



Research Article

Infertile Women with Diminished Ovarian Reserve have more Live Births Following Dehydroepiandrosterone Pre-Treatment

Siddhartha Chatterjee^{1,2*}, Anjana Ray Chaudhuri², Rajib Gon Chowdhury², Abira Datta^{1,2} and Bishista Bagchi²

¹Infertility specialist of Calcutta Fertility Mission, Kolkata, India

²Department of Reproductive Medicine, Calcutta Fertility Mission, Kolkata, India

³Clinical associate of Calcutta Fertility Mission, Kolkata, India

Abstract

Objective: Dehydroepiandrosterone (DHEA) has been proposed to improve ovulatory response in patients with Diminished Ovarian Reserve (DOR). The study was undertaken to find validity of the above fact, both for Timed Intercourse (TI) following OI and in IVF procedure.

Methods: 596 women aged between 25 and 42 years with DOR were detected by Ovarian Reserve Test (ORT). 551 of them were subjected to DHEA pre-treatment for 90 days followed by OI with Clomiphene Citrate (CC) and Gonadotrophin (Gn). 223 patients with DOR were subjected to IVF program. 186 of them received DHEA pre-treatment and 37 of them did not accept it. The analysis was performed using the statistical software R.

Result: Clinical Pregnancy (CP) and Live Birth (LB) following IVF (33.3% & 25.7% respectively) is almost 3 times more than TI group (12.8% & 9% respectively), when all groups are taken together. However, in cases of advancing age, chance of getting TI pregnancy was much less than IVF pregnancy, as found from Odds Ratio (OR).

Conclusion: DHEA is found to be effective in achieving spontaneous or IVF pregnancy in patients with poor ovarian reserve. IVF offers more live births in elderly women.

Keywords: DHEA; Diminished ovarian reserve; IVF; Live birth rate; Poor response; Timed intercourse

*Corresponding author: Siddhartha Chatterjee MBBS, DGO, DNB, FRCOG, FICOG, Department of Biochemistry and Endocrinology, Institute of Post Graduate Medical Education & Research, Kolkata, India, Tel: +91 9830387875; E-mail: sidchat54@gmail.com

Citation: Chatterjee S, Chaudhuri R, Chowdhury RG, Datta A, Bishista B (2019) Infertile Women with Diminished Ovarian Reserve have more Live Births Following Dehydroepiandrosterone Pre-Treatment. J Reprod Med Gynecol Obstet 4: 020.

Received: March 14, 2019; **Accepted:** March 29, 2019; **Published:** April 08, 2019

Copyright: © 2019 Chatterjee S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Key Message

Live birth rate improves after Dehydroepiandrosterone pre-treatment in patients with diminished ovarian reserve both for timed intercourse and IVF procedure, but IVF gives better results in elderly women.

Abbreviations

DHEA: Dehydroepiandrosterone

DOR: Diminished Ovarian Reserve

TI: Timed Intercourse

CC: Clomiphene Citrate

Gn: Gonadotrophin

CP: Clinical Pregnancy

LB: Live Birth

AFC: Antral Follicular Count

TVS: Transvaginal Ultrasonography

GCs: Granulosa Cells

OI: Ovulation Induction

PR: Pregnancy Rate

ORT: Ovarian Reserve Test

FET: Frozen Embryo transfer

IM: Intramuscular

SC: Subcutaneous

COS: Controlled Ovarian Stimulation

OPU: Ovum Pick Up

LBR: Live Birth Rate

CPR: Clinical Pregnancy Rate

FOR: Functional Ovarian Reserve

TOR: Total Ovarian Reserve

Introduction

In recent years, women delay their first conception till later years of reproduction. This may be due to building up of career in woman, late marriages, increased divorce, re-marriage, or some allied reasons. The advanced reproductive age is associated with reduction in fertility potential, due to decrease in follicular pool size with aging and also chromosomal aneuploidy in gametes. Decline in fertility accelerates after the age of 35 years which is called ovarian aging [1]. ORT consists of many investigations of which three are most important - Serum Follicular Stimulating Hormone (FSH) and Antral Follicular Count (AFC) in early follicular phase on day 2 or day 3 of period, or estimation of Serum Anti-Mullerian Hormone (AMH). The latter has been considered to be fairly constant parameter without inter cycle variability. It can be compared with AFC performed by Transvaginal Ultrasonography (TVS), which require expertise. Hence globally, AMH estimation is emerging as very important parameter to check ovarian reserve. AMH, a glycoprotein, belonging to transforming growth factor family [2], is produced by the Granulosa Cells (GCs)

of primary, pre-antral and small antral follicles in the ovary and then secreted in blood, exerting inhibitory effects on the recruitment of primordial follicles and response of growing follicles to FSH [3]. So far it is believed that decline in ovarian reserve is an irreversible process associated with reduction in fertility potential and increase in the risk of miscarriage. Recent researchers have found that androgens can rejuvenate the ovaries with better response, even in advanced age [4].

DHEA is one such molecule used in anti-aging treatment, has also proved to be beneficial to ovarian function. DHEA works in initial 60 days of folliculogenesis, starting from antral follicles which are non-responsive to Ovulation-Inducing (OI) agents. Although the mechanism of such benefits is not clearly understood till date, its promising pro-fertility action has been noted to improve both spontaneous and IVF Pregnancy Rates (PRs) clinically, in women having DOR [5]. Casson et al., [6] was the first to suggest that DHEA supplementation might improve some aspects of female ovarian functions, having DOR. The main idea came from a woman of advanced reproductive age, who underwent remarkable gains in her ovarian function, due to the effect of Insulin-like Growth Factor (IGF-1), after self-medication with DHEA [7]. It has also been observed that in IVF performed in patients with DOR, supplementation of DHEA improves response to ovarian stimulation with Gns, resulting in the increase of oocyte yield and embryo numbers [7,8]. The effect of DHEA picks at 3-4 months of treatment, a time span similar to complete follicular recruitment cycle, and this showed increase in follicular recruitment due to suppression of apoptosis [8,9]. Approximately 80% of spontaneous pregnancy losses result from chromosomal abnormalities [10], where aneuploidy elevates the rate of miscarriage [11,12]. Supplementation of DHEA reduces aneuploidy and miscarriage, thereby increasing the chances of LB in patients with DOR [13].

The primary end point of the study was to compare the CP and Live Birth Rate (LBR) between DHEA pre-treated and non-treated patients, after OI and after IVF treatment. The secondary end points were miscarriage rates, age-related PR and comparison between the success rates of IVF and conceiving spontaneously with OI at TI.

Materials and Methods

Selection of patients

The patients with DOR who never had DHEA treatment before aged between 25-42 years were included in the study.

Inclusion criteria

- Age between 25 years to 42 years of age with poor ovarian reserve with regular cycles
- FSH value >12 mIU/ml, AMH value <1.8 ng/ml and AFC <5
- Subjected to TI initially for 3 cycles only after OI or single attempt of IVF with COS and antagonist protocol

Exclusion criteria

- Irregular period or secondary amenorrhea
- Normal FSH and normal AMH value, AFC >5 and with any other endocrine defect like hypothyroidism and hyperprolactinemia

Poor Ovarian Response (POR) can be obtained mostly in stimulated cycle like IVF irrespective of ovarian reserve. POR requires at least one cycle of stimulation to detect it and may not recur in next

cycle. It is commonly observed in advanced maternal age, abnormal ovarian reserve test and in cases of previous POR [14,15]. In this case patients with DOR were only included in the study. DOR is commonly observed in women with any of the risk factors for POR and/or an abnormal ovarian reserve test (i.e., Antral Follicular Count (AFC) <5-7 follicles or AMH <0.5-1.1 ng/ml). But the hypothesis requires validation [16].

Study Design

Between June 2014 and June 2017, 596 patients between 25 years to 42 years of age with diminished ovarian reserves, attending Calcutta Fertility Mission were selected for the study. These women desired to have spontaneous conception attempts by TI. They were offered DHEA pre-treatment for 90 days before OI with daily 75 mg single dose orally. 551 of them accepted the pre-treatment and 45 of them did not agree for various reasons. ORT with those three parameters was performed initially in women more than 35 years of age and who could not produce at least 2 follicles with CC stimulation in the younger group women.

Sample size

During the same period, 223 patients with DOR with similar inclusion criteria selected for IVF procedure. They were offered DHEA pre-treatment at same dose for 90 days before COS was started. 186 patients accepted the treatment and 37 patients did not but wanted to have COS straightway. None of them had Intra-Cytoplasmic Sperm Injection (ICSI). They had single OPU cycle either with fresh or Frozen Embryo Transfer (FET) once only.

Consent

Written informed consent from study subject was also obtained prior to sample collection at the Calcutta Fertility Mission.

Ethical approval

A specific written consent was designed according to the ethical guidelines of Helsinki declaration, 1975 and received the ethical clearance from Calcutta fertility mission (Registration no: CFM/ETH-ICS/004).

Treatment protocol

Patients selected for TI had OI agents like CC, in a dose of 50 mg twice daily from D3-D7 of cycle. If failing to conceive by 3 cycles, injection Human Menopausal Gonadotrophin (hMG) 75 International Units (IU) was administered Intramuscularly (IM) from D4 of cycle on alternate days, total 3 such, along with above dose of CC to produce 18 mm follicles. All these patients attempted for TI on the basis of TVS findings only. The AFC was estimated in a Single Ultrasonography (USG) machine (Samsung Medison SONOACE R7) by a single observer, on Day 2 (D2) of cycle through TVS. The ovulation trigger was given with injection Human Chorionic Gonadotrophin (hCG) 5000 IU (IM) on the day the leading follicle/s measured 18mm. Luteal support was provided routinely with Dydrogesterone at twice-daily dose for 15 days, starting from the day following confirmed ovulation. COS was achieved in patients selected for IVF by administration of recombinant FSH (r-FSH) 225 IU Subcutaneously (S/C), starting from D3 of period for 3 days. Routinely, TVS was performed on D6 of cycle, to find out follicular recruitment. Recruitment of at least 3 growing follicles is aimed at. Further from D6 onward, injection

Human Menopausal Gonadotrophin (hMG) 150-300 IU by Intramuscular (IM) route was administered daily, depending on the number of follicles recruited. A maximum dose of 450IU (IM) of hMG injection was administered in some cases. When leading follicle(s) reach 14mm diameter, Gonadotrophin-Releasing Hormone Antagonist (GnRh-a) injection 0.25 mg S/C was started for down-regulating the pituitary. At least 3 shots, maximum of 5 injections of antagonists were used and on attaining 18 mm leading follicle size, ovulation was triggered either through injecting hCG 5000 IU (IM) or GnRh-a 1.0 mg S/C. Serum Estradiol (E2) value was estimated on hCG day monitoring. If E2 value is >greater than 2000 pg/ml, injection LhRh-a was used as ovulation trigger. 34-35 hours following ovulation trigger, Ovum Pick-Up (OPU) was performed by ultrasonography (TVS) route. These retrieved oocytes were inseminated as per conventional IVF techniques. The embryos formed following fertilization were transferred to mother's uterus after 48 hours of OPU, as per fresh Embryo Transfer (ET) cycle or after preparing the endometrium in subsequent cycles.

Hormonal measurements

Serum FSH level was estimated in our laboratory by Chemiluminescence Immunoassay (CLIA) with Monobind Acculite. FSH estimation kit is obtained from Lilac Medicare (P) Ltd, India. The reference interval of FSH level in follicular phase was 3.0-12.0 mIU/ml. In our laboratory, AMH is estimated by the AMH Gen II Enzyme-Linked Immunosorbent Assay (ELISA) kit from Beckman Coulter Inc., USA using Monobind Acculite Elisa reader (Eldex 3.8). According to our reference interval, an AMH level less than 1.8ng/ml is considered to be lower than normal (reference range: 2.0-6.8 ng/ml). Serum Estradiol (E2) value was estimated on hCG day monitoring so as to decide the ovulation trigger.

Statistical Analysis

P-values were calculated to find the significant difference of proportion between different groups. Odd ratios were used to measure the relative effect of different groups in comparison to reference group. All the statistical works were done using the statistical software MINITAB 17.

Results

In the TI group, after DHEA pre-treatment, the overall Clinical Pregnancy Rate (CPR) was found to be 12.9% while Live Born Rate (LBR) was 9.8% respectively, as compared to 4.44% and 2.2% respectively in non-treated patients. Similarly in IVF group, CPR and LBR were 33.3% & 25.7% respectively, and miscarriage rate was 7.3% (Table 1), after DHEA pre-treatment, as compared to 8.01% & 5.3% respectively, along with 2.8% miscarriage rate in no pre-treatment group, indicating that PR in cases of DHEA pre-treatment were more both for TI and IVF groups.

Table 2 presents age stratified difference in CPR and LBR in TI and IVF group. It shows that there was no statistically significant difference between CPR and LBR among age group 25-30 years and above 40 years (as per p-value). However, women of 30-40 years age group show statistically significant difference in both. Table 3 shows comparison of Odds Ratio (OR) of CP and Live Born (LB) as a whole in TI and IVF group. It was found that the OR was about 3 times more in IVF as compared to TI group in both CPR and LBR. When this age stratified OR for CP and LB in both TI and IVF group (Table 4) were plotted in chart, a significant uniform decrease in both CPR and LBR (Figure 1) was found with advancing age, and LBR decreased rapidly in TI group as compared to IVF group (Figure 2). The miscarriage rate was more in IVF group as compared to TI group (7.3% in IVF group versus 3.4% of TI group), even after DHEA pre-treatment.

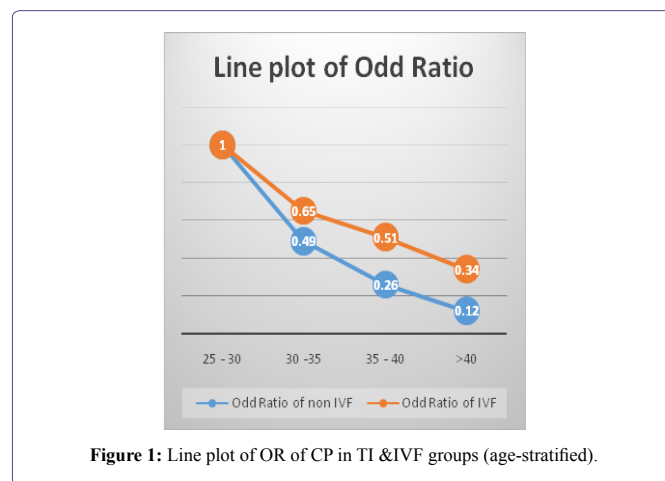


Figure 1: Line plot of OR of CP in TI & IVF groups (age-stratified).

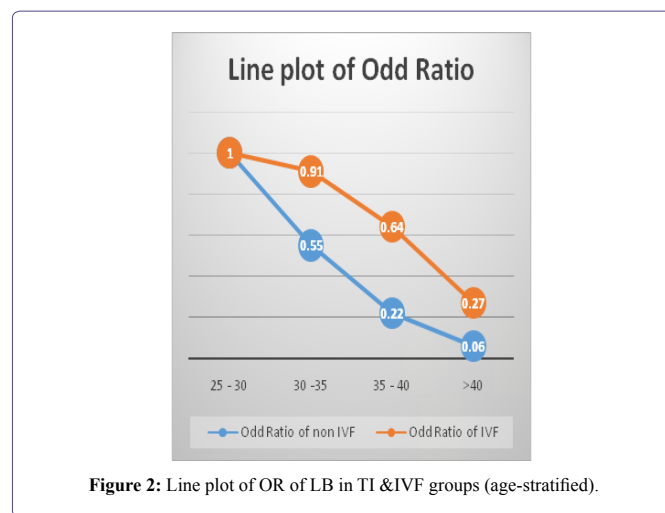


Figure 2: Line plot of OR of LB in TI & IVF groups (age-stratified).

Pre-treatment	Cases	CP/CPR	LB/LBR	Miscarr / MR	Cases	CP/CPR	LB/LBR	Miscarr/ MR
	TI				IVF			
NIL	45	2 (4.44%)	1 (2.2%)	1 (2.2%)	37	3 (8.01%)	2 (5.3%)	1 (2.8%)
DHEA	551	73 (12.9%)	63 (9.8%)	20 (3.4%)	186	52 (33.3%)	48 (25.7%)	14 (7.3%)

Table 1: Total CP and LB in TI and IVF Group with or without DHEA.

Ages	TI			IVF			P value 1	P value 2
	Cases	CP	LB	Cases	CP	LB		
25-30	114	29	22	22	10	7	0.078	0.237
30-35	181	26	21	74	26	22	0.001	0.002
35-40	181	15	9	74	22	17	0.000	0.000
>40	75	3	1	18	4	2	0.070	0.194

Table 2: Age-stratified comparison of CP and LB in TI and IVF Group.

	Cases	CP	Odd Ratio	Cases	LB	Odd Ratio
TI	551	73	1.00	551	53	1
IVF	186	62	3.27 (2.21,4.84)	186	48	3.27 (2.11,5.04)

Table 3: Odd ratio between CP and LB in TI and IVF groups.

Ages	TI			IVF			TI		IVF	
	Cases	CP	Odd Ratio 1	Cases	CP	Odd Ratio 1A	LB	Odd Ratio 2	LB	Odd Ratio 2A
25 - 30	114	29	1.00	22	10	1.00	22	1.00	7	1.00
30 -35	181	26	0.49 (0.27, 0.89)	74	26	0.65 (0.24, 1.71)	21	0.55 (0.28, 1.05)	22	0.91 (0.32, 2.53)
35 - 40	181	15	0.26 (0.13, 0.52)	74	22	0.51 (0.19, 1.34)	9	0.22 (0.09, 0.49)	17	0.64 (0.22, 1.82)
>40	75	3	0.12 (0.03, 0.41)	18	4	0.34 (0.08, 1.38)	1	0.06 (0.01, 0.42)	2	0.27 (0.05, 1.50)

Table 4: Age-stratified OR of CP achieved in women of TI and IVF groups.

Discussion

Poor response occurs due to the reduced active follicle content in ovary, which is otherwise called Functional Ovarian Reserve (FOR). FOR together with inactive or sleeping follicles constitute Total Ovarian Reserve (TOR). DHEA stimulates the sleeping follicular pool, to make them functional components. However it is noteworthy that in most of the cases, the underlying cause of poor response remains unidentified. This is especially true in young women [17-20]. Genetic aberrations particularly those involving genes encoding FSH Receptor (FSHR), in Granulosa Cells (GCs) and defective signal transduction following FSHR binding may cause poor ovarian response following stimulation [21-23]. In recent years, reduced expression of IGF-1 in the follicular fluid has been postulated as the possible explanation of low-peak E2 levels in women having reduced or decreased ovarian reserves, even after COS [24-26]. Low production of Gonadotrophin Surge-Attenuating Factor (GnSAF) following stimulation by FSH is associated with premature luteinization with poor response [1,27,28]. DHEA which was once considered to be anti-aging agent available over the counter, has emerged as a breakthrough medicine in patients with DOR to improve ovarian response, as unveiled by the pioneering work of Casson and his colleagues [6]. Due to methodological error in Casson's study, it was not universally accepted as a valid scientific study. Researchers like Gleicher, Barad or Wisner had demonstrated the beneficial effects of DHEA on poor responders [29]. The mechanism of action of DHEA still remains poorly understood. It has been postulated that DHEA helps in elevating the IGF-1 levels in the ovarian follicles of poor responders, and both in turn increases folliculogenesis and ovarian steroidogenesis by aging ovary showing characteristics of polycystic ovarian morphology. The elevation of intra-follicular androgens through supplementation of DHEA also leads

to improvement of the quality of oocytes. Hence, DHEA appears to increase both quality and quantity of follicular pool.

Dehydroepiandrosterone (DHEA) supplementation is being used by many IVF centers around the world in poor ovarian responders despite the lack of convincing data. About 25% of IVF programs use DHEA currently but large randomized prospective trials are needed and hence the present study [5]. In a study by DE Ikhenia et al., early follicular phase serum DHEAS levels were assessed in addition to markers of ovarian reserve (FSH, AMH, E2) in cycles of non-PCOS women (n=53) undergoing IVF. An inverse correlation was observed and this relationship was independent of age, BMI and smoking status (b coefficient -0.01, p=0.03). No relationship was seen between serum DHEAS levels and AMH nor with IVF cycle response or outcome [30]. In our study it has been found that FSH and AMH levels do not change significantly after DHEA pre-treatment; but the follicular development improves and more follicles are recruited after COS. This observation is similar to the study by Sonmezer M et al., which showed increased number of >17mm follicles and oocytes after DHEA supplementation [31].

It has been shown in the study that TI increases the CPR and LBR following OI following DHEA pre-treatment, as compared to no pre-treatment group. The CPR & LBR in IVF group were also found to be more after DHEA pre-treatment, as compared to TI group. More successful pregnancy occurred between 32-35 years and 35-40 years women both for TI and IVF group. But the PR (both CPR and LBR) was 3 times more in IVF group as compared to TI group after DHEA pre-treatment, as seen in statistical analysis (odds ratio). Poor PR in women less than 30 years and more than 40 years might be age related or other factors like genetic factors for DOR. When odds ratio

was line plotted during statistical analysis, it was observed that with advancing age, chances of conception diminish both in TI and IVF group but this was profound in TI group, indicating that it is better to offer IVF treatment in patients with advanced age as soon as possible. High miscarriage rate may be due to disturbed endometrial receptivity following COS and can decrease following DHEA supplementation according to previous studies [32]. But in our study the miscarriage rate was more in IVF group as compared to TI group (7.3% in IVF group versus 3.4% of TI group), even after DHEA pre-treatment.

Conclusion

To conclude, poor responders having DOR show improved LBR after DHEA pretreatment both for TI and IVF treatment but LBR in elderly patients in DOR improves more following IVF treatment.

Author Contributions

SC,RGC - collection of clinical materials, ARC, AD - hormone analysis and analysis of IVF patient parameters. SC,ARC, AD and BB were involved in designing the study and preparation of the manuscript.

Acknowledgment

Funding has been done from Institute's own fund. We, the authors acknowledge Ms. Orphi Bhattacharya for preparation of the manuscript and Dr. Arabinda Das, Assistant Professor in Statistics, Department of Statistics, Acharya Prafulla Chandra College, New Barrackpore, Kolkata 700 131, West Bengal, India, for preparation of statistical analysis.

Conflict of Interest

There is no conflict of interest.

References

1. Liu K, Case A, Reproductive Endocrinology and Infertility Committee (2001) Advanced reproductive age and fertility. J Obstet Gynaecol Can 33: 1165-1175.
2. Lukaszuk K, Ludwikowska B, Liss J, Kunicki M, Sawczak M, et al. (2014) Decreasing quality of the new generations of anti-Müllerian hormone assays. Biomed Res Int 2014: 165352.
3. Themmen AP (2005) Anti-Müllerian hormone: Its role in follicular growth initiation and survival and as an ovarian reserve marker. J Natl Cancer Inst Monogr: 18-21.
4. Gleicher N, Weghofer A, Barad DH (2011) The role of androgens in follicle maturation and ovulation induction: Friend or foe of infertility treatment? Reprod Biol Endocrinol 17: 116.
5. Fouany MR, Sharara FI (2013) Is there a role for DHEA supplementation in women with diminished ovarian reserve? J Assist Reprod Genet 30: 1239-1244.
6. Casson PR, Lindsay MS, Pisarska MD, Carson SA, Buster JE (2000) Dehydroepiandrosterone supplementation augments ovarian stimulation in poor responders: A case series. Hum Reprod 15: 2129-2132.
7. Barad DH, Gleicher N (2005) Increased oocyte production after treatment with Dehydroepiandrosterone. Fertil Steril 84: 756.
8. Barad D, Gleicher N (2006) Effect of dehydroepiandrosterone on oocyte and embryo yields, embryo grade and cell number in IVF. Hum Reprod 21: 2845-2949.
9. Barad D, Brill H, Gleicher N (2007) Update on the use of dehydroepiandrosterone supplementation among women with diminished ovarian function. J Assist Reprod Genet 24: 629-634.
10. Morales C, Sánchez A, Bruguera J, Margarit E, Borrell A, et al. (2008) Cytogenetic study of spontaneous abortions using semi-direct analysis of chorionic villi samples detects the broadest spectrum of chromosome abnormalities. Am J Med Genet A 146A: 66-70.
11. te Velde ER, Pearson PL (2002) The variability of female reproductive ageing. Hum Reprod Update 8: 141-154.
12. Pal L, Santoro N (2003) Age-related decline in fertility. Endocrinol Metab Clin North Am 32: 669-688.
13. Gleicher N, Weghofer A, Barad DH (2010) Dehydroepiandrosterone (DHEA) reduces embryo aneuploidy: Direct evidence from Preimplantation Genetic Screening (PGS). Reprod Biol Endocrinol 8: 140.
14. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, et al. (2011) ESHRE consensus on the definition of 'poor response' to ovarian stimulation for in vitro fertilization: The Bologna criteria. Hum Reprod 26: 1616-1624.
15. Frattarelli JL, Hill MJ, McWilliams GD, Miller KA, Bergh PA, et al. (2008) A luteal estradiol protocol for expected poor-responders improves embryo number and quality. Fertil Steril 89: 1118-1122.
16. Cohen J, Chabbert-Buffet N, Darai E (2015) Diminished ovarian reserve, premature ovarian failure, poor ovarian responder--a plea for universal definitions. J Assist Reprod Genet 32: 1709-1712.
17. de Carvalho BR, Sobrinho DBG, Vieira ADD, Resende MPS, Barbosa ACP, et al. (2012) Ovarian Reserve Assessment for Infertility Investigation. ISRN Obstet Gynecol 2012: 576385.
18. Practice Committee of the American Society for Reproductive Medicine (2015) Testing and interpreting measures of ovarian reserve: A committee opinion. Fertil Steril 103: 9-17.
19. Ubaldi F, Vaiarelli A, D'Anna R, Rienzi L (2014) Management of Poor Responders in IVF: Is There Anything New? BioMed Research International 352098: 10.
20. Badawy A, Wageah A, El Gharib M, Osman EE (2011) Prediction and Diagnosis of Poor Ovarian Response: The Dilemma. J Reprod Infertil 12: 241-248.
21. Oehninger S (2011) Poor responders in In Vitro Fertilization (IVF) therapy: The challenge continues. Facts Views Vis Obgyn 3: 101-108.
22. Yan Y, Gong Z, Zhang L, Li Y, Li X, et al. (2013) Association of follicle-stimulating hormone receptor polymorphisms with ovarian response in Chinese women: a prospective clinical study. PLoS ONE 8: 78138.
23. Achrekar SK, Modi DN, Desai SK, Mangoli VS, Mangoli RV, et al. (2009) Poor ovarian response to gonadotrophin stimulation is associated with FSH receptor polymorphism. Reprod Biomed Online 18: 509-515.
24. Greenseid K, Jindal S, Hurwitz J, Santoro N, Pal L (2011) Differential granulosa cell gene expression in young women with diminished ovarian reserve. Reprod Sci 18: 892-899.
25. Stadtmauer L, Vidali A, Lindheim Sr (1998) Follicular Fluid Insulin-Like Growth Factor-I and Insulin-Like Growth Factor-Binding Protein-1 and -3 Vary as a Function of Ovarian Reserve and Ovarian Stimulation. J Assist Reprod Genet 15: 587-593.
26. Paul S, Pramanick K, Kundu S, Kumar D, Mukherjee D (2010) Regulation of ovarian steroidogenesis *in vitro* by IGF-I and insulin in common carp, *Cyprinus carpio*: Stimulation of aromatase activity and P450arom gene expression. Mol Cell Endocrinol 315: 95-103.
27. Martinez F, Barri PN, Coroleu B, Tur R, Sorsa-Leslie T, et al. (2002) Women with poor response to IVF have lowered circulating Gonadotrophin Surge-Attenuating Factor (GnSAF) bioactivity during spontaneous and stimulated cycles. Hum Reprod 17: 634-640.

28. Messinis IE, Messini CI, Dafopoulos K (2014) Novel aspects of the endocrinology of the menstrual cycle. *Reprod Biomed Online* 28: 714-722.
29. Wisner A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, et al. (2010) Addition of Dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: A randomized prospective study. *Human Reprod* 25: 2496-2500.
30. Ikhen DE, Kallen A, Kodaman PH, Pal L (2013) Day 3 FSH is inversely correlated with serum DHEAS level in patients undergoing IVF. *Fertil Steril* 100: 508.
31. Sönmezer M, Ozmen B, Cil AP, Ozkavukçu S, Taşçı T, et al. (2009) Dehydroepiandrosterone supplementation improves ovarian response and cycle outcome in poor responders. *Reprod Biomed Online* 19: 508-513.
32. Gleicher N, Ryan E, Weghofer A, Blanco-Mejia S, Barad DH, et al. (2009) Miscarriage rates after Dehydroepiandrosterone (DHEA) supplementation in women with diminished ovarian reserve: A case control study. *Reprod Biol Endocrinol* 7: 108.



Journal of Anesthesia & Clinical Care
Journal of Addiction & Addictive Disorders
Advances in Microbiology Research
Advances in Industrial Biotechnology
Journal of Agronomy & Agricultural Science
Journal of AIDS Clinical Research & STDs
Journal of Alcoholism, Drug Abuse & Substance Dependence
Journal of Allergy Disorders & Therapy
Journal of Alternative, Complementary & Integrative Medicine
Journal of Alzheimer's & Neurodegenerative Diseases
Journal of Angiology & Vascular Surgery
Journal of Animal Research & Veterinary Science
Archives of Zoological Studies
Archives of Urology
Journal of Atmospheric & Earth-Sciences
Journal of Aquaculture & Fisheries
Journal of Biotech Research & Biochemistry
Journal of Brain & Neuroscience Research
Journal of Cancer Biology & Treatment
Journal of Cardiology & Neurocardiovascular Diseases
Journal of Cell Biology & Cell Metabolism
Journal of Clinical Dermatology & Therapy
Journal of Clinical Immunology & Immunotherapy
Journal of Clinical Studies & Medical Case Reports
Journal of Community Medicine & Public Health Care
Current Trends: Medical & Biological Engineering
Journal of Cytology & Tissue Biology
Journal of Dentistry: Oral Health & Cosmesis
Journal of Diabetes & Metabolic Disorders
Journal of Dairy Research & Technology
Journal of Emergency Medicine Trauma & Surgical Care
Journal of Environmental Science: Current Research
Journal of Food Science & Nutrition
Journal of Forensic, Legal & Investigative Sciences
Journal of Gastroenterology & Hepatology Research
Journal of Gerontology & Geriatric Medicine
Journal of Genetics & Genomic Sciences
Journal of Hematology, Blood Transfusion & Disorders
Journal of Human Endocrinology
Journal of Hospice & Palliative Medical Care
Journal of Internal Medicine & Primary Healthcare
Journal of Infectious & Non Infectious Diseases
Journal of Light & Laser: Current Trends
Journal of Modern Chemical Sciences
Journal of Medicine: Study & Research
Journal of Nanotechnology: Nanomedicine & Nanobiotechnology
Journal of Neonatology & Clinical Pediatrics
Journal of Nephrology & Renal Therapy
Journal of Non Invasive Vascular Investigation
Journal of Nuclear Medicine, Radiology & Radiation Therapy
Journal of Obesity & Weight Loss
Journal of Orthopedic Research & Physiotherapy
Journal of Otolaryngology, Head & Neck Surgery
Journal of Protein Research & Bioinformatics
Journal of Pathology Clinical & Medical Research
Journal of Pharmacology, Pharmaceutics & Pharmacovigilance
Journal of Physical Medicine, Rehabilitation & Disabilities
Journal of Plant Science: Current Research
Journal of Psychiatry, Depression & Anxiety
Journal of Pulmonary Medicine & Respiratory Research
Journal of Practical & Professional Nursing
Journal of Reproductive Medicine, Gynaecology & Obstetrics
Journal of Stem Cells Research, Development & Therapy
Journal of Surgery: Current Trends & Innovations
Journal of Toxicology: Current Research
Journal of Translational Science and Research
Trends in Anatomy & Physiology
Journal of Vaccines Research & Vaccination
Journal of Virology & Antivirals

Submit Your Manuscript: <http://www.heraldopenaccess.us/Online-Submission.php>