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Case Series

Reproductive outcome in congenital hypogonadotropic hypogonadism: our experience in a tertiary care centre

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ABSTRACT

Congenital hypogonadotropic hypogonadism (CHH) is a clinical syndrome characterised by low levels of gonadotropins due to impaired secretion of GnRH. It is a rare cause of infertility in females and managing such cases becomes a challenge at times. We present 4 cases of CHH cases who were managed in our centre and had successful pregnancy outcome. All the cases were initially given hormone replacement therapy (HRT) for 3-4 cycles as the uterus and endometrium were infantile due to hormone deficiency. Post HRT ovarian stimulation with gonadotropins and IUI cycles were attempted. 2 cases conceived with ovulation induction and IUI on the second attempt. The third and fourth case had to undergo IVF cycle with prolonged stimulation with gonadotropins for 15 days and 17 days respectively and they finally conceived after frozen embryo transfer. First three patients carried their singleton pregnancies till term and delivered healthy newborns. The fourth patient underwent early preterm emergency cesarean of the twins due to obstetrical indications.

Keywords: Congenital hypogonadotropic hypogonadism, IVF, Infertility, Reproductive endocrinology, IUI

INTRODUCTION

Hypogonadotropic hypogonadism (HH) is one of the least common aetiologies for female infertility. But appropriate management in most of the cases leads to successful outcome.[1] CHH is a rare disorder that results from the failure of the normal episodic GnRH secretion, leading to delayed puberty and infertility. In nearly 90% of the patients with CHH, the most prevalent presentation is primary amenorrhea. But in 10% cases with CHH had some menstrual bleeding at some point in time during adolescence (primary to secondary amenorrhea) before the chronic amenorrhea sets in.[2] In minority of women with CHH several studies have reported absent breast development prior to oestrogen replacement therapy. Data from various studies shows great variability in pubarche ranging from absent to almost normal pubic hair. Varying degrees of GnRH deficiency may impact ovarian androgen production differently. Furthermore, adrenarche leading to increased production of adrenal androgen (i. e., dehydroepiandrosterone, androstenedione) could also contribute to pubarche.[3,4]

Although the clinical presentation of CHH in adolescence is more common, many patients do not seek medical attention until adulthood. At this point, low libido, infertility, or less commonly bone loss and fractures are the most common complaints.[5] A small subset of patients presents with adult-onset HH (AHH). These patients report normal pubertal development followed later by the complete inhibition of the HPG axis leading to severe HH. Very rarely CHH is diagnosed at an older age.[6] Although CHH was previously considered as a lifelong condition, it is now known that a subset of patients with CHH

spontaneously recover function of their reproductive axis following treatment.[7]

We present four cases of CHH who had successful outcome following infertility treatment at our centre. Informed consent was taken from all four cases before writing this case series.

CASE SERIES

Case 1

29 years old nulligravida, married for 4 years, cohabiting with husband since marriage, reported to the infertility clinic with complaints of inability to achieve pregnancy. As per her history her menstrual cycles are only to withdrawal. She remembers she had attained her menarche very late after taking some medicines. Secondary sexual development was normal. On evaluation serum FSH and LH levels were significantly low. Serum FSH was 0.32 mIU/ml and LH was 0.02 mIU/ml. Serum AMH was 3.14. Other hormonal parameters were within normal limits. Karyotyping showed normal female karyotype. Ultrasound showed a small uterus with ovaries showing lesser number of antral follicles not corroborating with the serum AMH levels. Male factor evaluation revealed normal semen parameters.

After evaluation the patient was put on HRT for 3 months. Followed by this she was stimulated with high dose gonadotropins (both recombinant FSH and LH) from day 2 of her menses. Regular follicular monitoring was done by transvaginal ultrasound. After prolonged stimulation for about 15 days, two follicles of about 18 mm developed in bilateral ovaries and the trigger with recombinant HCG was given followed by IUI after 48 hrs (Figure 1). Patient conceived following first IUI cycle. Her pregnancy continued without any complications. She went into spontaneous labour at 38 weeks 4 days and delivered a healthy female child of 2.83 kg.

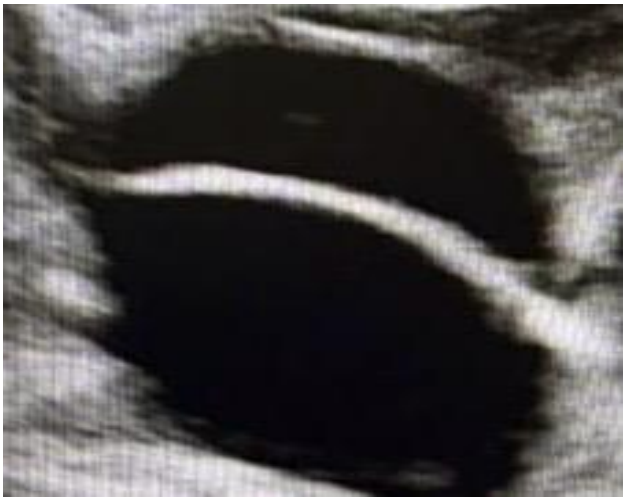

Figure 1: Two follicles in the left ovary post stimulation.

Case 2

26 years old nulligravida, married for 2 and half years was referred to the infertility centre as she was unable to get conceived after 2 years of cohabitation. She was diagnosed as a case of HH at 17 years of age after investigations for primary amenorrhea. Fertility evaluation revealed normal hysterosalpingogram (HSG) low serum FSH and LH levels (0.41 mIU/ml and 0.05 mIU/ml respectively) and a normal karyotype. Male factor was normal.

She underwent ovulation induction with gonadotropins followed by IUI. Patient conceived after 3rd IUI (Figure 2) attempt and her pregnancy continued till term and delivered a healthy male child of 3.1 kg at 39 weeks 2 days.

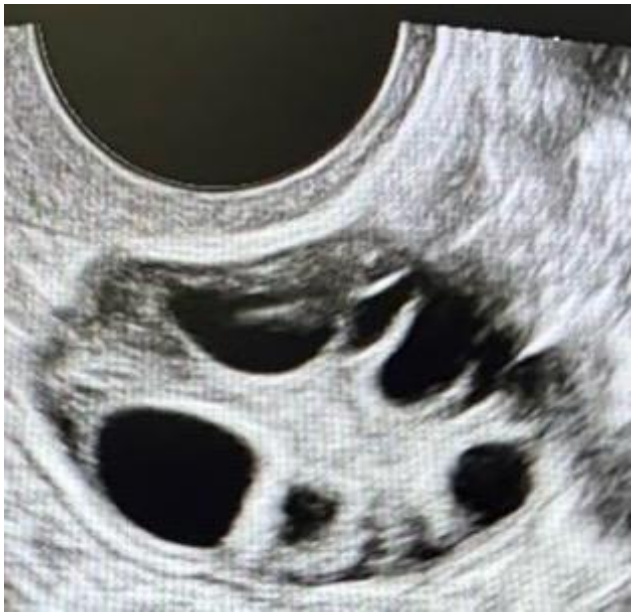

Figure 2: Right ovary post stimulation with gonadotropins.

Case 3

A 25 years old nulligravida, married in the last 3 years and cohabiting for 3 years referred to ART centre as a case of primary infertility. She had attained her menarche at 16 years of age and after that she gets her menses only after taking hormonal pills. Her ultrasound and MRI pelvis were suggestive of hypoplastic uterus and ovaries. Karyotype was 46XX. Serum FSH and LH were significantly low (0.43 mIU/ml and 0.07 mIU/ml respectively). Serum AMH levels were 2.19. Male factor evaluation revealed normal parameters.

She underwent HRT with oestrogen and progesterone for 3 months followed by 2 cycles of ovulation induction with gonadotropins and IUI. The 2 IUI cycles were unsuccessful. She was planned for IVF. After a prolonged 14 days of high dose recombinant FSH and LH, oocyte retrieval was done post trigger with recombinant hCG. 12 oocytes were retrieved (Figure 3). As the endometrial

thickness was not adequate plan was to freeze all embryos. 9 grade 1 embryos were frozen on day 3 at the 8-cell stage.

Patient underwent frozen embryo transfer one month later and conceived in the first attempt. She had developed gestational diabetes during pregnancy which was well controlled with diet and tablet metformin. The pregnancy continued till term without any major complications. Labor was induced with dinoprostone gel at 38 weeks. She underwent emergency caesarean for failed induction of labour with unfavourable cervix and delivered a male baby of 3.025 kg.

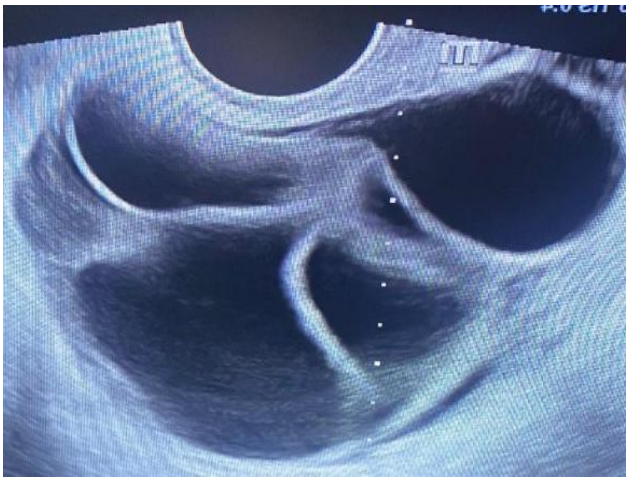

Figure 3: Left ovary on the day of oocyte retrieval.

Case 4

30 years old nulligravida, married for 9 years, cohabiting with husband for 6 years referred to the infertility clinic with complaints of inability to conceive and secondary amenorrhea. As per history she attained menarchy at 17 years of age and presently she gets menses only after taking hormonal pills. Serum FSH and LH levels were 1.21 mIU/ml and 1.23 mIU/ml respectively. Serum AMH was 1.18. Transvaginal ultrasound revealed a small hypoplastic uterus with ovaries showing no visible antral follicles. Karyotyping and MRI brain revealed no abnormalities. Male parameters were within normal limits.

She underwent HRT with oestrogen and progesterone for 4 months followed by an IUI cycle with gonadotropins. After 10 days of gonadotropins, IUI cycle was converted into IVF cycle because of multifollicular growth in bilateral ovaries. After 18 days of gonadotropins 4 oocytes were retrieved (Figure 4). Out of the 4 oocytes 3 fertilized and D3 embryos were cryopreserved. She later on underwent frozen embryo transfer and conceived with twins. Her antenatal period was uneventful till she went into preterm labour and underwent emergency caesarean at 28 weeks 2 days as both the twins were in breech presentation. She delivered twin female babies weighing 910 gm and 880 gm respectively. Second twin expired after 4 days of delivery.

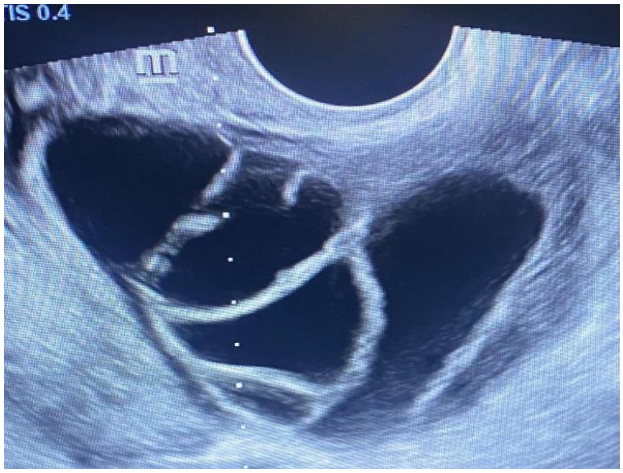

Figure 4: Ovary on the day of oocyte retrieval.

DISCUSSION

HH is the group I of ovulation disorders according to the WHO classification system.[8] It can be manifested by primary or secondary amenorrhea and low or normal serum gonadotropins. Women with HH and infertility can achieve successful pregnancies with appropriate treatment. The relatively high doses of gonadotropins needed to induce ovulation in a HH patient is well documented. In our study all the three cases required prolonged and higher doses of gonadotropins for the ovulation induction. Study conducted by Kumbak and Kahraman has also observed a longer stimulation duration and higher gonadotropin dose in patients with HH.[9] The need for prolonged stimulation in HH cases can be explained by the "dormant" ovaries that need to be primed before follicular response is achieved.

The study conducted by Ghaffari et al found that the implantation rates of the transferred embryos, pregnancy rates and the live birth rates in HH patients are comparable with the normal infertility controls.[10] In our study also the patient who had undergone IVF has conceived in very first attempt of the frozen embryo transfer.

Due to the deficiency of long-term hormonal stimulation, most of the patients with HH have small infantile uterus. Although uterine size can be improved with HRT prior to the ovulation induction, concerns still remains whether obstetric complications like preterm delivery are more common in HH cases. Study conducted by Zhang et al showed that pregnancy related complications are not raised in HH patients.[11] In our study also all the three HH cases conceived after infertility treatment carried their pregnancy till term without any major obstetrical complications.

CONCLUSION

The prognosis for women with HH and infertility is highly favourable with appropriate treatment. Most of the women with HH respond to the exogenous gonadotropins when

given for a prolonged duration and the live birth rates are comparable with those with other causes of infertility. Early diagnosis, individualized treatment and careful monitoring are the keys to ensure the best outcomes.

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