Review Article

Hypogonadotropic hypogonadism and assisted reproductive techniques: a review

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Abstract

Backgroud: Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disorder that manifests as absent or delayed pubertal development and infertility due to defective secretion or action of gonadotropin-releasing hormone (GnRH). The incidence is 1 in 10,000 in men and 1 in 50,000 in women. **Materials and Methods:** An online search was made on Google scholar and PubMed with search words hypogonadotropic hypogonadism (HHG), in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), intrauterine insemination, male, and female, and the retrospective/prospective studies that met the inclusion criteria were selected. **Inclusion criteria:** The studies included were retrospective and researched the effect of assisted reproductive techniques (ART) on women with CHH. The studies were included if they had any one of the following primary outcomes: fertilization rate (FR), implantation rate (IR), clinical pregnancy rate (PR) per cycle/embryo transfer (ET), and live birth rate (LBR). **Exclusion criteria:** (1) Review articles, (2) case reports, (3) duplication of studies, and (4) studies with no available endpoints. Secondary outcomes were any of the following: abortion rate, multiple gestations, ovarian hyperstimulation syndrome, and any adverse effect. The studies were reviewed for the demographic profile of the patients, drugs, and their doses used for stimulation protocol, fresh/frozen sample used, ART procedure, number of metaphase II (M II) oocytes retrieved, FR, IR, clinical PR, and adverse outcomes. **Results:** Seven studies have shown a statistically significant increased requirement of dose and duration of gonadotropins in women with CHH while reporting a comparable metaphase II (M II) oocyte recovery rate, FR, PR, IR, and LBR, when compared with controls. Five studies were selected for male HHG with ART, varying from a sample size of 4 to 31. Inj human chorionic gonadotropin (HCG) and Inj human menopausal gonadotropin (HMG)/recombinant follicle-stimulating hormone (rFSH) was used to induce spermatogenesis for a period of 6 to 24 months. In men with azoospermia/unable to conceive after gonadotropin therapy, ICSI was performed. Testicular sperm extraction (TESE) was used for the extraction of sperm in azoospermic men. FR from 41.7% to 82%, CPR from 17.6% to 51.5%, and LBR from 20% to 41.3% have been reported. **Conclusion:** Controlled ovarian hyperstimulation (COH) with IVF/ICSI should be offered to those patients who fail to conceive naturally or with intrauterine insemination/gonadotropin therapy. Newer regimes of COH (HCG with HMG/FSH), vitrified-thawed ET for female HHG, and pretreatment with FSH followed by HCG and follitropins for induction of spermatogenesis in male HHG look promising and need to be researched further.

Keywords: ART, hypogonadotropic hypogonadism, ICSI, infertility male/female, IVF

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INTRODUCTION

Congenital hypogonadotropic hypogonadism (CHH) is a rare genetic disorder that manifests as absent or delayed pubertal development and infertility due to defective secretion or action of gonadotropin-releasing hormone (GnRH).[1] It is associated with inappropriately low gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and sex steroids (testosterone or estradiol) in the absence of any functional or anatomical defect in the hypothalamic-pituitary gonadal axis (HPG).[2] The incidence is 1 in 10,000 in men and 1 in 50,000 in women.[3] Besides reproductive function, it is also often associated with other abnormalities such as cleft-lip, cleft-palate, deafness, renal abnormalities, neurodevelopmental delay, and cardiac and digital defects.[3-5] Hence, it has a negative impact on the patient's sexual, psychological, bone, and metabolic health.

Etiology

Hypogonadotropic hypogonadism (HHG) may be congenital or acquired. CHH may be broadly divided into anosmic CHH [Kallaman syndrome (KS)] and normosomic congenital HHG (nCHH) [Table 1].[2] While traditionally, KS was reported to be more common,[6] recent studies have now reported nCHH as the more common variant.[3,5] With the advent of next-generation massive parallel sequencing (NGS), such as whole-exome sequencing (WES), whole-genome sequencing (WGS), and targeted exome approach, several new genes have been identified.

Genetic origin

Both anosmic and normosmic have a variable pattern of genetic inheritance. Autosomal dominant/recessive, X-linked transmission have been identified. The variable phenotypes can be explained due to the oligogenic inheritance [the phenotype is expressed when there is more than 1 mutant Idiopathic HHG (IHH)/KS gene][6] seen in 10% to 20% cases.

In anosmic variant (KS), there is a defective embryonal migration of GnRH neuron (in association with olfactory receptor neurons) from the neural crest to hypothalamus. Some of the associated gene defects are KAL 1, FGFR1, FGF8, and PROK2.[7] In normosmic variant (nCHH), the mutations can be in the hypothalamic-pituitary region (DAX1, SRA1, etc.), GnRH pulse generator (TAC3, KISS1, KISS1R, GNRH1), pituitary gonadotropes (GNRHR, FSHB, LHB), or when associated with obesity (LEP, LEPR, PC1) and neurodegenerative syndromes [Gorden Holmes Syndrome, 4H syndrome (hypomyelination, HHG, and hypodontia), Martsolf syndrome, and DMXL2].[9]

Pathophysiology

An intact hypothalamic-pituitary-gonadal (HPG) axis is essential for normal pubertal development. The axis is active in utero (and early neonatal life in males), and then becomes dormant, to be reactivated at the time of puberty. The activation of the GnRH induced pulse of LH and FSH leads to the development of pubertal changes. Due to defective GnRH pulse, there is delayed/absent puberty, delayed bone fusion (eunuchoid habitus), and reduced bone mineral density due to decreased sex steroids.

In males, FSH stimulates the proliferation of Sertoli cells and the development of spermatogonia, whereas Leydig cells get stimulated by LH and lead to the production of testosterone. This high concentration of local testosterone leads to spermatogenesis. Due to the lack of HPG axis in utero and the neonatal life, males may present in the neonatal period with cryptorchidism or micropenis.[9,10]

TABLE 1: Causes of hypogonadotropic hypogonadism[8]

Congenital hypogonadotropic hypogonadiam	Acquired hypogonadotropic hypogonadism
Kallman syndrome	Pituitary lesion (tumor, granuloma, abscess)
Idiopathic hypogonadotropic hypogonadism	Cushing syndrome
Other genetic mutations	Drug use (opiates, alcohol abuse, steroids, chemotherapy)
Prader Willi syndrome	Pituitary irradiation, trauma, or surgery
Waardenburg syndrome	Iron overloadSarcoidosisHistiocytosisThalassemia
Gordon Holmes syndrome	Anabolic steroids use
Bardet Biedl syndrome	Hyperprolactinemia
CHARGE syndrome (coloboma, heart defects, choanal atresia, growth retardation, genital abnormalities, and ear defects)	MalnutritionEating disorderExcessive exercise
Septo-optic dysplasia	Chronic disease

In females, the early stage of follicular growth is independent of these hormones. However, at the time of puberty, LH stimulates theca cells to produce androgens, and FSH is required for final maturation of the follicle, and secretion of estradiol from the granulosa cells. Hence, it often goes unnoticed in females till puberty.

Clinical presentation

Females

Although the primary complaint in females is primary/ secondary amenorrhea, a few women have also reported spontaneous menses, and many have shown some development of secondary sexual characteristics [thelarche; pubarche, Tanners stage 3 (36.7%) or 4 (30%); axillary hair growth).[3,5] The other presenting complaints are decreased libido (83.3%), sleep disorder (53.3%), infertility (72.2%), vaginal dryness (40%), and eunuchoid habitus (76.7%).[5]

Males

In males, the chief complaints were micropenis (48.3%) and small testes (37.9%). Other complaints were sleep disorder (75.9%), erectile dysfunction and low libido (72.4%), fatigue (55.2%), high pitched voice (41.4%), and infertility (48%).[5]

CHH may also be associated with metabolic syndromes such as diabetes mellitus and obesity. Patients with KS may present with additional congenital anomalies such as cleft palate, unilateral renal agenesis, split hands, short feet, short metacarpals, deafness, and mirror movements (synkinesia).[9]

Diagnostic workup

Because CHH is a diagnosis of exclusion, it requires an extensive workup to exclude acquired causes of HHG and also to screen for associated defects and genetic mutations [Table 2]. Many patients present with infertility and hence, need to be evaluated for the same. Although semen analysis, gonadal ultrasound, and hormonal profile are done for the affected males, the affected women undergo tests for ovarian reserve, besides the hormonal profile and the complete infertility workup.

Antral follicle count (AFC) may be difficult to interpret in these women, due to the smaller size of the ovaries and low pool of antral follicles. Because of ovarian follicles up to 4 mm diameter act as the main source of serum anti-Mullerian hormone (AMH). AMH may be used to predict ovarian response and tailor the dose of gonadotropins for assisted reproductive techniques (ART) cycles in these women.[10,11]

Treatment

The treatment in adults is directed to the desire of the patient, whether they want fertility or not. In case they do not wish to conceive, they can be put on hormone replacement therapy (testosterone for the male, estrogen, and progesterone for the female). This will help improve bone mineral density, epiphyseal closure

TABLE 2: Investigations for CHH[2,4,8]

Investigation	Assessment
Complete blood count, renal and liver function test, C reactive protein, erythrocyte sedimentation rate	To screen for chronic disease/ marker for inflammation
Morning measurement [Serum LH, FSH, testosterone/estradiol, prolactin, free thyroxine, thyroid stimulating hormone, insulin-like growth factor- 1	Assessment of pituitary and thyroid functions
Serum GnRH,Inhibin B (optional)	Routine testing of GnRH is questioned as not of much use in diagnosis, if gonadotropins have been tested.
Anti-Mullerian hormone	Predictor of ovarian response
Semen analysis (Male)	Assessment of infertility
Adrenocorticotropic hormone, cortisol, free urinary cortisol, dexamethasone suppression test	Adrenal axis evaluation
Serum ferritin levels	To screen for Iron overload/ deficiency
Wrist X-ray (adolescents and children)	To determine bone age
Brain MRI	To screen for hypothalamo-pituitary lesion, abnormalities/ absence of olfactory placode
Renal ultrasound	To screen for renal agenesis
Pelvic ultrasound (female)	Assessment of gonads
Scrotal ultrasound (male)	Assessment of gonads
Bone densitometry (DXA)	To assess osteopenia
Karyotype or Comparative Genomic Hybridization(CGH) array	Screen for deletions/ insertions/gene syndromes
Gene screening: Sanger or next-generation sequencing: whole exome sequencing, whole genome sequencing	To identify genetic mutations/ KS genes
Olfactometry	To assess for anosmia
Ocular fundoscopy	Optic nerve hypoplasia

CHH, congenital hypogonadotropic hypogonadism; FSH, follicular stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MRI, magnetic resonance imaging.

(young adults), development of secondary sexual characteristics, improved libido, and help to restore self-confidence and a sense of wellbeing. In females, estrogen is started in a low dose of 1 to 2 mg/day, and gradually increased over a period of 12 to 24 months, to allow the development of secondary sexual characteristics. Then the patient is put on cyclic progesterone (200 mg for 14 days) to prevent endometrial hyperplasia. In men, testosterone enanthate 200 mg once a month then 2 to 3 weekly may be given. Lifelong therapy is required as the reversal is observed in only 10% to 20% of the cases.[8]

Genetic counseling

Genetic counseling should be initiated at the first visit itself. Counseling should be done regarding the phenotypic expression of the identified gene defects, for example, the possibility of renal agenesis if the mutation lies in ANOS1/KAL1 or primary adrenal failure and infertility if there is DAX1/NROB1 mutation. It is also important to counsel the patient regarding the risk of inheritance (Mendelian or oligogenic) and its expected phenotypic expression, when they seek treatment for infertility in adult life. For example, in the pedigrees indicating autosomal dominant transmission, whereas the risk of transmission to the offspring is 50%, the phenotypic expression is variable and difficult to predict.[6]

Treatment for infertility

A literature search for the available treatment options for a patient with HHG was made.

MATERIALS AND METHODS

An online search was made on Google scholar and Pubmed with search words "hypogonadotropic hypogonadism," "IVF," "ICSI," "IUI," "male," and "female," and the retrospective/prospective studies that met the inclusion criteria were selected.

Inclusion criteria

The studies included were retrospective and researched the effect of ART on women with CHH as there were no prospective studies. Studies were included if they had any one of the following primary outcomes: fertilization rate (FR), implantation rate (IR), clinical pregnancy rate (PR) per cycle/embryo transfer (ET), and live birth rate LBR.

Secondary outcomes were any of the following: abortion rate, multiple gestations, ovarian hyperstimulation syndrome, and any adverse effect.

Exclusion criteria

(1) Review articles, (2) case reports, (3) duplication of studies, and (4) studies with no available endpoints.

The studies were reviewed for the demographic profile of the patients, drugs and their doses used for stimulation protocol, fresh/frozen sample used, ART procedure, number of metaphase II (M II) oocytes retrieved, FR, IR, clinical PR, and adverse outcomes.

RESULTS

Nine studies were selected on ART in female HHG [Table 3], all were retrospective, with a sample size varying from 7 to 81. Seven of nine studies had a well-matched control group of either tubal factor, mild male factor, or unexplained infertility.

Most studies (six) have used human menopausal gonadotropin (HMG), supplementing it with either urinary/recombinant follicle-stimulating hormone (rFSH; two). Cechinno *et al.*[11] have used Luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and have reported a significantly higher dose of LH required in women with HHG.

Seven studies have shown a statistically significant increased requirement of dose and duration of gonadotropins in women with CHH, whereas reporting a comparable M II oocyte recovery rate, FR, PR, IR, and LBR, when compared with controls. However, Gaffari *et al.*[15] reported a statistically significant difference in the fertilization rate, but no difference in PR and LBR, when matched with controls.

Five studies were selected for male HHG with ART, varying from a sample size of 4 to 31 [Table 4]. None of them had a control group. Inj human chorionic gonadotropin (HCG) and Inj HMG/rFSH was used to induce spermatogenesis for a period of 6 to 24 months. In men with azoospermia/unable to conceive after gonadotropin therapy, intracytoplasmic sperm injection (ICSI) was performed. Testicular sperm extraction (TESE) was used for the extraction of sperm in azoospermic men. FR from 41.7% to 82%, CPR from 17.6% to 51.5%, and LBR from 20% to 41.3% have been reported.

Adverse events

Six studies commented on adverse events. Eight reported abortions and nine multiple pregnancies. None of the

TABLE 3: Female hypogonadotropic hypogonadism

Study	Number of patients	Mean age ± SD (years)	Mean BMI ± SD (kg/m^2)	Mean duration of Infertility (years)	Drug (IU)/Duration of treatment	Control group	Type of ART, Number of cycles	MI oocytes/ Total number of oocytes retrieved	Outcomes (PR, FR, IR, and LBR)	Adverse events
Kumbat *et al.*[12]	27	32.8 ± 4.9	25.7 ± 4.5	9.3 ± 6.1	Inj HMG and rFSH4537 ± 1887 (60 ampoules)/14 days (P = 0.001)	39/12 days, Antagonist protocol	Antagonist protocol with IVF + ICSI/ICSI(27 cycles)	72%	FR = 89% (P = 0.03), IR = 36.5%PR = 59.3%	Abortion rate=0
Ulug[13]	58	32.21 ± 5.2	21.09 ± 1.3	NA	Inj HMG (80.92 ± 21.8 ampoules) (P = 0.0001)/13.61 ± 2.1 (P = 0.0001)	116/11.69 ± 1.5 days, Gn RH agonist protocol	Inj HMG with IVF (53 cycles)	75.8% (NS)	FR = 73.9%(NS), IR = 32.4% (NS), PR = 56.6% (NS)	Multiple pregnancy = 13% (NS), Abortion<8%
Yildirim *et al.*[14]	10(13 cycles)	31.3 ± 5.6	25.3 ± 3.1	6.8 ± 3.6	Inj HMG, 3630 ± 1685 (P < 0.05)/ 13.0 ± 2.4 (P < 0.001)	20, 9.2 ± 0.8/r FSH ith Gn RH antagonist protocol	Inj HMG with ICSI (13 cycles)	5.9 ± 2.0/ 6.5 ± 3.1(NS)	FR = 81.9% (NS)IR = 38.3%(NS) PR = 80%(NS)LBR = 50%	Abortion= 25% Ectopic pregnancy (7.1%) in control group.
Ghaffari *et al.*[15]	81	33.5 ± 5.3	26.1 ± 4	8.9 ± 5.4	Inj HMG with/without rFSH (64. ± 30.2 ampoules) P < 0.001/ 13.8 ± 2.6, P < 0.001	84/10.4 ± 1.9	Inj HMG with/ without rFSH, 81 cycles	6.3 ± 4.7/ 8.3 ± 6(NS)	FR = 61.2% (P = 0.001)IR = 40% (NS)PR = 19.4% (NS)LBR = 15.2%(NS)	Twin pregnancy rate = 5.5% (NS)
Yilamz *et al.*[16]	33	32.5 ± 4.73	26 ± 3.81	NA	Inj HMG4741 ± 1912 (P < 0.001)/ 12.5 ± 2.06 (P < 0.001)	47/ 10.08 ± 1.62, GnRH agonist protocol with rec FSH	Inj HMG with IVF/ICSI	8.39(5.3)/10 (5.8) (NS)	PR = 30% (NS)	NA
Pandurangi *et al.*[17]	7	27	25.29 ± 3.77	NA	Inj HMG, uFSH, ICSI/29.28 days	NA	Inj HMG, uFSH, ICSI	70%	PR = 31.6%FR = 85%LBR = 85.7%	Abortion- 14.29% Multiple pregnancy- 14.29%
Jiang *et al.*[18]	46	30.93 ± 3.90	21.26 ± 1.89	3 (1–11)	Inj HMG, with low dose Inj HCG, IVF/ICSI, (13 (10–22) d(P < 0.001), 2959.78 ± 559.23 IU, (P = 0.005) 61 cycles	71, Triptorelin 3.75 mg, 5 weeks later Inj HMG	IVF/ICSI(61)	8.15 ± 5.04/ 8.96 ± 5.16 (NS)	FR = 82.13%(P = 0.03), Cleavage rate=99.68%(P = 0.001)IR=41.46%(P = 0.141) CPR=59.52%(P = 0.344)	Abortion (4%)(NS) Multiple pregnancy rate (41.67%)
Kuroda *et al.*[19]	91	32.6 ± 0.5	18.0 ± 0.3	NA	Inj HMG, 12.2 0.3/ 2292 96	NA	Gonadotropins/ 117 cycles/IVF-39, ICSI-37, IVF + ICSI-37	8.9 ± 0.6/ 9.9 ± 0.7	CPR=59.3%LBR=45.9%	Abortions(13.3%)
Cecchino *et al.*[11]	26	33	NA	NA	Gonadotropins/Antagonist protocol in some/13 (P < 0.001)/2700 (P = 0.038)	62/Antagonist protocol	Gonadotropins/ Antagonist protocol/IVF/ ICSI	8.5/13.5(NS)	FR=75.6%(NS)IR=59.2%(NS) PR=69.2% (NS)LBR=61.5%(NS)	NA

FR, fertilization rate; GnRH, gonadotropin-releasing hormone; HMG, recombinant follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IR, implantation rate; IVF, in vitro fertilization; LBR, live birth rate; NS, not significant; NA, not applicable; PR, pregnancy rate; rFSH, recombinant follicle stimulating hormone.

TABLE 4: Male hypogonadotropic hypogonadism

Study	Number of patients	Mean age/ SD (years)	Mean BMI/ SD (kg/ m^2)	Mean duration of Infertility (years)	Drug (IU)/ Duration of treatment	Control group	Type of ART, No. of cycles	Sperm retrieval	Fresh/ frozen semen	Outcomes (PR, FR,IR) and LBR	Adverse events
Fahmy *et al.*[20]	15(sperms retrieved in 11)	NA	NA	NA	Inj HCG, Inj HMG> 6 months	NA	TESE/ICSI (17 cycles)	11/15 (73%)	1frozen sperm,16 fresh (3 from ejaculate, 13 from TESE)	FR=41.7% CPR=17.6% Cumulative LBR=20%	1 twin pregnancy
Backircioglu *et al.*[21]	25	34.5 ± 5.2	NA	7.1 ± 4.0	Inj HCG + Inj Rfsh:9-12 months	NA	ICSI, 22 cycles	NA	Fresh/ frozen ejaculate	FR=65% PR=54.5%	AbortionsMultiple pregnancies
Resorlu *et al.*[22]	17 (Group-1:11- IHH. Group 2:6-secondary HHG)	Group 1:30.1 yearsGroup 2: 27.2 years	NA	NA	Inj HCG + Inj rFSH :18-24 months	NA	ICSI, 11 cycles	NA	Fresh semen	PR=54.5%	3 abortions,1 multiple pregnancy
Akarsu *et al.*[23]	4	36.25 years	NA	NA	InJ HCG + Inj HMG: 10 months	NA	TESE, ICSI, 6 cycles	4/4 (100%)	TESE: 4 Fresh/ 2 frozen thawed	FR=58% (Fresh TESE) FR=19% (Frozen-thawed TESE, PR=50%	1 abortion,1 twin pregnancy
Dokuzeyal *et al.*[24]	31	34.82 years	NA	NA	InJ HCG + Inj HMG	NA	Micro-TESE (34.5%), ejaculated sperm (65.5%)-ICSI, 29 cycles	NA	NA	FR=82% PR=51.7% LBR=41.3%	2 twin pregnancies

FR, fertilization rate; GnRH, gonadotropin-releasing hormone; HMG, recombinant follicle-stimulating hormone; ICSI, intracytoplasmic sperm injection; IR, implantation rate; IVF, in vitro fertilization; LBR, live birth rate; NS, not significant; NA, not applicable; PR, pregnancy rate; rFSH, recombinant follicle-stimulating hormone.

studies reported ovarian hyperstimulation syndrome (OHSS).

DISCUSSION

HHG is a rare cause of infertility (1%) hence, there were no prospective trials.[12] The studies available are few, have a small sample size, heterogeneous, and retrospective in design, which makes them prone to selection bias.

The women in these studies have been pretreated with combined estrogen and progesterone for 2 to 3 months before commencing ART cycle. The uterus is hypoplastic in these women, and it helps to regenerate the endometrium and increase the size of the uterus. Most of the studies (eight) have used HMG or combined FSH and LH for controlled ovarian hyperstimulation (COH) in women with CHH without pituitary suppression. Fig. 1

LH is required for androgen production from theca cells, which acts as a substrate for the aromatase enzyme and gets converted to estrogen by the granulosa cells. Although early ovarian follicles have receptors for FSH only, as they mature, they express receptors for both LH and FSH and get responsive to both. LH completes the meiotic division in the oocyte, releases oocytes, and causes the development of corpus luteum. Although FSH may be sufficient in eugonadotropic women, women with hypogonadotropic hypogonadism need either inj HMG or combined recombinant FSH and LH.[12]

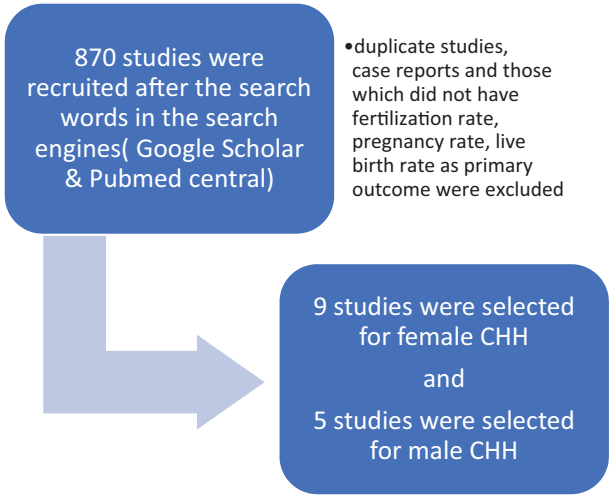

Figure 1: Selection of studies

A new protocol of low dose HCG (80–300 units) combined with HMG has been suggested by Jiang *et al.*[18] for COH in in vitro fertilization (IVF) cycles for women with HHG harvesting a comparable number of embryos without affecting embryo quality. It offers the added advantage of reduced duration of HMG use, making the cycle more convenient and cost-effective.

Effect of age

Gaffari *et al.*[15] reported a higher requirement of gonadotropins for women older than 35 years, with a lower recovery of total and M II oocytes, without affecting their FRs, IRs, PRs, and LBRs. However, older women had significantly lower PRs/cycle ($P = 0.01$). Yilmaz *et al.*[16] observed age to be a significant marker for ovarian response in women with HHG.

Frozen embryo transfer versus fresh cycle

Jiang *et al.*[18] have reported no statistical difference in the biochemical PR, clinical PR, multiple PR, ongoing PR per transfer, and IR after ET in frozen ET cycles and fresh cycles.

Kuroda *et al.*[20] reported outcome of 135 single ET after vitrified-warmed cleavage/blastocyst and the CPR and LBR were 34.6%, 26.9%, 65.1%, and 50.5%, respectively. Because COH in women with CHH requires prolonged and high doses of gonadotropins, it can cause embryo-endometrial asynchrony, a higher chance of multiple pregnancies, and OHSS. There was no case of multiple pregnancies or OHSS reported in the study. Hence, segmented cycles with single ET were suggested to improve ART outcomes.

Males

GnRH pulsatile therapy can induce spermatogenesis, but is usually not preferred, due to limited availability and requirement of infusion pumps. Conventionally, a trial of HCG for 3000 to 5000 IU/week for 6 months followed by HMG/FSH (75 IU three times per week) is prescribed. Both the drugs can be given together to induce spermatogenesis in men with small testicular volume (<4 ml) or with history of orchidopexy. A new approach is to pretreat the men with FSH to prime the Sertoli cells and seminiferous tubules, followed by administration of HCG, to prevent premature differentiation of Sertoli cells under the influence of LH-induced intratesticular testosterone. However, It may take around 6 months to 2 years to affect spermatogenesis with gonadotropins/HCG. The results may not be achieved in many (testicular volume < 4ml, h/o orchidopexy).[25]

Due to the prolonged course of treatment, and uncertain results, IVF or ICSI with TESE for testicular sperm extraction/semen is recommended if the initial trial with FSH/HCG fails to affect spermatogenesis, in order to shorten the treatment to pregnancy interval.

CONCLUSION

COH with IVF/ICSI should be offered to those patients who fail to conceive naturally or with intrauterine insemination/gonadotropin therapy. Newer regimes of COH (HCG with HMG/FSH), vitrified-thawed embryo transfer for female HHG, pretreatment with FSH followed by HCG, and follitropins for induction of spermatogenesis in male HHG look promising and need to be researched further.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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