Review Article

Role of growth hormone in ART cycles in poor responders: A literature review

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Abstract

Growth hormone (GH) has been used as an adjunct in the field of female infertility treatment for more than 25 years, although, apart from treating women with GH deficiency its role has not yet been clarified. In the current shift of trend of delaying marriage and childbearing due to career and various other reasons, many women across the world are opting for assisted reproductive techniques (ART). This poses a challenge to the ART experts due to diminished ovarian reserve with advancing age in women. Over the years, the definition of poor responder has also evolved and after the Bologna criteria in 2011 and Poseidon classification, most of the recent studies have used a uniform criterion to define poor responders. The current review recruited studies conducted over the past decade, to ensure uniform criterion for poor responders. After a thorough literature search, 12 studies were selected for review based on the selection criteria a total of 1774 women were included in the intervention group while 3167 women were included in the control group. The review lead us to the conclusion that GH adjuvant therapy in poor responders reduced the dose/duration of gonadotropin used, increased endometrial thickness, improved the number of M II oocytes retrieved, embryos formed, clinical pregnancy rate. However, it has not shown to improve live birth rates in ART cycles. Since there is some evidence that GH adjuvant therapy may benefit young Poor Ovarian Response (POR), more number of large clinical trials need to be performed for further subgroup analysis and benefitting these women seeking ART.

Keywords: embryo quality, growth hormone, IVF, ovarian reserve, poor responder

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INTRODUCTION

Infertility affects around 8% to 10% of couples worldwide, out of the 60 to 80 million couple affected, nearly 15% to 20% are from India.[1] There is a trend to delay marriage and childbearing and many women across the world are opting for assisted reproductive techniques (ART). This poses a challenge to the ART experts due to diminished ovarian reserve with advancing age in women.[2-6] Several studies have reported that ovarian reserve diminishes earlier in Indian women.[7,8] While, various adjuvants and therapies have been described in literature and used by experts for poor responders. However, most are without any proven benefits.[2,3,5,6,9]

Growth hormone (GH) has been used extensively in ART procedures, both in normal and poor responders. However, its use has been off label except in rare

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condition of GH deficiency. As shown in animal models, GH induces the production of Insulin like growth factor-1 (IGF-I), which helps in ovarian estrogen production and follicular development. It also stimulates granulosa cells and increases gonadotropin secretions.[2,3,5,6,9,10] Its role in POR is based on increased number of granulosa follicle stimulating hormone (FSH) and Leutinizing hormone (LH) receptors and enhanced mitochondrial activity.

While, there has been a considerable interest in the role of GH in poor responders, the literature is diverse, in terms of criteria used for poor responders, regimes of GH administration, and it is effect on the results of the ART cycle.

The definition of poor responder has also evolved and after the Bologna criteria in 2011 and Poseidon classification, most of the recent studies have used a uniform criteria to define poor responders.

MATERIALS AND METHODS

An online search was conducted on articles related to use of growth hormone (GH) in poor responders on PubMed, Google, Google scholar, Medline, Embase, Global health, Cochrane library. Search words "growth hormone," "poor responders," "poor," "ovarian reserve," "inadequate," and "suboptimal" were used. The studies which met the following criteria were recruited for analysis:

Inclusion criteria

(1) Used GH in the previous or the current cycle along with gonadotropins in poor responders undergoing in vitro fertilization (IVF)/intracytoplasmic injection (ICSI) and were controlled with poor responder women without use of GH in IVF/ICSI.
(2) Used clinical pregnancy as an endpoint.

Exclusion criteria

(1) Studies older than 10 years.

The current review recruited studies conducted over the past decade, to ensure uniform criterion for poor responders.

Outcome measures and definitions

The studies were evaluated for no. of oocytes (MII) retrieved, no. of embryos available for transfer, clinical pregnancy, live birth (if data available), miscarriage rates (Figure 1).

Clinical pregnancy: Presence of cardiac activity on ultrasound.

Live birth: Pregnancy delivered live beyond 24 weeks of gestation.

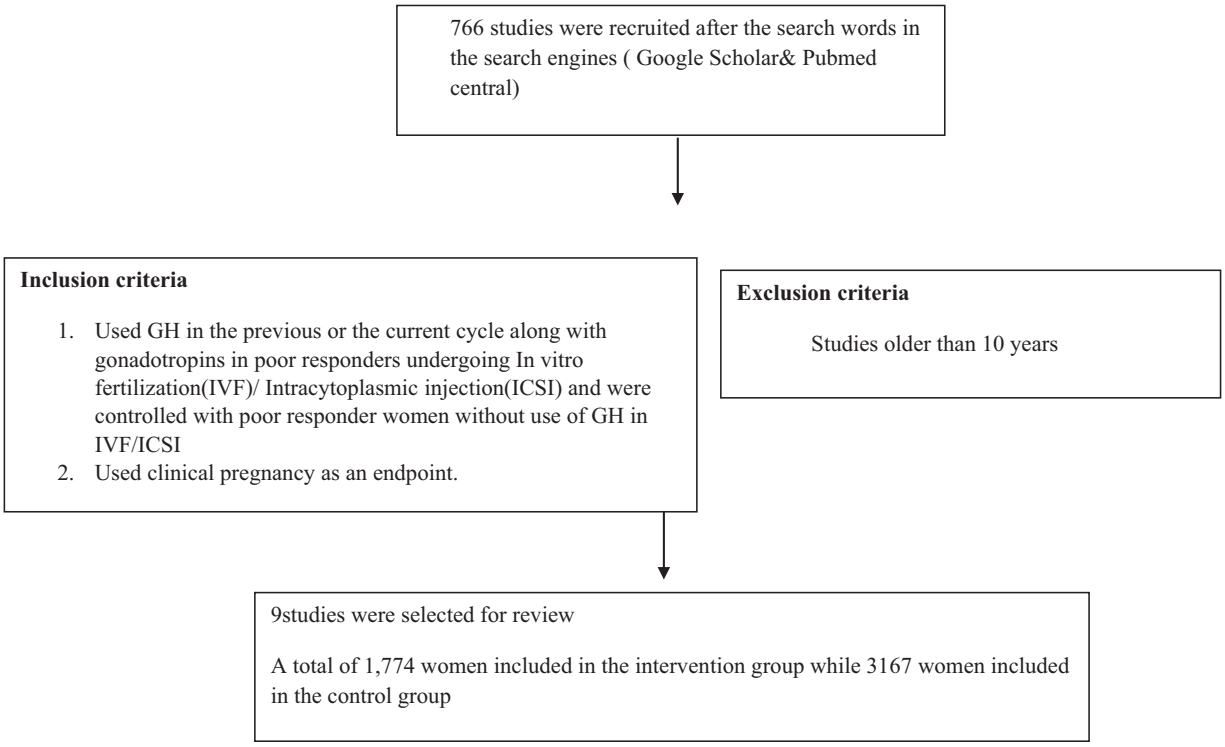

Figure 1: Selection of studies.

Miscarriage: Fetal loss before 20 weeks of gestation.

RESULTS

The literature search revealed 766 articles after the search words, which were narrowed down to 22 articles. Based on the selection criteria, only 12 studies were selected for review. A total of 1722 women were included in the intervention group while 3097 women were included in the control group. The main characteristics of the studies are given in Table 1 and the results in Table 2.

Most of the studies referred to Bologna criterion[3,4,5,9,11] for defining poor responders. Bologna criteria define poor responders with any two of the following:

(1) Age >40 years or any other factor for poor ovarian reserve.
(2) Previous poor ovarian response (≤3 oocytes on ART cycles).
(3) Poor ovarian reserve test (antral follicle count <5–7, anti-Mullerain hormone <0.5–1.1 ng/ml).

Zhu *et al.*[3] and Cai *et al.*,[5] further classified them into Poseidon group 3 and 4. Several studies have used the European Institute of Embryology & Infertility 2011 criterion[2,6,10,11] for defining poor responders.

The European Institute for Embryology and Infertility in 2011 gave the following definition of POR as follows (having at least two of the three following criteria):

(1) Age over 40 years,
(2) The evidences of POR as having a maximum of three oocyte following induction protocol), and
(3) Low ovarian reserve score (AFC less than 5–7, AMH less than 0.5–1.1 ng/ml).

While most of the studies were randomized clinical trials,[2-4,6,9,10,12,13] while one of it was a retrospective study.[5] Many studies had a small sample size.[2,4,6,9-13]

DISCUSSION

Poor responders remain one of the most challenging situations, now, with women delaying marriage and childbearing, it is becoming increasingly more prevalent in ART cycles. The current review intends to explore the role of GH in ART cycle.

The current data provides evidence, that supplementation of GH, might improve oocyte retrieved, number of embryos obtained for embryo transfer, clinical pregnancy, however, there was no increase in the live birth rate.

The studies are heterogenous in terms of protocol, dose, and type of GH used. Choe *et al.*[12] have used sustained release GH, Noeman *et al.*[13] have used recombinant GH. Irrespective of the dose/protocol used, most of the studies have demonstrated that use of GH decreases the dose/duration of gonadotropins.[2,3,6,9,10] The number of oocytes retrieved and embryos formed in GH treated cycle are significantly more.[2,6,9,10] GH improves oocyte quality by upregulating GH receptors on the oocytes and enhancement of its mitochondrial activity. This scientific evidence may support of the use of GH adjuvant therapy in poor responders.

Most of the studies failed to show any improvement in the clinical pregnancy rate with GH adjuvant therapy.[2,3,5,6,9,10,12] Li *et al.*[4] demonstrated a clinically significant increase in clinical pregnancy rate in women treated with GH. This could be explained by a smaller sample size in the study, and hence, it needs to be validated on a larger number of participants.

While some studies showed a higher endometrial thickness in women treated with GH,[4,9] it did not translate to higher clinical pregnancies.[2,3,5,6,9,10,12,13]

Zhu *et al.*[3] did a subgroup analysis and the results revealed that GH treatment significantly increased the number of day 3 embryos obtained in the subgroup of young PORs along with the long down-regulation protocol (63.11% vs. 49.35%; $P = 0.004$). GH treatment also reduced the risk of miscarriage in young PORs when used along with GnRH antagonist protocol (0.00% vs. 12%; $P = 0.023$).

The mechanism by which adjunct GH treatment improves IVF outcomes:

(1) It helps gonadotropin in follicle recruitment and development.
(2) It enhances oocyte maturation. It upregulates IGF-1 synthesis. Serum IGF-1 and IGFBP-3 increase following exogenous GH administration and lead to improved ovarian follicular maturation and steroidogenesis.[2,3,5,6,9,10]

No difference was observed in the miscarriage rate in both the treated and control group.[2–6,9–13]

Choe *et al.*,[12] used sustained release GH (20 mg three times: mid-luteal, late-luteal, menstrual cycle day 2)

Table 1: Characteristics of the studies

S. No.	Author (year)	Study design	Country/groups	Definition of poor responder and inclusion criteriaExclusion criteria	No. of participants	Limitations	GH regimen
1	Balasubramanyam S (2017)[11]	Case series	**India** A total of 24 women underwentThirty cycles of controlled ovarian stimulation.Ten patients out of24 had previous poor assisted reproductive technology<ST>Outcomes,of which four were poor responders.Group A: Previous poor response in 10 patientsGroup B: Response in this cycle after GH treatment	European Institute for Embryology and Infertility definition (2011)	24	Small sample sizeCase series reporting	Growth hormone 8 units per day subcutaneously from day 2 of the cycle until the day of the hCG trigger.
2	Safdarin L *et al.* (2018)[2]	Single-blinded clinical trial (RCT)	**Iran** 105 PORs, who referred to Dr Shariati Hospital between May 2016 and September 2017 in order to treat infertility.Group A – GH (Somatropin, 2.5 mg/day, subcutaneously from the eighth day of the cycle until the injection of HCG)Group B-GH (Somatropin, 0.1 mg/day, subcutaneously from the third day of the previous cycle)Group C-placebo (normal saline, 0.1 mg/day, subcutaneously) from the eighth day of the cycle until the injection of HCG).	European Institute for Embryology and Infertility definition (2011) POR due to-Aging-Ovarian surgery-Chemotherapy-Unknown reasons Women with high FSH levels (more than 20 IU/L)A history of infertility due to known non-POR causes such as azoospermiaDiabetes (type one or two)	105	Safety of long-term administration of GH on mothers and their children not studied	Group A – GH (Somatropin, 2.5 mg/day, subcutaneously from the eighth day of the cycle until the injection of HCG),Group B – GH (Somatropin, 0.1 mg/day, subcutaneously from the third day of the previous cycle)group C – placebo (normal saline, 0.1 mg/day, subcutaneously) from the eighth day of the cycle until the injection of HCG)
3	Zhu J *et al.* (2017–2018)[3]	RCT	**China** A total of 3080 expected PORs undergoing the first fresh in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles at Peking University Third Hospital**PG3 group** – 271 and 1021 women received or did not (control) receive GH adjuvant therapy, respectively.**PG4 group** – 557 and 1231 women receive and did not receive (control) GH adjuvant therapy, respectively.GH – GH recipientCN – control group	Bologna criteria Poseidon 3 (<35 years)Poseidon (≥35 years) Azoospermia or severe oligospermiaAbnormal karyotyping	3080	The study was mainly limited by the retrospective nature.This study did not include outcomes of cryopreservedembryos, thus the effectiveness of GH treatment in terms of acumulative LBR may be underestimated	4 IU/d of GH (Saizen; Merck Serono, Geneva, Switzerland), beginning on the initial day of gonadotrophin until the day of hCG injection.
4	Li J *et al.* (2017–2019)[4]	RCT	**China** 158 patients with poor embryo development were enrolled107 patients randomized for GH treatment **(GH group)** and 51 patients for untreated **(control group)** .	Bologna criteria At least one previous IVF cycle failure with no top-quality embryos (grade 1 or 2) Folliclestimulating hormone (FSH), luteinizing hormone (LH), and oestradiol (E2) concentrations in the normal range during the early follicular phaseAged 20–45-years oldUnexplained infertility with normal spermatozoa before IVF or subnormal spermatozoa justifying ICSIA normal uterine cavity with regular spontaneous menstrual cycles of 25–30 daysBody mass index (BMI) $< 25\ kg/m^2$	158	Not able to assess the cumulative live birth rate, because not all patients had all of their cryopreserved embryos transferred.	Three IU recombinant human GH (Jintropin AQ, Gensci, Changchun, China) per day, from the initial day of downregulation for the long protocol or stimulation for the antagonist protocol until the day of the hCG trigger

(*Continued*)

Table 1: (*Continued*)

S. No.	Author (year)	Study design	Country/groups	Definition of poor responder and inclusion criteriaExclusion criteria	No. of participants	Limitations	GH regimen
				Any genetic diseasePolycystic ovarian syndrome (PCOS) or endometriosisAzoospermia in the male partnerA history of endocrine disorders			
5	Cai M *et al*.[5] (2014–2016)	Retrospective study	**China** ART treatment in theReproductive Medicine Center of The Sixth Affiliated Hospitalof Sun Yat-Sen UniversityGH+:GH adjuvant groupGH-group: without GH pretreatment	Bologna Criteria Poseidon 3 (<35 years)Poseidon (≥35 years) abnormal chromosome, hydrosalpinx, endometriosis, hyperprolactinemia, thyroid diseases, uterine disorders that affected embryo implantation, severe oligoasthenozoospermia or azoospermia of the male partner	676	Small studyRetrospective analysis	2IU of GH in the form of Jintropin was administered during the preceding menstrual cycle on days 2–3, which included daily injection over a 6-week period in the lead-up to ovum pick-up (OPU).
6	Bassiouny YA *et al*. (2014)[6]	RCT	**Egypt** Randomized, open-label study was conducted in Kasr el Aini IVF Center, Cairo University,Group A (GH/hMG/GnRH antagonist)Group B (hMG/GnRHantagonist)	European Institute for Embryology and Infertility definition (2011) Women with previous ovarian surgery, women suffering from causes of infertility other than POR, and women refusing to be enrolled in the study were excluded.	141	Small sample sizeThe long-term safety of GH on the mothers and their children not studied	Growth hormone (Norditropin, Novo Nordisk) cotreatment was introduced on day 6 of hMG stimulation in a daily dose of 2.5 mg SC until the day of hCG triggering
7	Dakhly D MR *et al*. (2015–2017)[9]	Open label randomized control trial	**Egypt** Cairo University Hospital, Kasr Al-AiniGroup AGH/long protocolGroup BLong protocol only	Bologna Criteria Females above 45 years, or having FSH >20 IU/L, and those with other causes of infertility as tubal occlusion or severe male factor as severe azospermia or teratospermia, as well as couples who refused to participate were excluded from the trial.	240	Not performing a cost-effective analysis for the use of GH, especially that GH was used for a long duration in their protocol.	2.5 mg subcutaneous injection of GH (equivalent to 7.5 IU) (Norditropin pen, Novo Nordisk, Denmark) from day 21 of the previous cycle along with GnRHa, until the day of HCG
8	Bayoumi Y *et al*. (2014)[10]	A parallel, open-label, randomized controlled trial	**Egypt** Kasr Al Aini IVF Center, Cairo University, CairoGH+ groupGH-(Microflare Only Group)	2011 ESHRE criteria for POR - FSH levels greater than 20 IU/L- previous ovarian surgery- causes of infertility other than POR- polycystic ovary syndrome- anyendocrine disorder (e.g., diabetes mellitus or thyroid disease)- male factor infertility.	172	Study did not analyze the cost–benefit of each cycle among the two groupslimited number of patientsdata regarding the safety of GH treatment for patients and their offspring were lacking.	2.5 mg GH delivered subcutaneously on a daily basis from day 6 of HMG stimulation until ovulation could be induced with human chorionic gonadotropin (hCG)
9	Choe *et al*. (2017)[12]	Randomized, open-label, parallel study conductedin a single IVF center	**Germany** GH groupCN (control) group	Bologna Criteria - genetic causes of infertility- body mass index (BMI) >30 kg/m^2- abnormal uterine bleeding at the time of screening- ovarian tumor with borderline or higher malignancy-history of breast cancer- Hydrosalpinx-general contraindications for recombinant GH treatment were excluded	127	No comparison group with daily injection of recombinant GH.Did not measure IGF-1 and IGFBP-3 in follicular fluid to correlate with serum levels.	Sustained-release human GH (Eutropin Plus 20 mg, LG Life Sciences, Seoul, Korea) three times before and during COS (mid-luteal, late luteal, and menstrual cycle day 2)

(*Continued*)

Table 1: (*Continued*)

S. No.	Author (year)	Study design	Country/groups	Definition of poor responder and inclusion criteriaExclusion criteria	No. of participants	Limitations	GH regimen
10	Norman R J *et al.* (2019)[13]	Multicenter, double-blind, placebo-controlled trial	**Australia and New Zealand** HGHPlacebo (P)	- At least one IVF cycle in which there was a poor response (five or fewer oocytes) with recombinant-FSH stimulation of more than 250 IU/day.- Younger than 41 years of age, body mass index ≤32 kg/m^2 and never have had a recorded FSH above 15 IU/L. - Clinically significant systemic diseasehad undergone radiotherapy or chemotherapy-had any current history of malignant diseasepituitary or hypothalamic disease-had a current ovarian cyst >3 cm- had any chronic infectious diseasespolycystic ovary syndromeunexplained menstrual bleeding	130	Underpowered after recruitmentgives little hope to couples seeking to use this expensive adjunct to therapystudy does not show increased efficacy of HGH as an adjunct to FSH treatment in subjects receiving IVF who have been previous poor responders	Recombinant HGH (Saizen 8 mg, Merck, Australia), in a syringe of 24 IU with a daily administered dose of 12 IU. The placebo was an identical syringe provided by Merck but containing 0.3% metacresol in water. The syringes were reconstituted on Day 1 of stimulation and the injection site rotated daily. Dosage was stopped on the evening of human chorionic gonadotrophin (HCG) scheduling for oocyte retrieval
11	Nisha E *et al.* (2017)[14]	Retrospective, single center, interventional study	**India** 36 poor responders included in studyGroup A with growth hormone, and group B without growth hormone	Bologna Criteria - Age >35- Previous poor ovarian response (<3 oocyte cumulus complex)- Poor ovarian reserve AMH <1/AFC <5- Patient giving consent for the study - Patient having contraindication for gonadotrophins/growth hormone- Patient with DM or at risk with GDM- Patient with malignancy or prior history of malignancy-Poorly controlled thyroid disorder- Normo responders and hyper-responders	36	Study did not analyze the cost-benefit of each cycle among the two groupsLimited number of patientsdata regarding the safety of GH treatment for patients and their offspring were lacking	In group A injection human growth hormone 4 IU was included in the ovarian stimulation protocol from day 2 of the cycle when stimulation begins till HCG.
12	Regan P *et al.* (2018)[15]	Prospective randomized controlled trial	**Australia** PIVET Medical Centre Perth, Western AustraliaGroup A- without GHGroup B- with GH	Bologna criteria women were aged ≥39 years and had at least one failed IVF cycle - Endometriosis- Unusual medical conditions-Endocrine dysfunction- Polycystic ovarian syndrome	62	Study was not powered to detect an improvement in live birth rate; as such it would require a larger number of women compared with the 62 women recruited for the present study	GH (Saizen, Serono) over a period of 20–24 days in the lead-up to IVF. Specifically, a total of six injections of GH was administered to 10 patients on day 21 of the preceding cycle, and on days 2, 6, 8, 10, and 12 of the ensuing IVF cycle(10 IU per injection, a total of 60 IU)

Table 2: Results of the studies

S. No.	Author (year)	Duration of GN (no. of days)				No. of oocytes collected				ET (mm)				Clinical pregnancy				Miscarriage rates			
		Total dose of GN (IU)				MII oocytes				No. of transferred embryos				Live birth rates							
1	Balasubramanyam S (2017)[11]					A	B	*P* value						8/24 (33.3%)							
			5.1 (±3.6)	11.1 (±6.4)	0.0375		2.6 (±1.0)				4/24 (16.6%)										
			6.6 (±4.5)																		
2	Safdarin L *et al*. (2018)[2]	A	B	C	***P* value**	A	B	C	***P* value**	A	B	C	***P* value**	A	B	C	***P* value**	A	B	C	*P* value
		10.23 ± 1.03	10.37 ± 1.08	13.29 ± 1.38	0.051	7.14 ± 2.03	7.29 ± 2.16	5.17 ± 1.82	<0.001	10.51 ± 0.81	11.14 ± 0.77	10.54 ± 0.85	0.002	5 (14.3%)	8 (22.9%)	1 (2.9%)	0.047	9(25.7%)	10 (28.6%)	3(8.6%)	0.084
		3098.57 ± 510.	3140.00 ± 490.47	4662.86 ± 213.61	<0.001	6.09 ± 1.65	6.09 ± 2.00	3.46 ± 2.09	<0.001	2.49 ± 0.66	2.40 ± 0.88	1.63 ± 1.39	<0.001	1 (2.9%)	4 (11.4%)	0 (0.0%)	0.357				
3	Zhu J *et al*. (2017–2018)[3]	<35 years	GH	CN	*P* value	<35 years	GH	CN	*P* value	<35 years	GH	CN	*P* value	<35 years	GH	CN	*P* value	<35 years	GH	CN	*P* value
							6.56 ± 4.69	7.66 ± 5.09	0.001		10.57 ± 2.19	10.71 ± 1.79	0.342		75 (40.98%)	287 (41.65%)	0.824		4 (16%)	13 (12.26%)	0.740
			3.535 ± 1.289	3.492 ± 1.269	0.618						1.66 ± 0.61	1.69 ± 0.60	0.445		69 (37.70%)	238 (34.54%)	0.426				
		≥35 years				≥35 years	5.55 ± 3.93	5.40 ± 4.43	0.513	≥35 years	10.07 ± 1.98	10.10 ± 2.00	0.814	≥35 years	78 (24.38%)	189 (25.61%)	0.591	≥35 years	5 (25%)	14 (22.95%)	1.000
			3401 ± 1.382	3.577 ± 1.280	0.009						1.54 ± 0.70	1.59 ± 0.64	0.221		57 (17.81%)	132 (17.89%)	0.977				
4	Li J *et al*. (2017–2019)[4]	GH	CN	*P* value	GH	CN	*P* value	GH	CN	*P* value	GH	CN	*P* value	GH	CN	*P* value					
		10.11 ± 1.42	10.45 ± 1.94		10.29 ± 5.92	8.16 ± 4.17	0.022	9.62 ± 1.88	9.97 ± 1.92		47/91 (51.65%)	10/45 (22.22%)	0.002	3/91 (3.30%)	1/45 (2.22%)	1					
		2402.14 ± 648.33	2604.41 ± 853.42		9.08 ± 5.83	7.49 ± 3.98	0.040	1.92 ± 0.40	1.87 ± 0.40	0.464	44/91 (48.35%)	9/45 (20.00%)	0.003								
5	Cai M *et al*. (2014–2016)[5]	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value					
		9.81 ± 2.13	10.73 ± 1.99	<0.001	3.64 ± 2.83	3.54 ± 2.80	0.726	11.02 ± 2.07	11.22 ± 2.43	0.699	35.63%	32.68%	0.479	13.33% (4/30)	41.30% (19/46)	0.009					
		2358.28 ± 625.87	2474.19 ± 695.07	0.039				9	18	0.738	29.89%,	17.65%	0.028								
6	Bassiouny YA *et al*. (2014)[6]	A	B	*P* value	A	B	*P* value	A	B	*P* value	A	B	*P* value	A	B	*P* value					
		10.77	12.02	<0.001	7.58	4.90	<0.001	12.14	11.56	0.029	15/57 (26.3)	11/59 (18.6)	0.322	5/57 (8.8%)	3/59 (5.1%)	0.433					
		3.900	4.906	<0.001	4.53	2.53	<0.001	4.04	2.42	<0.001	10/57 (17.5)	8/59 (13.6)	0.553								
7	Dakhly D MR *et al*. (2015–2017)[9]	A	B	*P* value	A	B	*P* value	A	B	*P* value	A	B	*P* value	A	B	*P* value					
		11.1 ± 1.4	12.2 ± 1.5	<0.001	5.4 ± 1.7	4.3 ± 2.1	<0.001	11.8 ± 1.3	11.3 ± 1.2	<0.001	29/107, 27.1 %	23/103, 22.3 %	0.423	8/107, 7.5%	6/103, 5.8%	0.631					
		3386.2 ± 1113.7	4789.3 ± 1332.2	<0.001	4.1 ± 2.1	2.1 ± 1.4	<0.001	2.4 ± 0.9	1.6 ± 1.1	<0.001	28/140, 20%	20/119, 16.8%	0.509								

(Continued)

Table 2: (*Continued*)

S. No.	Author (year)	Duration of GN (no. of days)			No. of oocytes collected			ET (mm)			Clinical pregnancy			Miscarriage rates		
		Total dose of GN (IU)			MII oocytes			No. of transferred embryos			Live birth rates					
8	Bayoumi Y *et al.* (2014)[10]	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value
		10.3 ± 1.2	11.7 ± 1.2	<0.001	7.2 ± 1.5	4.7 ± 1.2	<0.001	11.9 ± 1.6	11.7 ± 1.7	0.590	24 (33.3)	15 (20.5)	0.083	2 (2.8%)	3 (4.1%)	>0.99
		3855.2 ± 895.5	4743.5 ± 1326.6	<0.001	5.2 ± 1.2	2.8 ± 1.0	<0.001	2.9 ± 0.3	2.1 ± 0.6	<0.001						
9	Choe *et al.* (2017)[12]	GH	CN	*P* value	GH	CN	*P* value	GH	CN	*P* value	GH	CN	*P* value	GH	CN	*P* value
					3.7 ± 2.6	3.4 ± 2.5	0.489	8.8 ± 2.2	9.1 ± 1.9	0.243	9.7 (6/62)	16.9 (11/65)	0.348	1.6%(1/62)	9.2% (6/65)	0.208
		2409.8 ± 991.7	2548.8 ± 814.4	0.394	2.5 ± 2.0	1.8 ± 1.8	0.018	1.7 ± 0.9	1.6 ± 1.0	0.309						
10	Norman RJ *et al.* (2019)[13]	HGH	*P*	95% CI	HGH	*P*	95% CI	HGH	*P*	95% CI	HGH	*P*	95% CI	HGH	*P*	95% CI
		9.3 (2.1)														
	9.9 (3.1)	0.93 (0.84, 1.04)										6/62 (9.7%)	3/51 (5.9)	1.71 (0.41, 7.22)		
	3/51 (5.9%)															
	1.71 (0.41, 7.22)															
		3383 (1073)														
	3786 (1684)	-403.5 (-885.1, 78.1)														
	29/31 (93.5)	25/33 (75.8)	4.64 (0.90, 23.9)		1.3 (0.7)	1.1 (0.7)	1.13 (0.80, 1.59)									
	1.1 (0.7)	1.13 (0.80, 1.59)														
	1.13 (0.80, 1.59)	2/29 (6.9)	3/25 (12.0)	0.54 (0.08, 3.54)												
	3/25 (12.0)	0.54 (0.08, 3.54)														
11	Nisha E *et al.* (2017)[14]	A	B	*P* value	A	B	*P* value	A	B	*P* value	A	B	*P* value	A	B	*P* value
					5.8	3.7	<0.0001				27.7%	16.6%	0.02			
								2-3	1-3	NS						
12	Regan P *et al.* (2018)[15]	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value	GH+	GH-	*P* value
					7.0 ± 4.7	5.3 ± 2.8	0.309	16	14	NS	6.2%	36%	0.044			
											6.2%	14%	0.464			

instead of recombinant GH to reduce the number of injections for patient convenience. However, the study failed to demonstrate any effect on number of MII oocytes retrieved, embryos available for transfer, Clinical Pregnancy Rate (CPR), or live births. Maybe, more experience is needed with the dosing and timing of sustained release preparation.

Norman *et al*.[13] conducted a multicentered double-blind, placebo controlled, randomized clinical trial comparing human GH to placebo with maximum stimulation in ART cycle. They recruited 62 for GH and 51 in control group. The study failed to demonstrate any effect of GH adjuvant therapy on CPR, live birth rates (LBR). This study was however, criticized because of the small sample size, failure to achieve randomization due to patient preference, frozen embryos were not utilized, and definition of poor responders was not as per the standard definitions.

A previous meta-analysis by Yu *et al*.[16] concluded that GH supplementation for IVF/ICSI in POR increases the number of MII oocyte, 2PN, and obtained embryos. However, it did not increase implantation rate and clinical pregnancy rates. The studies selected were much older (1995, 2006–2013) and hence, were more heterogenous as well as had differences in methodology. The current review has included more recent studies, with a more uniform definition of POR.

Lacunae

The studies available in the literature have not explored the long-term outcomes of GH on the women or their off springs. Most of the studies have not performed the cost-effective analysis of GH administration in the ART cycles, considering its added costs and doubtful benefits in increasing the live birth rates. Some studies,[3,4] have not included the outcomes of cryopreserved embryos, which may influence the cumulative LBR in GH treated cycles leading to its underestimation. Many have a small sample size[2,4,6,9,10,12,13] hence, are underpowered to reach a statistically significant conclusion. One was retrospective,[5] leading to an inherent bias.

CONCLUSIONS AND RECOMMENDATIONS

GH adjuvant therapy in poor responders reduced the dose/duration of gonadotropin used, increased endometrial thickness, improved the number of M II oocytes retrieved, embryos formed, clinical pregnancy rate, however, it has not shown to improve live birth rates in ART cycles.

Large clinical trials need to be performed for further subgroup analysis, as there is some evidence that GH adjuvant therapy may benefit young POR.

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Conflicts of interest

The authors report no conflicts of interest.

Commentary

Drs Kapoor and Nagma are to be commended for attempting to make sense of the literature concerning the role of growth hormone (GH) in the management of poor ovarian response (POR). They demonstrate the shortcomings in published studies, which make it difficult to understand the true role, if any, of this intervention. A major issue is the lack of an agreed preparation and dose of GH. Perhaps even importantly, how does one judge how much GH to give to a particular patient? As we are not treating a GH deficiency (other than in cases of hypopituitarism), so we do not know whether we can and should titrate the dose, or just use a standard dose in all cases. The growing acceptance of the Poseidon classification holds out some promise for future research, but studies so far suffer from a lack of standardised definition of POR. Taking a 'generous' view of the evidence, it is possible that GH use in women with POR may be associated with a reduced need for gonadotropins, and hence a saving in the cost of gonadotropins. However, this could easily be offset by the cost of GH itself. This underscores the importance of considering not only just clinical effectiveness, but also cost-effectiveness of treatments. Pending stronger evidence of a benefit in the chance of live birth, it appears that clinicians do not have a strong reason to prescribe GH to women with POR and normal pituitary function.

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