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Successful Pregnancy in A Woman with Primary Amenorrhea (Kallmann Syndrome)

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Abstract

Kallmann syndrome is congenital hypogonadotropichypogonadism associated with anosmia/hyposmia (loss or diminution of smell). The female patient with hypogonadotropichypogonadism initially presents with primary amenorrhea. The diagnosis can be made by absent or underdeveloped secondary sexual characteristics, small-sized uterus and ovaries, and absent or low levels of circulating gonadotropins. Sequential estrogen and progesterone administration restore menstruation during the therapy. Anovulation and infertility respond successfully to medical treatment with gonadotropins in most patients with established hypogonadotropichypogonadism. Fertility treatment involves ovarian stimulation with exogenous gonadotropins or pulsatile Gonadotropin-releasing hormone (GnRH) therapy.

1. Background

Kallmann syndrome was first identified by Maestre de San Juan in 1856, following which Kallmann et al. identified the genetic background of the condition a few years later. It is a congenital cause of hypogonadotropichypogonadism due to isolated Gonadotropin-releasing hormone (GnRH) deficiency and is classically associated with hyposmia or anosmia. The reason behind this association is that during embryogenesis, the GnRH neurons originate from the neural crest within the olfactory placode and migrate along with the olfactory neural fibers to undergo terminal differentiation.[1] Normal development and functioning of the hypothalamo-pituitary-gonadal axis is the fundamental requirement for puberty and further reproductive function. Pulsatile GnRH secretion stimulates the pituitary to produce Follicle stimulating hormone (FSH) and Luteinizing hormone (LH).[2] In the absence of these hormones, the ovaries are not stimulated; thereby, follicular growth and ovulation do not occur. Girls with Kallmann syndrome initially present with primary amenorrhea due to anovulation which also affects their reproductive function in their later life. The following is the summary of successful pregnancy and live birth in a woman with features of Kallmann syndrome.

2. Case details

A consultant endocrinologist referred a 26-year-old lady to a case of primary amenorrhea. Her spouse was a 27-year-old gentleman and was unaware of her menstrual history. The couple was married for five months and were anxious to conceive. She was never evaluated by a specialist for fear of shame and ridicule from family and friends. A detailed history pertaining to primary amenorrhea was obtained. She gave a history of anosmia since the time she remembered. There was no history of headache, visual disturbances, head trauma or surgery, intracranial infections, chronic intake of medications, chemotherapy, or radiation therapy. During her earlier visits with the doctor, she was prescribed combined estrogen and progesterone pills with which she had withdrawal bleeding. In contrast, she did not menstruate when progesterone alone was prescribed. This was suggestive of an intact end-organ (the uterus, in this scenario) and absence of estrogen, which could either be due to decreased production of gonadotropins or absent or non-functioning ovaries. Since then, she has been randomly medicating herself with combined oral contraceptive pills (estrogen and progesterone). She has been sexually active since marriage. On

examination, she was of normal build and was well nourished with a body mass index (BMI) of 27. She had breast and pubic hair development of Tanner Stage III, with normally developed external genitalia. Speculum and digital pelvic examination revealed a small-sized cervix and a small-sized mobile uterus. Transvaginal ultrasound showed a small-sized uterus and ovaries which could again be due to decreased production of gonadotropins or, absent or non-functioning ovaries. Our provisional diagnosis was hypogonadotropichypogonadism (Kallmann syndrome), confirmed by laboratory findings of very low circulating levels of serum gonadotropins [FSH – 0.28 mIU.mL-1 & LH – 0.05 mIU.mL-1 (Normal basal levels – 1.8-11.2 mIU.mL-1 & 2.0-9.0 mIU.mL-1, respectively).[3] She was counseled regarding the genetic component and the need for genetic evaluation, but she was not willing to undergo genetic testing.

As the couple was anxious about fertility treatment, the male partner underwent semen analysis as a part of the essential evaluation. In view of the confirmed diagnosis of hypogonadotropichypogonadism for the wife, it was decided to administer ovulation induction drugs in the form of gonadotropin injections. Before initiating ovulation induction, it was decided to prime her uterus for a few cycles with estrogen and progesterone to improve the uterine size before conception, in view of the long gap from previous hormonal treatment and the size of her uterus was small (Anteroposterior diameter – 14 mm; Normal 25-35 mm). Her treatment regimen consisted of 3 cycles of estradiolvalerate 4 mg daily for 28 days with vaginal micronized progestogens from Day 19 for 10 days. Withdrawal bleed was noted after every process, and there was an increase in the AP diameter of the uterus to 23 mm by the end of 3 cycles. The informed decision was taken for ovulation induction with consent from both partners. Ovulation induction with urinary HMG (Human Menopausal Gonadotropin) was started from day 3 of her cycle.

A chronic low-dose step-up protocol was followed to avoid hyperstimulation of ovaries. The protocol involves administering small daily doses of hMG (37.5-75 IU) for at least seven days, following which follicular growth is monitored. In the absence of a growing follicle, the dose is increased by 50%, or an additional 37.5 IU is added and continued for another seven days. The dose is maintained at the same level when a growing follicle is visualized in the ultrasound scan. Our patient developed a dominant follicle after 20 days of stimulation with gonadotropins and two small follicles. When the lead follicle reached a size of 15 mm, the gonadotropin injections were stopped, as the follicle becomes FSH-independent at this stage. The follicle got a mean diameter of 20 mm on Day 23 when we administered human Chorionic gonadotropin (hCG) injection of 5000IU to trigger ovulation, and the couple was advised to have coitus. Unfortunately, sexual contact was not possible due to erectile dysfunction due to extreme anxiety. Hence though ovulation induction was successful, pregnancy did not happen.

Further discussions and possible options led to another cycle of gonadotropin-induced ovulation with Intrauterine insemination (IUI) of the husband's prepared semen sample to avoid another situational sexual dysfunction. After establishing tubal patency with HSG (hysterosalpingogram), the second cycle of ovulation induction was successfully carried out with a low-dose step-up protocol of gonadotropins. IUI was proceeded 36 hours after hCG with a washed semen sample. Luteal support was achieved with continued estrogen and progestogen therapy through a corpus luteum was evident from ovulation. Physiologically, a small spike of LH is necessary for this menstrual cycle phase for sustained corpus luteal function. Due to the hypogonadotropic status, this spike is deficient in these women, and hence luteal support becomes inevitable till placental function establishes from 9-10 weeks of gestation. Live intra uterine twin pregnancy was confirmed at six

weeks, and the further course of pregnancy was uneventful with the birth of healthy twin girls at term.

The patient was advised regarding the need for continued hormone replacement therapy to avoid adverse health effects due to decreased estrogen, including osteoporosis.

2. Literature:

2.1. Infertility evaluation:

Although the evaluation for infertility is generally done after one year of regular, unprotected intercourse, some conditions like advanced age of the female partner, previous abdominal or pelvic surgeries, history of recurrent pelvic infections or abdominal tuberculosis, treatment of earlier malignancies, oligomenorrhea or amenorrhea and conditions in the male partner which may affect spermatogenesis warrant an earlier evaluation and intervention if required.[4] Women with amenorrhea do not ovulate, and those with oligomenorrhea have infrequent ovulation, which affects the probability of conception. Therefore, evaluating and treating these women at their earliest visit to the specialist is recommended.

2.2. Primary amenorrhea:

It is defined as the failure to attain menarche at 13 years of age in the absence of secondary sexual characteristics or 15 years of age, irrespective of the presence or absence of secondary sexual characteristics.[5]Various causes of primary amenorrhea are mentioned in table 1.

Table 1:
1.Outflow tract
i. Absent uterus Mullerian agenesis Androgen Insensitivity Syndrome ii. Ashermann's syndrome (Uterine synechiaie) iii. Obstruction Cervical agenesis Transverse vaginal septum Imperforate hymen
2.Ovary
i.Primary ovarian insufficiency (Turner's syndrome, Gonadal agenesis) ii.Premature ovarian failure (Turner's mosaic, Autoimmune disorders, Chemotherapy, Radiation therapy, Idiopathic)
3.Pituitary
i.Hyperprolactinemia ii.Infection iii.Inflammatory/infiltrative lesions iv.Vascular conditions – aneurysms v.Cranial radiation
4.Hypothalamic
i.Idiopathic (Kallmann syndrome) ii.Functional (Stress, Eating disorders) iii.Tumor iv.Vascular v.Infections vi.Chronic disease vii.Cranial radiation viii.Steroid abuse

2.3. Hypogonadotropichypogonadism (HH) and Kallmann syndrome:

In the above-mentioned conditions involving the hypothalamus or the pituitary, there is a diminished or absent secretion of gonadotropins. Kallmann syndrome is an isolated gonadotropin-releasing hormone (GnRH) deficiency where the absence of GnRH secretion results in low levels of circulating gonadotropins. Gonadotropins, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are responsible for stimulating ovaries, thereby initiating puberty and maintaining regular ovulation. When these hormones are not secreted in optimal amounts, there is no follicular growth, resulting in anovulation and hypoestrogenemia. Due to this hypoestrogenic state and non-estrogen-primed endometrium, withdrawal bleeding is not achieved with progesterone alone

in this group of patients. The estimated prevalence of HH ranges from 1:10,000 to 1:86,000 individuals.[6] The incidence in men is found to be around 1:10,000-30,000 whereas it is 1:50,000-1,25,000 in women.[7,8] Kallmann syndrome is congenital HH with associated anosmia, which occurs due to mutations in the KAL1 gene. The other genes implicated in the causation of the syndrome are FGFR1, FGF8, CHD7, PROKR2, and PROK2.[9] Genetic basis is seen in about 10-20% of cases, where the condition can be inherited as either X-linked, Autosomal dominant, or recessive inheritance.[10] Inheritance pattern is most commonly X-linked, which explains the significantly higher incidence in men.[9] Men present with azoospermia, whereas women present with anovulation and amenorrhea. The development of secondary sexual characteristics depends on exposure to exogenous hormone therapy. As the sensitivity of molecular testing is only around 30%, the diagnosis is primarily by clinical evaluation and confirmed by biochemical diagnosis.[11]

2.4. Infertility management in hypogonadotropichypogonadism

Oral ovulogens like selective estrogen receptor modulators (Clomiphene citrate) and aromatase inhibitors (Letrozole) require endogenous gonadotropins and gonadal steroids to promote follicular growth. Hence, these drugs are not suitable for patients with HH. Women with HH require exogenous gonadotropin injections or pulsatile GnRH therapy for follicular growth and maturity.[12]As evident from Figure 1, LH plays a major role in follicular growth and development; therefore, hMG injections (which have both FSH and LH) are preferred over recombinant FSH. Once the follicle reaches around 18-20 mm, ovulation may be triggered with either urinary or recombinant human chorionic gonadotropin (hCG). It is imperative to start with a lower dose of gonadotropin and step up in a gradual manner to avoid multiple follicles or ovarian Hyperstimulation syndrome (OHSS), which is a potentially life-threatening situation.[13]

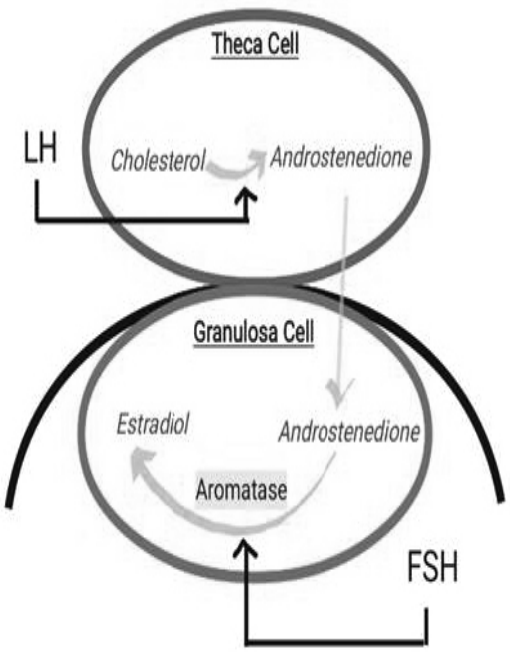

Figure 1: Two cell two gonadotropin theory

2.5. Luteal support:

The corpus luteum produces estrogen and progesterone to support the endometrium during pregnancy until the placenta takes over the function. The corpus luteum requires LH stimulation during the luteal phase to produce these hormones, and therefore, in the absence of LH, the luteal phase has to be supported with estrogen and progesterone supplements or hCG injections in these women until the luteoplacental shift happens, which is approximately around 8-9 weeks of gestational age.[12,14]

3. **Conclusion**

Endocrinologists primarily see hypogonadotropichypogonadism in men and most commonly in women for sexual infantilism/primary amenorrhea, which is the striking feature around puberty. Medical therapy is advantageous in inducing menstrual cycles and initiating spermatogenesis. Early referral to reproductive medicine consultants is essential for treating infertility due to anovulation.[15] Judicious management with Gonadotropin therapy is highly successful in inducing ovulation with a high

probability of pregnancy in patients with otherwise normal male and female factors.[16]

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