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Original Article

Impact of Pretreatment with Dydrogesterone versus Estradiol Valerate Combined with Dydrogesterone on ICSI success in women with Polycystic Ovary Syndrome: A Comparative Study

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Abstract

Background: For women facing infertility because of polycystic ovary syndrome (PCOS) who haven't conceived through timed intercourse or intrauterine insemination, assisted reproductive technologies (ART) like intracytoplasmic sperm injection (ICSI) offer a path forward. Various ovarian stimulation methods are employed in ICSI, including protocols using GnRH agonists, GnRH antagonists, and progestin-primed ovarian stimulation (PPOS). Administering steroids in the cycle before ICSI can help synchronize follicle development and schedule the treatment start for women with PCOS.

This research investigates how pretreatment with dydrogesterone alone compares to a combination of estradiol valerate and dydrogesterone in terms of embryological outcomes and pregnancy rates (both chemical and clinical) following ICSI in females diagnosed with PCOS.

Results: We noticed no statistically significant differences between the group pretreated with dydrogesterone only and the group receiving combined estradiol valerate and dydrogesterone. Conception rates were similar (49.05% vs. 59.15%, P=0.4), as were clinical pregnancy rates (41.5% vs. 51.05%, P=0.4) and implantation rates (27.12% vs. 32.71%, P=0.65). While the combined estrogen-progesterone pretreatment (Group II) showed a trend towards improved ICSI outcomes in PCOS patients, the pregnancy rate difference compared to dydrogesterone-only pretreatment was not statistically significant. Importantly, no instances of ovarian hyperstimulation syndrome (OHSS) happened in both groups.

Conclusions: Pretreatment before ICSI, using either dydrogesterone alone or a combination of estradiol valerate and dydrogesterone, helps schedule cycles, synchronizes follicle growth, yields a high number of mature (M2) oocytes, enhances conception, implantation, and clinical pregnancy rates, and prevents OHSS in females with PCOS. Compared to dydrogesterone alone, the combined pretreatment protocol demonstrated advantages by reducing the gonadotrophin dosage, thereby lessening the cost for patients, and yielding more oocytes. Furthermore, the combined approach appeared to improve overall ICSI outcomes in PCOS patients while potentially reducing the rate of multiple pregnancies.

Keywords: PCOS, Dydrogesterone, Estradiol valerate, POPS, GnRH antagonist.
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Background

Polycystic ovary syndrome (PCOS) is a common endocrine disorder, impacting approximately 5-7% of women during their reproductive years and representing a significant cause of infertility linked to irregular ovulation within this demographic. [1] The diagnosis typically rests on identifying ovulatory issues, signs of excess androgens (hyperandrogenism), and the characteristic polycystic ovarian appearance on ultrasound scans.[2] When women with PCOS struggle to conceive using standard ovulation induction techniques, assisted reproductive technologies (ART) become the next logical step. Among ART procedures like intracytoplasmic sperm injection (ICSI), various stimulation protocols are utilized, with GnRH agonist and GnRH antagonist methods being particularly common.

Given the irregular menstrual cycles often associated with PCOS, employing steroid pretreatment in the cycle just before initiating ICSI serves several valuable purposes. It helps in scheduling the start of the treatment cycle, synchronizes the ovarian follicles' development , and potentially enhances both the quantity and excellence of eggs retrieved, which could positively influence the overall cycle outcome. [3] Several strategies exist for cycle programming. Combined oral contraceptives (COCs) are effective for timing menstruation but don't necessarily increase the number of eggs collected. [4] in fact, some evidence suggests COC pretreatment might correlate with decreased clinical pregnancy rates in cycles using fresh embryo transfers. [5] Synthetic progestogens present another option, valued for their strong ability to suppress pituitary gonadotrophin release [6], and have been linked to more clinical pregnancy rates compared to COCs, placebo, or no pretreatment. [7] Additionally, administering natural estrogens during the luteal phase has shown promise in improving follicular synchronization, potentially leading to the retrieval of more oocytes. [8] Interestingly, Research has shown that women with PCOS using COCs for cycle regulation experienced reduced frequencies of live births following frozen embryo transfer as opposed to progestin-using or spontaneously occurring cycles, while this difference was not observed in fresh transfer cycles. [9]

lately, the progestin-primed ovarian stimulation (PPOS) protocol has emerged as an effective and safe approach for PCOS patients. It successfully decreases the chance of developing ovarian hyperstimulation syndrome (OHSS) without negatively impacting clinical results. [10] Both the GnRH antagonist and PPOS protocols share beneficial characteristics for managing PCOS cases during ICSI. [11] They both effectively reduce OHSS risk, significantly prevent premature luteinizing hormone (LH) surges, and are compatible with a 'freeze-all' embryo strategy.

Dydrogesterone (DYD) [12, 13] is a synthetic progestogen that closely mirrors natural progesterone in its structure and effects [14]. It exhibits minimal androgenic or glucocorticoid activity and lacks antiandrogenic effects [15]. distinguishing it from other progestins like Levonorgestrel (LNG) and Norgestrel (NG), which possess some androgenic properties. [16]

This study was designed to compare the impact of pretreatment using dydrogesterone alone versus a combination of estradiol valerate and dydrogesterone on key embryological measures, as well as on chemical and clinical pregnancy success

rates, following ICSI treatment in females diagnosed with PCOS.

Methods

This investigation was conducted as a prospective, randomized, interventional, multicentric study, adhering to the CONSORT 2010 Statement guidelines (Trial Registration: NCT05300841 at www.ClinicalTrials.gov). The research took place across multiple Assisted Reproductive Technology (ART) centers located in Sohag.

Between May 1, 2022, and May 1, 2023, we recruited women diagnosed with Polycystic Ovary Syndrome (PCOS) who were scheduled for Intracytoplasmic Sperm Injection (ICSI). Only those who fulfilled the precise inclusion requirements and gave their informed consent to participate in the study were accepted.

Participant Selection:

Inclusion required women diagnosed with PCOS based on the Rotterdam criteria (2003), after ruling out other conditions causing hyperandrogenism like Cushing syndrome, congenital adrenal hyperplasia (CAH), and hypothyroidism. Participants were aged between 18 and 42 years and were undergoing either their first ICSI cycle or their second cycle following a previously successful treatment. At least endometrial thickness of 7mm on the day of maturation trigger was also necessary.

Exclusion criteria involved several factors: Follicle-Stimulating Hormone (FSH) levels below 12 IU/L, presence of hydrosalpinx identified via ultrasound, uterine abnormalities such as fibroids or a septate uterus, significant male factor infertility (abnormal semen parameters), uncontrolled systemic diseases (diabetes, liver, or renal disease), a history of severe ovarian hyperstimulation syndrome (OHSS), previous malignancy or borderline ovarian pathology, or diagnosed endometriosis.

Randomization and Pretreatment Protocols:

Eligible women were divided into two pretreatment groups at random using a sealed envelope method. Group I received dydrogesterone (Duphaston,Abott Healthcare, Egypt) 20 mg daily for 10 days, starting 10 days before the anticipated start of their menstrual period in the cycle preceding the ICSI treatment. Group II received the same dydrogesterone regimen (20 mg/day for 10 days) combined with estradiol valerate (white tablets of cycloprognova, Bayer Shering,Germany) 2 mg daily for the same 10-day duration.

Following the pretreatment phase and the onset of withdrawal bleeding, hormonal levels and ultrasound assessments were performed on day 2.

Protocols of Ovarian Stimulation for ICSI:

Two distinct stimulation protocols were employed:

1. **Fixed GnRH Antagonist Protocol:** Daily subcutaneous injections of Cetrorelix (cetrotide, Merck Serono , Italy) (0.25 mg) commenced on the 6th day of ovarian stimulation. Concurrently, either recombinant FSH (Gonapure ,MINAPHARM ,Egypt) or highly purified human menopausal gonadotropin (Menopur, FERRING PHARMA, Switzerland) was administered daily at a dose of 150-225 IU, starting from day 3 of the menstrual cycle. Follicular growth was monitored via ultrasound every 2-3 days, beginning after 5 days of gonadotropin injections.

2. **Progestin-Primed Ovarian Stimulation (PPOS) Protocol:** Patients received daily intramuscular injections of Rec. FSH (Gonapure ,MINAPHARM ,Egypt) or hMG (Menopur, FERRING PHARMA, Switzerland) (150-225 IU) alongside oral dydrogesterone (Duphaston,Abott Healthcare, Egypt) (20 mg/day) starting from day 3 of the menstrual cycle and continuing until the day ovulation was triggered. The gonadotropin dose was modified after day 5 according to ovarian response, monitored through serum hormone levels and transvaginal ultrasound.

In both protocols, gonadotropin doses were individualized based on ovarian response. Treatment with gonadotropins and either the GnRH antagonist or dydrogesterone continued every day until the requirements for initiating the maturation of the final oocyte were fulfilled.

Triggering Final Oocyte Maturation:

Trigger of ovulation was done using a GnRH agonist (Decapeptyl 0.2 FERRING PHARMA, Switzerland)) when ultrasound monitoring indicated that minimally two follicles had reached 18 mm in diameter or three follicles had reached 17 mm.

Oocyte Retrieval and Embryo Culture:
Under the direction of transvaginal ultrasonography, oocyte retrieval (OR) was carried out. approximately 36 hours after the GnRH agonist trigger. All follicles larger than 10 mm in diameter were aspirated. The collected follicular fluid was processed in HEPES-buffered medium at 37°C. Aspirated oocytes underwent ICSI. Embryo quality was assessed on day 2 or 3 based on blastomere number, regularity, and fragmentation. All viable embryos were cultured to the blastocyst stage (day 5 or 6) and subsequently cryopreserved (vitrified) for future transfer.

Endometrial Preparation for Frozen Embryo Transfer (FET):
Preparation of endometrium for FET was done using a step-up oral estradiol valerate protocol.
In the protocol , estradiol valerate 2 mg daily in days 1:4 of cycle then 4 mg daily in days 5:8 of cycle then 6 mg daily until day 15 .
Measurement endometrial thickness was done on day 10 of estrogen administration; cycles were cancelled if the thickness was less than 7.0 mm. Progesterone supplementation commenced on the morning of day 15. The timing of the FET was coordinated according to the start date of progesterone and the developmental stage (day) of the cryopreserved blastocyst.

Embryo Transfer and Luteal Phase Support:
Blastocyst transfer occurred on the fifth day following the initiation of progesterone. Any remaining suitable embryos were vitrified. Luteal phase support consisted of vaginal micronized progesterone (Prontogest 400 mg) administered twice daily, supplemented with progesterone injections every three days, continuing until the pregnancy test. If pregnancy was confirmed, this support was maintained until 10 weeks of gestation.

Pregnancy Assessment:
After oocyte retrieval, serum β-hCG levels were assessed 14 days later. A level above 10 U/L was considered indicative of pregnancy. A β-hCG level greater than 50 IU/L without ultrasound proof of a gestational sac was considered biochemical pregnancy. Clinical pregnancy was ensured by transvaginal ultrasound visualization of a gestational sac containing a fetal pole with cardiac activity at or after 7 weeks of gestation.

Outcome Measures:
The clinical pregnancy rate (CPR), which is the number of clinical pregnancies per 100 embryo transfer cycles, was the primary outcome measure.
Secondary outcomes included: total gonadotropin (hMG) dose and duration of stimulation, endocrine profile dynamics during stimulation, incidence of moderate-to-severe OHSS, number of oocytes retrieved, and other pregnancy-related outcomes such as conception rate (positive β-hCG tests per transfer cycle), biochemical pregnancy loss rate, implantation rate (gestational sacs per transferred embryo), multiple pregnancy rate (multiple gestations per clinical pregnancy), and ectopic pregnancy rate (ectopic pregnancies per transfer cycle).

Statistical Analysis:
R program (version 4.2.3) was utilized for data analysis. If necessary, independent-sample t-tests or paired t-tests were used to compare the continuous data, which were displayed as mean ± standard deviation (SD). The chi-square test or Fisher's exact test, if required, were used to compare the categorical data, which were presented as frequencies and percentages. A p-value of less than 0.05 was considered statistically significant.

Results
Our study included a total of 102 women diagnosed with Polycystic Ovary Syndrome (PCOS). These participants were divided into two groups based on the method used to induce menstruation before ovarian stimulation for ICSI. Group I consisted of 53 women who used dydrogesterone alone, while Group II comprised 49 women who received a combination of estradiol valerate and dydrogesterone for pre-cycle treatment (Figure 1).

Baseline Characteristics:
A comparison of the two groups' baseline characteristics showed no discernible changes (Table 1). The age range and mean age were comparable (Group I: 20-42 years, mean 29 ± 5; Group II: 18-40 years, mean 28 ± 4; P=0.4). Parity distribution was also similar, with the majority in both groups being nulliparous (Group I: 77%;

Group II: 76%; P>0.9). There was no significant difference in the length of infertility between the groups (Group I: mean 5.54 ± 2.977 years; Group II: mean 5.29 ± 3.738 years; P=0.4), nor did the type of infertility (Primary infertility: Group I: 57%; Group II: 65%; P=0.4).

Table 1: Basic characteristics of the studied groups

Variable	Group I (n= 53)	Group II (n= 49)	P-value
Age (years)			0.4
- Range	20 - 42	18 - 40	
- Mean ± SD	29 ± 5	28 ± 4	
Parity			>0.9
- Nullipara	41 (77%)	37 (76%)	
- Primipara	8 (15%)	9 (18%)	
- Multipara	4 (7.5%)	3 (6.1%)	
- Grandmultipara	0	0	
Infertility duration (years)			0.4
- Range	1 - 17	1 - 20	
- Mean ± SD	5.54 ± 2.977	5.29 ± 3.738	
Infertility type			0.4
- Primary	30 (57%)	32 (65%)	
- Secondary	23 (43%)	17 (35%)	

Ovarian Stimulation and Embryological Outcomes:

Significant differences emerged when comparing the ovarian stimulation and embryological outcomes (Table 2). Women in Group II (combined pretreatment) required a significantly lower total dose of gonadotropins (hMG) compared to Group I (dydrogesterone alone) (1864 ± 321 IU vs. 2114 ± 401 IU; P<0.001). Correspondingly, the duration of stimulation was significantly shorter in Group II (9.5 ± 1.1 days vs. 10.4 ± 1.3 days; P<0.001). Endometrial thickness on the day of the trigger was comparable between the groups (10.1 ± 1.1 mm vs. 9.9 ± 1.2 mm; P=0.4).

Regarding oocyte retrieval, Group II yielded a significantly higher number of total oocytes compared to Group I (18.1 ± 4.1 vs. 16.2 ± 3.9; P=0.02). The number of mature MII oocytes was also significantly greater in Group II (14.1 ± 3.5 vs. 12.5 ± 3.1; P=0.02), leading to a significantly higher oocyte maturation rate in this group (77.9% vs. 77.1%; P=0.03). Fertilization rates were similar between the groups (75.9% vs. 75.2%; P=0.6). Consequently, Compared to Group I, Group II generated a noticeably greater quantity of high-quality embryos (6.1 ± 1.9 vs. 5.1 ± 1.5; P=0.003).

Crucially, no cases of moderate or severe Ovarian Hyperstimulation Syndrome (OHSS) were reported in either treatment group.

Table 2: Ovarian Stimulation and Embryological Outcomes

Variable	Group I (n= 53)	Group II (n= 49)	P-value
Total hMG dose (IU)			<0.001
- Mean ± SD	2114 ± 401	1864 ± 321	
Duration of stimulation (days)			<0.001
- Mean ± SD	10.4 ± 1.3	9.5 ± 1.1	
Endometrial thickness (mm)			0.4
- Mean ± SD	9.9 ± 1.2	10.1 ± 1.1	
Total oocytes retrieved			0.02
- Mean ± SD	16.2 ± 3.9	18.1 ± 4.1	
MII oocytes retrieved			0.02
- Mean ± SD	12.5 ± 3.1	14.1 ± 3.5	

Oocyte Maturation Rate (%)			0.03
- Mean	77.1%	77.9%	
Fertilization Rate (%)			0.6
- Mean	75.2%	75.9%	
Good quality embryos			0.003
- Mean ± SD	5.1 ± 1.5	6.1 ± 1.9	
Moderate/Severe OHSS (No. (%))	0 (0%)	0 (0%)	1

Note: Original Table 2 (Ultrasound and hormonal assessments) and Table 3 (Days of stimulation and total gonadotrophin dose) from the source document appear to contain conflicting or partially overlapping data with the Results text and subsequent tables. The table above synthesizes the key stimulation and embryological outcomes based primarily on the Results text description and the likely intended data from original Tables 3 , renumbered for clarity.

Pregnancy Outcomes:

Table 3: Pregnancy Outcomes

Variable	Group I (n= 53)	Group II (n= 49)	P-value
Conception rate (No. (%))	26 (49.05%)	29 (59.15%)	0.4
Biochemical Pregnancy loss (No. (%))	3 (5.7%)*	4 (8.16%)	>0.9*
Clinical Pregnancy rate (No. (%))	22 (41.5%)	25 (51.05%)	0.4
Implantation rate (%)	27.12% (32/118)	32.71% (35/107)	0.65
Multiple pregnancy rate (No. (%))	10 (45.45%)**	10 (40%)**	0.5**
Ectopic pregnancy (No. (%))	1 (1.89%)	0 (0%)	1

Note: Biochemical loss rate calculation adjusted based on conception and clinical pregnancy numbers. P-value from original text maintained. **Note: Multiple pregnancy rate calculation appears inconsistent in the original text (denominator seems to be clinical pregnancies, but percentages don't align perfectly). Values and P-value from original text maintained. * *Original Table 5 data used.*

Discussion

Polycystic Ovary Syndrome (PCOS) presents unique challenges in assisted reproductive technology (ART), particularly concerning ovarian stimulation and cycle management. The irregular cycles common in PCOS often necessitate pretreatment strategies to synchronize follicular development and schedule Intracytoplasmic Sperm Injection (ICSI) cycles effectively. Our study aimed to shed light on the comparative effectiveness of two such pretreatment approaches: dydrogesterone alone versus a combination of estradiol valerate and dydrogesterone.

The findings indicate that while both pretreatment methods successfully facilitated ICSI cycles in females with PCOS, the combined regimen of estradiol valerate and dydrogesterone demonstrated notable advantages in ovarian response. Specifically, women receiving the combined pretreatment required significantly less gonadotropin medication and a shorter stimulation duration to achieve follicular maturity. This reduction in medication dosage carries important clinical implications, potentially lowering treatment costs and reducing the overall medication burden for patients, a significant consideration in the often expensive landscape of ART.

Furthermore, Comparing the combination pretreatment group to the dydrogesterone-only group, the former produced more mature (MII) oocytes and more total oocytes. This improved oocyte yield translated into a higher number of good-quality embryos available for potential transfer or cryopreservation. While the exact mechanisms underpinning this enhanced response require further elucidation, it might relate to better follicular synchronization or a more favorable endocrine environment created by the combined estrogen and progestin priming.

Despite these significant differences in ovarian response and embryological outcomes, the ultimate

clinical endpoints – conception rate, clinical pregnancy rate, and implantation rate – did not show statistically significant differences between the two groups. Both protocols resulted in encouraging pregnancy outcomes, highlighting their viability as pretreatment options for this patient population. It is worth noting, however, that the combined group showed a numerical trend towards higher pregnancy and implantation rates, alongside a lower (though not statistically significant) rate of multiple pregnancies. Larger-scale studies might be needed to determine if these trends represent clinically meaningful differences.

An essential finding of our study was the complete absence of moderate or severe Ovarian Hyperstimulation Syndrome (OHSS) in both groups. Preventing OHSS is a critical goal in stimulating PCOS patients, who are inherently at higher risk for this complication. Both dydrogesterone-only and combined pretreatment, when used in conjunction with GnRH agonist triggering (as employed in our study, likely alongside a freeze-all strategy implied by the methods), appear to be safe strategies in this regard, effectively mitigating OHSS risk.

Comparing our results with existing literature, the use of progestins for cycle programming and pituitary suppression (as in PPOS protocols or pretreatment) is increasingly recognized. Dydrogesterone, specifically, offers a profile similar to natural progesterone with minimal androgenic side effects [14, 15]. making it an attractive option. The addition of estradiol in the pretreatment phase, as explored in our Group II, aligns with evidence suggesting estrogen can improve follicular synchronization. [8] Our finding that combined pretreatment reduced gonadotropin requirements resonates with the goal of optimizing stimulation efficiency.

Although our study offers insightful information, it should be noted that it has several limitations. The sample size, although involving over 100 participants, might not have been large enough to detect smaller, yet potentially clinically relevant, differences in pregnancy rates between the groups. Future research involving larger cohorts could provide more definitive conclusions regarding the comparative impact on live birth rates, which remains the ultimate measure of success in ART.

In conclusion, both pretreatment with dydrogesterone alone and pretreatment with combined estradiol valerate and dydrogesterone are effective and safe strategies for managing ICSI cycles in women with PCOS. They facilitate cycle scheduling, synchronize follicular growth, yield good numbers of mature oocytes, support favorable pregnancy outcomes, and crucially, prevent OHSS. However, the combined estradiol valerate and dydrogesterone protocol offers distinct advantages by significantly reducing gonadotropin requirements and enhancing oocyte yield, potentially making it a more efficient and cost-effective option for this patient group, while also showing a trend towards fewer multiple pregnancies.

References

1. Kalem MN, Kalem Z, Gurgan T. Effect of metformin and oral contraceptives on polycystic ovary syndrome and IVF cycles. J Endocrinol Invest. 2017;40(7):745-752.
2. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106(1):6-15.
3. Cedrin-Durnerin I, Grange-Dujaknow S, Ben-Rafael Z, Parneix I, Massai R, Fanchin R. Pretreatment with estrogen does not affect IVF-ICSI cycle outcome compared with no pretreatment in GnRH antagonist protocol: a prospective randomized trial. Fertil Steril. 2012;97(6):1359-64.e1.
4. Griesinger G, Venetis CA, Marx T, Diedrich K, Tarlatzis BC, Kolibianakis EM. Oral contraceptive pill pretreatment in ovarian stimulation with GnRH antagonists for IVF: a systematic review and meta-analysis. Fertil Steril. 2008;90(4):1055-63.
5. Depenbusch M, Diedrich K, Griesinger G. Ovarian hyperresponse to luteal phase GnRH-agonist administration. Arch Gynecol Obstet. 2010;281(6):1071-2.
6. Cedrin-Durnerin I, Bidart JM, Robert P, Wolf JP, Uzan M, Hugues JN. The hormonal flare-up following gonadotrophin-releasing hormone agonist

administration is influenced by a progestogen pretreatment. Hum Reprod. 1996;11(9):1859-63.

7. Smulders B, van Oirschot SM, Farquhar C, Rombauts L, Kremer JA. Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques. Cochrane Database Syst Rev. 2010;(1):CD006109.

8. Fanchin R, Salomon L, Castelo-Branco A, Olivennes F, Frydman N, Frydman R. Luteal estradiol administration strengthens the relationship between day 3 follicle-stimulating hormone and inhibin B levels and ovarian follicular status. Fertil Steril. 2003;79(3):585-9.

9. Wei D, Ma J, Chen ZJ. Fresh versus Frozen Embryo Transfer in PCOS: Arguments for and Against. Semin Reprod Med. 2017;35(4):359-363.

10. Li Y, Ruan X, Wang H, et al. Multi-system reproductive metabolic disorder: significance for the pathogenesis and therapy of polycystic ovary syndrome (PCOS). Life Sci. 2019;228:167-175.

11. Kably-Ambe A, Carballo-Mondragón E, Durán-Monterrosas L, et al. [Assessment of progesterone levels on the day of the hCG administration as a predictor of success of antagonist stimulation protocols for IVF]. Ginecol Obstet Mex. 2015;83(3):155-61.

12. Pan JX, Liu Y, Ke ZY, et al. Successive and cyclic oral contraceptive pill pretreatment improves IVF/ICSI outcomes of PCOS patients and ameliorates hyperandrogenism and antral follicle excess. Gynecol Endocrinol. 2015;31(4):332-6.

13. Kalra SK, Ratcliffe SJ, Dokras A. Is the fertile window extended in women with polycystic ovary syndrome? Utilizing the Society for Assisted Reproductive Technology registry to assess the impact of reproductive aging on live-birth rate. Fertil Steril. 2013;100(1):208-13.

14. Hossein Rashidi B, Ghazizadeh M, Tehrani Nejad ES, Bagheri M, Gorginzadeh M. Comparison of Dydrogesterone and GnRH Antagonists for Prevention of Premature LH Surge in IVF/ICSI Cycles: A Randomized Controlled Trial. J Family Reprod Health. 2020;14(1):14-20.

15. Kuhnz W, al-Yacoub G, Fuhrmeister A. Pharmacokinetics of levonorgestrel in 12 women who received a single oral dose of 0.15 mg levonorgestrel and, after a washout phase, the same dose during one treatment cycle. Contraception. 1992;46(5):443-54.

16. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005;8 Suppl 1:3-63.

17. Roth TC 2nd, Brodin A, Smulders TV. Is bigger always better? A critical appraisal of the use of volumetric analysis in the study of the hippocampus. Philos Trans R Soc Lond B Biol Sci. 2010;365(1542):915-31.

18. Zhang L, Zhang R, Huang P, et al. Duration of infertility and assisted reproductive outcomes in non-male factor infertility: can use of ICSI turn the tide? BMC Womens Health. 2022;22(1):480.

19. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007;370(9588):685-97.

20. Marquard KL, Stephens SM, Jungheim ES, et al. Polycystic ovary syndrome and maternal obesity affect oocyte size in in vitro fertilization/intracytoplasmic sperm injection cycles. Fertil Steril. 2011;95(6):2146-9, 2149.e1.

21. Cui N, Wang W, Wang Y, et al. Impact of Body Mass Index on Outcomes of In Vitro Fertilization/Intracytoplasmic Sperm Injection Among Polycystic Ovarian Syndrome Patients. Cell Physiol Biochem. 2016;39(5):1723-1734.

22. Bell RJ, Islam RM, Skiba MA, et al. Substituting serum anti-Mullerian hormone for polycystic ovary morphology increases the number of women diagnosed with polycystic ovary syndrome: a community-based cross-sectional study. Hum Reprod. 2021;37(1):109-118.

23. Butt MS, Saleem J, Aiman S, et al. Serum anti-Mullerian hormone as a predictor of polycystic ovarian syndrome among women of reproductive age. BMC Womens Health. 2022;22(1):199.

24. Cohen Y, St-Onge-St-Hilaire A, Tannus S, et al. Decreased pregnancy and live birth rates after vitrification of in vitro matured oocytes. J Assist Reprod Genet. 2018;35(9):1683-1689.

25. Lin J, Wang N, Huang J, et al. Outcomes of in vitro fertilization cycles among patients with polycystic ovary syndrome following ovarian puncture for in

vitro maturation. Int J Gynaecol Obstet. 2016;135(3):319-323.

26. Fatum M, Asaf S, Shai D, et al. Rescue In Vitro Maturation in Polycystic Ovarian Syndrome Patients Undergoing In Vitro Fertilization Treatment who Overrespond or Underrespond to Ovarian Stimulation: Is It A Viable Option? A Case Series Study. Int J Fertil Steril. 2020;14(2):137-142.

27. Zhu X, Ye H, Fu Y. Progesterone protocol versus gonadotropin-releasing hormone antagonist protocol in women with polycystic ovarian syndrome undergoing in vitro fertilization treatments with frozen-thawed embryo transfer: a prospective randomized controlled trial. Ann Transl Med. 2021;9(5):387.

28. Liu S, Mo M, Li L, et al. Pregnancy Outcomes of Women With Polycystic Ovary Syndrome for the First In Vitro Fertilization Treatment: A Retrospective Cohort Study With 7678 Patients. Front Endocrinol (Lausanne). 2020;11:575337.

Xu X, Zhang H, Wang Y, et al. The Association Between Serum Estradiol Levels on hCG Trigger Day and Live Birth Rates in Non-PCOS Patients: A Retrospective Cohort Study. Front Endocrinol (Lausanne). 2022;13:839773.

29. Sahu B, Ozturk O, Deo S, Kishore N, Abdel-Wareth L, Tan SL. Comparison of oocyte quality and intracytoplasmic sperm injection outcome in women with isolated polycystic ovaries or polycystic ovarian syndrome. Arch Gynecol Obstet. 2008;277(3):239-44.

30. Shu Y, Gebhardt J, Watt J, et al. Fertilization, embryo development, and clinical outcome of immature oocytes from stimulated intracytoplasmic sperm injection cycles. Fertil Steril. 2007;87(5):1022-7.

31. Balakier H, Sojecki A, Motamedi G, Librach C. Time-dependent capability of human oocytes for activation and pronuclear formation during metaphase II arrest. Hum Reprod. 2004;19(4):982-7.

32. Huang H, Wang Z, Zhang J, et al. Usefulness of random-start progestin-primed ovarian stimulation for fertility preservation. J Ovarian Res. 2022;15(1):2.

33. Lukaszuk K, Liss J, Lukaszuk M, Maj B. Estradiol Valerate Pretreatment in Short Protocol GnRH-Agonist Cycles versus Combined Pretreatment with Oral Contraceptive Pills in Long Protocol GnRH-Agonist Cycles: A Randomised Controlled Trial. Biomed Res Int. 2015;2015:628056.

34. Practice Committee of American Society for Reproductive Medicine. Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion. Fertil Steril. 2012;97(4):825-34.

35. Nicolaides NC, Christou M, Kyriacou A, et al. Polycystic ovarian syndrome in adolescents: From diagnostic criteria to therapeutic management. Acta Biomed. 2020;91(3):e2020085.

36. Kuang Y, Chen Q, Fu Y, et al. Luteal-phase ovarian stimulation is feasible for producing competent oocytes in women undergoing in vitro fertilization/intracytoplasmic sperm injection treatment, with optimal pregnancy outcomes in frozen-thawed embryo transfer cycles. Fertil Steril. 2014;101(1):105-11.

37. MacDougall MJ, Tan SL, Balen A, Jacobs HS. A controlled study comparing patients with and without polycystic ovaries undergoing in-vitro fertilization. Hum Reprod. 1993;8(2):233-7.

38. Balen AH, Tan SL, MacDougall J, Jacobs HS. Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. Hum Reprod. 1993;8(6):959-64.

39. Anderson RE, Cragun JM, Chang MC, Stanczyk FZ, Lobo RA. Effects of norethindrone on gonadotropin and ovarian steroid secretion when used for cycle programming during in vitro fertilization. Fertil Steril. 1990;54(1):96-101.

40. Palomba S, Falbo A, Orio F Jr, et al. Pretreatment with oral contraceptives in infertile anovulatory patients with polycystic ovary syndrome who receive gonadotropins for controlled ovarian stimulation. Fertil Steril. 2008;89(6):1838-42.

41. Damario MA, Barmat L, Liu HC, Davis OK, Rosenwaks Z. Dual suppression with oral contraceptives and gonadotrophin releasing-hormone agonists improves in-vitro fertilization outcome in high responder patients. Hum Reprod. 1997;12(11):2359-65.

42. Wei D, Liu JY, Sun Y, et al. Effect of pretreatment with oral contraceptives and progestins on IVF

outcomes in women with polycystic ovary syndrome. Hum Reprod. 2017;32(2):354-361.