Concept 2017; 11: 5.

22. World Health Organization. WHO Laboratory Manual for the Examination and Processing of Human Semen. 5th ed. Geneva, Switzerland: WHO Press; 2010.

23. Scholtes MW, Zeilmaker GH. A prospective, randomized study of embryo transfer results after 3 or 5days embryo culture in in vitro fertilization. Fertil Steril 1998; 65:1245-8.

24. Levron J, Shulman A, Bider D, Seidman D, Levin T, Dor J, et al. A prospective randomized study comparing day 3 with blastocyst-stage embryo transfer. Fertil Steril2002;77:1300-1.

25. Skarin G, Nillius SJ, Wide L. Failure to induce early abortion by huge doses of super active LHRH agonist in women. Contracept. 1982; 26: 457-463.

26. Isik AZ, Caglar GS, Sozen E, Akarsu C, Tuncay G, Ozbicer T, Vicdan K. Single-dose GnRH agonist administration in the luteal phase of GnRH antagonist cycles: a prospective randomized study. Reprod Biomed Online. 2009;19:472–477.

27. Pirard C, Loumaye E, Laurent P, Wyns C. Contribution to more patient-friendly ART treatment: Efficacy of continuous low-dose GnRH agonist as the only luteal support- results of a prospective, randomized comparative study. Int J Endocrinol 2015; 2015; 727569.

28. Ata B, Urman B. Single dose GnRH agonist administration in the luteal phase of assisted reproduction cycles: is the effect dependent on the type of GnRH analogue used for pituitary suppression? Reprod Biomed Online. 2010;20:165–166.

Table 1: Socio-demographic variables

Variables	Frequency	Percent (%) N=150
Age Wife (years)		
<25	1	0.7
25-34	100	66.7
≥35	49	32.6
Mean -	32.8±4.0	
Age Husband (years)		
<40	107	71.3
40-49	42	28.0
≥50	1	0.7
Mean-	37.7±4.3	
Parity		
0-3	147	98.0
>3	3	2.0
Mean		
Duration Infertility (years)		
≤1	7	4.7
>1	143	95.3
Mean-	4.7±2.9	
Type of Infertility		
Primary	91	60.7
Secondary	59	39.3

Table 2: IVF Parameters/Indices and Pregnancy outcome

Variables		Frequency	Percent (%) N=150
Number of oocyte retrieved			
<10		63	42.0
≥10		87	58.0
Mean-	11.2±5.1		
Number fertilized			
<10		117	78.0
≥10		33	22.0
Mean-	7.3±3.2		
Number of embryo			
<10		145	96.7
≥10		5	3.3
Mean	4.9±2.3		
Protocol			
Antagonist		150	100
Support			
Agonist		75	50.0
No Agonist		75	50.0
Pregnancy outcome			
Negative		82	54.7
Positive		68	45.3
Miscarriage n=68			
Yes		20	29.4
No		48	70.6
OHSS*			
No		132	88.0
Yes		18	12.0
Duration FSH (days)			
<15		107	71.3
≥15		43	28.7
Mean-	13.6±1.9		
FSH AMP			
<30		49	32.7
≥30		101	67.3
Mean-	32.3±4.8		
Endometrial Thickness			
<10		99	66.0
≥10		51	34.0
Mean-	8.8±2.0		

***Ovarian Hyper-stimulation Syndrome**

Table 3: Association between Use of support, parameters and outcomes of IVF

Variable p value	Agonist	Support (%)	No Agonist (%)	χ^2	df
Number of oocyte					
<10	30 (47.6)	33 (52.4)	0.25	1	0.741[a]
≥10	45 (51.7)	42 (48.3)			
Number Fertilized					
<10	54 (46.2)	63 (53.8)	3.15	1	0.114[a]
≥10	21 (63.6)	12 (36.4)			
Number of Embryo					
<10	72 (49.7)	73 (50.3)	0.21	1	1.000[a]
≥10	3 (60.0)	2 (40.0)			
Pregnancy outcome					
Negative	34 (41.5)	48 (58.5)	5.27	1	0.016
Positive	41 (60.3)	27 (39.7)			
Miscarriage n=68					
No	35 (72.9)	13 (27.1)	14.55	1	0.001
Yes	5 (25.0)	15 (75.0)			
Duration of Infertility					
≤1	3 (42.9)	4 (57.1)	0.15	1	1.000
>1	72 (50.4)	71 (49.6)			
OHSS					
No	67 (50.8)	65 (49.2)	0.25	1	0.802[a]
Yes	8 (44.4)	10 (55.6)			
Duration FSH					
<15	58 (54.2)	49 (45.8)	2.64	1	0.148[a]
≥15	17 (32.0)	36 (68.0)			
FSH AMP					
<30	24 (49.0)	25 (51.0)	0.03	1	1.000[a]
≥30	51 (50.5)	50 (49.5)			
Endom. Thickness					
<10	51 (51.5)	48 (48.5)	0.27	1	0.730[a]
≥10	24 (47.1)	27 (52.9)			

[a] **Fischer Exact**