Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article ISSN: 2059-4828

Subcutaneous progesterone (Prolutex)® for luteal phase support in cycles of in vitro fertilization–embryo transfer- A retrospective cohort study

Ali Hibshi, Amani Aldriweesh, Bahjat Saeed, Serdar Coskun and Khalid Awartani*

Reproductive Medicine, Department of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Centre Riyadh, Kingdom of Saudi Arabia

Abstract

Background: The requirement of luteal phase support in in vitro fertilization cycles is necessary. However, the route and the dose of progesterone is still debated. Recently a water-soluble injectable progesterone complex became available for subcutaneous administration. The purpose of this study was to see the effect of the water-soluble injectable progesterone complex (Prolutex)® in luteal phase support during in vitro fertilization – embryo transfer cycles in Saudi population.

Methods: A retrospective cohort study, including the women who underwent IVF-ET treatment at KFSH & RC IVF unit from June 2017 to December 2017. The pregnancy rate in patients who received subcutaneous progesterone supplementation for luteal phase support after IVF-ET cycles were compared to the patients who received intravaginal Cyclogest.

Results: A total of 447 patients underwent IVF treatment during the study period between two groups. There were 167 in Prolutex and 280 in Cyclogest groups. Live birth rates in patients who received Prolutex and Cyclogest were similar.

Conclusion: Prolutex is safe and effective in supporting the luteal phase in IVF patients.

Abbreviation: IVF-ET: In Vitro fertilization-Embryo transfer, KFSH & RC: King Faisal Specialist Hospital and Research Centre, IVF: In Vitro fertilization, LPS: Luteal Phase Support, COS: Controlled Ovarian Stimulation, LH: Luteinizing Hormone, P: Progesterone, hCG: Human Chorionic Gonadotropin, GnRH: Gonadotropin Releasing Hormone, ART: Assisted Reproductive Technology, IM: Intramuscular, SC: Subcutaneous, OPU: Ovum Pick Up, PGT: Pre-Implantation Genetic Testing, CD: Cycle Day, TV: Transvaginal, hMG: Human Menopausal Gonadotropin, U/S: Ultrasound.

Background

The requirement for luteal phase support (LPS) in stimulated IVF cycles is well established, however, drug choice, route of administration and duration of use are still debated [1]. The pulsatile secretion of Luteinizing Hormone (LH), by the anterior pituitary is disrupted during controlled ovarian stimulation (COS) [2] It was suggested that both the use of gonadotropin releasing hormone analogues to prevent the LH surge and aspiration of granulosa cells during the oocyte retrieval may impair the ability of the corpus luteum to produce sufficient progesterone [3]. Endometrium needs to be supported exogenously which can be achieved by progesterone (P), human chorionic gonadotropin (hCG) or gonadotropin releasing hormone (GnRH) agonists [3]. American Society for Reproductive Medicine (ASRM) Position Statement asserts that "based on available data, progesterone supplementation in IVF cycles yields significantly higher pregnancy rates compared with placebo or no treatment and lower risks for ovarian hyper stimulation syndrome compared with supplementation with hCG [4]. Moreover, a recent Cochrane meta-analysis discussing luteal phase support for ART cycles confirmed that P has a significantly positive effect on clinical pregnancy, live birth and ongoing pregnancy rates [5,6]. Progesterone supplementation is available in multiple preparations, including intramuscular, vaginal, oral or in a newly developed subcutaneous preparation. In our population, we have assessed patient preference in the past and found out that 46 % of the patient preferred the injectable route [7]. Although patients satisfaction and pregnancy rates were similar between vaginal and intramuscular progesterone supplementation in the study, almost half of the patients have concern using vaginal preparation due to cultural reasons [7]. Parenteral P in the form of IM injections in oil gained and retained popularity because of its consistent and measurable serum levels. Patients and clinicians continue to favor a medication that they could be certain was "being absorbed" although the significant clinical drawbacks of these IM injections, which include pain, low patient acceptance, and the logistics associated with IM injections, which cannot be self-administered, and complications such as irritation, and occasionally sterile abscess formation [8-10]. Patient preference for vaginal over IM administration, as found by Levine and later Yanushpolsky et al., is clearly related to the pain and inconvenience associated with IM injections, which are difficult to self-administer and are painful, even when the injection is performed by a health care professional [11,12]. Contemporary IVF, however, relies

***Correspondence to:** Khalid Awartani, Reproductive Medicine, Department of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Centre Riyadh, Kingdom of Saudi Arabia, E-mail: kawartani@kfshrc.edu.sa

Key words: *luteal phase support, in vitro fertilization, embryo transfer, prolutex, cyclogest*

Received: May 13, 2020; **Accepted:** June 02, 2020; **Published:** June 08, 2020

otherwise almost entirely on SC injections for agonist, antagonist, and gonadotropin therapy, and women feel confident and comfortable in self-administering these injections. Some women are reluctant to use medications that require vaginal insertion and are concerned about the leakage associated with gels and pessaries. Data from different sources showed that vaginal route is not free of side effects [13,14]. Recently, a water-soluble injectable progesterone complex has been developed for subcutaneous administration [15]. It has been shown that the bioavailability of Prolutex (IBSA, Lamone-Switzerland) administered SC is equivalent to the IM oil preparation, even though the absorption is definitely more rapid [16]. Although IM P in oil and SC (Prolutex)® result in higher serum levels than vaginal administration, levels in the endometrium are actually lower [17]. However, the endometrial levels obtained with 25 mg/d and 50 mg/d were sufficient to induce a correct endometrial decidualization [17]. This new product may therefore be a good alternative for these patients. Since there is a problem with the availability of intramuscular progesterone supplementation, we have started using subcutaneous progesterone since June 2017 and the aim is to report our early experience using SC P.

Material and methods

Study design and ethics approval

This retrospective cohort study approved by KFSH&RC institutional review board included women who underwent IVF-ET treatment at KFSH&RC IVF unit from June 2017 to December 2017. A total of 447 patients had completed a fresh IVF-ET cycles in this period. Healthy Saudi women between 18 and 45 years of age, with a history of infertility or genetic disease requiring IVF or Pre-Implantation Genetic Testing (PGT) and a normal uterine cavity were included. Outcomes were compared in patients who received (Prolutex) ® to other patients in the same study period who received Cyclogest (L.D. Collin, Barnstaple, UK). Of those patients, 280 received Cyclogest and 167 received Prolutex. In both groups, P luteal phase support started on the day one post OPU and continued until a negative pregnancy test was confirmed, pregnancy loss occurred, or up to 10 weeks gestation was achieved (ongoing pregnancy). During their second visit after 2 weeks post ET, pregnancy test was done. If not pregnant, treatment was stopped. If positive, a repeat serum pregnancy test was performed after 2 days and 7 days. At about 3 weeks after a positive serum pregnancy test, a pregnancy ultrasound was performed.

Treatment protocol

All patients started treatment cycle at follicular phase between cycle day (CD) 2 to CD 5 according to the plan of the treating physician, GnRH agonist long protocol, GnRH agonist short protocol or GnRH antagonist protocol without oral contraceptive. In the GnRH agonist long protocol, one dose of Lupron depot 3.75 mg injection (AbbVie Limited, New Zealand) is administered IM during the follicular phase between CD 2 and CD 5 then a follow up appointment was given after 19 to 23 days to conduct a baseline ultrasound. At baseline, documentation of the down-regulation of the pituitary and ovaries was confirmed by endometrial lining <5 mm and no evidence of ovarian cysts on the transvaginal (TV) ultrasound. Ovarian cysts were defined as ovarian follicles with a mean diameter ≥ 15 mm. After documentation of adequate down-regulation of the pituitary/ovarian axis, gonadotropin treatment was started with the use of human menopausal gonadotropin (hMG) (Menogon; Ferring Pharmaceuticals, Parsippany, NJ) or recombinant FSH (Gonal F, Merck Pharmaceuticals, Whitehouse Station, NJ, USA). In GnRH short protocol, patient started Buserelin 0.4 mg SC daily from the day of gonadotropin start. In fixed GnRH antagonist protocol, Ganirelix (Merck Pharmaceuticals, Whitehouse Station, NJ, USA) 0.25 mg SC started on day 7 of stimulation. In flexible GnRH antagonist protocol, Ganirelix started whenever the dominant follicle reaches to 14 mm size. All women received at least one vial of gonadotropin daily during the period of COH. For most patients, the daily dose was between 150 IU to 300 IU based on their ovarian reserve or their response to previous stimulation. Type of gonadotropin either Menogon or Gonal F were chosen based on preference of the treating physician. Ovulation was triggered by administration of 5000 IU or 10,000 IU hCG (IBSA, Switzerland) when three or more follicles had reached a diameter of 17 mm or greater. Oocytes were retrieved 36 h later by using single lumen needle. Eggs were inseminated by conventional IVF or injected by intracytoplasmic sperm injection (ICSI) as appropriate. Oocytes from patients with tubal factor or without fertilization failure from previous IVF cycles were inseminated by IVF. Patients with unexplained infertility with more than 6 oocytes were split between IVF and ICSI. In case the number of oocytes less than six and in the rest of the cases, ICSI was performed. A maximum of two cleavage stage or two blastocyst stage embryos were transferred on either post retrieval day 3 or days 5, depending on the quality and quantity of embryos available. P for LPS started on day one post OPU and continued until a negative pregnancy test confirmed, pregnancy loss occurred, or until up to 10 weeks of gestation achieved (ongoing pregnancy). About 2 weeks after embryo transfer, a serum pregnancy test was performed to document pregnancy. If not pregnant, treatment was stopped. If positive, a repeat serum pregnancy test was performed after 2 days and 7 days. Approximately 3 weeks after a positive serum pregnancy test, a pregnancy ultrasound was performed. All data is recorded prospectively in our database. Pregnancy rate defined as patient having pregnancy test positive. Clinical pregnancy is defined as the presence of one or more gestational sacs with positive fetal heartbeat detected on ultrasound scan performed 5 weeks after embryo transfer. Pre-clinical pregnancy loss defined as either dropping HCG titer before ultrasound time, or non-viable pregnancy at 7 weeks ultrasound scan.

Statistical analysis

Data were analyzed using SPSS version 23 software. Two-tailed t-test was used for parametric data, Mann-Whitney test for non-parametric data and Chi-squared test for binomial data. A p value of <0.05 was considered statistically significant.

Results

A total of 447 patients completed a fresh IVF-ET treatment cycle during the study period. Of those, 280 received Cyclogest and 167 received Prolutex. Patients characteristics were compared between two groups according to the age, BMI, number of previous cycles, antral follicle count (AFC), indication for treatment and the causes of infertility. The two groups were similar in age, BMI, the number of previous cycles and the indication for the treatment (Table 1). However, the Cyclogest group had significantly higher AFC compared to the Prolutex group. In terms of causes of infertility, the Cyclogest group also had significantly higher number of male factor infertility and the Prolutex group had significantly more unexplained infertility patients (Table 1).

The cycle characteristics were also compared between the Prolutex and Cyclogest groups according to duration of stimulation in days, total doses of stimulation drugs, endometrial thickness at day of HCG, stimulation protocols, number of oocytes retrieved, number of ICSI, split ICSI, conventional IVF cycles, fertilization rate, number of transferred embryos, number of available embryos, number of good

quality embryos and day of embryo transfer. There were no significant differences between the two groups except Prolutex group had more day 5 transfers compared to Cyclogest group (Table 2).

The pregnancy, clinical pregnancy and live birth rates were similar in patients who received Prolutex and Cyclogest for luteal phase support after IVF-ET cycles (Table 3).

Moreover, there is no significant difference in terms of pregnancy and clinical pregnancy rates between Prolutex and Cyclogest when analyzed according to BMI, days of embryo transfer and causes of infertility (Table 4).

Discussion

This study is the first in our population to check the effect of Prolutex, a new water-soluble SC P for LPS in IVF and ICSI treatment cycles compared with vaginal P Cyclogest. Prolutex was found to have a similar live birth rate compared to Cyclogest vaginal P as LPS following embryo transfer. In our unit, patients are given the choice to select between Prolutex and Cyclogest since similar efficacy has been demonstrated in earlier randomized controlled trials [1,18]. A further meta-analysis of phase III trials also demonstrated no significant difference in clinical outcomes between two routes, SC and

Table 1. Patient characteristics

Criteria		Mean Standard Deviation (Prolutex) n = 167	Mean Standard Deviation (Cyclogest) n = 280	P-Value
Age		31.9 ± 4.6	32.5 ± 5	0.2
BMI		28.8 ± 5.4	28.6 ± 5.3	0.6
No. of previous cycles		2.4 ± 1.7	2.7 ± 1.8	0.08
AFC mean		20.8	24	0.03
Indication for treatment	**Infertility**	144 (86.2%)	226 (80.7%)	0.2
	PGT	23 (13.8%)	54 (19.3%)	0.2
Causes of Infertility	**Male**	51 (35.4%)	116 (51.3%)	0.003
	Tubal	5 (3.5%)	19 (8.4%)	0.08
	PCOS	11 (7.6%)	19 (8.4%)	0.08
	Endometriosis	3 (2.1%)	2 (0.9%)	0.8
	Anovulation	0	2 (0.9%)	0.5
	Combined	30 (20.8%)	28 (12.3%)	0.4
	Unexplained	44 (30.6%)	40 (17.8%)	0.005

Table 2. Cycle characteristics

		Prolutex n = 167	Cyclogest n = 280	P-Value
	Duration of stimulation in days	11.8 ± 2.6	12.3 ± 2.7	0.08
	Total doses of gonadotropin (IU)	3845 ± 2225	3803 ± 2341	0.8
	Endometrial thickness at day of HCG (mm)	10.23 ± 0.34	10.29 ± 0.23	0.43
Stimulation protocol	**Antagonist**	49 (29.3%)	92 (32.9%)	0.46
	Long	109 (65.3%)	170 (60.7%)	0.36
	Short	9 (5.4%)	18 (6.4%)	0.69
Insemination type	**ICSI**	144 (86.2%)	225 (80.4%)	0.1
	Split ICSI	17 (10.2%)	36 (12.9%)	0.5
	Conventional IVF	6 (3.6%)	19 (6.7%)	0.2
	No. of oocyte retrieved	12 ± 6.9	12 ± 7.1	0.7
	Fertilization rate (per retrieved oocytes)	51.2 ± 18	49 ± 2	0.2
	No. of embryo transferred	1.8 ± 0.4	1.88 ± 0.35	0.35
	No. of available embryos	701	1114	0.2
	No. of good quality embryos	346 (49.4 %)	532 (47.8%)	0.5
Day of embryo transfer	**Day 3**	93 (55.7%)	184 (65.7%)	0.04
	Day 5	74 (44.3%)	96 (34.3%)	0.04

Table 3. Pregnancy outcome

	Prolutex	Cyclogest	P value
Number of cycles performed	167	280	
Pregnancy rate	66 (39.5%)	90 (32%)	0.12
Clinical pregnancy	44 (26.3%)	74 (26.4%)	1
Live birth	41 (24.5)	59 (21.1%)	0.4

Table 4. Comparison of clinical pregnancy rates between Prolutex and Cyclogest groups according to the stimulation protocols, BMI, day of transfer and causes of infertility

		Prolutex n = 167	Cyclogest n = 280	P value
BMI < 30	N	101	167	
	Pregnancy rate	36 (35.6 %)	52 (31.1 %)	0.5
	Clinical Pregnancy	26 (25.7%)	40 (23.9 %)	0.7
BMI 30	N	66	113	
	Pregnancy rate	30 (45.4 %)	38 (33.6%)	0.17
	Clinical Pregnancy	19 (28.8%)	32 (28.3 %)	0.8
Day 3	N	93	184	
	Pregnancy rate	29 (31.2%)	44 (23.9%)	0.25
	Clinical Pregnancy	19 (20.4%)	39 (21.2%)	1
Day 5	N	74	96	
	Pregnancy rate	37 (50%)	46 (47.9%)	0.88
	Clinical Pregnancy	25 (33.8%)	35 (36.5%)	0.75
Male factor	N	51	116	
	Pregnancy rate	16 (31.3%)	38 (32.8%)	1
	Clinical Pregnancy	12 (23.5%)	27 (23.3%)	1
Unexplained infertility	N	44	40	
	Pregnancy rate	17 (38.6%)	12 (30%)	0.5
	Clinical Pregnancy	10 (22.7%)	12 (30%)	0.47

vaginal [19]. The clinical pregnancy rates in two RCTs were 27.4% in Lockwood et al. and 41.6 % in Baker et al. studies [1,18]. In our study, the clinical pregnancy rate (26.3%) in Prolutex group is comparable to Lockwood et al., study. The ongoing pregnancy and live birth rates reported in Baker et al. is 10% higher than those reported by Lockwood et al [1,18]. Nonetheless, both studies demonstrated non inferiority of subcutaneous to vaginal progesterone [1,18]. This consistency is reassuring given that similar results could be obtained in different patient populations. Baker et al. study was conducted in United States of America (USA) while Lockwood et al., study was in Europe [1,18]. The higher ART success rates in USA have been the subject of earlier debates [20]. Approach to ovarian stimulation and likely other factors between the USA and Europe could explain such difference. Women treated in the USA tend to produce more embryos to choose from and have higher number of embryos transferred, inevitably resulting in a high incidence of multiple births [21]. The trend in the USA in the recent years for single embryo transfer has been increased and the rate of multiple birth is declining [21].

There were earlier reports showing the difference in the bioavailability between obese and non-obese patients following SC injection of some medications [22]. Therefore, we compared the pregnancy rates in women with BMI less than 30 to BMI more than 30 and found the rates were similar between Cyclogest and Prolutex. The current study is retrospective in nature and there were statistical differences in the AFC mean, the number of male or unexplained infertility and the number of day 3 and 5 embryo transfer between two groups which required further comparison to eliminate whether similar pregnancy rates were related to such differences.

The Cyclogest group had significantly more AFC compared to Prolutex group. However, this was not translated into more oocytes retrieved between the two groups. In the meta-analysis of Doblinger et al. the number of oocytes has been reported to be significant predictor of the outcome [19]. Since the number of oocytes were the same between both groups in our study, we do not expect to have impact of higher AFC in Cyclogest group in the outcome. To further rule out the effect of differences in the number of male and unexplained infertility and the number of day 3 and 5 embryo transfer between two groups, we compared the pregnancy rates for each parameter. There was no difference in pregnancy and clinical pregnancy rates between Cyclogest and Prolutex when compared to different days of embryo transfers and causes of infertility as shown in Table 4. Our patients in both groups continued LPS until 10 weeks of pregnancy. Similarly, worldwide LPS is continued until 10 to12 weeks of gestation in 66.5% of cycles although the evidence base that P may be withdrawn on the day of positive pregnancy test or the demonstration of fetal heart beat without impact on the miscarriage rate [23-25]. Since similar efficacy has been demonstrated between SC and vaginal route in our and earlier studies [1,18]. A reasonable approach is to consider providing women the choice to choose the route. In our population, although the vaginal route has been consistently shown to have similar results to injectable route, the selection of SC route was made by a good number of patients 37.4%, which is similar to earlier study with IM P [7]. Preference of the injectable route in our population despite possible minor pain and discomfort at or post administration may be due to cultural sensitivity regarding use of vaginal route. The limitation of our study is being retrospective in nature.

Conclusion

The present study provides evidence that Prolutex is safe and effective in supporting the luteal phase in IVF patients. The option of administering P SC for LPS in ART will broaden the spectrum of available treatments, an advantage for women needing sustained LPS or disliking vaginal treatments for cultural, personal, or medical reasons [26].

Declarations

Ethical approval and consent to participate

A retrospective cohort study approved by KFSH&RC institutional review board, included women who underwent IVF-ET treatment at KFSH&RC IVF unit from June 2017 to December 2017 and had subcutaneous progesterone for LPS that started on the day one post ovum pick up (OPU). RAC#2181101. The consent to participate is not applicable.

Consent for publication

Not applicable.

Availability of data and material

It is attached as Excel document.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

This study was designed and Finalized by all Authors. Amani Aldriweesh and Bahjat Saeed acquired the data, Ali Hibshi wrote the manuscript. Khaled Awrtani performed the statistical analysis and interpreted the data, and Serdar Coskun critically revised the manuscript.

References

1. Lockwood G, Griesinger G, Cometti B (2014) Subcutaneous progesterone versus vaginal progesterone gel for luteal phase support in in vitro fertilization: a non-inferiority randomized controlled study. *Fertil Steril* 101: 112-119. [Crossref]

2. de Ziegler D, Ayoubi JM, Frydman R, Fanchin R (2018) Luteal phase support in assisted reproductive technologies: from here to there. *Fertil Steril* 109: 57-58. [Crossref]

3. Daya S (2009) Luteal support: progestogens for pregnancy protection. *Maturitas* 65 Suppl 1: S29-S34. [Crossref]

4. ASRM Practice Committee (2008) Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. ASRM practice committee position statement. *Fertil Steril* 90: S150-S153. [Crossref]

5. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M (2011) Luteal phase support for assisted reproduction cycles. *Cochrane Database Syst Rev* CD009154. [Crossref]

6. Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin (2008) Practice Committee of American Society for Reproductive Medicine in collaboration with Society for Reproductive Endocrinology and Infertility. *Fertil Steril* 90(5 Suppl): S150-S153. [Crossref]

7. Zaman AM, Coskun S, Alsanie AA, Awartani KA (2017) Intramuscular progesterone (Gestone) versus vaginal progesterone suppository (Cyclogest) for luteal phase support in cycles of in vitro fertilization–embryo transfer: patient preference and drug efficacy. *Fertil Res Pract* 3: 17. [Crossref]

8. Tavaniotou A, Smitz J, Bourgain C, Devroey P (2000) Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. *Hum Reprod Update* 6: 139-148.

9. Propst AM, Hill JA, Ginsburg ES, Hurwitz S, Politch J, et al. (2001) A randomized study comparing Crinone 8% and intramuscular progesterone supplementation in in vitro fertilization-embryo transfer cycles. *Fertil Steril* 76: 1144–1149.

10. Costabile L, Gerli S, Manna C, Rossetti D, Di Renzo GC, et al. (2001) Aprospective randomized study comparing intramuscular progesterone and 17alpha-hydroxyprogesterone caproate in patients undergoing in vitro fertilization-embryo transfer cycles. *Fertil Steril* 76: 394-396. [Crossref]

11. Levine H (2000) Luteal support in IVF using the novel vaginal progesterone gel Crinone 8%: results of an open-label trial in 1184 women from 16 US centers. *Fertil Steril* 74: 836-837. [Crossref]

12. Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M (2010) Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective randomized study. *Fertil Steril* 94: 2596-2599.

13. Donders GG, Van Bulck B, Caudron J, Londers L, Vereecken A, et al. (2000) Relationship of bacterial vaginosis and mycoplasmas to the risk of spontaneous abortion. *Am J Obstet Gynecol* 183: 431-437. [Crossref]

14. Flynn CA, Helwig AL, Meurer LN (1999) Bacterial vaginosis in pregnancy and the risk of prematurity: a meta-analysis. *J Fam Pract* 48: 885-892. [Crossref]

15. Zoppetti G, Puppini N, Pizzutti M (2007) Water soluble progesterone–hydroxypropyl-β-cyclodextrin complex for injectable formulations. *J Incl Phenom Macrocycl Chem* 57: 283-288.

16. Sator M, Radicioni M, Cometti B, Loprete L, Leuratti C, et al. (2013) Pharmacokinetics and safety profile of a novel progesterone aqueous formulation administered by the s.c. route. *Gynecol Endocrinol* 29: 205-208. [Crossref]

17. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, et al. (2000) Direct transport of progesterone from vagina to uterus. *Obstet Gynecol* 95: 403-406. [Crossref]

18. Baker VL, Jones CA, Doody K, Foulk R, Yee B, et al. (2014) A randomized, controlled trial comparing the efficacy and safety of aqueous subcutaneous progesterone with vaginal progesterone for luteal phase support of in vitro fertilization. *Human Reprod* 29: 2212-2220. [Crossref]

19. Doblinger J, Cometti B, Trevisan S, Griesinger G (2016) Subcutaneous progesterone is effective and safe for luteal phase support in IVF: An individual patient data meta-analysis of the phase III trials. *PLoS One* 11: e0151388. [Crossref]

20. HI Abdalla (2010) Are US results for assisted reproduction better than the rest? Is it a question of competence or policies? *Reprod BioMed Online* 21: 624-630.

21. Toner JP, Coddington CC, Doody K, Voorhis BV, Seifer DB, et al. (2016) Society for assisted reproductive technology and assisted reproductive technology in the united states: a 2016 update. *Fertil Steril* 106: 541-546.

22. Chan CC, Hung-Yu E, Chan MM, Tang OS, Lau EY, et al. (2003) Bioavailability of hCG after intramuscular or subcutaneous injection in obese and non-obese women. *Human Reprod* 18: 2294-2297,

23. Nyboe AA, Popovic-Todorovic B, Schmidt KT, Loft A, Lindhard A, et al. (2002) Progesterone supplementation during early gestations after IVF or ICSI has no effect on the delivery rates: a randomized controlled trial. *Hum Reprod* 17: 357-361.

24. Liu XR, Mu HQ, Shi Q, Xiao XQ, Qi HB (2012) The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a meta-analysis. *Reprod Biol Endocrinol* 10: 107-114. [Crossref]

25. Aboulghar MA, Amin YM, Al-Inany HG, Aboulghar MM, Mourad LM, et al. (2008) Prospective randomized study comparing luteal phase support for ICSI patients up to the first ultrasound compared with an additional three weeks. *Hum Reprod* 23: 857-862. [Crossref]

26. Engmann L, Benadiva C (2012) Agonist trigger: what is the best approach? Agonist trigger with aggressive luteal support. *Fertil Steril* 97: 531-533. [Crossref]