Hypergonadotropic hypogonadism: looking beyond ovarian senescence

Richa Vatsa1*, Vanita Suri2, Neelam Choudhary2, Aashiama Arora2, Shruti Sharma2

1Department of Obstetrics and Gynaecology, AIIMS, New Delhi, India
2Department of Obstetrics and Gynaecology, PGIMER, Chandigarh, Punjab, India

Received: 26 November 2020
Accepted: 04 January 2021

*Correspondence:
Dr. Richa Vatsa,
E-mail: dr.richavatsa@gmail.com

ABSTRACT
Gonadotropin resistant ovary syndrome (GROS) is a rare cause of primary infertility where ovarian reserve is present but they fail to respond to gonadotropin stimulation. This condition can be easily confused with premature ovarian insufficiency (POI) if thorough workup is not done as in both the cases serum FSH is high, but ovarian reserve is normal in GROS and low or absent in POI. So, we are presenting this case of GROS. A 28-year-old lady presented with oligomenorrhoea since menarche and primary infertility. On workup her serum FSH and LH levels were markedly elevated, serum estradiol was normal. Markers of ovarian reserve, ante Mullerian hormones (AMH) and antral follicle count (AFC), were normal. Her autoantibody assay was also normal. She did not respond to stimulation with high doses of gonadotropins (uHMG). Hypergonadotropic hypogonadism is not always POI. We should not miss diagnosis of GROS where it is possible to have own biological child by in vitro maturation of immature oocytes, whereas in POI donor oocyte is the only fertility option.

Keywords: Gonadotropin resistant ovary syndrome, Infertility, In vitro maturation

INTRODUCTION
GROS also known as savage syndrome is a rare cause of infertility characterized by hypergonadotropic hypogonadism.1 Infertility is a common complaint of woman presenting with GROS, and fertility aspects are poor in these patients.

This condition can be misdiagnosed easily as POI without complete infertility workup. Measurement of markers of ovarian reserve like AMH and AFC can differentiate these two conditions. In vitro maturation (IVM) of oocyte has started emerging as treatment modality to have their own biological child.2,3 Whereas there is no hope of pregnancy with own oocytes in women with POI. So, this condition should be differentiated from GROS. Here we are presenting a case of GROS who came to us with infertility.

CASE REPORT
A 28-year-old lady presented to with complains of oligomenorrhoea since menarche and primary infertility for 10 years. Menstrual cycles were of 40-60 days duration. There were no symptoms, hot flushes or vaginal dryness, related to menopause. She had a body mass index (BMI) of 21.6, no significant finding in general physical examination and gynaecological examination. Her sexual maturity rating was A+B4. On workup her serum FSH and LH levels were markedly elevated, serum estradiol was normal. Markers of ovarian reserve, ante Mullerian hormones (AMH) and antral follicle count (AFC), were normal. Her autoantibody assay was also normal. She did not respond to stimulation with high doses of gonadotropins (uHMG). Hypergonadotropic hypogonadism is not always POI. We should not miss diagnosis of GROS where it is possible to have own biological child by in vitro maturation of immature oocytes, whereas in POI donor oocyte is the only fertility option.
husband semen analysis and hysterosalpingography, were normal.

![Transvaginal ultrasonography of ovary with antral follicles.](image)

**Figure 1: Transvaginal ultrasonography of ovary with antral follicles.**

**Table 1: Result of various investigations done.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value 2013</th>
<th>Value 2017</th>
<th>Value 2018</th>
<th>Normal value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D3 FSH (IU/L)</td>
<td>30.66</td>
<td>62.42</td>
<td>55.35</td>
<td>3.5-12.5</td>
</tr>
<tr>
<td>D3 LH (mIU/ml)</td>
<td>30.56</td>
<td>16.69</td>
<td>40.67</td>
<td>2.2-12.6</td>
</tr>
<tr>
<td>AMH (ng/ml)</td>
<td>10.9</td>
<td>4.78</td>
<td>1.0-3.5</td>
<td></td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>72.64</td>
<td>12.5-166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>1.6</td>
<td>0.2-2.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH (μIU/ml)</td>
<td>2.73</td>
<td>0.5-4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (μg/L)</td>
<td>12.8</td>
<td>4.7-23.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti TPO (IU/ml)</td>
<td>11.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA-tTG (U/ml)</td>
<td>&lt;0.1</td>
<td>&lt;7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI brain</td>
<td>Normal study (2018)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype</td>
<td>46XX</td>
<td></td>
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</tr>
</tbody>
</table>

After complete infertility evaluation patient, with a possible diagnosis of GROS, patient was started on ovarian stimulation with highly purified urinary human menopausal gonadotropin. However, after administration of 10 days in the dose 150 IU there was no follicular recruitment. Dose was increased to 225 IU/day for 8 days, but there was no response after total duration of 18 days and a dose of 3300 IU. In next cycle we planned her stimulation after down regulation with gonadotropin releasing hormone agonist (GnRHa) depot (leuprolide acetate 3.75 mg IM), again after 15 days of stimulation, starting with 150 IU and increasing the dose up to 300 IU (total dose 3375 IU), there was no follicular recruitment and cycle abandoned. After two failed cycles of gonadotropin stimulation, we referred her to centre with facility for in vitro maturation but patient refused any further treatment due to financial constraints.

**DISCUSSION**

GROS is well known entity and rare cause of infertility. Patients present with oligomenorrhea or amenorrhea and workup show hypergonadotropic hypogonadism. These patients may have mutation in FSH receptor. Total of 17 inactivating mutations have been identified. Case report has described galactosemia and antigonadotropin antibodies also as a cause of gonadotropin resistance. The condition can be easily confused with POI as both present with raised FSH. One study showed that as many as 11-20% patients with diagnosis of POI may turn out to be GROS on detailed workup. Older times ovarian biopsy was used to diagnose ROS, showing various primordial follicles and absence of graffian follicles. With good quality ultrasound, AFCs helps in non-invasive diagnosis of this condition. Further AMH and inhibin B can also differentiate these conditions. These markers of ovarian reserve will be normal in GROS but low in POI. It is important to differentiate these two conditions as pregnancy with self-oocyte is possible in former condition not in later one. Follicles often fail to respond when stimulated with gonadotropin. Clinicians have tried suppression of FSH and LH with oral contraceptive pills (OCPs) and GnRHa followed by gonadotropin stimulation but without success in most cases. Clinicians have tried suppression of FSH and LH with oral contraceptive pills (OCPs) and GnRHa followed by gonadotropin stimulation (recombinant FSH and highly purified urinary HMG) in a patient of GROS due to antigonadotropin antibody followed by IVF, resulting in successful live birth. Authors hypothesized that down regulation of endogenous gonadotrophins for three cycles might have contributed in desensitization of autoantibodies and up regulation of follicular FSH receptors. However, titers of gonadotrophins were not measured to prove this point. The pregnancy is possible in GROS by IVM of immature oocytes followed by IVF and intracytoplasmic sperm injection (ICSI) cycle. First birth in woman with ROS by this modality was reported by Grynberg et al in 2013. Further more cases of live birth in these patients with IVM have been reported till date. Galvão et al performed 24 IVM cycles in 9 patients with resistant ovary syndrome. Average of 11.5±10.4 cumulus oocyte complexes (COC) was retrieved, and IVM resulted in 3.4±3.1 mature oocytes. Eight patients became pregnant after ICSI and transfer of 23 cleavage stage embryos, resulting in five healthy live births, live birth rate was 16.7% per started cycle and 33.3% per patient. So, pregnancy is possible in these patients with IVM of self-oocytes followed by IVF/ICSI should be considered first line infertility treatment before embarking for donor oocyte IVF.
Due to rarity of this condition, there is lack of evidence-based management for GROS. We do not know why gonadotropin stimulation after suppression with OCPs and GnRHa was effective in some cases but ineffective in others.\textsuperscript{2,5,10,11} Further mechanism needs to be established by which \textit{in vitro} gonadotropins becomes effective on oocytes, same was not effective \textit{in vivo}. Studies are needed to get these answers.

**CONCLUSION**

Hypergonadotropic hypogonadism does not mean POI always. Clinician should do complete work up of these patients who present with infertility. Markers of ovarian reserve will differentiate these two conditions.

**Funding:** No funding sources  
**Conflict of interest:** None declared  
**Ethical approval:** Not required

**REFERENCES**
