Original Article

# Improvement of reproductive outcome in hypo-responders using genomics evidence based controlled ovarian stimulation (COS) – Demonstration through case presentations

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## Abstract

**Aim:** To identify genomic variants associated with hypo-response to COS in patients with repeated intrauterine insemination (IUI) and/or in vitro fertilization (IVF) failures and devise appropriate management strategies. **Materials and methods:** Twelve patients with a history of IUI/IVF failures were included in the study. Next generation sequencing (NGS) based genomic analysis on peripheral blood, designed for Indian population was performed to identify risk genotypes. Multiple causative and susceptibility genotypes associated with oogenesis, fertilization, implantation failure, pregnancy loss, premature ovarian insufficiency, oocyte quality, response to COS, and pharmacogenomic correlations were part of the genomic panel. **Results:** A total of six variants were reported with poor or slow response to controlled ovarian stimulation in AMH, AMHR2, ESR1, FSHR, and LHCGR genes. In two cases, thrombophilia related variants in VEGFA and MTRR genes were also identified. Based on the genotypes identified with ovarian response correlations, stimulation protocols were modified and better outcome was recorded. **Conclusion:** We demonstrate identification of hypo-responders and customization of controlled ovarian stimulation protocols based on genomic analysis combined with clinical parameters leading to reduction in number of cycles and improving outcome or reproductive success.

**Keywords:** AMH, AMHR2, controlled ovarian stimulation, ESR1, FSHR, genotypes, IUI, IVF, LHCGR, pharmacogenomics, polymorphisms

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**Submission:** 14–06–2023, **Revised:** 9–08–2023, **Accepted:** 8–09–2023, **Published:** 30–September–2023

## INTRODUCTION

Retrieval of good number of oocytes with controlled ovarian stimulation (COS) is a crucial prerequisite for the success of assisted reproductive technology (ART). Further, the number of oocytes retrieved might be used as an independent predictor of the live birth rate of the treatment cycle.[1] However, the great range of variability among women undergoing COS and inability to predict response accurately is a frequent challenge faced by infertility clinics. Although clinical parameters such as low anti-Mullerian hormone (AMH $< 1.2$ ng/mL), low antral follicle count (AFC $< 5$), high follicle-stimulating hormone (FSH), high estradiol (E2), and advanced

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| Quick Response Code: | Website: www.fertilityscienceresearch.org |
| | DOI: 10.4103/fsr.fsr_27_23 |



**How to cite this article:** Achuri A, Udumudi A. Improvement of reproductive outcome in hypo-responders using genomics evidence based controlled ovarian stimulation (COS) – Demonstration through case presentations. Fertil Sci Res 2023;10:145-50.

maternal age add value as indicators of poor ovarian response, none are absolute measures, and they only serve as broad indicators.[2,3] Low AMH, although a frequently used ovarian reserve marker, does not reflect the quality of oocytes retrieved in ART.[4] In current practice, these clinical markers, either independently or in a combined manner, contribute significantly to predicting poorer prognosis in patients, but frequently fail to identify hypo-responders. According to the novel POSEIDON criteria, the hypo-responders, or the "unexpected POR," group 1 (<35 yrs) and group 2 (>35 yrs) are women who unexpectedly show a low ovarian response (< 4 oocytes) or suboptimal (4–9 oocytes retrieved) to ovarian stimulation with exogenous gonadotropins despite the presence of adequate ovarian reserve indicated by ovarian reserve markers.[5] In the IUI cycle, hypo-response criteria are met when there is delayed follicle growth, regression of follicle, or the need for multiple dosages of gonadotrophins in women with normal BMI and no PCOS.[6] This group of hypo-responders clearly needs further work to predict response to COS.

With the advancement in genomics and the availability of genome-wide association studies (GWAS), data are accumulating on genetic variability in population groups. The rapidly emerging data demonstrate association of single nucleotide polymorphisms with female infertility, folliculogenesis, and response to controlled ovarian stimulation. Researchers in the field have predicted that genetic biomarkers in synergy with hormonal and functional tests may provide the best tools to guide individualized treatment.[7] Information about the genetic profile of the woman is crucial to understanding the pharmacogenomic implications of IVF treatment, which helps in determining the suitable drug and dosage to achieve optimal oocyte retrieval.[8] Multiple genes and their polymorphisms are reported to be associated with controlled ovarian stimulation, such as *AMH, AMHR2, BMP15, CYP19A1, COMT, ESR1, ESR2, FSHR, GDF9, HRG, KISS1, KISS1R, LHB, LHCGR, PAI1, P53, SHBG, SOD2, VEGFA, TNF,* etc. We present 12 cases of repeated IVF/IUI failures, the identification of genomic variants associated with hypo-response to COS and follow-up management.

## SUBJECTS AND METHODOLOGY

The subjects were 12 patients who were undergoing fertility treatment at a single fertility center. A detailed patient and family history were taken at our clinic. Anti-Mullerian Hormone (AMH) was tested for all subjects at a single lab facility by Electrochemiluminescence immunoassay (ECLIA). Antral follicle count (AFC) was measured by transvaginal ultrasound, and all follicles measuring 2–10 mm on both ovaries were counted on day 2 or 3 of the menstrual cycle. Our inclusion criteria included women with failed IVF and/or IUI cycles, retrieval of lower than expected oocytes, poor response to stimulation, delayed ovulation/failed ovulation noted in multiple cycles with a BMI not more than 28. Women above 40 years and with a BMI >28 were excluded to avoid age- and obesity-related decrease in fertility factor. We have also excluded women with polycystic ovarian syndrome (PCOS) who fall under the definition of the Rotterdam consensus, where PCOS is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism, and polycystic ovaries (≥12 follicles measuring 2–9 mm in diameter and/or an ovarian volume >10 mL in at least one ovary.[9] All patients had atleast one failed ART cycle (IUI or IVF) and as per POSEIDON eight cases were group 1 (cases 1, 2, 3, 5, 7, 10, 11, 12), two cases group 2 (cases 8, 9), one case group 3 (case 4), and one case group 4 (case 6). None of them had any significant family history and karyotypes of all couples were normal.

Genomic gap - Gene Femina designed for the Indian population (GeneFemina) was carried out on the peripheral blood samples of the subjects using next-generation sequencing (NGS) technology to identify associated genotypes. DNA corresponding to targeted genomic regions is amplified using the Ion AmpliSeq library 2.0 and custom-designed primers. The purified library is quantified and sequenced on a S5 platform (Thermo Fisher, USA) aligned to hg38 with uniform coverage ~99% and a mean read depth 150X. Variants are called using Torrent Variant Caller and annotated using Ion Reporter Software. Analytical sensitivity, specificity, and test reproducibility ~99%. Variant analysis and interpretation were done using Genomic Fertility Analysis (GFA) software. Multiple risk genotypes associated with oogenesis, fertilization, implantation failure, pregnancy loss, premature ovarian insufficiency, oocyte quality, response to COS, and pharmacogenomic implications were tested in the study. Follow-up management was done based on the genotype–phenotype correlations and recommended measures to achieve an optimal response to stimulation.

## RESULTS

A total of six variants were reported with poor or slow response to controlled ovarian stimulation in AMH,

AMHR2, ESR1, FSHR, and LHCGR genes [Table 1]. As the test is a multigene panel including implantation failure and pregnancy loss correlations, in two cases, thrombophilia-related variants in the VEGFA and MTRR genes were identified as secondary variants. Based on the genomics evidence and interpretation provided along with the results, stimulation protocols were modified, and good ovarian response was achieved in all 12 cases. Table 2 provides case history, pre-test ART details, genomic analysis, and post-test ART details and outcome. Out of 12 cases presented, 6 cases reported a full-term delivery of a healthy baby, four cases have ongoing advanced pregnancy, and two cases are awaiting embryo transfer.

## DISCUSSION

Out of 12 cases except case 6 (PG-4) and case 4 (PG-3) with borderline AMH (1.1 ng/mL), all other cases were not indicative of poor response to ovarian stimulation and had AMH and AFC within the range. However, genomic fertility analysis by GeneFemina identified six gene variants in the AMH, AMHR2, ESR1, FSHR, and LHCGR genes associated with poor or slow responses to controlled ovarian stimulation in all 12 cases.

Anti-Mullerian Hormone (*AMH*) c.146G>T genotype is reported in case 5. The AMH gene has a crucial role in ovarian function, and its gene variations are associated with reduced bioactivity of AMH, low oocyte numbers in untreated females, and poor response to controlled ovarian stimulation.[10] The patient was treated with DHEA and higher gonadotropins dose was used for stimulation in subsequent cycle. Even though the use of DHEA and its role in clinical pregnancy outcomes are controversial, DHEA supplementation is reported to augment ovarian stimulation in poor responders, especially in women with low AMH.[11] The Anti-Mullerian Hormone Receptor (*AMHR2*) c.622-6C>T genotype is reported in case 7. The *AMHR2* genotype is reported to be associated with a poor ovarian response to standard gonadotropin stimulation, affecting mainly the follicular growth, resulting in smaller follicles and requiring modulation of ovarian stimulation.[12] A higher gonadotropin dose was used for the case. The Estrogen Receptor Alpha (*ESR1*) c.453-397T>C genotype is reported in cases 6, 8, and 10. ESR1 mediates estrogen effects on follicle growth, maturation, oocyte release, and implantation. ESR1 gene variants are associated with idiopathic female infertility, poor ovarian reserve, low oocyte retrieval rates, requiring longer induction period, and higher doses of rFSH which were provided in subsequent cycles to the patient.[13] Follicle stimulating hormone receptor (*FSHR*) c.2039G>A genotype is reported in cases 5, 8, 9, 10, 11, and 12. *FSHR* plays a central role in oogenesis, maturation of follicles, proliferation of granulosa cells, and in the recruitment of the dominant follicle. The genotype is reported extensively in poor responders who are comparatively more resistant to FSH action and require a stronger stimulus.[8] All cases were given a higher gonadotropins dose subsequently. Luteinizing hormone Choriogonadotropin Receptor (*LHCGR*) c.161 +4491T>G and c.935A>G genotypes are reported in cases 1, 2, 3. The LHCGR gene plays an important role in female reproductive development and ovulation. Both the reported *LHCGR* variants are recognized as pharmacogenomic markers in ovarian stimulation, with carriers of the risk genotypes showing a better response to exogenous LH stimulation.[14] Exogenous LH was provided subsequently for women with *LHCGR* genotypes. A recent study on 312 Indian women demonstrated a strong association between *AMH, AMHR2, ESR1, FSHR*, and *LHCGR* genotypes and poor or hyporesponse to COS, along with a multi-gene cumulative risk analysis that offers an additional tool for accurate prediction of poor response to COS.[15]

Based on the identified gene variants in the analysis, stimulation protocols were modified, which resulted in successful stimulation with good oocyte retrieval. For all 12 cases, a minimum gap of 3 months was given between the pre-test and post-test stimulations, and there was no significant change in the weight of the patients in this interval. For all IVF cases (1, 2, 3, 4, 6, 8, 9, 12) r-hCG 0.25 mg was used as trigger and for IUI cases (5, 7, 10, 11) urinary hCG of 10,000 units was used. Table 2 gives particulars of the stimulation protocols used for each

**Table 1: Details of Gene variants reported with COS association in all cases**

| Gene | Loci | rsID | Genotype | Outcome | Recommendation | Case no. |
|---|---|---|---|---|---|---|
| AMH | c.146G>T | rs10407022 | TT | Poor response to COS | DHEA supplementation augments COS | 5 |
| AMHR2 | c.622-6C>T | rs2071558 | TT | Poor response to COS | Higher dose of gonadotropins favourable | 7 |
| ESR1 | c.453-397T>C | rs2234693 | TT | Poor response to COS | Higher dose of gonadotropins favourable | 6, 8, 10 |
| FSHR | c.2039G>A | rs6166 | GG | Poor response to COS | Higher dose of gonadotropins favourable | 5, 8, 9, 10, 11, 12 |
| LHCGR | c.161+4491T>G | rs13405728 | AA | Slow response to COS | Exogenous LH stimulation and higher LH dose favourable | 1, 3 |
| LHCGR | c.935A>G | rs2293275 | GG | Slow response to COS | Exogenous LH stimulation and higher LH dose favourable | 2, 11 |

**Table 2: Genomics evidence based COS modulation with pre-test, post-test details and outcome**

| Case | Age (BMI) | AMH (ng/mL) | AFC | Indication for ART | Pre Test ART details | Genotypes | Post test ART details | ART outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 32 yrs (26) | 2.1 | 7+8 | Unexplained infertility, failed OI, IUI | **IVF** – rFSH 225 + rLH 75 for 4 days, changed to hmg 450 for 2 days in view of poor response. Only three follicles seen growing after 6 days, cycle abandoned at patients' request | LHCGR (rs13405728) *VEGFA* (rs2146323) | **IVF** – rFSH 300 + rLH 150, 10 oocytes retrieved, 7M2, 4 grade A blastocysts on day 5, 2 average grade blastocysts on day 6, frozen ET (2 embryos transferred) | Conceived, currently 7 months pregnant, LMWH was started after ET in view of VEGFA genotype |
| 2 | 32 yrs (22) | 1.3 | 10+5 | B/L Tubal Block | **IVF** – rfsh 225 – stimulation 9 days – 6 oocytes retrieved – 4M2 – 1 grade B day 3 embryo – FET negative | LHCGR (rs2293275) | **IVF** – rFSH 300 + rLH 150, 7 oocytes, 6M2 – 4 good grade blasts on day 5,Frozen single ET | Conceived, delivered a healthy baby |
| 3 | 28 yrs (23) | 3 | 8+7 | Bilateral tubal block | **IVF** – rFSH 300 for 10 days, 5 follicles >15 mm (21, 19.5 × 2, 18.5, 15.5 mm), 2 follicles >14 mm, empty follicles, no oocyte retrieved | AMH (rs10407022) FSHR (rs6166) LHCGR (rs13405728) | **IVF** – rfsh 300 + rLH 150 for 9 days, 18 oocytes retrieved, 15M2, 7 good grade blastocysts frozen on day 5 | Awaiting ET |
| 4 | 34 yrs (28) | 1.1 | 7+8 | Unexplained infertility, failed IUI, IVF | **IVF** – done at a different center, 2M2, no fertilization (protocol details unavailable) | LHCGR (rs2293275) | **IVF** – rfsh 300 + rLH 150 for 11 days, 8M2, 4 blastocysts on day 5, 3 Euploid by PGT-A, frozen single ET | Conceived, delivered a healthy baby |
| 5 | 31 yrs (26) | 2 | 12+12 | RPL, male partner oligospermia | **IUI** – Post IUI 2 missed abortions at 6 wks | AMH (rs10407022) FSHR (rs6166) MTRR (rs1801394) | **IUI** –Stimulation with high dose gonadotrophins (150iu HMG), 2 dominant follicles on day 12, LWMH started in luteal phase in view of MTRR genotype | Conceived, delivered a healthy baby |
| 6 | 36 yrs (20) | 0.7 | 5+6 | Diminished ovarian reserve, male partner OATS | **IVF** – done in USA, 2M2, 1 embryo, fresh ET, negative, 2nd cycle in USA (agonist protocol), no eggs | AMH (rs10407022) ESR1 (rs2234693) LHCGR (rs13405728) | **IVF** – rFSH 300 + rLH 150 for 9 days, 13 oocytes retrieved, 8M2, 3 Blastocysts on day 5, Frozen | Awaiting ET |
| 7 | 31 yrs (26) | 3 | 11+12 | Unexplained infertility, failed OI, IUI | **IUI** – multiple failed OI and IUI, delayed and poor response to stimulation | AMHR2 (rs2071558) | **IUI** – stimulation with high dose gonadotrophins (150iu HMG), 2 dominant follicle seen on day 12 | Conceived, delivered a healthy baby |
| 8 | 36 yrs (26) | 2.5 | 10+5 | Male partner Azoospermia, TESA sperms available | **IVF** – done at a different center, rFSH 225iu, 14 days stimulation, 1 embryo on day 3, FET, failed | ESR1 (rs2234693) FSHR (rs6166) | **IVF** – rFSH 300 + hMG 150 for 10 days, 10M2, Fresh ET on day 3 (3 embryos transferred), Remaining 6 embryos frozen | Conceived, delivered a healthy baby |
| 9 | 36 yrs (28) | 2.9 | 10+11 | Unexplained infertility, failed IUI | **IUI** – 6 failed IUI | FSHR (rs6166) | **IVF** – rFSH 300 + hMG 150 for 9 days, 12 oocytes retrieved, 10M2, Fresh embryo transfer on day 3 (3 embryos transferred), remaining 5 embryos frozen | Conceived, delivered a healthy baby |
| 10 | 32 yrs (25) | 3 | 10+12 | Unexplained infertility, failed OI, IUI | **IUI** – Multiple failed OI, IUI | ESR1 (rs2234693) FSHR (rs6166) | **IUI** – Stimulation with high dose gonadotrophins (150iu HMG), 3 dominant follicles seen on day 12 | Conceived, delivered a healthy baby 1 year old |
| 11 | 28 yrs (20) | 2.4 | 12+12 | Unexplained infertility, failed IUI | **IVF** – IVF done elsewhere, 6 oocytes retrieved, 4M2, 2 embryos transferred on day 2 twice, both failed | FSHR (rs6166) | **IUI** – Stimulation with high dose gonadotrophins (150iu HMG) 3 dominant follicles seen on day 9 | Conceived, 7 months pregnant |
| 12 | 26 yrs (25) | 4.9 | 12+12 | Male partner oligospermia | **IUI** – multiple failed OI, IUI | FSHR (rs6166) | **IVF** – rFSH 300+ hMG 150 for 8 days, 13M2, Fresh ET (2 days 5 embryos transferred) | Conceived, delivered a healthy baby |

patient, oocyte retrieval results, and outcome details. Out of 12 cases presented, 67% reported live births, 17% with current ongoing advanced pregnancy, and two cases are awaiting embryo transfer.

As the panel used in the methodology includes multiple genes associated not only with an ovarian response but also implantation failure and pregnancy loss, in cases 1 and 5, we identified two thrombophilia-related variants in the *VEGFA* (c.659-111C>A) and *MTRR* (c.66A>G) genes as secondary findings. Both of these variants are associated with implantation failure and recurrent pregnancy loss-related risk in Indian women.[16] Administration of a therapeutic anticoagulant dose was used as a preventive measure in case 5 with history of previous pregnancy losses, who conceived and delivered a healthy baby, and in case 1 pregnancy is advancing well and is in the 3rd trimester. Although the use of low molecular weight heparin is controversial, its use in subgroups showing inherited thrombophilia polymorphisms is evidenced to have a beneficial effect on live birth rates and reduce adverse pregnancy outcomes.[17-20]

## CONCLUSION

We demonstrate the identification of hypo-responders using genomic analysis and the customization of controlled ovarian stimulation protocols based on the results to reduce failed cycles and to improve outcome or reproductive success. Pharmacogenomics is a promising approach in the field of individualized medicine and is fast approaching the ART segment. The unique genetic information of each infertile woman, in combination with clinical parameters, may lead to a better prediction of ovarian response and is therefore anticipated to greatly benefit the process of controlled ovarian stimulation. Larger studies are required to further calibrate the various genotypes and associations with ovarian stimulation, especially in the Indian population.

### Ethical statement

The ethical clearence taken from Institutional Committe.

### Authors' contributions

Author A. Achuri was involved in conceptualisation, analysis, and manuscript writing. Author A Udumudi was involved in study design, analysis, and interpretation of results and manuscript writing.

### Acknowledgment

The authors would like to thank the patients for consenting to participate in the study.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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