Journal of Clinical Obstetrics, Gynecology & Infertility

Case Report
Published: 22 Jul, 2023

Successful IVF Outcome Using Modified Luteal Phase Support with Multi-Dose GnRh Agonist in a Case of Resistant Infertile PCOS – Case Report and Review of Literature

Rohitha C, Reeta M, Monika S and Monika R*

Department of Obstetrics & Gynecology, All India Institute of Medical Sciences, India

Abstract

Objective: Infertile polycystic ovarian syndrome women are challenging to manage and severe form hinders their response to any forms of therapy. Owing to its multifactorial cause, multiple approach-based therapy helps to curb each etiological factor in different ways helping the woman holistically. This case report aims to discuss the levels of management in a case of resistant PCOS.

Case Report: We present a case of severe form of lean PCOS woman in which timed multiple approaches resulted in a successful ongoing pregnancy.

Conclusion: Modified luteal phase support with multiple GnRh agonist therapy may be considered useful in PCOS women where there is risk of OHSS, agonist trigger and freezable embryos are not available.

Keywords: Agonist trigger; Clomiphene resistance; Fresh embryo transfer; GnRH luteal phase support; IVF; PCOS

Introduction

Polycystic ovarian syndrome affects 8% to 13% of reproductive age women and is the most common cause of anovulatory infertility. It is characterized by oligo-anovulation, clinical and/or biochemical hyperandrogenism and polycystic ovarian morphology [1]. Chronic anovulation and poor oocyte quality are the main cause of infertility in PCOS and treatment modalities include lifestyle modification, oral ovulation induction agents, insulin sensitizers, laparoscopic ovarian drilling and *In-Vitro* Fertilization (IVF). Risk associated with Controlled Ovarian Stimulation (COS) include risk of ovarian hyperstimulation syndrome, poor oocyte quality, luteal phase defect, poor implantation rates, clinical pregnancy rates and live birth rates. We report a case of resistant infertile PCOS where an individualized approach resulted in successful IVF outcome and ongoing pregnancy after long standing infertility.

Case Presentation

This is a case of a woman in her late 30's who consulted first time in our outpatient clinic in 2008 (25 years) with infertility 2 years. She gave history of prolonged cycles (up to 90-120 days) since menarche. She had clinical hyperandrogenism with mFG score of 8 and ultrasound showed polycystic ovaries with BMI of 21 Kg/M^2. Based on the above features, a diagnosis of lean PCOS with phenotype A was made. She had no family history of PCOS or diabetes in the family. Table 1 describes the hormonal profile of the patient over last 13 years. Trans-vaginal ultrasound revealed bilateral bulky ovaries with antral follicle count >25 in each ovary and volume of 11 cc and 10 cc in right ovary and left ovary respectively. In 2008, after initial investigations, patient was diagnosed with PCOS A and primary infertility. Ovulation induction was given Clomiphene Citrate (CC) 50 mg. Two cycles were deferred since she did not ovulate despite multiple doses of gonadotropins. In view of failed response to CC and requiring high doses of gonadotrophins in each cycle, ovarian drilling was planned. She underwent laparoscopy + hysteroscopy + bilateral ovarian drilling in 2009 (26 years) following which she received 6 more cycles of ovulation induction with intrauterine insemination over 1 year, but did not conceive. Couple left the treatment in between and then decided to go for IVF in 2013. Antagonist protocol with Gonal F 150 IU was given for 9 days of

OPEN ACCESS

Correspondence:
Reeta Mahey, Department of Obstetrics & Gynecology, All India Institute of Medical Sciences, No. 3090 A, Teaching Block, New Delhi- 110029, India

Received Date: *28 Jun 2023*
Accepted Date: *17 Jul 2023*
Published Date: *22 Jul 2023*

Citation:
Rohitha C, Reeta M, Monika S, Monika R. Successful IVF Outcome Using Modified Luteal Phase Support with Multi-Dose GnRh Agonist in a Case of Resistant Infertile PCOS – Case Report and Review of Literature. J Clin Obstet Gynecol Infertil. 2023; 7(1): 1057.

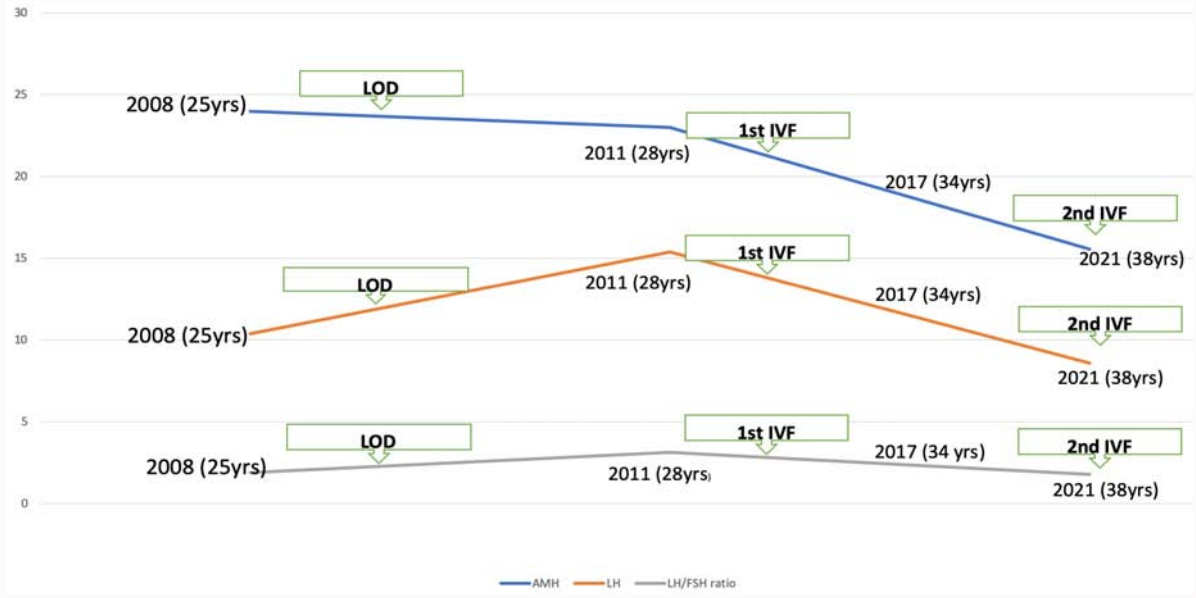

Figure 1: Timeline of events and hormonal profile of the patient. (LOD: Laparoscopic Ovarian Drilling; IVF: In Vitro Fertilization).

Table 1: Hormonal profile and biochemical markers over time.

Year (Age)	2008 (25 years)	2011 (28 years)	2017 (34 years)	2020 (37 years)	2021 (38 years)
FSH	5.47 mIU/L		4.89 mIU/L		5.95 mIU/mL
LH	10.4 mIU/L		15.39 mIU/L		7.9 mIU/mL
LH/FSH Ratio	1.9				1.32
AMH	23 ng/mL	24 ng/mL	>23 ng/mL	16.56 ng/mL	7.91 ng/mL
Total testosterone	0.65 ng/mL				
TSH	4.36 IU/L				
Total cholesterol	176 mg/dL	176 mg/dL			
Triglycerides	64 mg/dL	178 mg/dL			
LDL	88 mg/dL	94 mg/dL			
HDL	44 mg/dL	46 mg/dL			
VLDL	13 mg/dL	36 mg/dL			
Oral GTT (mg/dL)	83/105/90				
Fasting Insulin		8.38 mIU/mL			

stimulation. Total dose required in the stimulation was 3000 IU. Three oocytes were retrieved and all of them were grade 3 and cycle landed up in fertilization failure and no embryo transfer. She developed early onset severe OHSS from day 4 of oocyte retrieval and required hospitalization and ICU monitoring for severe OHSS. After a break in treatment for 1 year, she consulted again in 2020 for second IVF cycle, antagonist protocol started with Gonal-F (recombinant FSH) 267 IU. She received 9 days of stimulation. Her estradiol levels on the day of trigger were >3000 ng/mL, progesterone was 6.05 ng/mL (premature LH surge). GnRh agonist trigger was given in view of PCOS and previous history of severe OHSS. Ten oocytes were retrieved. Grades of oocytes cumulus complex were as follows [2]: 4 were of grade I, 2 were of grade II and 4 of grade III. The fertilization of the oocytes was assessed 18 h to 20 h after IVF with the observation of the presence of two pronuclei. Day 2 embryos (42 h to 44 h after IVF) were classified according to the size, nucleation, and cytoplasmic morphology of the blastomeres and fragmentation. Provisional plan was for freeze all in view of LH surge and previous history of OHSS. But as a surprise, out of 7 fertilized oocytes, only 2 for cell grade B embryos were left on day 2 which showed more than 50% fragmentation and granular cytoplasm and were not of freezable quality.

The dilemma was: (a) Potential chances of poor cryosurvival rate in view of only 2 poor quality embryos. (b) LH surge had happened in this cycle which might have caused endometrial-embryo asynchrony; (c) In view of previous history of OHSS, GnRh agonist had been given for ovulation trigger which is not suitable for fresh embryo transfer; (d) Risk of OHSS with hCG injection in view of previous OHSS.

After discussing with all options with couple, decision for fresh day 2 embryo transfer along with rescue Luteal Phase Support (LPS) with pulse GnRH agonist was planned. Multiple GnRH agonist (Inj Leuprolide 0.5 mg s/c) injections were given on post ovum pick up day 3, 5, 7, 9 and 11 with routine LPS. Rescue hCG as LPS was refrained because of past history of OHSS. After 15 days, urine pregnancy test was positive with beta HCG levels of 999 ng/mL which increased to 4,026 in 48 h. Clinical pregnancy was documented at 6 weeks with

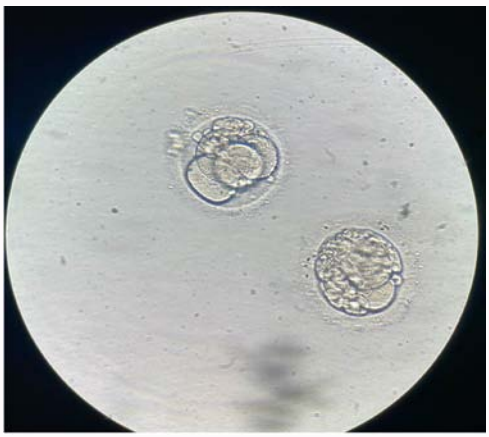

Figure 2: Day 2 embryos showing >50% fragmentation and granular cytoplasm.

fetal cardiac activity and live birth at term (Figure 1, 2).

Discussion

This case shares an important message about individualized management options in a case of resistance infertile PCOS. Anovulation is one of the main causes of infertility in PCOS. Ovulation induction with letrozole, clomiphene citrate and gonadotrophins are first line of treatment in infertile PCOS women. Failure to this, further options include Laparoscopic Ovarian Drilling (LOD) followed by IVF. Choosing next step after failed IVF in resistant PCOS becomes challenging for both infertile couple and clinician.

Although PCOS women are usually hyper-responders with surplus number of oocytes are retrieved, they are often of poor quality, leading to lower fertilization, cleavage and implantation rates and higher miscarriage rates [3,4]. In addition, few resistant PCOS phenotype patients may require higher dose of gonadotrophins during IVF and poor oocyte yield. First IVF cycle in our patient yielded only 3 oocytes leading to fertilization failure along with early onset severe OHSS. The impaired oocyte maturation and embryo developmental competence in PCOS might be due to altered endocrine and paracrine factors, metabolic dysfunction, impaired follicular milieu during early follicular development and maturation [5].

In the present case, severe OHSS in 1st IVF cycle may be explained by long interval between drilling and IVF cycle. Different between our current case and previously reported case was that the current case was 38 years and her AMH was 7.91 ng/mL and her cycles were ovulatory now. As we had to choose between repeat LOD or repeat IVF, option of IVF (antagonist protocol- GnRh agonist trigger-elective freezing-frozen embryo transfer) was chosen in view of advanced maternal age and not very high AMH levels.

The concept of GnRh agonist as trigger was first used given by Nakano et al. in 1973 [6]. The principle behind agonist triggering is that it is able to prevent OHSS completely; basis of which is complete luteolysis [7]. But compromised pregnancy rates in fresh embryo transfer with this trigger precluded the usage of this novel and absolute therapy of OHSS prevention. Segmented cycles and freeze all have been considered as the safer options in hyper-responders but practically not applicable in all cases.

Picard et al. in 2005 first used agonist for LPS in IUI cycle [8]. They could attain sufficient luteal phase duration and increased progesterone and a reasonably good pregnancy rate. One of the hypotheses is that GnRH agonist acts on pituitary cells and secretes LH [9,10]. Another theory suggests that LH release has a positive effect on the endometrium by regulating angiogenetic factors and cytokines thus enhancing implantation rates [11,12]. There are studies reported on usage of multiple doses of GnRH agonist for LPS in IVF cycles before [13]. Wiser et al. in 2019 [14] reported first prospective study using alternate day subcutaneous GnRH agonist trigger similar to the present case report where they compared with hCG micro-dose group. They achieved a clinical pregnancy rate of 43.6% with GnRH agonist luteal support. Hormone dynamics during the stimulation cycle reflected rising LH and progesterone concentrations after the introduction of GnRH agonist support. In our study, we did not monitor serum progesterone levels.

When compared to Good Quality Embryos (GQE), Poor Quality Embryos (PQE) result in higher miscarriage rates and lower ongoing pregnancy rates [15]. However, poor quality embryo may also have the chance of live birth. An important concern with PQE is aneuploidy. Hence it is very crucial to have a thorough discussion with couple to prepare their expectations based on quality of embryos transferred. In our case, we had to transfer day 2 embryos based on embryologists' opinion as they were highly fragmented and there were probabilities of getting arrested low cryo-survival rates.

Individualized approach and usage of multiple pulsatile GnRH agonist therapy has allowed for a fresh transfer where otherwise cycle would be cancelled. Hence this case report emphasizes on clinical application of LOD, GnRH agonist trigger and modified LPS with GnRH agonist on an individualized basis in PCOS women.

Conclusion

High AMH are associated with poor IVF outcome, low oocyte yield, poor quality and high risk of OHSS. Decision between drilling and IVF should be chosen according to age of the patient, previous response and AMH levels. Modified luteal phase support with multiple GnRh agonist therapy may be considered useful in PCOS women where there is risk of OHSS, agonist trigger and freezable embryos are not available.

References

1. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;29(2):181-91.
2. Lin Y-C, Chang S-Y, Lan K-C, Huang H-W, Chang C-Y, Tsai M-Y, et al. Human oocyte maturity *in vivo* determines the outcome of blastocyst development *in vitro*. J Assist Reprod Genet. 2003;20(12):506-12.
3. Boomsma CM, Fauser BCJM, Macklon NS. Pregnancy complications in women with polycystic ovary syndrome. Semin Reprod Med. 2008;26(1):72-84.
4. Weghofer A, Munne S, Chen S, Barad D, Gleicher N. Lack of association between polycystic ovary syndrome and embryonic aneuploidy. Fertil Steril. 2007;88(4):900-5.
5. Dumesic DA, Meldrum DR, Katz-Jaffe MG, Krisher RL, Schoolcraft WB. Oocyte environment: Follicular fluid and cumulus cells are critical for oocyte health. Fertil Steril. 2015;103(2):303-16.
6. Nakano R, Mizuno T, Kotsuji F, Katayama K, Wshio M, Tojo S. "Triggering" of ovulation after infusion of synthetic Luteinizing hormone Releasing Factor (LRF). Acta Obstet Gynecol Scand. 1973;52(3):269-72.
7. Fatemi HM, Polyzos NP, Van Vaerenbergh I, Bourgain C, Blockeel C, Alsbjerg B, et al. Early luteal phase endocrine profile is affected by the

mode of triggering final oocyte maturation and the luteal phase support used in recombinant follicle-stimulating hormone-gonadotropin-releasing hormone antagonist in vitro fertilization cycles. Fertil Steril. 2013;100(3):742-7.

8. Pirard C, Donnez J, Loumaye E. GnRH agonist as novel luteal support: Results of a randomized, parallel group, feasibility study using intranasal administration of buserelin. Hum Reprod Oxf Engl. 2005;20(7):1798-804.
9. Tesarik J, Hazout A, Mendoza-Tesarik R, Mendoza N, 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 Oxf Engl. 2006;21(10):2572-9.
10. 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.
11. Kung H-F, Chen M-J, Guua H-F, Chen Y-F, Yi Y-C, Yen-Ping Ho J, et al. Luteal phase support with decapeptyl improves pregnancy outcomes in intracytoplasmic sperm injection with higher basal follicle-stimulating hormone or lower mature oocytes. J Chin Med Assoc JCMA. 2014;77(10):524-30.
12. Stewart EA. Gonadotropins and the uterus: is there a gonad-independent pathway? J Soc Gynecol Investig. 2001;8(6):319-26.
13. Bar-Hava I, Mizrachi Y, Karfunkel-Doron D, Omer Y, Sheena L, Carmon N, et al. Intranasal gonadotropin-releasing hormone agonist (GnRHa) for luteal-phase support following GnRHa triggering, a novel approach to avoid ovarian hyperstimulation syndrome in high responders. Fertil Steril. 2016;106(2):330-33.
14. Wiser A, Klement AH, Shavit T, Berkovitz A, Koren RR, Gonen O, et al. Repeated GnRH agonist doses for luteal support: A proof of concept. Reprod Biomed Online. 2019;39(5):770-76.
15. Lai I, Neal M, Gervais N, Amin S, Taerk E, Faghih M. Transfers of lower quality embryos based on morphological appearance result in appreciable live birth rates: A Canadian center's experience. FS Rep. 2020;1(3):264-9.