

Pregnancy outcome of assisted reproductive technology cycle in patients with hypogonadotropic hypogonadism

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Received: 18.04.2015
Review completed: 10.07.2015
Accepted: 13.08.2015

ABSTRACT

CONTEXT: Ovulation induction in patients with hypogonadotropic hypogonadism (HH) is a challenge to the treating physician. The threshold for ovarian response in HH may differ substantially from that of normal patients. To reach that threshold levels of follicle stimulating hormone, in a step-up protocol longer duration of stimulation is required in some cases so as to prevent multiple pregnancy and to eliminate the risk of ovarian hyperstimulation syndrome. **AIM:** To evaluate the duration of stimulation, quality of oocytes, and embryo, and the pregnancy outcome in the assisted reproductive technology (ART) cycles in patients with HH. **MATERIALS AND METHODS:** Over the period of 4 years, we had 14 patients with HH in whom 21 cycles of ovulation induction were done. Of these 7 patients underwent oocyte retrieval and intracytoplasmic sperm injection (ICSI). We present a retrospective study of these 7 patients who underwent ART to evaluate the duration of stimulation, quality of oocytes and embryo, and the pregnancy outcome. **RESULTS:** In the study group on ovulation induction with gonadotropins, only one patient had the duration of stimulation of the standard 12 days, the remaining 6 patients took ≥ 12 days to respond to stimulation (maximum being 54 days). Mean ET in these patients was 8.9 mm. Six patients had $>70\%$ good quality MII oocytes. One patient responded poorly and had only 2 good quality MII oocytes (50%). After ICSI procedure, resultant embryos were of grade 1 and 2 in all the patients irrespective of the duration of stimulation. Fertilization rate in these patients was 85% (except in one 50% fertilization rate), and the cumulative pregnancy rate was 68.6%. **CONCLUSION:** In the patients with HH the quality of oocytes and embryos, and the pregnancy rate is not affected even if the duration of stimulation is prolonged.

KEY WORDS: Embryo, gonadotropins, hypogonadotropic hypogonadism, intrauterine insemination, oocytes, ovulation induction

INTRODUCTION

Hypogonadotropic hypogonadism (HH) is the 2nd most frequent cause of ovarian failure in young women in whom pulsatile GnRh therapy or replacement of gonadotropin can restore ovulation. The threshold for ovarian response in HH may differ substantially from that established for normal patients. These patients require a combination of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) for inducing ovulation. The success of ovulation induction is reported to be as high 60–80% with a high multiple pregnancy rate (20–50%).^[1] In order to avoid higher order pregnancies these patients may require a longer duration of stimulation^[2]

with gradually stepping up the dose in order to reach the threshold of FSH and LH. Assisted reproductive technology (ART) is beneficial in this group of patients to prevent higher order multiple pregnancy or to increase the chance

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How to cite this article: Pandurangi M, Tamizharasi M, Reddy NS. Pregnancy outcome of assisted reproductive technology cycle in patients with hypogonadotropic hypogonadism. *J Hum Reprod Sci* 2015;8:146-50.

Access this article online

Quick Response Code:



Website:

www.jhrsonline.org

DOI:

10.4103/0974-1208.165141

of pregnancy whenever there is poor response on ovarian stimulation. We present 7 cases of HH, who underwent ART to evaluate the duration of ovarian stimulation, quality of oocytes and embryo, and the pregnancy outcome in the ART cycle in patients with HH.

MATERIALS AND METHODS

Over the period of 4 years, we had 14 patients with HH in whom 21 cycles of ovulation induction were done. 7 patients underwent ART. 3 of the 7 patients were initially planned for ovulation induction and intrauterine insemination (IUI) but later converted to ART cycle while 4 patients were planned directly for controlled ovarian hyperstimulation and intracytoplasmic sperm injection (ICSI). All these patients had amenorrhea, and they were evaluated for it. Serum prolactin and thyroid function test were normal in all the patients. Serum FSH, LH, estradiol, anti-mullerian hormone (AMH), ultrasonography (USG) pelvis, and magnetic resonance imaging (MRI) were done for all patients and the findings are tabulated in Table 1.

Before ovulation induction, adequate size of the uterus (at least >5 cm) was obtained by giving cyclical estrogen and progesterone therapy for a minimal of 3 months. Tubal patency was established by doing HSG. Semen analysis of husband was done for all the patients and was found to be normal in all of them. Patients planned for ovulation induction and IUI were started on injection human menopausal gonadotropins (HMG) 75 IU for 7 days, later the dose was gradually stepped up with injection HMG

with or without injection urinary FSH (uFSH) depending upon the response with the aim to obtain 2 or 3 follicles. Whenever there was hyper response or poor response during ovulation induction for IUI these patients were counseled for conversion to an ART cycle. In patients planned for ART higher dose of injection HMG 150 IU in combination with injection uFSH 150–225 IU was started depending upon the age and AMH of the patient. When 3 follicles had reached ≥ 18 mm urinary human chorionic gonadotropin 10,000, IU IM trigger was given, and oocyte retrieval was done 36 h later using 17 g needle, under short GA anesthesia under TVS guidance. ICSI was done for all patients and grading of embryos was done by Veeck’s scoring system. Embryo transfer was done using Labotect catheter on day 3 after retrieval. When there was a high risk of ovarian hyperstimulation syndrome (OHSS), fresh embryo transfer was avoided, and embryos were frozen. In such patients later frozen embryo transfer was done after hormone replacement therapy. In the fresh cycle, luteal phase was supplemented for all patients with estradiol valerate 2 mg twice daily orally and micronized progesterone 200 mg thrice daily vaginally. Serum beta human chorionic gonadotropin was estimated 14 days after embryo transfer.

The stimulation details as in Table 2.

RESULTS

In the study group, 4 patients had primary amenorrhea remaining 3 had presented as a case of secondary

Table 1: Base line profile of the HH patients who underwent oocyte retrieval

Patient	Age in years	Primary/secondary amenorrhea	MRI	BMI (kg/m ²)	Ovarian volume and AFC	FSH (mIU/ml)	LH (mIU/ml)	Estradiol (pg/ml)	AMH (ng/ml)
1	30	Primary amenorrhea	Normal	24	Right ovary: Volume - 2.0 cc, 10 AF (PCOM) Left ovary: Volume - 1.5 cc, 10 AF (PCOM)	5.6	7.7	28.8	4.0
2	21	Primary amenorrhea	Normal	25	Right ovary: Volume - 1.9 cc, 10 AF (PCOM) Left ovary: Volume - 2.1 cc 10 AF (PCOM)	3.2	2.36	20.8	6.8
3	26	Primary amenorrhea	Empty sella on MRI	23	Not seen	0.4	0.2	30	0.7
4	24	Primary amenorrhea	Normal	23	Not seen	0.05	1.0	17	3.6
5	26	Secondary amenorrhea	Normal	21	Not seen	0.3	0.3	43.5	1.4
6	28	Secondary amenorrhea	Normal	31	Right ovary: Volume - 5.4 cc, 7 AF Left ovary: Volume - 2.9 cc, 5 AF	5.5	6.8	24.5	3.2
7	34	Secondary amenorrhea on antipsychotic medications drug induced hyperprolactinemia and hypogonadism	Normal	30	Right ovary: Volume - 1.5 cc, 8 AF Left ovary: Volume - 2.6 cc, 5 AF	3.0	1.9	17	1.7

BMI= Body mass index, HH= Hypogonadotropic hypogonadism, AFC= Antral follicle count, FSH= Follicle-stimulating hormone, LH= Luteinizing hormone, AMH= Anti-Mullerian hormone, PCOM= Polycystic ovarian morphology, MRI= Magnetic resonance imaging

amenorrhea. Ovaries were visualized in 4 patients, and two of these showed polycystic ovarian morphology (PCOM) features, but volume was <12 cc. Only in two patients the exact cause was identified (one case was having features of empty sella on MRI and the other had secondary hypogonadism due to anti psychiatric medications). FSH and LH were low in 4 patients and in the remaining 3 patients the levels were near normal values. In the later three patients, the history of amenorrhea and serum estradiol levels of <30 pg/ml helped us to make the diagnosis of hypogonadism. Only one patient had the duration of stimulation of the standard 12 days, the remaining 6 patients took >12 days to respond to stimulation (maximum being 54 days). Mean ET in these patients was 8.9 mm. Six patients

had >70% good quality MII oocytes (One patient who had poor response had only 2 MII good quality oocytes). After ICSI, resultant embryos were of grade 1 and 2 in all patients. Fertilization rate in these patients was 85% (except in one who had 50% fertilization rate), and the cumulative pregnancy rate was 68.6%. The details of the quality of oocyte and embryos and pregnancy outcome are tabulated in Table 3.

DISCUSSION

HH is a rare disorder of reproductive function characterized by the absence of normal hypothalamic – pituitary synchronous activity. These patients belong to WHO

Table 2: Ovarian stimulation details

Case number	Total dose of gonadotropin			Number of follicles on the day of HCG		Duration of stimulation (days)	Endometrial thickness (mm)	Serum estradiol (pg/ml)	Serum progesterone (ng/ml)
	Starting dose	uFSH IU	uHMG IU	>17 mm	12-17 mm				
1	Injection HMG 75 IU	1612.5	3375	6	4	30	8.8	2007.2	-
2	Injection HMG 75 IU	11,912.5	5325	15	11	54	14	6571.7	-
3	Injection HMG 75 IU	7087.5	7087.5	5	1	52	9.8	538.65	0.6
4	Injection uFSH 150 + Injection HMG 75 IU	1650	2250	8	5	20	8.2	4499.02	1.48
5	uFSH 300 IU + injection HMG 150 IU	3900	1950	4	4	14	7.3	998.9 (on day 9)	-
6	uFSH 150 IU + injection HMG 150 IU	2100	2100	5	4	14	7.5	1583.05	0.8
7	uFSH 225 IU + injection HMG 150 IU	2250	1800	2	3	12	9	1108.92	1.15

FSH= Follicle-stimulating hormone, HMG= Human menopausal gonadotropin, HCG= Human chorionic gonadotropin

Table 3: Quality of oocyte and embryos

Case number	Duration of stimulation (days)	M2/total oocytes	Quality of M2 oocytes*	Injected/ fertilized oocytes	Grade of embryo**	Number of embryos transferred	Pregnancy outcome
1	30	12/12	Good quality	12/12	Grade 1: 7 Embryos Grade 2: 5 Embryos	Frozen transfer of 2 embryos	Singleton pregnancy term delivery
2	54	17/19	Good quality	17/14	Grade 1: 10 Embryos Grade 2: 4 Embryos	Frozen transfer of 3 embryos	Twins delivered at 36 weeks
3	52	2/4	Good quality	2/1	Single embryo of grade 1	Fresh transfer of the single embryo	Singleton pregnancy term delivery
4	20	12/12	Large vacuoles in - 2 oocytes Fragmented polar body - 5oocytes	12/7	All embryos of grade 1	Fresh transfer of 2 embryos	Singleton pregnancy term
5	20	3/4	Wide perivitelline space in all eggs	3/3	Grade 1: 2 Embryos Grade 2: 1 Embryos	Fresh transfer of 3 embryos	Nil pregnancy
6	17	7/10	Good quality	7/7	Grade 1: 5 Embryos Grade 2: 2 Embryos	Fresh transfer of 3 embryos Frozen transfer of 2 embryos	Fresh embryo transfer nil pregnancy Frozen embryo transfer - Singleton pregnancy followed up till 12 wks
7	12	7/9	One giant oocytes remaining good oocytes	6/6	All embryos of grade 1	Fresh transfer of 3 embryos	Spontaneous abortion at 13 weeks

*Quality of oocytes: Granular oocytes, oocytes containing vacuoles, dark cytoplasm, debris and inclusions are considered as poor quality oocytes, **Grade of embryo – by Veeck's scoring method

Group 1 anovulation which account for 10% of cases for anovulation and present with the history of amenorrhea, hypogonadism (<30 pg/ml of estradiol)^[3] and the gonadotropin levels low or in the low normal range. In the present study 5 pts had low FSH & LH levels while the remaining 2 patients had normal to near normal FSH & LH levels. In the later 2 patients serum estradiol levels were <30 pg/ml which pointed to the diagnosis of HH.

Prediction of an individual patient to respond to gonadotropin treatment in HH cannot be based on baseline LH and FSH estimation, which we usually use for other patients. AMH may be useful to some extent.^[4] Ovaries may or may not be seen on USG in these patients. Only after a patient is subjected to gonadotropin stimulation, we can estimate her pattern of response. The threshold for ovarian response in HH may differ substantially from that established for normal patients.

Gonadotropin treatment in patients with HH is the accepted method of ovulation induction. In such patients, optimal clinical results are achieved by using FSH combined with LH,^[5] which is accomplished by administration of HMG, recombinant LH or low dose human chorionic gonadotropin. Multifetal pregnancy is the most frequent complication of ovulation induction with gonadotropin in these patients. In order to decrease the incidence of multiple pregnancies, if step-up protocol is used it results in a longer duration of stimulation. In two patients (case 1 and 2) in spite of step-up hyper response could not be avoided though they took a longer time to respond (30 days and 54 days) details in Table 2. In both of these patients, ovaries were seen and showed PCOM with a low volume of the ovary. These patients underwent rescue *in vitro* fertilization (IVF) with freezing of the embryos due to the risk of OHSS. Later frozen embryo transfer was done and both the patients conceived. The hyper response might have been due to underlying PCOS, which may get unmasked after giving gonadotropin as shown by Wang and Lobo.^[6] AMH in both these patients was >3.7 ng/ml suggesting high risk for hyper response. The second patient had moderate OHSS and was managed conservatively. GnRh agonist trigger to avoid OHSS cannot be used in these patients due to endogenous deficiency of gonadotropin.

The third patient was stimulated by step-up protocol but when she did not show any response till the 36th day, serum AMH was done which was 0.7 ng/ml. Tran *et al.*^[7] mentioned in the clinical case seminar "The role of AMH in Assessing Ovarian Reserve" that AMH has limitations because it only reflects the growing follicular pool that is responsive to gonadotropins. Hence, conditions that cause a permanent or sustained interruption of gonadotropin release may lead to a decrease AMH levels and therefore an underestimation of the true ovarian reserve suggesting that AMH may not be a

very good predictor of ovarian reserve in patients with HH. They reported a case with HH in which during the 16-week course of treatment with HMG, follicular development was observed. Both AMH and antral follicle count (AFC) gradually increased during treatment from the initial AMH and AFC of 0.20 ng/ml and zero, and peaked to 1.26 ng/ml and 6, respectively. Considering this we convinced the patient as she was young (26 years) and decided to continue stimulation until the maximum dose of gonadotropin 600 IU/day was used or till response was noted whichever was earlier. The couple agreed to continue the gonadotropins injections and on the 47th day of stimulation with uFSH 225 IU and HMG 225 IU ovaries were seen and the same dose was continued. On the 52nd day patient developed 5 follicles of >17mm. The couple was counseled for oocyte retrieval as she was a poor responder and had responded after a long course of gonadotropin, details in Tables 2 and 3. This patient required higher dose to respond, and she formed relatively less number of follicles compared to patients who had higher AMH.^[6]

Last four cases (4th to 7th) were planned for ART hence these patients were stimulated with a higher dose gonadotropin, and they responded relatively faster.

The quality of oocytes and embryo in all these 7 patients were good irrespective of the duration of stimulation as shown in Table 3 proving that long duration of stimulation in HH did not affect the quality of oocytes or embryo. Lewit and Kol^[8] has also reported successful stimulation after 29 days of gonadotropin in a patient in whom twice stimulation was cancelled after 20 days due to nonresponse to gonadotropin. They concluded that patients with HH undergoing ovarian stimulation for IVF should be carefully assessed on a trial and error basis for ovarian response before we give up on obtaining fertilizable oocytes. Our observation also helps us to confidently continue ovulation induction in patients with HH in step-up protocol till follicular response is seen irrespective of duration of stimulation. Juan Balasch has suggested to use step-down and step-up approach where patients receive 2 or 3 ampoules of HMG daily (depending upon the patient's body mass index) for 2 days later one ampoule from day 3 to 7. From day 8 onward, HMG is administered on the principles of step-up regimen as per the requirement of the patient.^[8] This might reduce the duration and the cost of the ovarian stimulation.

CONCLUSIONS

Ovulation induction in a patient with HH is a challenge to the treating physician. Ovarian reserve is difficult to assess in these patients as AMH levels in these patients have to be interpreted cautiously. When planned for ovulation induction we must be prepared for longer duration of stimulation which does not affect the quality of oocytes and

embryo, and the pregnancy rate. The treating physician and the patient need a lot of patience and motivation to continue the treatment for longer duration.

Acknowledgment

This work was supported by the staff and the Reproductive Medicine DM postgraduates in the Department of Reproductive Medicine, Sri Ramachandra Medical College and Research Institute, Sri Ramachandra University.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Allahbadia G. Manual of Ovulation Induction. 1st ed. Rotunda Medical Technologies PVT .LTD; 2001. p. 93-4.
2. Kumbak B, Kahraman S. Women with hypogonadotropic hypogonadism: Cycle characteristics and results of assisted reproductive techniques. *Acta Obstet Gynecol Scand* 2006;85:1453-7.
3. Aboulghar M, Rizk B. Ovarian Stimulation. 1st ed. Cambridge University Press; 2011. p. 162-8.
4. Sönmezer M, Özmen B, Atabekoglu CS, Papuccu EG, Ozkavukcu S, Berker B, *et al.* Serum anti-mullerian hormone levels correlate with ovarian response in idiopathic hypogonadotropic hypogonadism. *J Assist Reprod Genet* 2012;29:597-602.
5. Burgués S; Spanish Collaborative Group on Female Hypogonadotropic Hypogonadism. The effectiveness and safety of recombinant human LH to support follicular development induced by recombinant human FSH in WHO group I anovulation: Evidence from a multicentre study in Spain. *Hum Reprod* 2001;16:2525-32.
6. Wang JG, Lobo RA. The complex relationship between hypothalamic amenorrhea and polycystic ovary syndrome. *J Clin Endocrinol Metab* 2008;93:1394-7.
7. Tran ND, Cedars MI, Rosen MP. The role of anti-müllerian hormone (AMH) in assessing ovarian reserve. *J Clin Endocrinol Metab* 2011;96:3609-14.
8. Lewit N, Kol S. The low responder female IVF patient with hypogonadotropic hypogonadism: Do not give up! *Fertil Steril* 2000;74:401-2.