Review / Derleme

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The effects of growth hormone supplementation in poor ovarian responders undergoing In vitro fertilization or Intracytoplasmic sperm injection: A systematic review and meta-analysis of randomized controlled trials

İn vitro fertilizasyona veya intrasitoplazmik sperm enjeksiyonuna zayıf yumurtalık yanıtı veren kadınlarda büyüme hormonu takviyesinin etkileri: Randomize kontrollü çalışmaların sistematik bir derlemesi ve meta-analizi

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Abstract

To evaluate the effect of growth hormone (GH) supplementation on outcomes of in vitro fertilization (IVF) or Intracytoplasmic sperm injection (ICSI) for women with poor ovarian response. Relevant randomized controlled trials (RCTs) were obtained through search in several databases including PubMed, Scopus, Clinicaltrials.gov, Google Scholar, and Cochrane Library. Outcome measures included live birth rate, clinical pregnancy rate, cycle cancelation rate, number of retrieved oocytes, number of transferred embryos, total dose of gonadotropin, duration of gonadotropin treatment, and peak estradiol level. Additionally, a meta-regression analysis was performed to acknowledge any potential linear relationships between these outcomes and IVF success. After analyzing 18 RCTs comprising of 1870 patients, the study found that GH supplementation improved the number of retrieved oocytes [standardized mean difference (SMD), 0.65; 95% confidence interval (CI), 0.29-1.00] and transferred embryos group (SMD, 0.80, 95% CI, 0.39, 1.21) as well as peak E2 level (SMD, 1.20; 95% CI, 0.59, 1.81). While reduced the total dose and duration of gonadotropin treatment (SMD, -0.82, 95% CI, -1.25, -0.39, and SMD, -0.63, 95% CI, -1.04, -0.22, respectively). The meta-regression analysis found no linear relationship between clinical pregnancy, live birth rate, or cycle cancelation rate and the outcomes measured ($p>0.1$). Based on the available evidence, GH supplementation appears to improve the outcomes of IVF or ICSI in women with poor response. However, there is a need for further RCTs with larger sample sizes to determine the cost-effectiveness of adding GH to conventional protocols of IVF/ICSI for treating infertility in women with poor ovarian response.

Keywords: Growth hormone, gonadotropin, IVF, meta-analysis, systematic review

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Öz

Bu çalışmanın amacı zayıf yumurtalık yanıtı olan kadınlarda büyüme hormonu (GH) takviyesinin in vitro fertilizasyon (IVF) veya intrasitoplazmik sperm enjeksiyonu (ICSI) sonuçları üzerindeki etkisini değerlendirmektir. İlgili randomize kontrollü çalışmalar (RKÇ) PubMed, Scopus, Clinicaltrials.gov, Google Scholar ve Cochrane Kütüphanesi dahil olmak üzere çeşitli veri tabanlarında arama yapılarak elde edildi. Sonlanım ölçümleri arasında canlı doğum oranı, klinik gebelik oranı, siklus iptal oranı, alınan oosit sayısı, transfer edilen embriyo sayısı, toplam gonadotropin dozu, gonadotropin tedavisinin süresi ve en yüksek östradiol seviyesi yer aldı. Ek olarak, bu sonuçlar ile IVF başarısı arasındaki olası doğrusal ilişkileri belirlemek için bir meta-regresyon analizi gerçekleştirildi. Toplam 1870 hastayı kapsayan 18 RKÇ'nin analizinden sonra, GH desteğinin alınan oosit sayısını [standartlaştırılmış ortalama fark (SOF), 0,65; %95 güven aralığı (GA), 0,29-1,00] ve transfer edilen embriyo grubunu (SOF, 0,80, %95 GA, 0,39, 1,21) ve pik E2 seviyesini (SOF, 1,20; %95 GA, 0,59, 1,81) iyileştirdiği; Gonadotropin tedavisinin toplam dozunu ve süresini azalttığı (sırasıyla SOF, -0,82, %95 GA, - 1,25, -0,39 ve SOF, -0,63, %95 GA, - 1,04, -0,22) bulundu. Meta-regresyon analizi klinik gebelik, canlı doğum oranı veya siklus iptal oranı ile ölçülen sonlanımlar arasında doğrusal bir ilişki bulamadı (p>0,1). Mevcut kanıtlara göre, GH takviyesi zayıf yanıt veren kadınlarda IVF veya ICSI sonuçlarını iyileştiriyor gibi görünmektedir. Ancak, zayıf yumurtalık yanıtı olan kadınlarda kısırlığı tedavi etmek için IVF/ICSI'nın geleneksel protokollerine GH eklemenin maliyet etkinliğini belirlemek için daha büyük örneklem boyutlarına sahip daha fazla RKÇ'ye ihtiyaç vardır.

Anahtar Kelimeler: Büyüme hormonu, gonadotropin, IVF, meta-analiz, sistematik inceleme

Introduction

Diminished ovarian reserve (DOR) affects a significant percentage of women, between 8-15%, and its incidence increases in women over 40, affecting more than half of them[1]. Poor responders (POR) are women with DOR who experience difficulties producing enough mature oocytes, leading to lower embryo quality and higher cycle cancellation rates[2]. The European Society for Human Reproduction and Embryology introduced a standardized set of criteria named Bologna in 2011 to diagnose women with poor ovarian response[3]. To diagnose a patient with POR, at least two of the following three criteria must be met: (i) advanced maternal age (40 years or older) or another risk factor for POR; (ii) a history of poor ovarian response (three or fewer oocytes retrieved or a previous cycle that was canceled); and (iii) abnormal results from ovarian reserve tests (antral follicle count [AFC] of less than 5-7 follicles or Anti-Mullerian hormone [AMH] levels below 0.5-1.1 ng/mL). If a patient experiences two instances of POR despite receiving maximal stimulation, she can be diagnosed with the condition, even if the other criteria are not met. When considering treatment strategies for stimulating ovarian function in POR, one potential option is to administer gonadotropin-releasing hormone (GnRH) agonists[4]. While this approach has shown promise, it can also have its limitations. For example, it may inhibit ovarian function and response and require an increased dose of gonadotropin, thus leading to early luteinizing hormone (LH) secretion and potentially contributing to in vitro fertilization (IVF) failure rates[5]. In an effort to improve outcomes, various ovarian hyper-stimulation protocols have been explored, including the use of growth hormone as an additional treatment in stimulation protocols. However, an ideal protocol for POR has yet to be established, and more research is needed to optimize treatment strategies.

GH is a protein originating from the ovary and pituitary gland that targets the uterine and ovarian tissues in the female reproductive system. In general, GH promotes the overall ovarian health through its antioxidant effect[6]. However, the specific effects of GH are mediated by its receptors in myometrium[7], uterine decidua[8], granulosa cells and stroma of human ovary[9]. Ovarian GH, by creating a GH-GH receptor complex, increases the phosphorylation of janus kinase-2 and subsequently activates STAT molecules, thereby changing gene expression and cell performance. It also intercedes the development of primordial follicles to pre-antral in a paracrine manner. With gonadotropin receptors upregulation, GH increases the sensitivity of granulosa cells to follicle-stimulating hormone (FSH) and LH. Moreover, some studies have suggested its steroidogenesis effect, too. Additionally, GH enhances the oocytes quality by increasing the nucleal and cytoplasm maturation, which is done by the inhibitory effect of GH on connexin 43 and the increase of cumulus cells. Finally, GH improves implantation through its proliferative effect on uterine decidua cells[6]. Growth hormone is primarily released by the pituitary gland and plays a key role in cell growth, development, and metabolism.

GH is secreted mostly by pituitary gland, and affects cell growth, development as well as metabolism[10]. The use of GH as a co-treatment for various ovarian stimulation protocols in reproductive medicine has been the subject of extensive research. GH stimulates insulin-like growth factor 1 (IGF-1) production in both the liver and ovarian follicles. IGF-1 helps regulate steroidogenesis, enhances gonadotropin effect on granulosa and theca cells, and increases ovarian sensitivity to gonadotrophins, thereby advancing early follicular development, preventing of antral follicles involution, and promoting oocyte maturation[11-13]. Furthermore, recent studies indicate that GH takes part in enhancing follicular survival and cell proliferation as well as promoting high-quality embryos and increasing implantation rate[14,15]. However, the effect of GH administration on IVF/intracytoplasmic sperm injection (ICSI), outcomes is still not clearly understood, with studies showing contradictory results. While some research has shown that growth hormone (GH) positively affects oocytes, the endometrium, and improves embryo development outcomes, others have not replicated these results[16-19]. In conclusion, t the majority of evidence suggests GH is crucial for follicular development, estrogen production, and the maturation of

oocytes via IGF-1, while its effect on the efficacy of IVF or ICSI techniques remains a subject of ongoing research.

The addition of GH to IVF/ICSI protocols has been the subject of several recent studies, including a 2020 meta-analysis which reported improved outcomes for poor ovarian responders[20]. Since then, several new randomized controlled trials (RCTs) have been published investigating the influence of GH on IVF/ICSI outcomes. To provide a thorough understanding of the subject, our aim is to conduct a rigorous meta-analysis of the available evidence from relevant RCTs to date.

Materials and Methods

In this meta-analysis, we aim to investigate the impact of GH supplementation on the outcomes of IVF or ICSI in poor ovarian responders. We have taken measures to ensure the rigor and transparency of our study, including registering our research protocol on the Open Science Framework and utilizing a checklist for search strategy, screening, and data selection. Our methodology conforms to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to maintain a high standard of reporting[21]. The systematic review protocol was registered in Open Science Framework (https://osf.io/bv9zm).

Literature Search

A comprehensive literature search was conducted up to May 25, 2023 to identify relevant RCTs and systematic reviews. The following databases were searched: Cochrane Library, PubMed, SCOPUS, Google Scholar, and Clinical Trials. To generate subsets of relevant citations, we used a combination of Medical Subject Headings (MESH) and text words. Two subsets were created for studies of poor ovarian response, using keywords related to "reserve" and "poor". Additional two subsets were also created for studies on IVF/ICS and GH supplementation, using relevant keywords. the subsets were combined using the "AND" operator to generate a refined set of citations, and a publication type filter was applied to obtain only RCTs and systematic reviews. To adhere to the search engine specifications for each database, the search strategy was adjusted accordingly. There were no restrictions on language or date. Additionally, we screened the reference lists of relevant systematic reviews and included studies to identify any additional articles that met our inclusion criteria. Two independent reviewers conducted the search and screened all records for eligibility. Any differences were addressed through discussion and agreement among the reviewers.

Criteria for Selecting Studies

Prior to conducting the literature search, we established the inclusion and exclusion criteria for this meta-analysis. To be considered for inclusion, studies had to be RCTs that met the following criteria: inclusion of women characterized as POR, women subjected to IVF or ICSI with any ovarian stimulation protocol, and reporting of clinical pregnancy outcomes. Studies that used adjuvant treatments alongside GH or lacked a comparison group not using GH were excluded from the analysis.

Extraction of Relevant Data

Two reviewers (AA, FA) undertook a meticulous evaluation of each study's title and abstract to determine its eligibility for inclusion in this meta-analysis. Studies that did not meet the inclusion criteria were excluded. The complete texts of the remaining studies were reviewed to confirm they met the eligibility criteria for the data extraction process. Next, the following information was selected for extraction in three sets: 1. patient-specific factors [i.e. what POR criteria are met, age, body mass index (BMI), and the duration of infertility], 2. study design (i.e. number of participants, details of IVF or ICSI protocol, doses and details of GH administration), 3. outcomes (i.e. pregnancy rate, live birth rate, number of retrieved oocytes, number of transferred embryos, rate of cycle cancellation, and total dose of gonadotropins administered, and peak estradiol level).

Study Quality Assessment

To ensure the reliability and accuracy of the meta-analysis, two independent authors (FZ, QB) evaluated the quality of the included literature using the Cochrane risk of bias assessment tools for RCTs. Any inconsistencies in the evaluations were resolved by a third author, (FA).

Statistical Analysis

This meta-analysis was conducted on the effects of co administration of gonadotropins and GH during the ovarian stimulation on IVF outcome for POR's patients compared to a control group using Stata version 15 (Stata Corp, College Station, TX, USA). After the authors have extracted data, meta-analysis has been on the adequate data. We have gathered all information in Tables 1-3 to be systematically studied and explained in the result section. Standardized mean difference (SMD) between the control and the patient's group was selected as the main unit of analysis for each variable. The cut-off values have been set by Cohen for the interpretation of medium, small, and large effect sizes (0.5, 0.2, and 0.8, respectively). Analyses have been performed employing the random effects model. The authors have assessed heterogeneity by I2 statistics and values larger than 50% were announced as moderate to high heterogeneity. We also have done meta-regression when we found enough studies to examine the relationship between pregnancy rate, and live birth rate as potential effect modifiers. Publication bias was assessed visually using funnel plots and quantitatively through Begg's and Egger's regression tests.

Results

Study Selection and Included Studies

After an extensive search using MESH terms, a total of 234 studies were identified. Of these, 37 duplicates were removed.

Table 1. Characteristics of the studies included

Publication, country of origin	Population (GH + control)	Inclusion criteria	Intervention	Gonadotropins treatment	Stimulation protocol	Selected outcomes
Safdarian et al.[24] 2019, Iran	70 (35+35)	Bologna criteria	2.5 mg/day GH CD8-trigger	300 IU/day CD3-trigger	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Duration of gonadotropin treatment Total doses of gonadotropin No. of collected oocytes No. of transferred embryos Clinical pregnancy rate, live birth rate, cycle cancelation rate
Bassiouny et al.[16] 2016, Egypt	141 (68+73)	Bologna criteria	2.5 mg/day GH CD6-trigger	300-450 IU/day HMG IM CD2-trigger	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Total dosage of HMG Duration stimulation No. of collected oocytes No. of embryos transferred Clinical pregnancy rate Live birth rate Cycle cancelation rate
Bayoumi et al.[17] 2015, Egypt	172 (84 + 88)	Bologna criteria	2.5 mg/day GH CD6-trigger	300-450 IU/ day HMG three days after GnRh-a until trigger	GH: Microflare stimulation protocol C: Microflare stimulation protocol	Total dosage of HMG Duration of stimulation No. of embryos transferred No. of collected oocytes Clinical pregnancy rate, cycle cancelation rate
Choe et al.[28] 2018, South Korea	127 (62+65)	Bologna criteria	20 mg GH three times at mid-luteal, late luteal, and menstrual cycle day 2	225-375 IU/day FSH from CD3-trigger	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Total doses of gonadotropin No. of collected oocytes No. of embryos transferred Clinical pregnancy rate
Dakhly et al.[22] 2018, Egypt	240 (120+120)	Bologna criteria	2.5 mg GH from previous cycle day 21 until trigger	300 IU/day FSH from CD2/3-trigger	GH: Long GnRH agonist protocol C: Long GnRH agonist protocol	Duration of stimulation, Dosage of gonadotropins E2 levels No. of collected oocytes No. of transferred embryos Canceled cycles rate, Clinical pregnancy rate, Live birth rate
Dor et al.[29] 1995, Israel	14 (7+7)	Oestradiol <500 pg/ mL, less than three oocytes retrieved in two previous IVF cycles	18 IU GH on days 2, 4, 6 and 8 of the cycle	300 IU/day FSH on CD3-CD7 and 300 IU/day HMG On CD8-trigger	GH: GnRH agonist short protocol C: GnRH agonist short protocol	Total dosage of HMG No. of collected oocytes No. of transferred embryos
Eftekhar et al.[18] 2012, Iran	82 (40+42)	Failed IVF cycles ≥1; oocytes ≤3; E2 levels <500 pg/mL on HCG day	4 IU/day GH from previous cycle day 21 until trigger	IU/day of HMG on CD2-trigger	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Duration of stimulation Total dosage of HMG E2 levels Cancelation rate No. of collected oocytes No. of embryos transferred Clinical pregnancy rate
Lee et al.[30] 2019, Taiwan	184 (94+90)	Bologna criteria	4, 4, 2 IU GH for three days in a row	NA	GH: Ultra-long GnRH agonist protocol C: Ultra-long GnRH agonist protocol	Total dosage of HMG E2 levels No. of collected oocytes No. of embryos transferred Clinical pregnancy rate

Table 1. Continued

Publication, country of origin	Population (GH + control)	Inclusion criteria	Intervention	Gonadotropins treatment	Stimulation protocol	Selected outcomes
Kucuk et al.[5] 2008, Turkey	61 (31+30)	Responded poorly to high dose gonadotropin in first cycle	4 mg/day GH from previous cycle day 21	450 IU/day rFSH until trigger (starting day: NA)	GH: GnRH agonist long protocol C: GnRH agonist long protocol	Duration of stimulation, Total dosage of FSH E2 levels No. of embryos transferred, Pregnancy rate
Zafardoust et al.[25] 2022, Iran	194 (97+97)	Bologna criteria	5 mg/day GH from previous cycle day 21 until trigger	75-300 IU/ day of FSH on CD2/3-trigger	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Duration of stimulation Total dosage of FSH E2 levels Cancelation rate Clinical pregnancy rate Live birth rate
Mohammad et al.[23] 2021, Egypt	156 (78+78)	Bologna Criteria W/O advanced maternal age	4 IU/day GH from CD2 - 1 day before oocyte retrieval	450 IU/day HMG from CD2-trigger	GH: Ultra-short GnRH antagonist C: Ultra-short GnRH antagonist	Duration of stimulation E2 levels Cancelation rate No. of collected oocytes No. of embryos transferred Clinical pregnancy rate
Norman et al.[31] 2019, Australia	130 (65+65)	At least one IVF cycle with oocytes ≤5; age ≤ 41; FSH ≤15 IU/l	12 IU/day GH from CD1- trigeer	NA	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Total dosage of rFSH duration of stimulation No. of collected oocytes No. of embryos transferred live birth rate Clinical pregnancy rate, cancelation rate
Owen et al.[32] 1991, UK	25 (13+12)	At least one previous IVF cycle with poor response (e.g. oocytes ≤6, embryos ≤3)	24 IU GH on alternate days during stimulation	225 IU/day HMG from CD1 until trigger	GH: Microflare protocol C: Microflare protocol	Duration of HMG Total dosage of HMG No. of embryos No. of collected oocytes Pregnancy rate, live birth rate
Suikkari et al.[33] 1996, Finland	22 (16+6)	Oocytes ≤2 or ≥48 amples of HMG	4 IU/day or 12 IU/day GH from menstrual cycle day 3 d until trigger	300 IU/day FSH from from menstrual cycle day 3 until trigger	GH: GnRH-a flare up protocol C: GnRH-a flare up protocol	Cancelation rate Total dosage of FSH E2 levels No. of collected oocytes Pregnancy rate Live birth rate
Gong et al.[26] 2020, China	105 (52+53)	Bologna criteria	4 IU/day GH on day 2 of the previous menstrual cycle until trigger	FSH from day 2 of the menstrual cycle	GH: GnRH antagonist protocol C: GnRH antagonist protocol	Total dosage of FSH Duration of stimulation E2 levels No. of collected oocytes No. of embryos Cancelation rate Clinical pregnancy rates
Bergh et al.[34] 1994, Sweden	20 (10+10)	Failed IVF attempts ≥2, oocytes <5, age 25-38 years	0.1 IU/kg GH during stimulation for a maximum of 25 days	75-300 IU/day HMG or rFSH for 10 to 25 days	GH: GnRH agonist long protocol C: GnRH agonist long protocol	Total dosage of gonadotropins Duration of stimulation E2 levels No. of collected oocytes Cancelation rate Clinical pregnancy rates

Table 1. Continued

Publication, country of origin	Population (GH + control)	Inclusion criteria	Intervention	Gonadotropins treatment	Stimulation protocol	Selected outcomes
Tesarik et al.[35] 2005, Spain	100 (50+50)	Age 41-44 years	8 IU/day GH from CD7	450 IU/day of rFSH and 150 IU/day of HMG for 5 days (adjusted until trigger)	GH: GnRH agonist long protocol C: GnRH agonist long protocol	Total dosage of gonadotropins Duration of stimulation E2 levels No. of collected oocytes No. of embryos Live birth rate Clinical pregnancy rates Cancelation rate
Zhuang et al.[27]1994, China	27 (12+15)	Previous poor response	12 IU GH on alternate days	2 IU HMG given on alternate days for 12 days (at same time as GH)	GH: GnRH agonist long protocol C: GnRH agonist long protocol	Total dosage of gonadotropins Duration of stimulation E2 levels No. of collected oocytes No. of embryos Live birth rate Clinical pregnancy rates Cancelation rate

GH: Growth hormone, CD: Cluster of differentiation, C: Control, HMG: Human menopausal gonadotropin, GnRH: Gonadotropin-releasing hormone, IVF: In vitro fertilization, HCG: Human chorionic gonadotropin, FSH: Follicle-stimulating hormone, rFSH: Recombinant follicle stimulating hormone

Table 2. The results of subgroup analysis

	Number of study	Standard mean difference	95% CI	I2
Age	14	-0.02	-0.14, 0.11	41.9%
BMI	12	-0.05	-0.16, 0.06	15.5%
Duration of infertility	8	-0.00	-0.12, 0.12	0.0%
Oocytes retrieved	13	0.65	0.29, 1.00	90.6%
Total gonadotropin	11	-0.82	-1.25, -0.39	92.8%
Duration of gonadotropin stimulation	11	-0.63	-1.04, -0.22	91.7%
Transferred embryo	11	0.80	0.39, 1.21	91.4%
Peak E2 level	11	1.20	0.59, 1.81	96.1%

CI: Confidence interval, BMI: Body mass index

Then, the abstracts of the remaining articles went through further assessment, which resulted in exclusion of 163 studies for not meeting the inclusion criteria. The full text of the remaining 34 studies were retrieved, and 16 of them were excluded following the reasons outlined in Figure 1. At last, only 18 studies matched the selection criteria and were included for meta-analysis. Eligible studies were published from 1991-2022, and included a total of 1870 women identified as POR. Among them, 934 women received GH co-treatment during ovarian stimulation and were assigned to the intervention group,

Table 3. The results of meta-regression analysis

	Primary outcomes	Coef (95% confidence interval)	p-value
Oocyte retrieved			
	Cycle cancellation rate	0.019 (-1.86, 1.80)	0.982
	Clinical pregnancy rate	-0.740 (-5.73, 4.25)	0.750
	Live birth rate	-3.154 (-10.83, 4.52)	0.318
Total gonadotropin			
	Cycle cancellation rate	3.166 (-1.44, 7.77)	0.152
	Clinical pregnancy rate	0.753 (-7.74, 9.25)	0.845
	Live birth rate	8.183 (-8.23,24.60)	0.239
Duration of gonadotropin			
	Cycle cancellation rate	1.337 (-0.61,3.29)	0.156
	Clinical pregnancy rate	-19.455 (-53.96, 15.03)	0.170
	Live birth rate	4.551 (-7.22, 16.32)	0.343
Transferred embryo			
	Cycle cancellation rate	-1.743 (-4.95, 1.47)	0.241
	Clinical pregnancy rate	0.495 (-8.65, 9.64)	0.905
	Live birth rate	-9.305 (-48.57, 29.96)	0.415
Peak E2 level			
	Cycle cancellation rate	-1.743 (-4.95, 1.47)	0.247
	Clinical pregnancy rate	0.495 (-8.65, 9.64)	0.905
	Live birth rate	-9.305 (-48.57, 29.96)	0.415

while the remaining 936 women, who received conventional COS, were assigned to the comparison group. The definition of poor ovarian response was not consistent across the studies due to some being published before the establishment of the Bologna criteria. Out of articles included, four were carried out in Egypt[16,17,22,23], three were from Iran[18,24,25], two from China[26,27], and one from South Korea[28], Israel[29], Taiwan[30], Turkey[5], Australia[31], UK[32], Finland[33], Sweden[34], and Spain[35]. All articles aimed to determine whether GH co-treatment could enhance IVF or ICSI outcomes for patients with poor ovarian response. GnRH agonists were used in 10 studies[5,17,22,23,29,30,32-35], and total of five RCTs used GnRH antagonists[16,18,24,25,28]. Detailed information on these studies can be found in Table 1.

Demographics

A total of 14, 12, and 8 studies reported the age[5,16-18,22-26,28,30,31,34,35], and duration of infertility[18,22-24,26,28] of the study participants, respectively. The findings of the analysis indicated that there was no significant difference with regard to these demographic factors among studies, exhibiting low to moderate heterogeneity (age: I2=41.9%, BMI: I2=15.5%, duration of infertility: I2=0.0%). Nevertheless, a random-effects model was used as illustrated in Figure 2.

Number of Retrieved Oocytes

A total of 15 studies reported number of retrieved oocytes. two of which[29,32] did not provide standard deviation of data, finally, 13 studies[16-18,22-24,26-28,30,31,34,35] including 1554 patients (770 in the GH group and 784 in the control group) were included in the meta-analysis. A significant increase in the number of retrieved oocytes was found in the GH group compared to the control group (SMD, 0.65; 95% CI, 0.29-1.00), as shown in

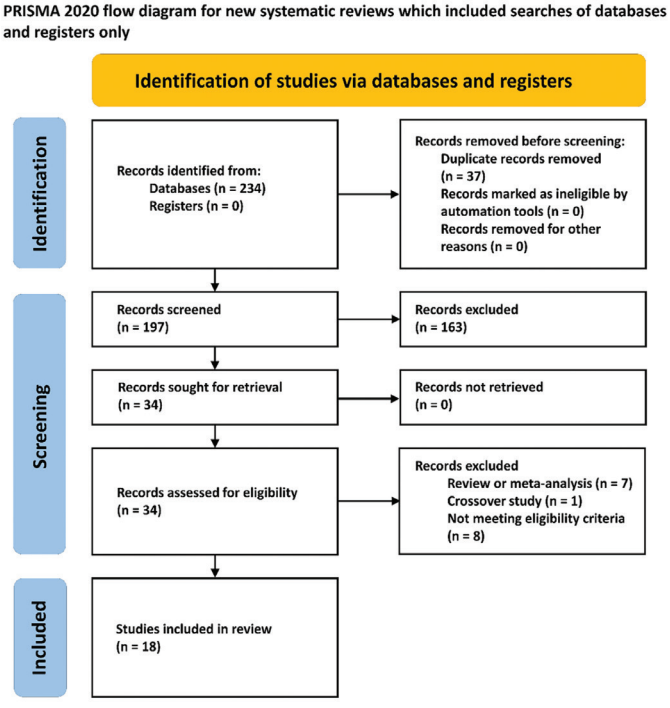

Figure 1. PRISMA flow diagram for current systematic review

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols

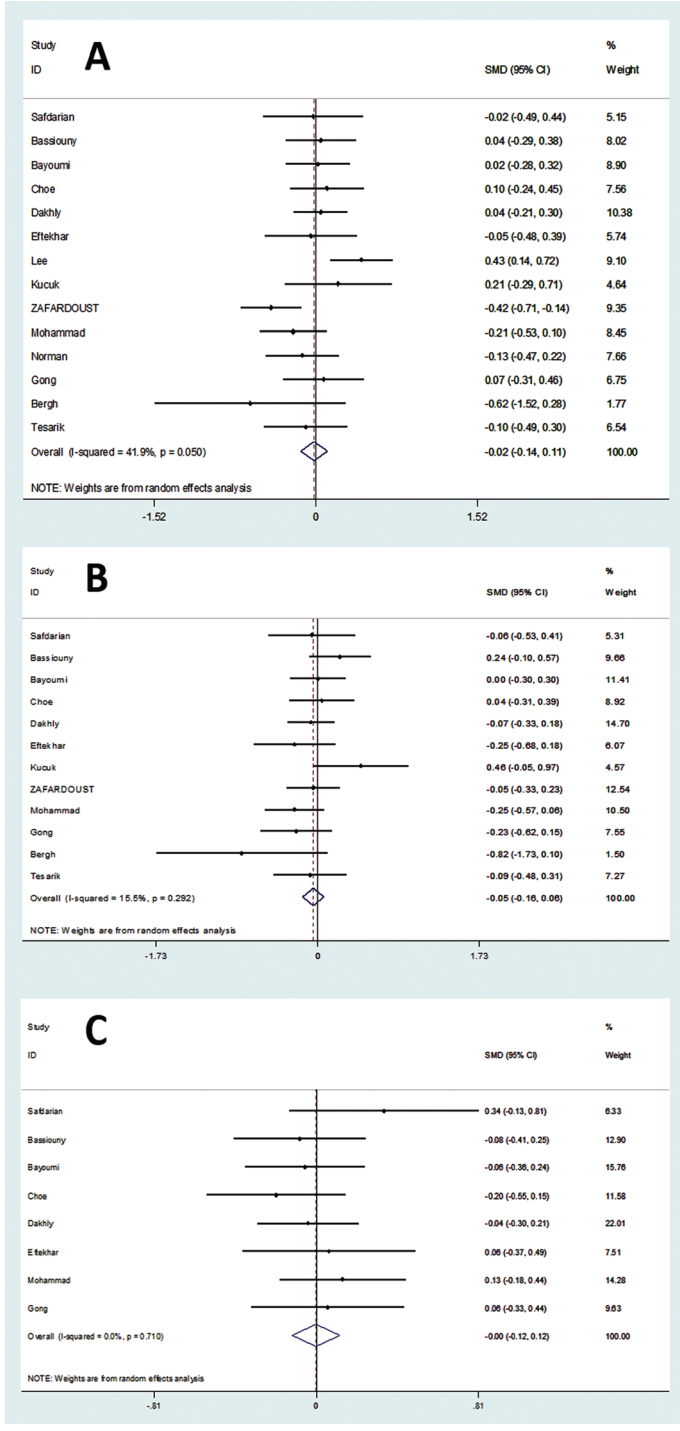

Figure 2. Forest plot for demographics; A) Age, B) BMI, C) Duration of infertility

CI: Confidence interval, SMD: Standardized mean difference, BMI: Body mass index

Figure 3A. However, significant heterogeneity was observed among these studies (I2=90.6%), as a result, the random effects model was applied.

Number of Transferred Embryo

A total of 15 studies reported the number of transferred embryo, four of which[22,29,32,35] did not provide standard deviation of data or lacked specific data required for a meta-analysis. The meta-analysis finally included 11 studies[5,16-18,23,24,26-28,30,31] for 1255 patients (621 in the GH group and 634 in the control group). The result showed a significant increase in the number of transferred embryo in the group given GH o-treatment compared to the control group (SMD, 0.80, 95% CI, 0.39, 1.21). A random effects model was applied due to the significant heterogeneity among these studies. (I2=91.4%), as shown in Figure 3B.

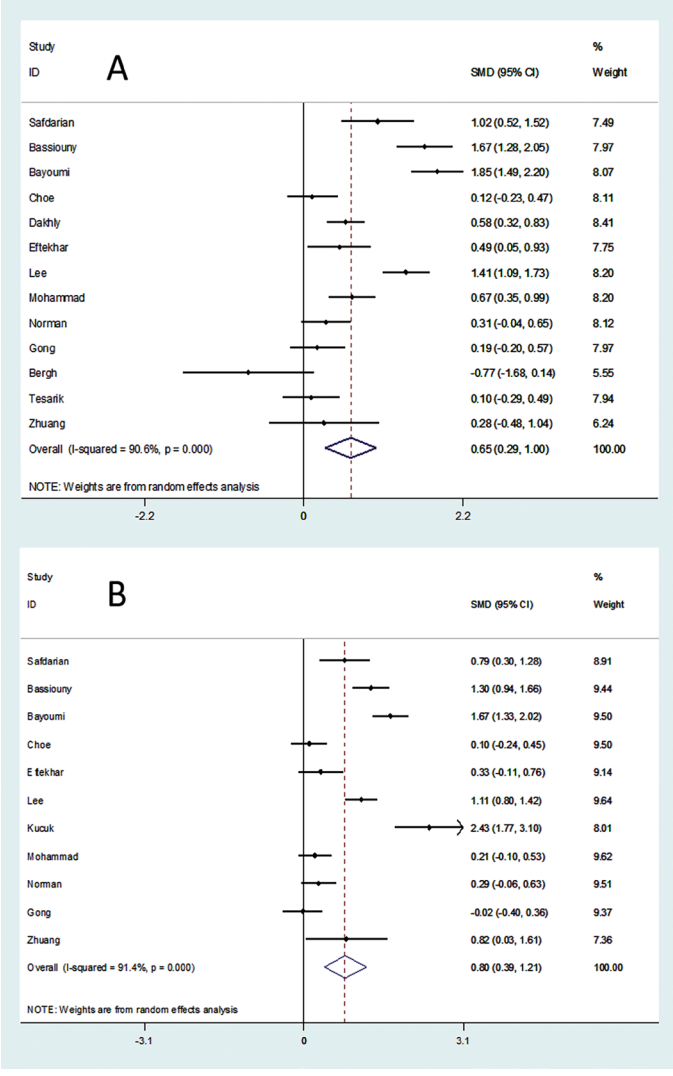

Figure 3. Forest plot for Secondary outcomes; A) Number of retrieved oocytes, B) Number of transferred embryo

CI: Confidence interval, SMD: Standardized mean difference

Total Dose of Gonadotropin

A total of 15 studies reported total dose of gonadotropin, four of which[29,32-34] did not provide standard deviation of data or lacked specific data required for a meta-analysis. The meta-analysis finally included 11 studies[5,16-18,22,24-28,31] for 1449 patients (716 in the GH group and 733 in the control group). The result indicated a significant decrease in the gonadotropin dosage with the administration of GH [SMD=-0.82, 95% CI=(-1.25, -0.39)]. A random effects model was applied due to the significant heterogeneity among these studies. (I2=92.8%), as shown in Figure 4A.

Duration of Gonadotropin Therapy

A total of 14 studies reported the duration of gonadotropin therapy, three of which[22,32,34] did not provide standard deviation of data or lacked specific data required for a meta-analysis. The meta-analysis finally included 11 studies[5,16-18,23-27,31,35] for 1478 patients (732 in the GH group and 746 in the control group). The findings showed a notable reduction in gonadotropin dosage with GH administration (SMD, -0.63, 95% CI, -1.04, -0.22). A random effects model was applied due to the significant heterogeneity among these studies (I2=91.7%), as shown in Figure 4B.

Peak E2 Level

A total of 14 studies reported peak E2 level. Three of which[32-34] did not provide standard deviation of data, Finally, 11 studies[5,16-18,22,23,26-28,30,35] including 1395 patients (691 in the GH group and 704 in the control group) were eligible for the meta-analysis. A significant increase in the level of peak E2 was observed in the GH group compared to the control group (SMD, 1.20; 95% CI, 0.59, 1.81), as shown in Figure 4C. However, significant heterogeneity was observed among these studies (I2=96.1%), therefore, the random effects model was applied.

Meta-regression Analysis

A meta-regression analysis was conducted to investigate whether the differences of reported outcomes in GH and control group were correlated to effectiveness of intervention in regards to cycle cancellation rate, pregnancy rate, and live birth rate. The findings of the meta-regression analysis indicated that there was no significant linear relationship between the effectiveness of intervention and any of the reported outcomes, including the number of retrieved oocytes, the total dose of gonadotropin, the duration of gonadotropin therapy, the number of transferred embryos, and the peak E2 level. Further details can be found in Table 3.

Sensitivity and Bias Analysis

The sensitivity analysis indicated that no single study or group of similar studies significantly affected the SMD and its corresponding CI, suggesting the overall findings are robust. Also, Egger's regression test, Begg's test, and funnel plot analysis were performed to detect publication bias in relation

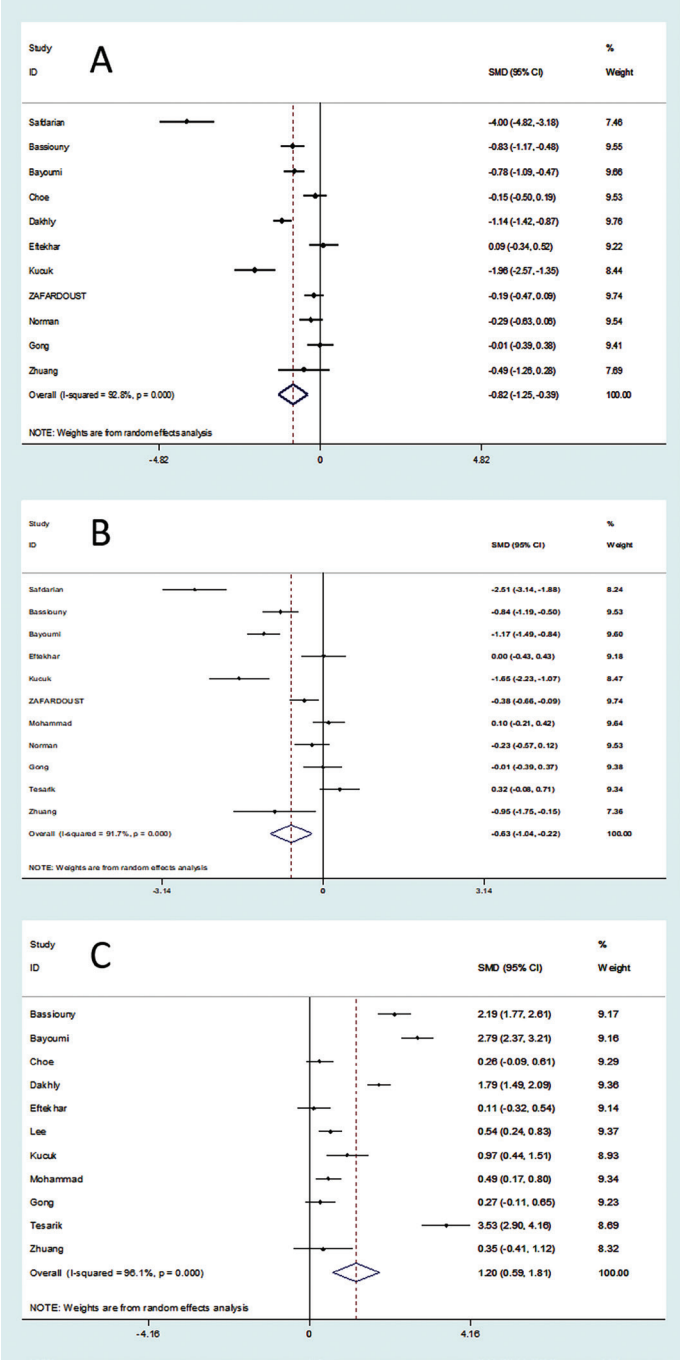

Figure 4. Forest plot for secondary outcomes; A) Total gonadotropin, B) Duration of gonadotropin therapy, C) Peak E2 level

CI: Confidence interval, SMD: Standardized mean difference

to the number of retrieved oocytes. Both Egger's regression test and Begg's test did not reveal any evidence of publication bias (p>0.1), and funnel plot analysis yielded a symmetric plot for the number of retrieved oocytes (Figure 5). Therefore, giving no indication of publication bias.

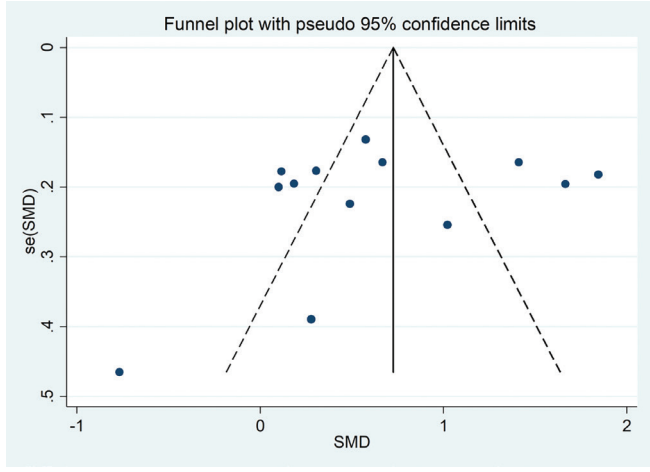

Figure 5. Funnel plot of the studies represented in the meta-analysis

SMD: Standardized mean difference

Discussion

This systematic review and meta-analysis included 18 studies involving 1870 participants. The findings revealed a significant correlation between the usage of GH and various factors, such as the number of retrieved oocytes, embryo transfer, total dose of gonadotropin, duration of gonadotropin therapy, and peak E2 level. However, there was no significant association between the improvement in these factors and the success of IVF, including LBR, pregnancy rate, and cycle cancellation rate. Several studies, consistent with our findings, demonstrated a concurrence regarding the number of retrieved oocytes[5,16-18,22-24]. GH is believed to play a crucial role in enhancing ovarian function by stimulating follicular growth, gametogenesis, increasing estrogen production, and promoting oocyte maturation[16,18,23]. It facilitates the growth of small follicles, increasing gonadotropin sensitivity, and reduces follicular degeneration and atresia before ovulation, thus improving ovulation[18]. Additionally, GH stimulates the synthesis of IGF-1 by influencing granulosa cells, which mediates the action of GH[24]. Lower doses of GH have shown more favorable responses on the ovary[30]. Although some studies did not support this outcome and did not report a significant relationship in terms of oocyte retrieval[29,31].

Another aspect investigated in this study was the number of transfer embryos, which exhibited a significant improvement, consistent with several other studies[18,22-24,30]. Nonetheless, conflicting results were reported in some studies[29,31].

Our study observed a correlation between the usage of GH and a decrease in the dose and duration of gonadotropin use, supported by several studies[5,16,17,22,31]. GH concentration in follicular fluid plays a role in enhancing ovarian response to gonadotropin[22]. Together with IGF-1, GH enhances the function of FSH, leading to a reduction in the required dose

and duration of gonadotropins[22,32]. However, this effect was more pronounced in patients with poor ovarian response, whereas patients with normal ovarian response required higher doses of gonadotropin, resulting in a less favorable response[32]. Taking a lower dose of GH has been reported to increase the need for gonadotropin and reduce ovarian response[30], while a higher dose of GH has the opposite effect[5]. Another mechanism that may explain this effect is the acceleration of ovarian follicle development and earlier oocyte production during GH administration, thereby reducing the need for higher gonadotropin doses[31].

GH induces changes in the hormonal profile of patients, with one of the most notable effects being the increase in peak E2 levels, supported by several studies[5,17,23]. Elevated E2 levels indicate an increase in the number of follicles stimulated by GH and, consequently, an increase in the number of produced oocytes[17]. It is proposed that GH may enhance the chance of pregnancy by elevating the E2 level in follicular fluid[5,23]; however, this outcome was not observed in our study.

Theoretically, GH can influence the pregnancy rate through various mechanisms, such as improving oocyte quantity and quality, enhancing embryo quantity and quality, increasing the number of transferable embryos, and promoting implantation potential[5,16,17,22]. GH may improve the success of embryo implantation by enhancing endometrial blood supply and increasing endometrial receptivity[30]. Even though a study by Safdarian et al.[24] reported a notably higher clinical pregnancy rate, although there was no significant difference in LBR. Nevertheless, our study, along with several others, supports the notion that improving these factors does not significantly impact the outcomes of IVF[16-18,22,28].GH consumption affect the quality and quantity of oocyte production but does not have significant correlation with pregnancy rate and LBR[16,17,22]. While the administration of a high dose of GH in the late luteal phase demonstrated an increase in the pregnancy rate in Kucuk et al.'s study[5], that was not statistically significant.

Overall, the effectiveness of GH is influenced by various factors, including the hormonal background, patient characteristics, and GH dosage[24]. GH deficiency may be a necessary condition for its effectiveness in IVF[24]. The timing of GH administration during the cycle is another influential factor[28]. It has been reported that the effect of GH administration is more pronounced in PORs compared to normal responders, particularly in terms of qualitative response rather than quantitative response[28]. Furthermore, increasing age leads to a decrease in GH, making older women with GH deficiency an ideal group to receive GH supplementation[22].

Study Limitations

This study encompassed diverse ethnic groups, thereby enhancing the generalizability of the results to other populations. However, our study had some limitations, too. Included studies had used various criteria for diagnosing POR, although the dominant method was the Bologna criterion. Also, some studies had small populations, which indicates the requirement of future studies with larger populations.

Conclusion

In summary, this systematic review and meta-analysis investigated the relationship between GH usage and factors related to IVF. The findings indicate a significant association between GH and improved outcomes such as the number of retrieved oocytes, transferable embryos, total gonadotropin dosage, duration of gonadotropin therapy, and peak E2 levels. However, despite these positive effects, there was no significant impact on the success of IVF in terms of LBR, pregnancy rate, and cycle cancellation rate. The effectiveness of GH appears to depend on individual factors and the timing and dosage of administration. Further research is needed to clarify its role in IVF outcomes and identify the specific patient groups that may benefit most from GH supplementation.

Ethics

Authorship Contributions

Concept: F.Z., N.D., Design: F.Z., A.A., N.D., Data Collection or Processing: Q.B., A.A., R.K., Analysis or Interpretation: F.Z., Q.B., Literature Search: R.P., F.A.M., Writing: F.Z., Q.B., R.P., A.A.

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