Efficacy and safety of human chorionic gonadotropin for follicular phase stimulation in assisted reproduction: a systematic review and meta-analysis

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Objective: To assess the efficacy and safety of hCG to induce follicular stimulation.
Design: Systematic literature searches of PubMed, EMBASE, CENTRAL, and SciSearch databases. Randomized controlled trials (RCTs) using hCG in early or late follicular phases were included.
Setting: Three reproductive medicine services of gynecology in Spain and two universities.
Patient(s): A total of 1,068 women treated in 11 RCTs were included.
Intervention(s): Use of hCG versus other hormone treatments, no administration, or placebo during the period of follicular stimulation.
Main Outcome Measure(s): Live birth, clinical pregnancy, mature oocytes, miscarriage, ovarian hyperstimulation syndrome (OHSS), and FSH doses.
Result(s): No differences in live birth, miscarriage, and OHSS rates between hCG (given at either the early or late follicular phases) and different control regimens were found. Pooled analysis for clinical pregnancy showed significant differences in favor of hCG at the late follicular phase. The doses of FSH were lower in women treated with hCG at either the early or late follicular phase than in those treated with FSH alone.
Conclusion(s): The use of hCG in the early and late follicular phase in controlled ovarian stimulation has the advantage of decreasing the doses of FSH. (Fertil Steril® 2012;97:1343–50. ©2012 by American Society for Reproductive Medicine.)
Key Words: hCG, follicular maturation, controlled ovarian stimulation, FSH doses, systematic review, meta-analysis

Controlled ovarian hyperstimulation for IVF is usually achieved using FSH or LH. HCG purified from the urine of pregnant women (u-hCG) or produced by recombinant DNA technology (r-hCG) is one of the hormones used to trigger ovulation. Usually one injection of 5,000–10,000 IU of u-hCG or 250 μg of r-hCG is administered when one or more follicles measuring >17 mm in diameter are observed on ultrasound. Various hormone treatment protocols include the administration of 5,000 IU of hCG for luteal phase support (1). However, the use of hCG in more initial phases of the stimulated cycle to enhance follicular growth is infrequent and poorly characterized.

The main objective of this systematic review was to assess the efficacy of hCG to induce follicular development during controlled ovarian hyperstimulation. A secondary objective was to evaluate the safety of this approach according to data provided in the studies included in the review.

MATERIALS AND METHODS

The study was exempt from Institutional Review Board approval (not appropriate) because this was a systematic review and meta-analysis and did not involve interventions on human beings.

Search Strategy

We performed an exhaustive electronic search in the following databases: MEDLINE (from 1950 until March 2011), EMBASE (from 1980 until March 2011), and the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1, 2011). The search combined terms and descriptors related to IVF, controlled ovarian hyperstimulation, and hCG. The search strategy was modified to fit with the syntaxes used in each database that was consulted. We added validated filters to that strategy to retrieve clinical trials (2, 3). Moreover, we searched for ongoing trials at the main clinical trials registers, including www.controlled-trials.com, www.clinicaltrials.gov, and the World

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Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch). No language limits were placed. Reference lists of all identified articles and overviews, and a Science Citation Index Search (SciSearch, ISI Web of Knowledge) of relevant articles, provided additional sources of potentially eligible clinical trials.

Eligibility Criteria

The review included randomized controlled clinical trials (RCTs) of women undergoing treatment for infertility of subinfertility independent of whether the cause of infertility is in the male or the female partner. The type of intervention evaluated was the administration of u-hCG versus other hormone treatments, no administration, or the administration of placebo during the period of follicular stimulation. Parallel or crossover RCTs were included in the study. To avoid the potential of a carryover bias, crossover designs were eligible if data for the first treatment before assignment to the second treatment being tested were available.

Outcome Measures

Main outcomes of interest for the review were live birth rate (per women randomized), clinical pregnancy (per women randomized) rate, number of mature oocytes, doses of FSH, adverse events, including miscarriage (per women randomized), and ovarian hyperstimulation syndrome (OHSS) as defined by International Committee Monitoring Assisted Reproductive Technologies (4).

Data Extraction

Data were collected using standard forms in which characteristics of the study design, participants, interventions, comparisons, and main results were recorded. Two independent reviewers (M.J.M., J.V.) judged study eligibility, assessed quality, extracted data-solving discrepancies by agreement, and, if needed, reached consensus with a third author (J.J.E.). Agreement between reviewers was analyzed using the weighted kappa for each inclusion criterion (5) and kappa with quadratic weighting for the quality components (6).

Assessment of Risk of Bias

The risk of bias of the studies included in the review was evaluated according to the Cochrane Collaboration's recommended tool (7), which is a two-part tool that addresses six specific domains (sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and "other issues") and answers a prespecified question about the adequacy of the study in relation to the entry. A judgment of "yes" for all domains indicates a low risk of bias, a judgment of "no" for one or more domains indicates a high risk of bias, and a judgment of "unclear" for at least one domain indicates an unclear risk of bias.

Analysis

To determine the pooled effect of each variable, a random-effects model was used. The relative risk (RR) for dichotomous data and the mean difference (MD) for continuous data accompanied by the 95% confidence intervals (CIs) were calculated. Statistical significance was set at $P<.05$. We evaluated the degree of variation across studies attributable to heterogeneity with the I^2 statistic (8). We conducted meta-analyses using Review Manager software.

RESULTS

A total of 1,865 studies were retrieved in the initial electronic search, but 1,786 were excluded at title/abstract screening. The remaining 80 studies were considered eligible by one or both reviewers. During the second phase of the inclusion process, 69 were excluded because the inclusion criteria were not fulfilled (n = 49) or because of administration of hCG for indications other than follicular stimulation (n = 20). The flow chart of the 11 trials included in the meta-analysis is shown in Supplemental Figure 1. The two reviewers achieved good agreement in the selection of trials for inclusion (weighted kappa, 0.73; 95% CI, 0.58–0.89).

Description of Included Studies

Eleven RCTs evaluating hCG during the period of follicular stimulation in women undergoing assisted reproduction met the inclusion criteria (9–19). The sample size ranged from 20 to 300 women, with a total of 1,068 women. Ages of the participants ranged between 20 and 40 years. A total of 283 (four studies) women participated in studies in which hCG was administered in the early follicular phase and 785 (seven studies) in which hCG was administered in the late follicular phase. In seven studies, one control group was included (9–13, 15, 19), whereas in the remaining four studies, two controls groups were included (14, 16–18). The main causes of infertility were male factor, tubal factor, ovulatory factor, endometriosis, and unexplained etiology. Characteristics of the studies included in the meta-analysis are shown in Table 1.

Internal Validity of Included Studies

As shown in Supplemental Figure 2, the risk of bias was important in most studies, particularly because blinding of the randomization process and the interventions was not mentioned. Except for the clinical trial of Lossl et al. (11), the risk of bias was high or unclear for the majority of studies.

Main Outcomes

Live birth. Only the study of Lossl et al. (11) provided data on the use of hCG in the early phase of the cycle (103 women) for the outcome of live birth rate. As shown in Supplemental Figure 3, there were no significant differences in the number of live births between the intervention and the control group (RR = 0.78; 95% CI, 0.43–1.41). Four studies assessing the administration of hCG in the late follicular phase (13, 17–19) reported quantitative information on the number of live

TABLE 1

Characteristics of the clinical trials included in the review.

Author, year (reference)	Total patients	Age years	hCG group No.	hCG group Treatment	Control group No.	Control group Treatment	Main causes of infertility	Dropouts, %
HCG at early follicular phase:								
Beretsos, 2009 (9)	50	33	19	200 IU/d for 7 d	27	RFSH 200 IU/d	Male, tubal, other	8
Drakakis, 2009 (12)	120	36.8 ± 3	58	200 IU/d IM for 4 d	56	rLH 200 IU/d for 4 d	Male, tubal, other	5
Filicori, 1999 (10)	20	32.5 ± 1	10	50 IU/d SC for 14 d	10	HP-FSH 150 IU/d SC for 14 d	Male, unexplained	NA
Lossl, 2008 (11)	103	32.5	53	1,250 IU SC cycle day 2	50	rFSH 150 IU/d (flexible protocol)	Male, tubal, other	NA
HCG at late follicular phase:								
Blockeel, 2009 (13)	70	29.8 ± 3.4	29	200 IU/d, 6 follicles >12 mm, E_2 >600 ng/L	32	rFSH 200 IU/d	Not stated	12.8
Dehghani-Firouzabay, 2006 (19)	60	26.5 ± 3.8	30	250 IU/d SC, leading follicle >14 mm	30	hMG 150 IU/d	Male, unexplained	NA
Filicori, 2005 (15)	48	33.6 ± 0.5	24	200 IU/d SC, 6 follicles >12 mm, E_2 >600 pg/mL	24	rFSH or hMG 225–300 IU/d	Male	NA
Gomes, 2006 (18)	51	29.5	17	200 IU/d IM, leading follicle >12 mm	17 and 17	hMG 225 IU/d IM; and rFSH 200 IU/d SC	Tubal, male, other	NA
Kyono, 2004 (14)	73	<40	24	200 IU/d, follicles reached 14 mm	26 and 23	uFSH 225-300 IU/d; and uFSH + GnRH antagonist 0.25 mg	Not stated	NA
Serafini, 2006 (16)	323	33.8 ± 0.4	106	200 IU/d, leading follicle 13–14 mm	96 and 98	rFSH + GnRH antagonist; and rFSH + GnRH agonist	Not stated	NA
Kyono, 2006 (17)	192	32.7 ± 0.3	63	200 IU/d, follicular diameter 14 mm	66 and 63	uFSH + nasal GnRH agonist; and uFSH + GnRH antagonist	Male, tubal, other	NA

Checa. Controlled ovarian stimulation with hCG. Fertil Steril 2012.

births, with percentages ranging between 10% and 46%. The pooled analysis with all four trials did not show statistically significant differences between hCG and control treatments (RR = 1.42; 95% CI 0.97–2.08, $I^2 = 0\%$; Supplemental Fig. 3).

Clinical pregnancy. Three studies (9, 11, 12) with a total of 263 women reported data for the outcome of clinical pregnancy with the use of hCG at the early follicular phase. The pooled analysis with these three trials did not show significant differences between the hCG and control groups (RR = 1.30; 95% CI, 0.89–1.91; $I^2 = 52\%$; Fig. 1). Five studies have assessed the administration of hCG at the late follicular phase (13, 16–19) for the outcome of clinical pregnancy. The pooled analysis showed statistically significant differences in favor of the hCG group (RR = 1.32; 95% CI, 1.06–1.64; $P=.01$; $I^2 = 0\%$; Fig. 1). The stratified analysis according to treatment of the control group showed no significant differences when hCG was compared with highly purified FSH (HP-FSH) or hMG. However, the comparison of hCG with recombinant human FSH (rFSH) showed a statistically significant difference for the hCG group ($P=.04$; Fig. 1).

Retrieved metaphase II oocytes. Pooled analysis of three studies (13, 15, 16) that evaluated the administration of hCG in the late follicular phase versus FSH, in association with agonists and antagonists of GnRH in both study groups, with a total of 313 women, showed that there were significant differences in the mean (±SD) number of mature oocytes retrieved for the FSH (10.6 ± 0.5) versus hCG protocols (10.3 ± 0.5; MD, −0.30, 95% CI, −0.44 to −0.16; $I^2 = 0\%$; Fig. 2).

Doses of FSH. The mean (±SD) doses of FSH were lower for women treated with hCG (1,725 ± 265.6 IU) than for those treated with FSH alone (2,670 ± 518.6 IU), both in the two studies in which hCG was administered in the early follicular phase (9, 11) (MD, −1,094.34; 95% CI, −1,374.73 to −813.96) and in the five studies (12–16) in which hCG was given in the late follicular phase. Mean doses of FSH were 1,647.7 ± 611.5 IU in the hCG group, as compared with 2,156.7 ± 799.9 IU in the FSH group (MD, −514.68; 95% CI, −672.86 to −356.51.93; Fig. 3).

Adverse Events

Miscarriage. Only the study of Filicori et al. (10) provided data on the number of miscarriages when hCG was administered at the early follicular phase, and significant differences between the study groups were not found (MD, 0.20; 95% CI, 0.01–3.70). When hCG was administered in the late follicular phase (16–18), differences in the miscarriage rate between the hCG protocol and either urinary FSH (uFSH) or rFSH protocols were not observed (RR = 1.40; 95% CI, 0.51–3.82, $I^2 = 0\%$).

OHSS. Only two studies reported data on development of OHSS for the use of hCG in the early follicular phase (11, 12). In the study of Lossl et al. (11), no case of OHSS was observed, whereas in the study of Drakakis et al. (12), seven patients in each group (hCG and recombinant LH [rLH]) developed OHSS (RR = 0.97; 95% CI, 0.36–2.58). Seven studies (13–19) provided data on OHSS for the administration of hCG in the late follicular phase. Pooled analysis showed no statistically significant differences for the comparison of hCG with hMG, rFSH, or HP-hMG (RR = 0.57; 95% CI, 0.31–1.04; $I^2 = 0\%$).

DISCUSSION

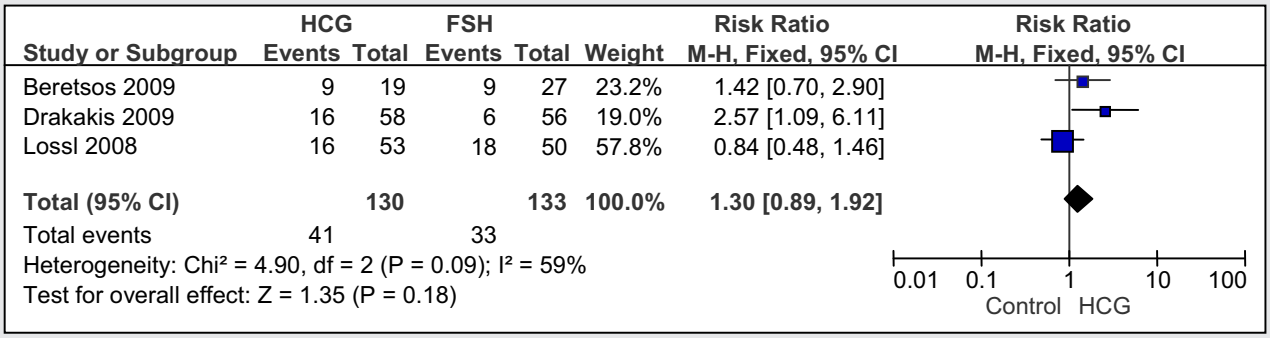
This is the first meta-analysis that evaluates the efficacy and safety of the administration of hCG for the stimulation of follicles. According to the present findings, the use of hCG to induce follicular stimulation seems to be associated with results similar to those obtained with standard FSH regimens. Usually, hCG has been used as a substitute for the midcycle LH surge because of the degree of homology between the two hormones (20). HCG has a slower plasma metabolic clearance, which consists of a rapid phase in the first 5–9 hours after IM administration and a slower phase in the first 1-3 days. Both LH and hCG are complex heterodimeric glycoproteins with molecular weights of ~30 and 40 kD, respectively (21). These two hormones have identical α-subunits and a high cysteine content. Most importantly, they have the same natural function—to cause ovulation and support lutein cells. The major differences between hCG and LH include the sequence of the β-subunit, the regulation of the secretion of the two hormones, and the pharmacokinetics of clearance of hCG as opposed to LH (22). The longer half-life and greater affinity for the LH/hCG receptor of hCG account for a potency ratio estimate of hCG-to-LH of around 1:6 (23).

The theoretical possibility of the use of hCG refers to two specific situations, the first in ovarian priming before the use of FSH at the beginning of the cycle, and the second in the late follicular phase at the time of the appearance of LH receptors. These two possibilities were analyzed in this study. The dose of hCG used for priming ranged between 200 and 1,250 IU. The action of LH/hCG in preantral and small antral follicles is limited to its stimulatory action on theca cells in conjunction with local growth factors, to induce the formation of the androgen substrate needed for the conversion of granulosa cells into E_2, which helps in follicular differentiation. Moreover, after 14 days of pituitary desensitization, LH can be abnormally low, so LH or hCG is normally added to prevent this and to ensure adequate androgen production in theca cells (24). Although in this meta-analysis an increase in the number of live births was not found (RR, 0.78; 95% CI, 0.43–1.41), a higher number of mature oocytes was observed, which were probably induced by the previous androgenization that was induced by hCG.

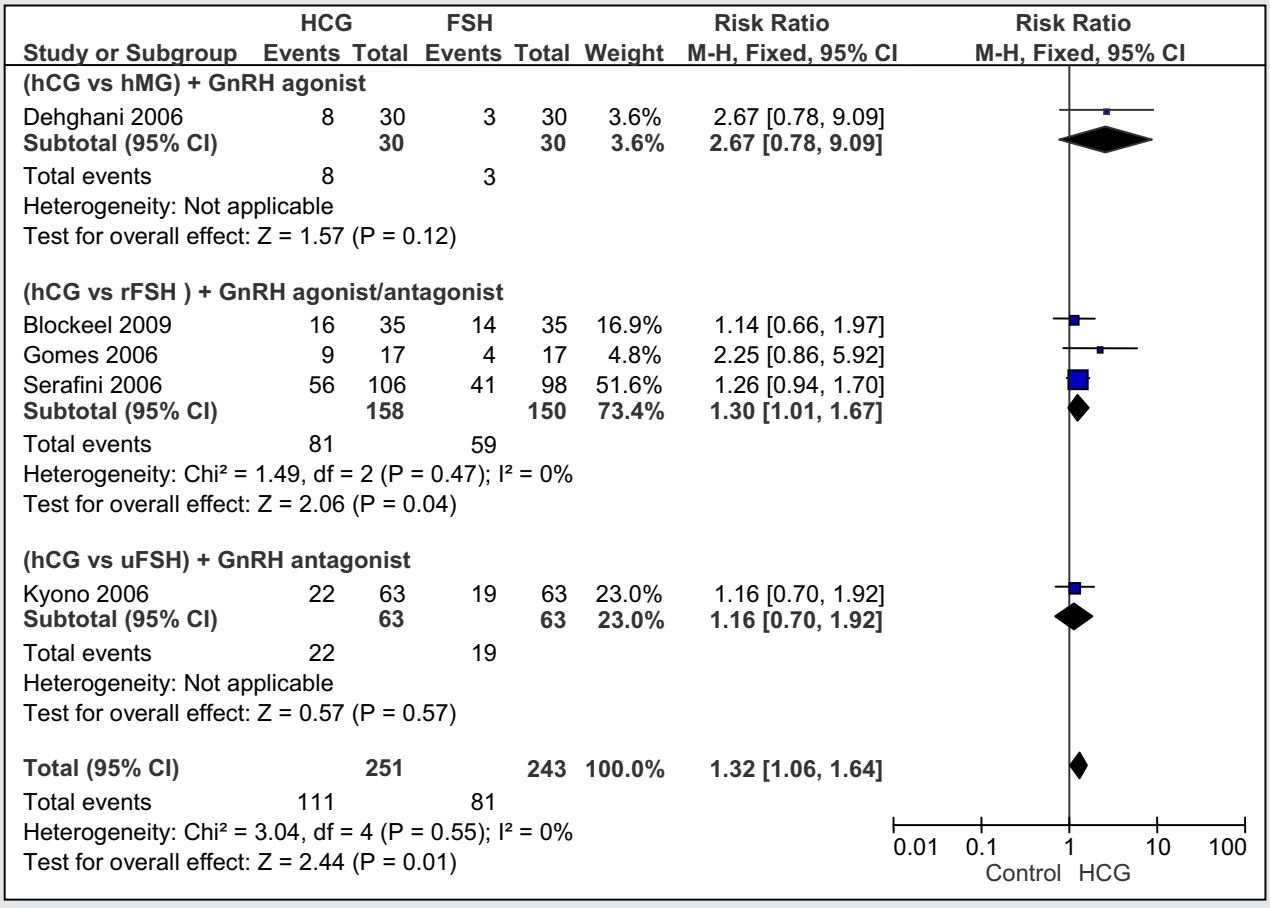
At the late follicular phase, hCG was administered at doses of 200 IU/day when follicles reached 12–14 mm in diameter in both the GnRH agonist and antagonist cycles. In physiological conditions, in this second part of the follicular phase, there is a decrease in FSH levels and LH plays a critical role in the control of folliculogenesis (25). Low-dose hCG may promote the growth of intermediate-sized follicles that have LH/hCG receptors expressed in the granulosa cells, potentially resulting in effective and safe induction of ovulation until the final stages without the presence of FSH (26). In relation to the final outcome (i.e., live births), hCG and control treatments were similar, with an RR of 1.42 (95% CI, 0.97–2.08). The

FIGURE 1

Early follicular phase



Late follicular phase



Effectiveness of hCG supplementation versus standard stimulation protocols for the outcome of clinical pregnancy.

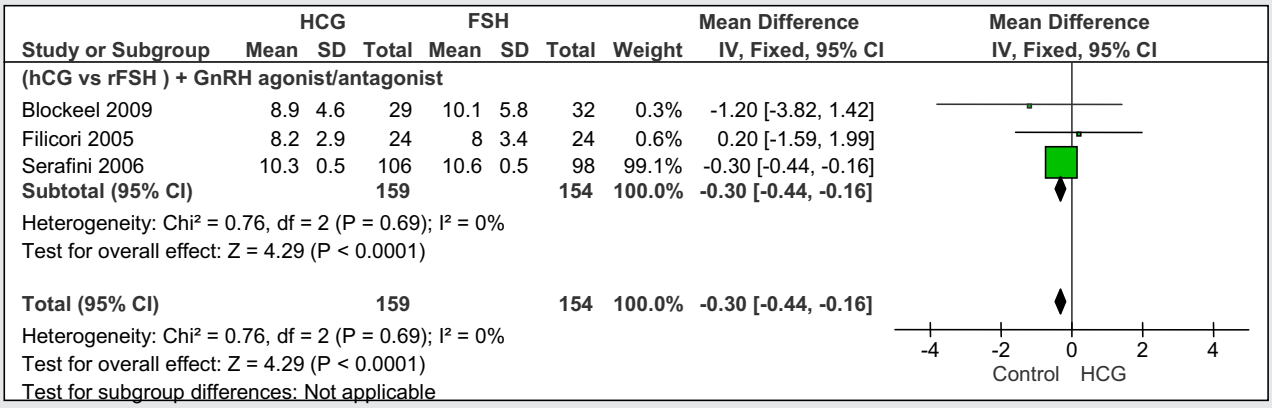
Checa. Controlled ovarian stimulation with hCG. Fertil Steril 2012.

clinical pregnancy rate in the hCG group was significantly higher than that in the standard FSH group (RR, 1.32; 95% CI, 1.06–1.64). Although a lower number of metaphase II oocytes was obtained (MD, −0.3; 95% CI, −0.44 to −0.16), a better oocyte quality may be the reason for a higher number of clinical pregnancies. HCG activity is present in HP-FSH, and in the MERIT clinical trial, better embryo quality in patients treated with HP-FSH was also reported (27).

In relation to OHSS, which is particularly associated with hCG for triggering ovulation (28), in the present meta-

FIGURE 2

Late follicular phase



Effectiveness of hCG supplementation versus standard stimulation protocols for the outcome of retrieved metaphase II oocytes.

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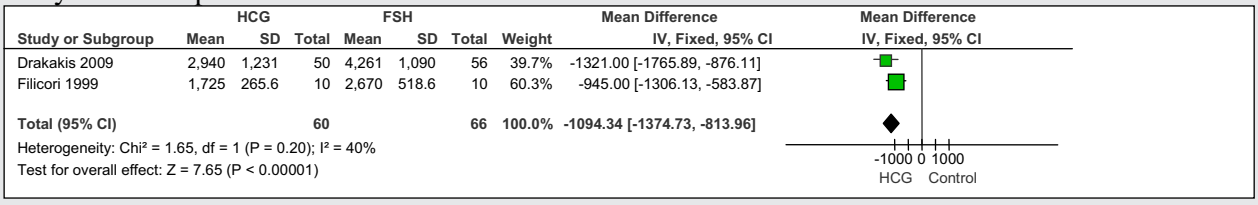
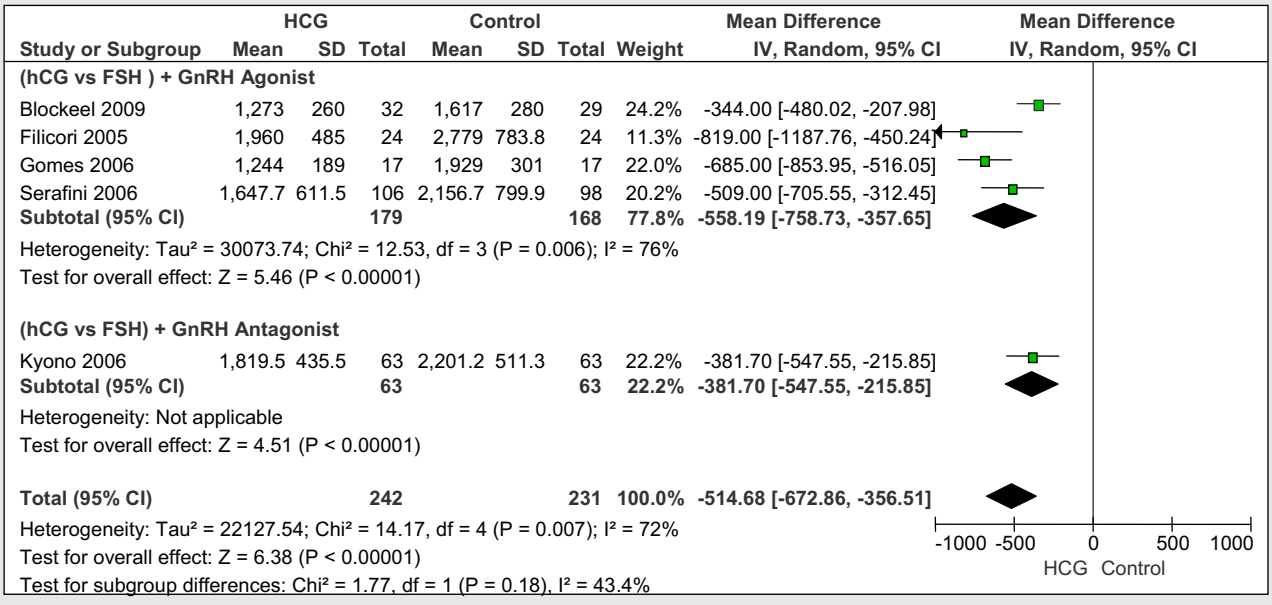
FIGURE 3

Early follicular phase



Late follicular phase



Mean differences in the FSH doses used.

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analysis, a higher number of cases of OHSS in the hCG group was not detected. We observed a lower number of metaphase II oocytes in the group of women treated with hCG. In our opinion, the doses of hCG used for oocytes maturation are lower than those used for triggering ovulation and therefore would trigger fewer hyperesponses; also hCG-mediated LH effect would allow the growth of larger follicles and the atresia of small-sized follicles without expression of LH receptors (26). Moreover, low responders were included in some of the studies, which would justify a lower risk of ovarian hyperstimulation.

The use of hCG may have the advantage of a reduction in the FSH doses used in the controlled ovarian hyperstimulation cycles, and in this meta-analysis a reduction of the total dose of FSH in the groups who were given hCG as a supplement to treatment was observed. According to these data, both hCG and FSH protocols for follicular stimulation are equally effective and safe, but the low cost of hCG stimulation makes this alternative more efficient.

The current study has several potential limitations but also some strengths. Systematic reviews have become standard practice in medical research to synthesize the best available evidence, but a potential risk for publication bias remains. However, publication bias seems unlikely given that no single study included in the meta-analysis concluded in favor of the use of hCG to increase the rate of live birth. In making health care management decisions, patients and clinicians must trade off the benefits and downsides of alternative strategies; thus they need to know how much confidence they can place in the estimates of effect. In this systematic review, the most relevant limitations are those related to the lack of information regarding the design and execution (methodological limitations) of the included studies, some degree of heterogeneity, and, more importantly, a low number of events and hence a low degree of precision. Except for the study of Lossl et al. (11), the risk of bias was high or unclear for the majority of studies. The overall quality of the evidence was therefore considered low, which decreases our confidence in the estimate of effect showed by adding hCG in controlled ovarian hyperstimulation. Differences in the regimens and the low number of events for the outcomes of live birth and clinical pregnancy would determine that the present results are susceptible to be modified by results of further RCTs reporting a larger number of events.

The heterogeneity of treatments used in the different studies makes the overall interpretation of data difficult. In the group of studies assessed for the early follicular phase, the series of Filicori et al. (10) is the only study in which hCG was administered during the entire follicular phase from the early to the late follicular phase, whereas in the majority of studies, hCG was given either in the early or in the late phase. In our opinion, hCG should be administered through the entire follicular phase to achieve a higher recruitment during the first phase and to activate LH receptors in the late phase.

In summary, the administration of hCG in the initial follicular phase appears to be associated with results similar to those obtained with conventional regimens used in controlled ovarian stimulation but has the advantage of decreasing the doses of FSH. In terms of safety, the incidence of OHSS is similar to that of standard protocols without hCG. For this reason, hCG may be a valid alternative to decrease the dose of FSH in the treatment of infertility. This possibility, however, is based on a limited number of studies with different protocols for follicular stimulation. Owing to the methodological limitations of the studies and different ovarian stimulation regimens, well designed clinical trials are necessary to define better whether hCG is useful for ovarian growth stimulation at the early follicular phase.

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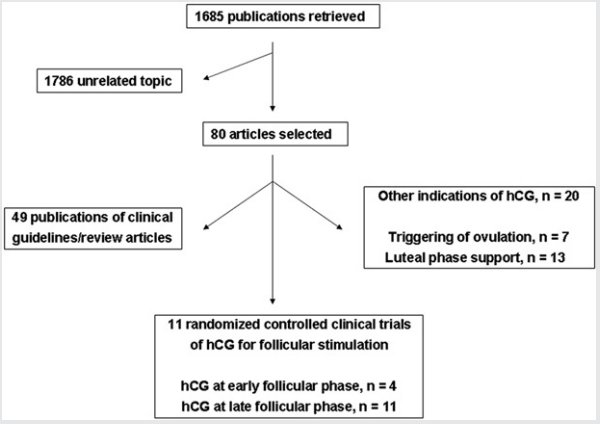
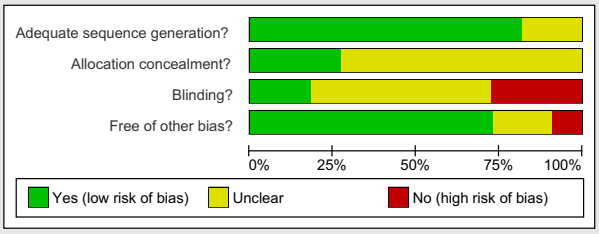
SUPPLEMENTAL FIGURE 1



Flow chart for the trial identification and selection process.

Checa. Controlled ovarian stimulation with hCG. Fertil Steril 2012.

SUPPLEMENTAL FIGURE 2



Risk of bias for the 11 RCTs included in the meta-analysis.

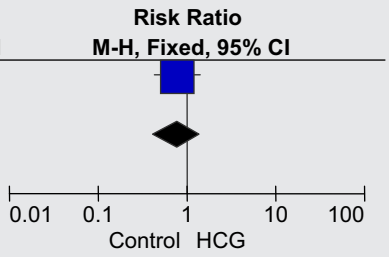
Checa. Controlled ovarian stimulation with hCG. Fertil Steril 2012.

SUPPLEMENTAL FIGURE 3

Early follicular phase

Study or Subgroup	HCG Events	HCG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lossl 2008	14	53	17	50	100.0%	0.78 [0.43, 1.41]
Total (95% CI)		**53**		**50**	**100.0%**	**0.78 [0.43, 1.41]**
Total events	14		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



Late follicular phase

Study or Subgroup	HCG Events	HCG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
(hCG vs hMG) + GnRH agonist						
Dehghani 2006	8	30	3	30	9.1%	2.67 [0.78, 9.09]
Subtotal (95% CI)		**30**		**30**	**9.1%**	**2.67 [0.78, 9.09]**
Total events	8		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

(hCG vs rFSH) + GnRH agonist/antagonist						
Blockeel 2009	11	35	8	35	24.2%	1.38 [0.63, 3.00]
Gomes 2006	6	17	3	17	9.1%	2.00 [0.60, 6.72]
Subtotal (95% CI)		**52**		**52**	**33.3%**	**1.55 [0.80, 2.97]**
Total events	17		11			

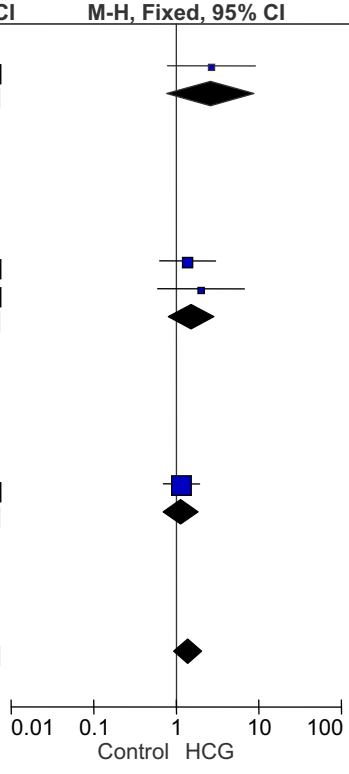
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)

(hCG vs uFSH) + GnRH antagonist						
Kyono 2006	22	63	19	63	57.6%	1.16 [0.70, 1.92]
Subtotal (95% CI)		**63**		**63**	**57.6%**	**1.16 [0.70, 1.92]**
Total events	22		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

Total (95% CI)		**145**		**145**	**100.0%**	**1.42 [0.97, 2.08]**
Total events	47		33			

Heterogeneity: Chi² = 1.96, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)



Effectiveness of hCG supplementation versus standard stimulation protocols for the outcome of live birth.

Checa. Controlled ovarian stimulation with hCG. Fertil Steril 2012.