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*Systematic Review*

# Corifollitropin Alfa Compared to Daily Recombinant FSH in *in Vitro* Fertilization Programmes: A Meta-Analysis of Randomized-Controlled Trials

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**Abstract**

**Background**: Corifollitropin alfa (CFA) is a long-acting recombinant follicle-stimulating hormone (rFSH) used for controlled ovarian stimulation (COS). Several studies analyzing the clinical efficacy and safety of CFA compared to daily rFSH during COS have been carried out. The present study offers a meta-analysis of the randomized controlled trials (RCTs) on this topic. **Methods**: A computerized search of the published literature was carried out using PubMed, MEDLINE, Science direct and Google Scholar databases. The comparison between CFA and daily rFSH treatments during COS were investigated only in RCTs. The primary endpoint of the study is represented by the number of total oocytes retrieved at ovum pick-up. The studies included in the analysis were pooled together in order to estimate the log odds ratio (OR) or the mean difference (MD) along with the corresponding 95% confidence intervals (CI) by using a random effects model. The heterogeneity between the studies was evaluated with the Higgins and Chi-square tests. **Results**: The study examined a total of twelve RCTs published from 2004 to date and included a total of 4980 patients, with 2664 receiving CFA and 2316 patients receiving daily rFSH for COS. Women treated with CFA had higher number of total oocytes retrieved at ovum pick-up (MD 0.91, 95% CI [0.34, 1.49], $p = 0.001$), and higher number of metaphase II (MII) oocytes (MD 1.00, 95% CI [0.37, 1.62], $p = 0.002$) compared to those receiving daily rFSH. There were no significant differences between the two study groups regarding the other outcomes analyzed. The subgroup analysis performed comparing "normal" versus "poor" responders revealed that normal responders receiving CFA showed an higher cancellation rate, with respect to those receiving rFSH. **Conclusions**: This study shows that COS with CFA results in a higher number of oocytes retrieved at ovum pick-up in comparison with daily rFSH.

**Keywords:** corifollitropin alfa; FSH; randomized controlled trials; controlled ovarian stimulation; *in vitro* fertilization

## 1. Introduction

Corifollitropin alfa (CFA) is a long-acting recombinant follicle stimulating hormone (rFSH) used for the controlled ovarian stimulation (COS) during *in vitro* fertilization (IVF) programs [1].

The molecular structure of CFA is a heterodimer composed by the FSH $\alpha$-subunit and a chimeric $\beta$-subunit constituted by the fusion of the FSH $\beta$-subunit and the C-terminal peptide (CTP) of the human chorionic gonadotropin (hCG) $\beta$-subunit [2,3]. The addition of the CTP to new recombinant proteins allows to prolog their circulating lifetime [2]. In fact, contrarily to conventional recombinant FSH (rFSH) preparations characterized by a relatively short half-life and rapid metabolic clearance, a single injection of CFA can initiate and sustain the multiple follicular growth for the first seven days of COS, due to a slower absorption and a much longer elimination half time [1,4–6]. For this reason, the main clinical advantage offered by CFA is represented by the reduced number of subcutaneous injections that are needed during one treatment cycle, resulting in a mitigation of the patient burden [1,2,5,6].

CFA is administered as a single injection from day 2 or 3 of menstrual cycle and, if needed, daily injections of rFSH are given from day 8 of stimulation [7]. Age and weight of patients are factors to consider when determining the optimal CFA dose. The optimal doses are 100 $\mu$g in women who weigh less than or equal to 60 kilograms and 36 years old or younger; and 150 $\mu$g in women weighing more than 60 kilograms regardless of age and women who weigh 50 kilograms or more and who are older than 36 years of age [6].

The clinical effectiveness and safety of CFA compared to daily rFSH during COS represent the topic of several randomized controlled trials (RCTs). The aim of this study is to provide an updated meta-analysis pooling the data of the RCTs published to date on this matter.

## 2. Materials and Methods

The results of this study are reported according to the guidelines outlined in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [8].

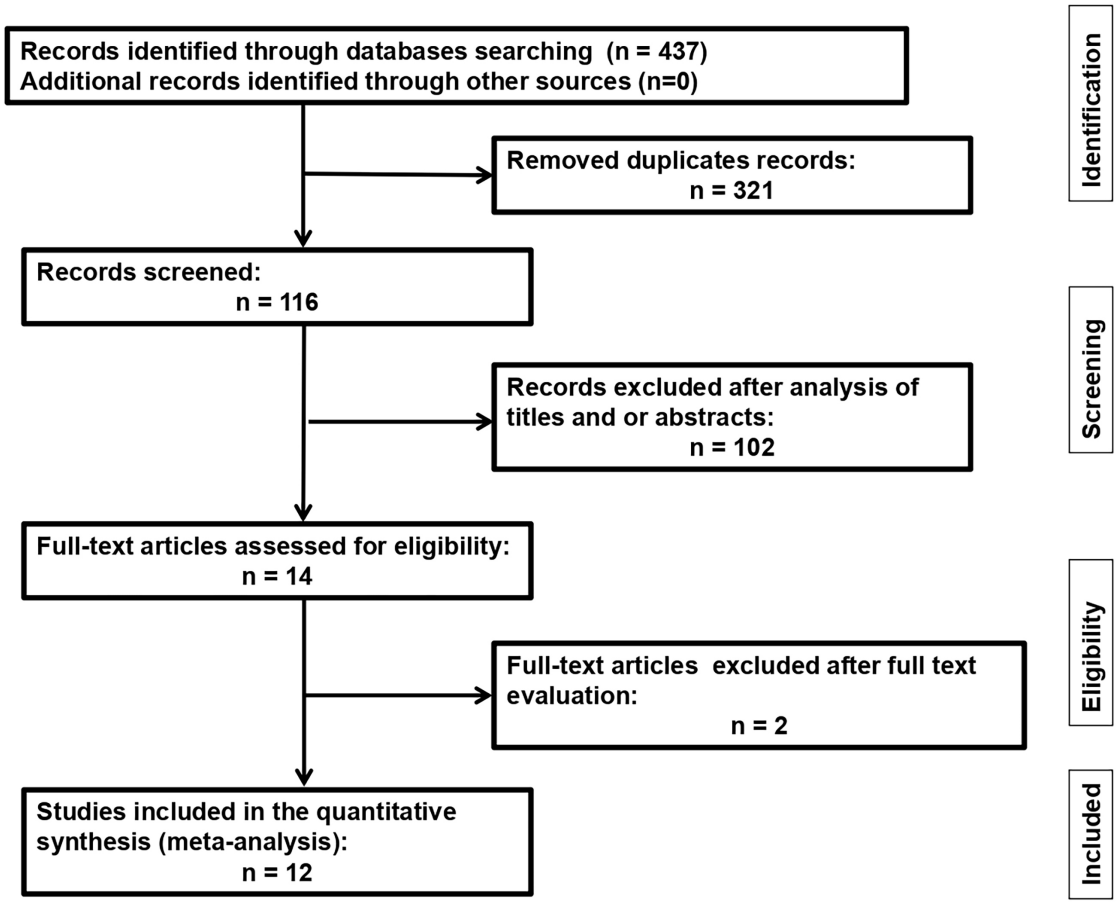


**Fig. 1. Flow chart of the studies selection.**

*2.1 Selection Criteria*

The target population was represented by infertile couples undergoing IVF/intracytoplasmic sperm injection (ICSI) or eggs donation. Only RCTs comparing CFA and daily rFSH treatments during COS and RCTs assessing the clinical effectiveness and safety of CFA were analyzed.

The primary endpoint of the present meta-analysis is represented by the number of oocytes retrieved at ovum pick-up, as suggested by the European medicines agency (EMA) for the comparison between gonadotropins [9].

The additional considered outcomes were: total duration of stimulation, cycle cancellation rate, number of metaphase II (MII) oocytes retrieved, fertilization rate, number of embryos obtained, implantation rate, clinical pregnancy rate, ongoing pregnancy rate, live birth rate, miscarriage rate, and incidence of ovarian hyperstimulation syndrome (OHSS). Randomized controlled trials with primary endpoints different from IVF outcomes but likewise exploring the clinical parameters considered in our study were also included in the present meta-analysis.

Articles not written in English and studies different from RCTs together with abstracts, editorials, letters to the editor, comments and studies with no control group were excluded.

*2.2 Search Strategy*

A computerized search of the published literature was carried out using PubMed, MEDLINE, Science direct and Google Scholar databases. We considered RCTs published up to 2020. The search strategy included different terms such as ART, CFA, rFSH, IVF programs. In PubMed we utilized keywords as follows: ("IVF" OR *in vitro* fertilization) OR ("ART" OR assisted reproductive technology) and ("CFA" OR corifollitropin alpha) OR ("rFSH" OR recombinant follicle stimulating hormone).

*2.3 Data Collection Process and Data Items*

Two investigators independently screened titles and abstracts of the studies. The same authors independently assessed the RCTs for inclusion according to the selection criteria and extracted data about study features. The investigators manually collected data from the studies. The items collected from each study were as follows: the first author's name, the year of publication, study design, study setting, participant characteristics (intervention and control groups), CFA administration during COS and IVF outcomes. Any disagreements about inclusion were resolved through discussion or by consultation with a third researcher.

**Table 1. Characteristics of the studies included in the meta-analysis.**

| Authors | Participants | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Devroey *et al.* (2004) [13] | Patients randomized:<br>n = 75 with CFA<br>n = 24 with rFSH<br><br>Patients treated:<br>n = 74 with CFA<br>n = 24 with rFSH<br><br>Characteristics:<br>-Women aged 18–39 years, BMI 17–31 kg/m$^2$<br>-Regular menstrual cycle (24–35 days). | -From day 2 or 3 of the menstrual cycle: single s.c injection of CFA (120, 180, or 240 µg) + 150 IU rFSH from stimulation day 8 up to and including the day of hCG<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) starting on the day that the leading follicle had reached 14 mm<br>-Final oocyte maturation trigger: 10000 IU hCG<br>-Luteal phase support: vaginal micronized P (600 mg/d) or i.m P (≥50 mg/d) | -From day 2 or 3 of menstrual cycle: fixed daily s.c dose of 150 IU rFSH up to and including the day of hCG<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) starting on the day that the leading follicle had reached 14 mm<br>-Final oocyte maturation trigger: 10000 IU hCG<br>-Luteal phase support: vaginal micronized P (600 mg/d) or i.m progesterone (≥50 mg/d) | -Higher mean number of oocytes recovered per started cycle in CFA group compared to rFSH group<br>-No differences in the number of good quality embryos between the two study groups<br>-Equal numbers of embryos available for ET between the two study groups |
| Corifollitropin alfa dose-finding, (2008) [14] | Patients randomized:<br>n = 242 with CFA<br>n = 83 with rFSH (follitropin beta)<br><br>Patients treated:<br>n = 234 with CFA<br>n = 81 with rFSH<br><br>Characteristics:<br>-Women aged 20–39 years<br>-Normal menstrual cycle (24–35 days)<br>-BMI 17–31 kg/m$^2$ | -From day 2 or 3 of the menstrual cycle: single s.c dose of 60, 120, or 180 µg corifollitropin alfa + 150 IU (from stimulation day 8) rFSH (follitropin beta) up to the day of hCG<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) from stimulation day 5 up to and including the day of hCG<br>-Final oocyte maturation trigger: 10000 IU hCG<br>-Luteal phase support: P administered daily | -From day 2 or 3 of the menstrual cycle: 150 IU rFSH up to the day of hCG<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) from stimulation day 5 up to and including the day of hCG<br>-Final oocyte maturation trigger: 10000 IU hCG<br>-Luteal phase support: P administered daily | -Dose-related increase in multifollicular development and in the number of retrieved oocytes in CFA group<br>-The optimal dose for a 1-week interval is higher than 60 µg and lower than 180 µg |

**Table 1. Continued.**

| Authors | Participants | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Devroey *et al.* (2009) [15] | Patients randomized:<br>n = 757 with CFA<br>n = 752 with rFSH (follitropin beta)<br><br>Patients treated:<br>n = 756 with CFA<br>n = 750 with rFSH<br><br>Characteristics:<br>-Women aged 18–36 years with a body weight >60 kg up to and including 90 kg<br>-BMI of 18–32 kg/m$^2$<br>-Menstrual cycle length of 24–35 days | -From menstrual cycle day 2 or 3: s.c injection of 150 µg CFA, or matching placebo + rFSH from day 8 up to and including the day of hCG administration<br>-GnRH antagonist (ganirelix, 0.25 mg) once daily s.c. starting on stimulation day 5 up to and including the day of hCG<br>-Final oocyte maturation trigger: 5000–10000 IU urinary hCG<br>-Luteal phase support: P ≥600 mg/d vaginally or at least 50 mg/d i.m. | -From menstrual cycle day 2 or 3: placebo + 200 IU rFSH up to and including the day of hCG<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) starting on stimulation day 5 up to and including the day of hCG<br>-Final oocyte maturation trigger 5000–10000 IU urinary hCG<br>-Luteal phase support: P ≥600 mg/d vaginally or at least 50 mg/d i.m. | -Ongoing pregnancy rates of 38.9% for the CFA group and 38.1% for rFSH<br>-Higher follicular response with CFA with higher number of COCs compared with rFSH<br>-Equal median duration of stimulation and incidence of OHSS between the study groups |
| Corifollitropin alfa Ensure study group (2010) [16] | Patients randomized and treated:<br>n = 268 with CFA<br>n = 128 with rFSH<br><br>Characteristics:<br>-Women aged 18–36 years with body weight ≤60 kg<br>-BMI 18–32 kg/m$^2$<br>-Normal menstrual cycle length (24–35 days) | -From day 2 or 3 of menstrual cycle: single s.c injection of 100 µg CFA + ≤200 IU rFSH (from stimulation day 8 up to the day of hCG administration)<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) starting on stimulation day 5<br>-Final oocyte maturation trigger: 5000–10000 IU urinary hCG<br>-Luteal phase support: P ≥600 mg/d vaginally or at least 50 mg/d i.m. | -From day 2 or 3 of menstrual cycle: placebo + 150 IU rFSH (follitropin beta) + ≤200 IU rFSH (from stimulation day 8 up to the day of hCG administration)<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) starting on stimulation day 5<br>-Final oocyte maturation trigger: 5000–10000 IU urinary hCG<br>-Luteal phase support: P ≥600 mg/d vaginally or ≥50 mg/d i.m. | -The mean ± SD number of oocytes retrieved per started cycle of 13.3 ± 7.3 for CFA versus 10.6 ± 5.9 for rFSH<br>-The incidence of moderate and severe OHSS of 3.4% for CFA group and 1.6% for rFSH |

**Table 1. Continued.**

| Authors | Participants | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Requena *et al.* (2013) [17] | Patients randomized:<br>n = 63 with CFA<br>n = 68 with rFSH (follitropin beta)<br><br>Patients treated:<br>n = 59 with CFA<br>n = 61 with rFSH<br><br>Characteristics:<br>-Oocyte donors aged 18–35 years with a regular menstrual cycle<br>-No hereditary or chromosomal diseases, normal karyotype, negative when screened for sexually transmitted diseases<br>-At least 7 antral follicles at the beginning of the cycle<br>-Body weight $\geq$60 kg and BMI $\leq$29 kg/m$^2$ | -Oral contraceptive pill for a maximum of 21 days preceded ovarian stimulation<br>-After a wash-out period of 5 days after the last pill: single injection of 150 µg CFA + daily s.c. administration of rFSH 200 IU (if needed) from stimulation day 8<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) started on day 5 of stimulation<br>-Final oocyte maturation trigger: single dose of 0.1 mg GnRH agonist | -Oral contraceptive pill for a maximum of 21 days preceded ovarian stimulation<br>-After a wash-out period of 5 days after the last pill: daily s.c doses of 200 IU rFSH<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) started on day 5 of stimulation<br>-Final oocyte maturation trigger: single dose of 0.1 mg GnRH agonist | -Significant difference in the median duration of stimulation, between stimulation with CFA and daily rFSH (10.83 $\pm$ 1.7 and 9.39 $\pm$ 2.2 days, respectively; $p = 0.002$)<br>-No significant differences in clinical parameters between the two protocols |
| Kolibianakis *et al.* (2015) [18] | Patients randomized and treated:<br>n = 40 with CFA<br>n = 39 with rFSH (follitropin beta)<br><br>Characteristics:<br>-Women with previous poor response to ovarian stimulation ($\leq$4 COCs) after maximal stimulation<br>-Age <45 years<br>-Regular spontaneous menstrual cycle<br>-BMI of 18–32 kg/m$^2$ and basal follicle stimulating hormone $\leq$20 IU/L | -From day 2 of menstrual cycle: single s.c dose of 150 µg CFA + 450 IU of rFSH administered from Day 8 of stimulation until the day of hCG administration<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) when the leading follicle reached 14 mm in average diameter up to the day of hCG administration<br>-Final oocyte maturation trigger: 250 µg of rhCG<br>-Luteal phase support: vaginal micronized P (600 mg/day) | -From day 2 of menstrual cycle: seven fixed daily doses of 450 IU rFSH<br>-GnRH antagonist (ganirelix acetate, 0.25 mg) when the leading follicle reached 14 mm in average diameter up to the day of hCG administration<br>-Final oocyte maturation trigger: 250 µg of rhCG<br>-Luteal phase support: vaginal micronized P (600 mg/day) | -Number of COCs retrieved not statistically different between the two study groups<br>-No significant difference regarding the probability of live birth between the two study groups |

**Table 1. Continued.**

| Authors | Participants | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Boostanfar *et al.* (2015) [19] | Patients randomized:<br>n = 695 with CFA<br>n = 696 with rFSH<br><br>Patients treated:<br>n = 694 with CFA<br>n = 696 with rFSH<br><br>Characteristics:<br>-Women aged ≥35 to ≤42 years with a body weight of ≥50 kg and a BMI of ≥18 and ≤32 kg/m$^2$<br>-History of regular spontaneous menstrual cycles (cycle length, 24–35 days)<br>-Patients with normal thyroid function<br>-Access to ejaculatory sperm for IVF or intracytoplasmic sperm injection (ICSI) | -From day 2 or 3 of menstrual cycle: single injection of 150 µg of CFA + seven injections of placebo rFSH from stimulation days 1–7 + treatment with open-label daily ≤300 IU of rFSH from stimulation day 8 until the criterion to trigger final oocyte maturation<br>-GnRH antagonist (ganirelix acetate, 0.25 mg/d) starting on stimulation day 5<br>-Final oocyte maturation trigger: rhCG<br>-Luteal phase support: intravaginal P gel | -From day 2 or 3 of menstrual cycle: injection of placebo CFA + seven injections of 300 IU rFSH from stimulation days 1–7 + treatment with open-label daily ≤300 IU of rFSH from stimulation day 8 until the criterion to trigger final oocyte maturation<br>-GnRH antagonist (ganirelix acetate, 0.25 mg/d) starting on stimulation day 5<br>-Final oocyte maturation trigger: rhCG<br>-Luteal phase support: intravaginal P gel | -Vital PRs per started cycle of 23.9% in the CFA group and 26.9% in the rFSH group<br>-Mean (SD) number of recovered oocytes per started cycle of 10.7 (7.2) and 10.3 (6.8) in the CFA and the r FSH groups, respectively<br>-LBRs per started cycle of 21.3% in the CFA group and 23.4% in the rFSH group<br>-Incidence of SAEs of 0.4% versus 2.7% in the CFA and rFSH groups<br>-OHSS (all grades) of 1.7% in both groups |
| Drakopoulos *et al.* (2017) [20] | Patients randomized:<br>n = 77 with CFA<br>n = 75 with rFSH<br><br>Patients treated:<br>n = 77 with CFA<br>n = 72 with rFSH<br><br>Characteristics:<br>-Patients younger than 40 years old, fulfilling the Bologna criteria for poor ovarian response<br>-Patients with the cut-off of AMH <1.1 ng/mL for prediction of poor response<br>-Patients with AFC (measured on Day 2–4 of a previous cycle) with the cut-off <7 | -From day 2 of menstrual cycle: single s.c injection of 150 $\mu$g CFA + daily dose of hp-HMG (300 IU/day) from stimulation day 8 up to the day of hCG administration<br>-GnRH antagonist ganirelix acetate (0.25 mg/d) starting on stimulation day 6<br>-Final oocyte maturation trigger: 10000 IU hCG<br>-Luteal phase support: progesterone tablets intravaginally | -From day 2 of the menstrual cycle: daily dose of rFSH (300 IU/day) administered up to the day of hCG administration<br>-GnRH antagonist ganirelix acetate (0.25 mg/d) starting on stimulation day 6<br>-Final oocyte maturation trigger: 10000 IU hCG<br>-Luteal phase support: progesterone tablets intravaginally | -No differences in the ongoing pregnancy rates between the two study groups<br>-Biochemical pregnancy rate, CPRs, LBR and number of oocytes retrieved comparable between the two groups<br>-More patients in the CFA group with cryopreserved embryos compared to the rFSH group (28.6% versus 14.3%, respectively)<br>-Asian patients with significantly lower cancellation rates compared to European poor responders (3.1% versus 20.4%, respectively) |

**Table 1. Continued.**

| Authors | Participants | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Cruz *et al*. (2017) [21] | Patients randomized:<br>n = 68 with CFA<br>n = 69 with rFSH<br><br>Patients treated:<br>n = 59 with CFA<br>n = 63 with rFSH<br><br>Characteristics:<br>-Healthy women aged between 18 and 35 years<br>-Regular menstrual cycles<br>-No hereditary or chromosomal diseases, with normal karyotype and negative for sexually transmitted<br>-At least six antral follicles per ovary at the beginning of the cycle<br>-Weigh less than 60 kg | -Oral contraceptive pill taken for a maximum of 21 days, starting on day 1 or 2 of menses of the previous cycle<br>-After a wash-out period of 5 days after the last pill: 100 µg of CFA + daily administration of rFSH from stimulation day 8<br>-GnRH antagonist ganirelix acetate (0.25 mg/d) starting on stimulation day 6<br>-Final oocyte maturation trigger: 0.1 mg GnRH agonist | -Oral contraceptive pill taken for a maximum of 21 days, starting on day 1 or 2 of menses of the previous cycle<br>-After a wash-out period of 5 days after the last pill: daily doses of 150 IU rFSH or 225 IU hp-HMG<br>-GnRH antagonist ganirelix acetate (0.25 mg/d) starting on stimulation day 6<br>-Final oocyte maturation trigger: 0.1 mg GnRH agonist | -No statistical differences in the mean of transferred embryos or frozen embryos in each treatment group<br>-Implantation rate and CPRs similar among the groups of study |
| Vuong *et al*. (2017) [22] | Patients randomized and treated:<br>n = 200 with CFA<br>n = 200 with rFSH (follitropin beta)<br><br>Characteristics:<br>-Patients from Vietnam aged 35–42 years with a body weight of $\geq$50 kg and BMI $\geq$18 to $\leq$32 kg/m$^2$ undergoing IVF and/or ICSI<br>-Regular spontaneous menstrual cycle<br>-AMH $\geq$1.38 ng/mL or AFC of 7–20, measured within 2 months of ovarian stimulation | -From day 2 or 3 of the menstrual cycle: single s.c injection of CFA 150 µg + daily doses of rFSH from stimulation day 8, up to the day before the final trigger of ovulation<br>-GnRH antagonist (ganirelix acetate 0.25 mg in 0.5 ml s.c) from day 5 of stimulation<br>-Final oocyte maturation trigger: rhCG<br>-Luteal phase support: 50 mg P i.m and estradiol (2 mg/day orally) | -From day 2 or 3 of the menstrual cycle: daily injection of rFSH 300 IU/day continuing up to and including stimulation day 7 + daily dose of rFSH from stimulation day 8 up to the day before the final trigger of ovulation<br>-GnRH antagonist (ganirelix acetate 0.25 mg in 0.5 mL SC) from day 5 of stimulation<br>-Final oocyte maturation trigger: rhCG<br>-Luteal phase support: 50 mg P i.m and estradiol (2 mg/day orally) | -No significant difference between the CFA and rFSH groups for the number of oocytes retrieved<br>-Similar ongoing pregnancy rate and LBRs in both the treatment groups<br>-Low and similar complication rates in the CFA and rFSH groups<br>-No significant differences in obstetric outcomes between the study groups |

**Table 1. Continued.**

| Authors | Participants | Intervention | Comparator | Outcomes |
|---|---|---|---|---|
| Sorouri *et al*. (2019) [23] | Patients randomized and treated:<br>n = 54 with CFA<br>n = 55 with rFSH<br><br>Characteristics:<br>-Age between 18–36 years<br>-Regular menstruations<br>-Body mass index (BMI) between 19–30 kg/m$^2$<br>-Presence of two ovaries, having an ultrasound within the last 6 weeks and no problems in the uterus<br>-FSH on second-fourth day of menstruation below 10<br>-Normal thyroidstimulating hormone<br>-Sperm analysis at acceptable level for ICSI (sperm count being not less than 5 million) | -From day 2 or 3 of the menstrual cycle: single s.c injection of CFA 150 µg + daily doses of rFSH from stimulation day 8, up to the day before the final trigger of ovulation<br>-GnRH antagonist (ganirelix acetate 0.25 mg in 0.5 mL SC) from day 5 of stimulation<br>-Final oocyte maturation trigger: rhCG<br>-Luteal phase support: 100 mg per day progesterone from the day of OPU and 150 mg per day after embryo transfer | - From day 2 or 3 of the menstrual cycle: 150 IU of daily r-FSH<br>-GnRH antagonist (ganirelix acetate 0.25 mg in 0.5 mL SC) from day 5 of stimulation<br>-Final oocyte maturation trigger: rhCG<br>-Luteal phase support: 100 mg per day progesterone from the day of OPU and 150 mg per day after embryo transfer | -No significant difference between the two groups in terms of stimulation duration, number of follicles, number of oocytes, total number of embryos, and number of transferred embryos<br>-No significant differences regarding the pregnancy outcomes including chemical pregnancy rate (positive pregnancy test), clinical pregnancy rate (detection of fetal heart), the rate of ovarian hyper-stimulation syndrome, multiple pregnancy, ectopic pregnancy, and miscarriage between the two study groups |
| Fusi *et al*. (2020) [24] | Patients randomized and treated:<br>n = 136 with CFA<br>n = 136 with rFSH<br><br>Characteristics:<br>-AFC <5<br>-AMH <1.1 ng/mL<br>-Less than three oocytes obtained in the previous cycle<br>-Age >40 years | -From day 1 or 2 of the menstrual cycle: injection of CFA 100 µg or 150 µg + 300 IU rFSH and 150 IU rLH from the 5th day after CFA injection<br>-GnRH antagonist (ganirelix acetate 0.25 mg) when the leading follicle reached 13 mm<br>-Final trigger of oocyte maturation: 10000 IU of hCG | -From day 3 of the menstrual cycle: administration of 300 IU of rFSH and 150 IU rLH or 300 IU HMG<br>-GnRH antagonist (ganirelix acetate 0.25 mg) when the leading follicle reached 13 mm<br>-Final trigger of oocyte maturation: 10000 IU of hCG | -Number of retrieved oocytes different between CFA protocols and the control group<br>-Higher pregnancy rates, especially in the long protocol with CFA<br>-Shorter length of stimulation with CFA treatments compared to rFSH |

P, Progesterone; AFC, antral follicle count; AMH, anti-mullerian hormone; AEs, adverse effects; BMI, body mass index; CFA, corifollitropin alfa; COCs, cumulus-oocyte complexes; COS, controlled ovarian stimulation; CPRs, clinical pregnancy rates; ET, embryo transfer; FSH, follicle stimulating-hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; HP-HMG, highly purified human menopausal gonadotropin; i.m, intramuscular; LBR, live birth rate; LH, luteinizing-hormone; OHSS, ovarian hyperstimulation syndrome; P, progesterone; PRs, pregnancy rates; rFSH, recombinant follicle stimulating-hormone; rhCG, recombinant human chorionic gonadotropin; s.c, subcutaneous; SAEs, severe adverse effects; SD, standard deviation.

### 2.4 Study Quality Evaluation

The critical assessment of the study quality was performed in accordance with the Cochrane Risk Assessment Tool [10] by two researchers who worked independently. The tool includes the following domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each domain was assessed and classified as low, unclear, or high risk of bias. Any discrepancies in the evaluation of studies quality were resolved by discussion with a third investigator.

### 2.5 Statistical Analysis

The current meta-analysis was conducted using the R Package Metafor version 2.1–0 (Wolfgang Viechtbauer, Maastricht, The Netherlands) [11]. We considered a group of women treated with CFA and a control group treated with daily rFSH. The studies included in the analysis were pooled together. According to the nature of data, we used as outcome measure the log odds ratio (OR) or the raw mean difference (MD) and calculated the summary estimates along with the corresponding 95% confidence intervals (CI) by using a random effects model, i.e., assuming that data were drawn from a hierarchy of different populations. Where studies reported data in terms of mean and range instead of standard deviation (SD), the SD was approximated by one-fourth of the range of data [12]. The Higgins index ($I^2$) and a Chi-square test ($\chi^2$) were used to evaluate the statistical heterogeneity between the studies. A $p$-value $< 0.05$ referred to the overall effect was considered statistically significant. We addressed the problem of heterogeneity by conducting two subgroup analyses: (i) normal responders versus poor responders, and (ii) low versus high starting dose of daily rFSH. To evaluate the robustness of the findings, we have also performed for each outcome the sensitivity analysis. Finally, we used the normal quantile plot to search for publication bias.

## 3. Results

### 3.1 Selection Process and Quality of Included Studies

The studies selection is summarized in Fig. 1. After reading the article titles and abstracts, 116 studies were screened, and 102 studies were discarded because they did not respect the study selection criteria. Of the remaining 14 studies, 2 were excluded after a full text evaluation. A total of 12 studies were included in the present meta-analysis [13–24]. The publication years ranged from 2004 to date and the characteristics of the included studies are summarized in Table 1 (Ref. [13–24]).

We notice that all analyses were carried out with an intention-to-treat approach. Twelve RCTs have been included in the analysis, considering a total of 4980 patients (2664 receiving CFA and 2316 receiving daily rFSH). Data were typically presented per woman randomized or started cycle. However, the implantation and fertilization rates were restricted only to patients with embryo transfer and subjects undergoing IVF and/or ICSI, respectively, whereas the miscarriage rate was presented per clinical pregnancy.

### 3.2 Risk of Bias in RCTs Included in the Meta-Analysis

A summary of risk of bias is presented in Fig. 2. Selection bias in the included studies was "unclear" considering that not all the trials reported adequate random sequence generation and detailed methods of allocation concealment. All the studies are blinded with "low" risk of performance with the exception of Devroey *et al.* [13] Corifollitropin alfa dose-finding [14], Requena *et al.* [17], Drakopoulos *et al.* [20], Cruz *et al.* [21], Sorouri *et al.* [23] and Fusi *et al.* [24]. No studies were assessor blinded and for this reason they were judged to be at "unclear" risk of detection bias, while regarding the attrition bias not all the studies reported complete outcome data with the exception of Devroey *et al.* [15], Boonstanfar *et al.* [19] and Vuong *et al.* [22]. Low risk of bias was reported concerning the reporting bias and no other sources of bias were detected but we judged these as "unclear" risk of bias.

### 3.3 Outcome Measures

#### 3.3.1 Ovarian Stimulation Outcomes

3.3.1.1 Total duration of stimulation. There was no evidence of a statistically significant difference (MD –0.17, 95% CI [–1.13, 0.79], $p = 0.73$; 9 RCTs, n = 4420; substantial heterogeneity: $I^2 = 98.7\%$, $p < 0.0001$) between the CFA compared with daily rFSH (Fig. 3).

3.3.1.2 Number of oocytes retrieved (Primary outcome). There was a statistically significant higher number of oocytes retrieved (MD 0.91, CI [0.34, 1.49], $p = 0.001$; 8 RCTs, n = 3700; substantial heterogeneity: $I^2 = 69.6\%$, $p = 0.01$) in the CFA group (Fig. 4).

3.3.1.3 Number of MII oocytes retrieved. There was a statistically significant higher number of MII oocytes retrieved (MD 1.00, CI [0.37, 1.62], $p = 0.002$; 9 RCTs, n = 3314; substantial heterogeneity: $I^2 = 90\%$, $p < 0.0001$) in the CFA group (Fig. 5).

3.3.1.4 Fertilization rate. There was no evidence of a statistically significant difference (OR 0.94, CI [0.81, 1.08], $p = 0.38$; 6 RCTs, n = 3584; no heterogeneity: $I^2 = 0\%$, $p = 1.00$) between the two groups (Fig. 6).

3.3.1.5 Number of embryos obtained. There was no evidence of a statistically significant difference (MD 0.30, CI [–0.35, 0.96], $p = 0.36$; 7 RCTs, n = 3999; substantial heterogeneity: $I^2 = 94.3\%$, $p < 0.0001$) between the two groups (Fig. 7).

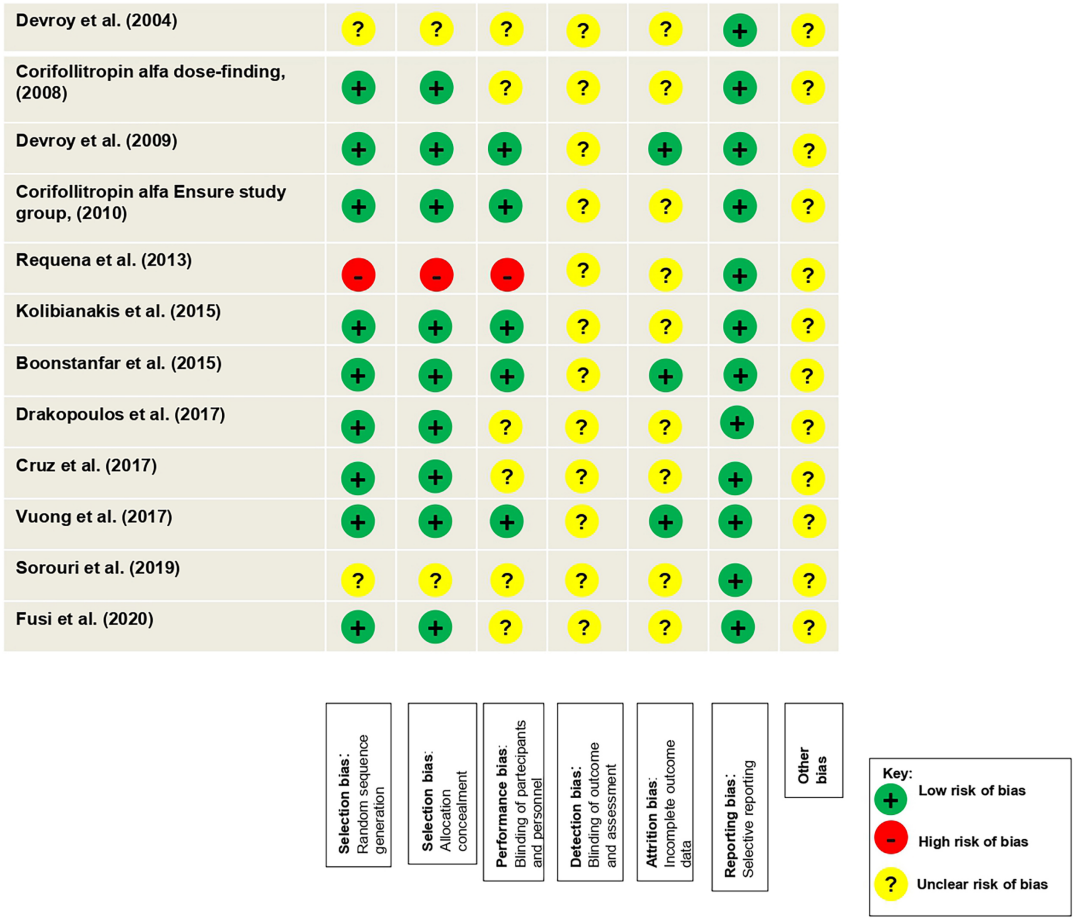


**Fig. 2. Risk assessment of bias for the randomized controlled studies (RCTs) included in the meta-analysis.**

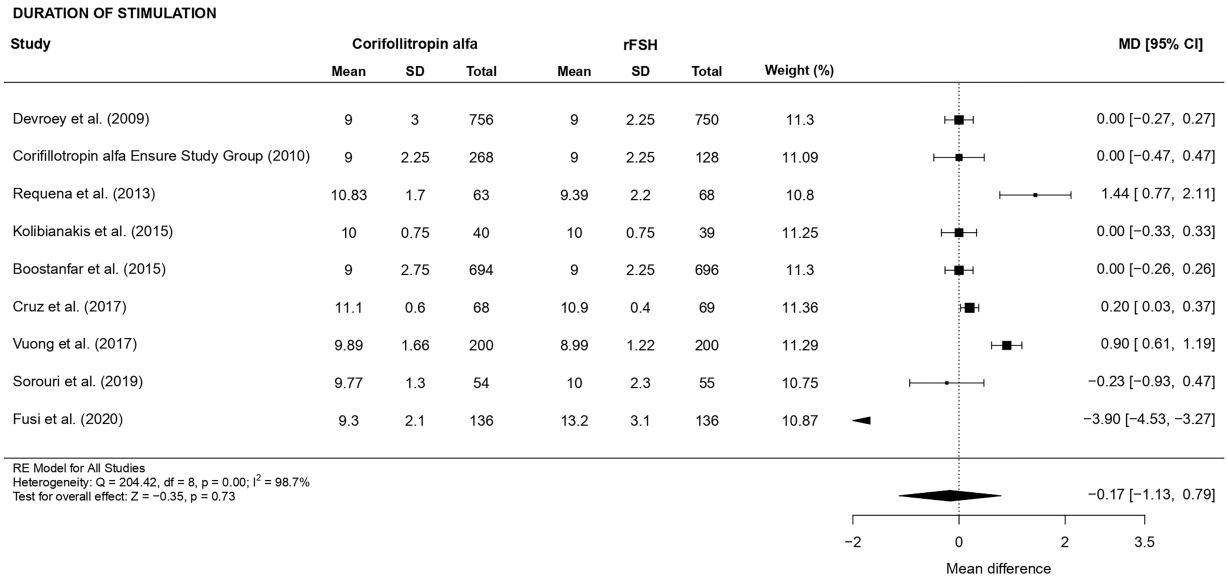


**Fig. 3. Forest plot of the total duration of stimulation.**

3.3.2 Pregnancy Outcomes

3.3.2.1 Implantation rate. There was no evidence of a statistically significant difference (OR 0.92, 95% CI [0.75, 1.13], $p$ = 0.44; 5 RCTs, n = 2300; no heterogeneity: $I^2$ = 0%, $p$ = 0.89) between the two groups (Fig. 8).

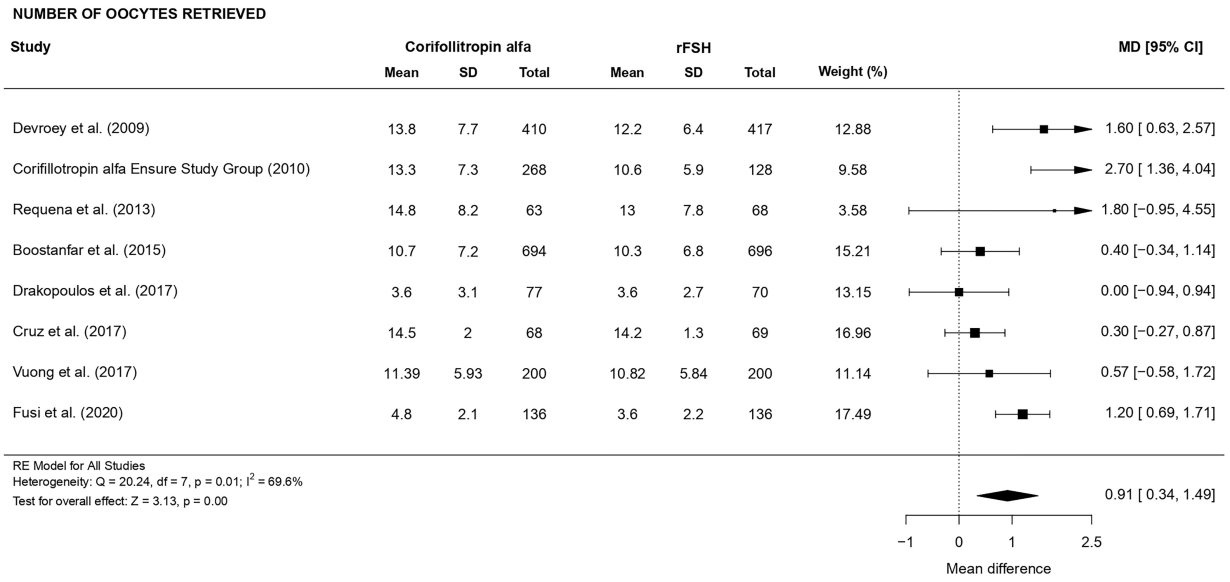


**Fig. 4. Forest plot of the number of oocytes retrieved.**

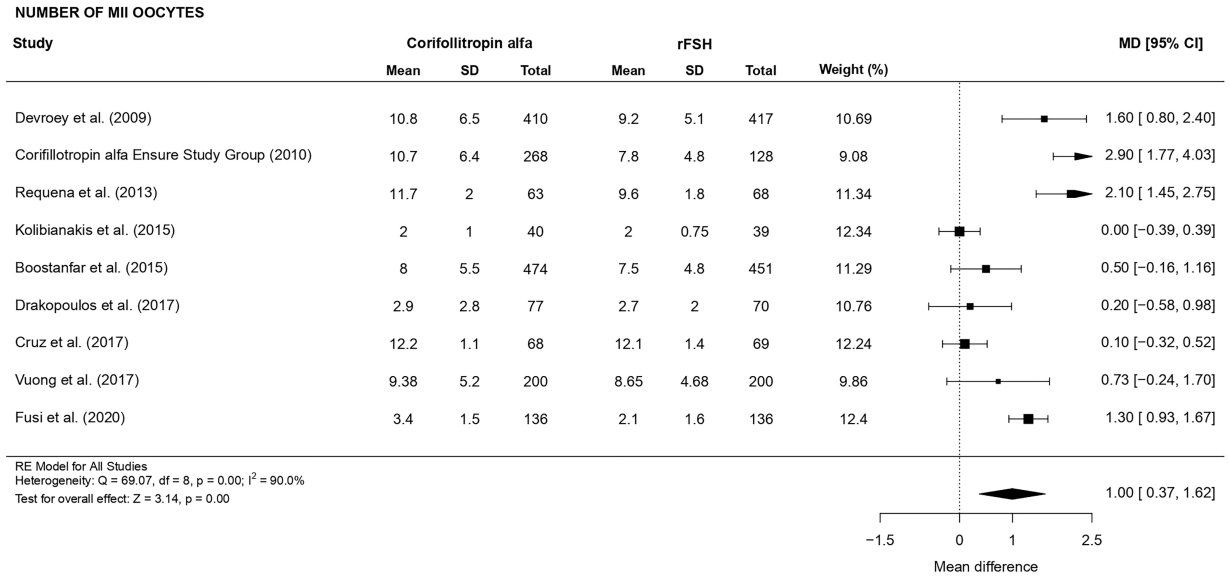


**Fig. 5. Forest plot of the number of MII oocytes.**

3.3.2.2 Clinical pregnancy rate. As for the clinical pregnancy rate there was no evidence of a statistically significant difference (OR 0.94, 95% CI [0.82, 1.08], $p = 0.41$; 10 RCTs, n = 4515; low heterogeneity: $I^2 = 5.1\%$, $p = 0.77$) between the CFA and rFSH groups (Fig. 9).

3.3.2.3 Ongoing pregnancy rate. Concerning the ongoing pregnancy rate, there was no evidence of a statistically significant difference (OR 0.93, 95% CI [0.81, 1.08], $p = 0.35$; 8 RCTs, n = 4524; low heterogeneity: $I^2 = 3.3\%$, $p = 0.31$) between the two groups (Fig. 10).

3.3.2.4 Live birth rate. A total of 2013 women have been analyzed. There was no evidence of a statistically significant difference in live birth rate (OR 0.90, 95% CI [0.73, 1.13], $p = 0.37$; 4 RCTs, n = 2013; no heterogeneity: $I^2 = 0\%$, $p = 0.76$) between the two groups (Fig. 11).

3.3.2.5 Miscarriage rate. There was no evidence of a statistically significant difference (OR 1.03, 95% CI [0.68, 1.55], $p = 0.90$; 4 RCTs, n = 1191; low heterogeneity: $I^2 = 13.3\%$, $p = 0.50$) between the two groups (Fig. 12).

3.3.3 Safety-Related Outcomes

3.3.3.1 Incidence of OHSS. There was no evidence of a statistically significant difference (OR 1.08, 95% CI [0.79, 1.49], $p = 0.63$; 7 RCTs, n = 4214; no heterogeneity: $I^2 = 0\%$, $p = 0.91$) between the two groups (Fig. 13).

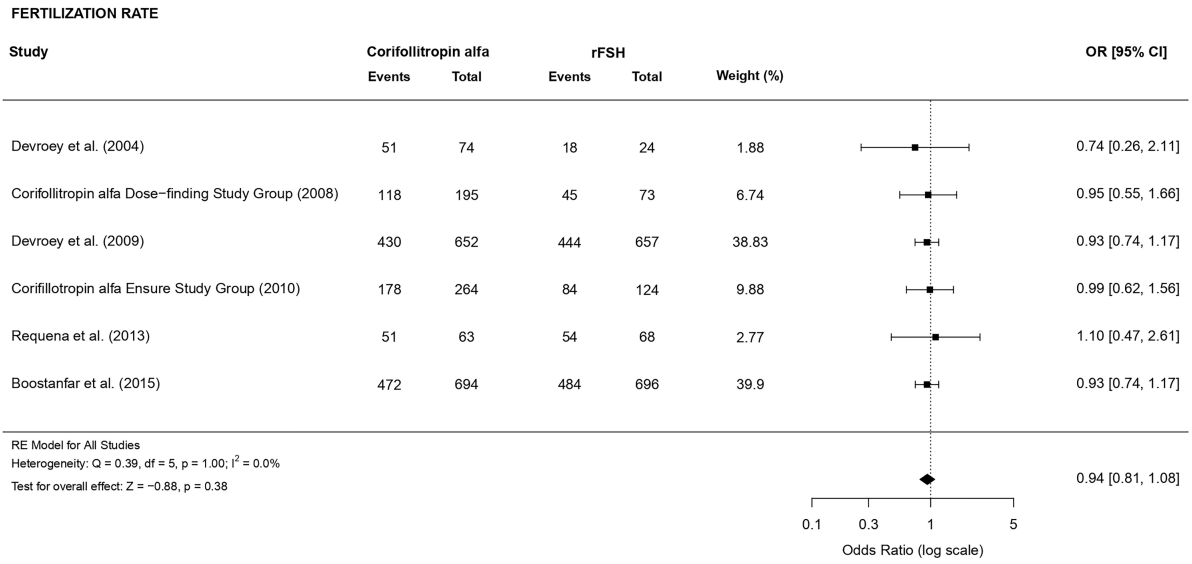


**Fig. 6. Forest plot of the fertilization rate.**

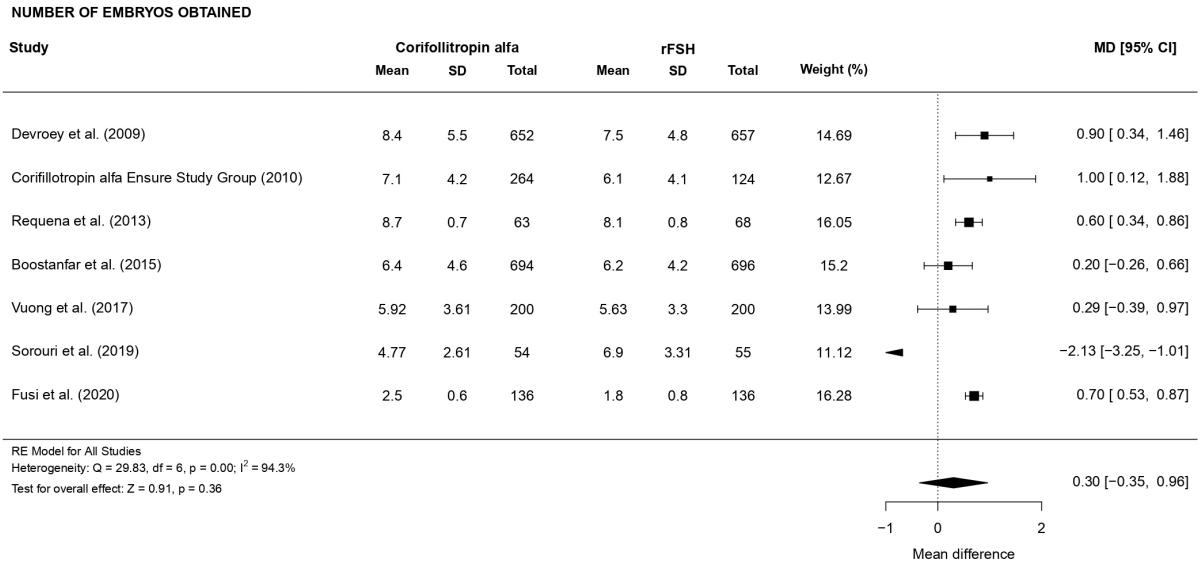


**Fig. 7. Forest plot of the number of embryos obtained.**

3.3.3.2 Cycle cancellation. A total of 4557 women have been analyzed. There was no evidence of a statistically significant difference (OR 1.25, 95% CI [0.89, 1.75], $p = 0.20$; 8 RCTs, n = 4557; moderate heterogeneity: $I^2 = 28.8\%$, $p = 0.17$) between the two groups (Fig. 14).

### *3.4 Subgroups Analyses and Sensitivity Analysis*

To address the problem of heterogeneity and evaluate the robustness of our findings, we have carried out two subgroup analyses and performed, for each outcome, the sensitivity analysis.

The first subgroup analysis, identified according to the patient characteristic "normal" versus "poor" responders, did not reveal significant differences between subgroups for all the considered outcomes, except for the number of oocytes retrieved (primary outcome), number of MII oocytes and cancellation rate, which exhibited, for the normal responders' group, a significant difference between patients receiving CFA and daily rFSH. Specifically, normal responders receiving CFA showed an increased number of oocytes retrieved (MD 1.05, 95% CI [0.28, 1.82], $p = 0.01$; 6 RCTs, n = 3281; high heterogeneity: $I^2 = 70.99\%$, $p = 0.01$) (Fig. 15), a higher number of MII oocytes retrieved (MD 1.27, 95% CI [0.43, 2.11], $p = 0.003$; 6 RCTs, n = 2816; substantial heterogeneity: $I^2 = 88.01\%$, $p < 0.001$) (Fig. 16), and a higher cancellation rate (OR 1.37, 95% CI [1.03, 1.80], $p = 0.03$; 6 RCTs, n = 4138; no heterogeneity: $I^2 = 0\%$, $p = 0.42$), with respect to patients receiving rFSH (Fig. 17).

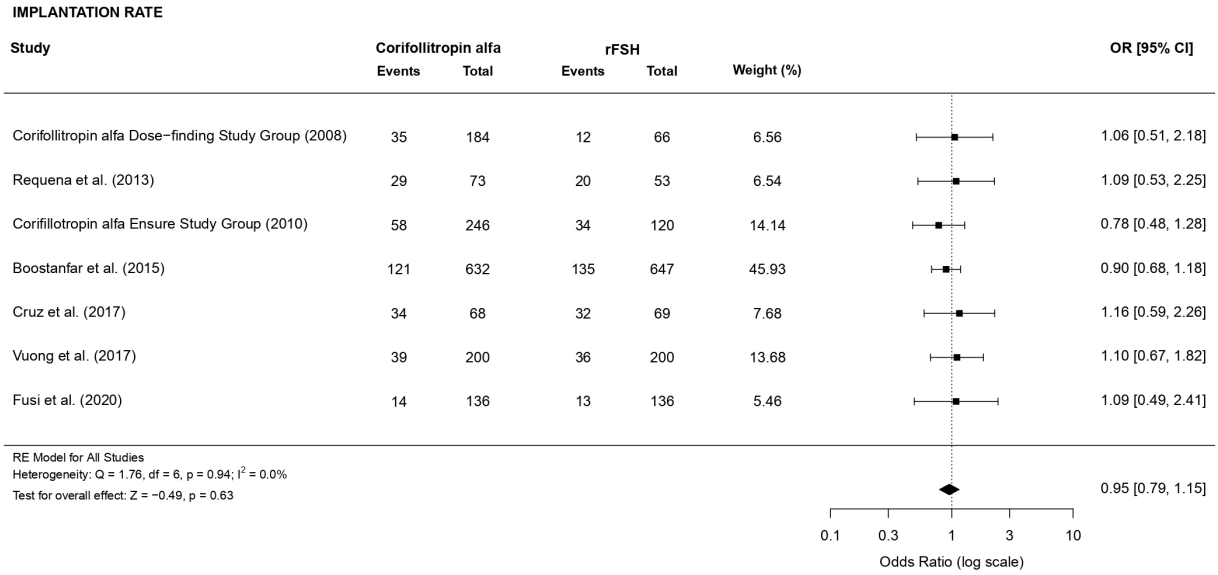


**Fig. 8. Forest plot of the implantation rate.**

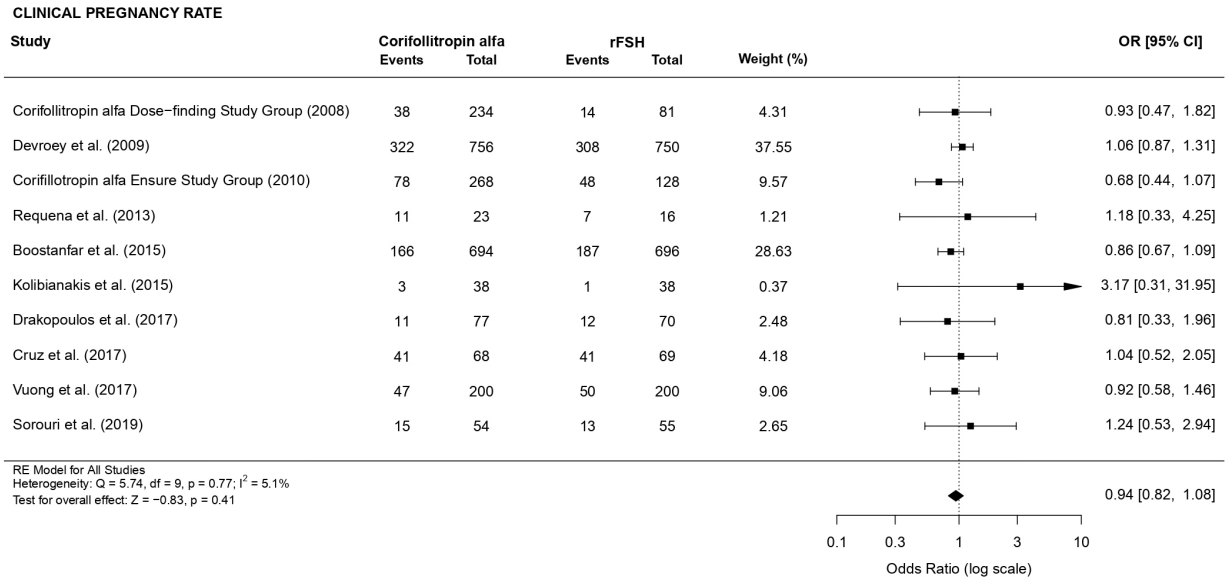


**Fig. 9. Forest plot of the clinical pregnancy rate.**

The second subgroup analysis has been performed according to the starting dose of daily rFSH. For the group where daily doses greater than 150 International unit (IU) of daily rFSH were given, we obtained a higher number of oocytes retrieved (MD 0.82, 95% CI [0.29, 1.35], $p = 0.002$; 6 RCTs, n = 3167; moderate heterogeneity: $I^2 = 48.78\%$, $p = 0.10$) (Fig. 18), MII oocytes (MD 0.91, 95% CI [0.33, 1.50], $p = 0.002$; 7 RCTs, n = 2781; substantial heterogeneity: $I^2 = 85.39\%$, $p < 0.0001$) (Fig. 19), and embryos obtained (MD 0.61, 95% CI [0.45, 0.77], $p < 0.0001$; 5 RCTs, n = 3502; low heterogeneity: $I^2 = 20\%$, $p = 0.21$) (Fig. 20) in the group of patients treated with CFA.

Both the subgroup analyses did not reveal any significant difference between subgroups in terms of duration of stimulation, which is an outcome with substantial heterogeneity. However, we noticed that, in the group of patients treated with a low dose of daily rFSH, when excluding the study of Sorouri *et al.* [23], the duration of stimulation appears to be significantly higher in the group of patients treated with CFA (MD 0.18, 95% CI [0.02, 0.34], $p = 0.03$; 2 RCTs, n = 533; no heterogeneity: $I^2 = 0\%$, $p = 0.44$).

The leave-one-out sensitivity analysis, conducted by serially excluding each study, confirmed the pooled results for almost all the outcomes, with the two following exceptions. When excluding the study by Fusi *et al.* [24] we obtained a significantly higher cycle cancellation rate in the CFA group (OR 1.39, 95% CI [1.06, 1.81], $p = 0.02$; 7 RCTs, n = 4285; no heterogeneity: $I^2 = 0\%$, $p = 0.53$). Fi-

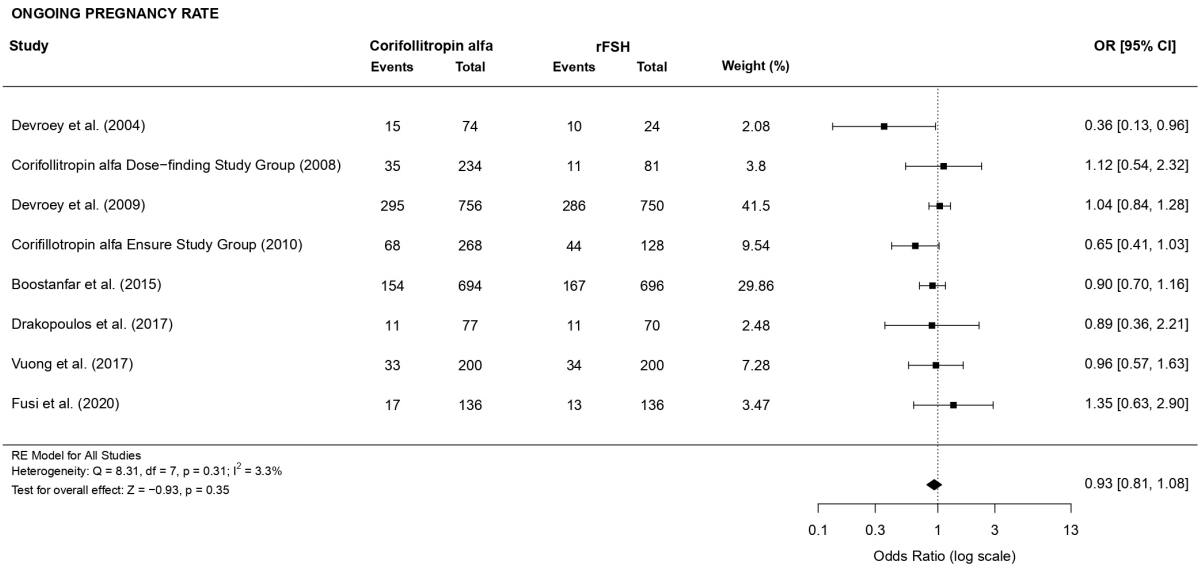


**Fig. 10. Forest plot of the ongoing pregnancy rate.**

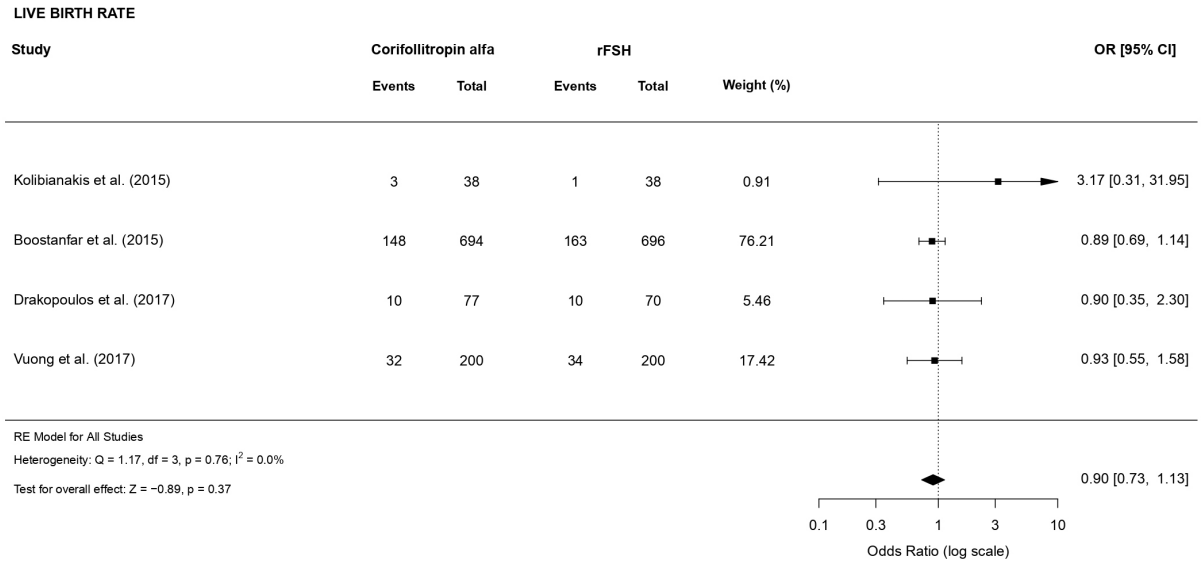


**Fig. 11. Forest plot of the live birth rate.**

nally, when excluding the study by Sorouri *et al.* [23] a significantly higher number of embryos obtained in the CFA group was observed (MD 0.63, 95% CI [0.49, 0.77], $p < 0.0001$; 6 RCTs, n = 3890; low heterogeneity: $I^2 = 7.16\%$, $p = 0.26$).

## 4. Discussion

The present meta-analysis pooled the data from twelve RCTs focusing on the clinical effectiveness and safety of CFA compared to conventional daily rFSH.

The analysis shows that treatment with CFA results in an increased number of total oocytes retrieved at ovum pick-up and increased number of MII oocytes compared to patients receiving daily conventional rFSH during COS. No statistically significant differences were noted for the other outcomes analyzed in this study.

Previous meta-analyses have been published with the aim to compare the ovarian stimulation with CFA and daily rFSH [25–28]. With respect to the latest recently published meta-analysis [28], the strengths of the present study comprise that our data updated the results by including four additional studies [17,21,23,24] and 640 more patients. More to the point, the present meta-analysis also combined the data regarding five outcomes previously not examined by Cozzolino and colleagues (2019) (duration of stimulation, cancellation rate, fertilization rate, implantation rate and miscarriage rate). We also included RCTs on egg donors [17,21] and poor responders [18,20,24] that represent two subgroups of IVF patients.

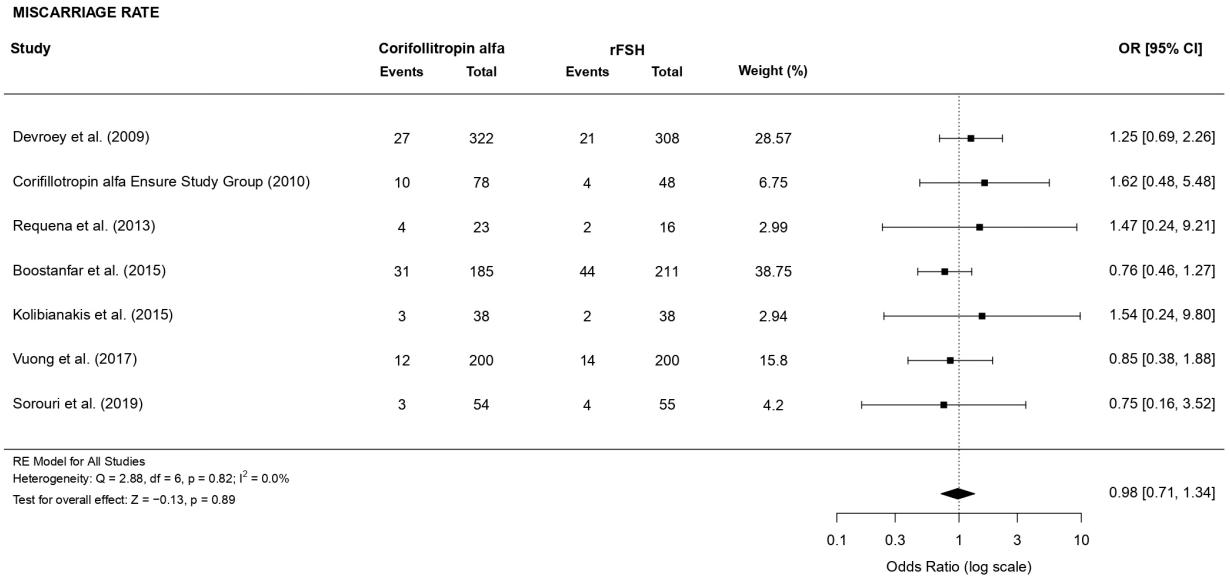


**Fig. 12. Forest plot of the miscarriage rate.**

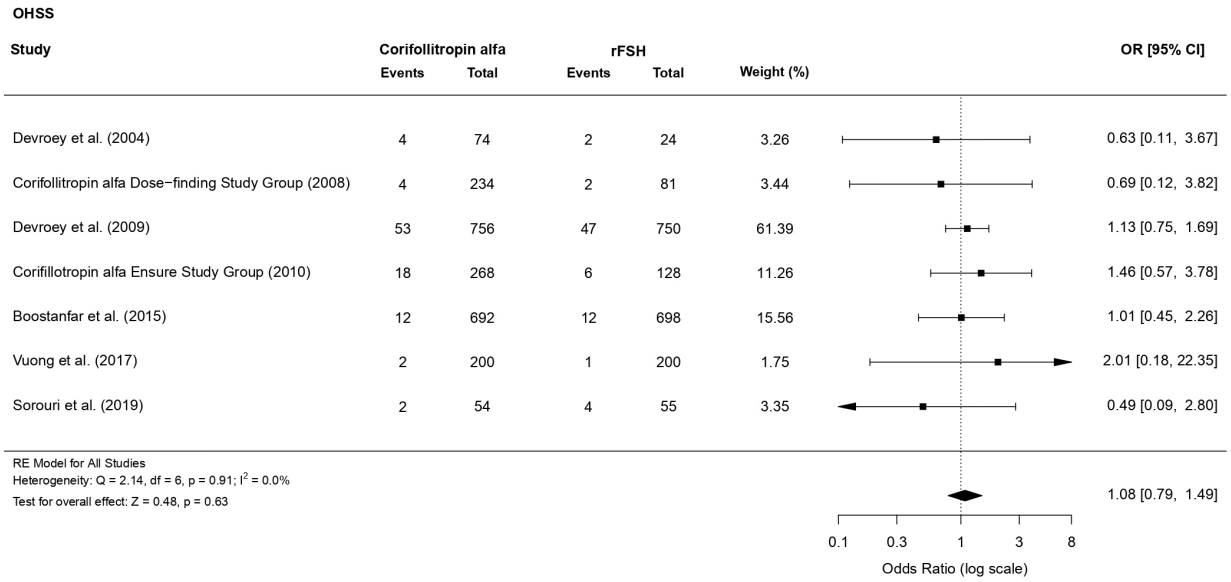


**Fig. 13. Forest plot of the risk of OHSS.**

The number of retrieved oocytes at ovum pick-up represents one of the main parameters in the comparison between gonadotropins according to the European Medicines Agency (EMA) [9]. This parameter was considered as primary endpoint in the majority of the studies included in the present meta-analysis [14–16,24]. The CFA protocol resulted in an higher number of oocytes retrieved at ovum pick up compared to daily rFSH [14,16,24]. These data reveal the efficacy of this novel FSH formulation but advises against the possible increased risk of developing OHSS during COS with CFA [6]. The present meta-analysis reassured about this concern considering that no differences in OHSS incidence have been found between CFA and daily rFSH treatments (OR 1.08, 95% CI [0.79, 1.49], $p = 0.63$). However, the heterogeneity between the included studies in relation to the patients' characteristics and the ovarian stimulation protocols recall the need for specific studies on this matter. In this context, the study of Tarlatzis *et al.* [29] was conducted with the aim to assess the incidence of OHSS after CFA treatment by pooling the cases of OHSS from three large phase III trials primarily designed to analyse the efficacy of CFA treatment in a GnRH antagonist protocol [15,16,30]. The pooled data demonstrated that the risk of OHSS tends to be slightly higher with CFA than with daily rFSH treatment, but the overall incidence of OHSS (5.6%) together with the timing of occurrence and the severity in all the three phase III trials are in line with those obtained with daily rFSH treatment [29].

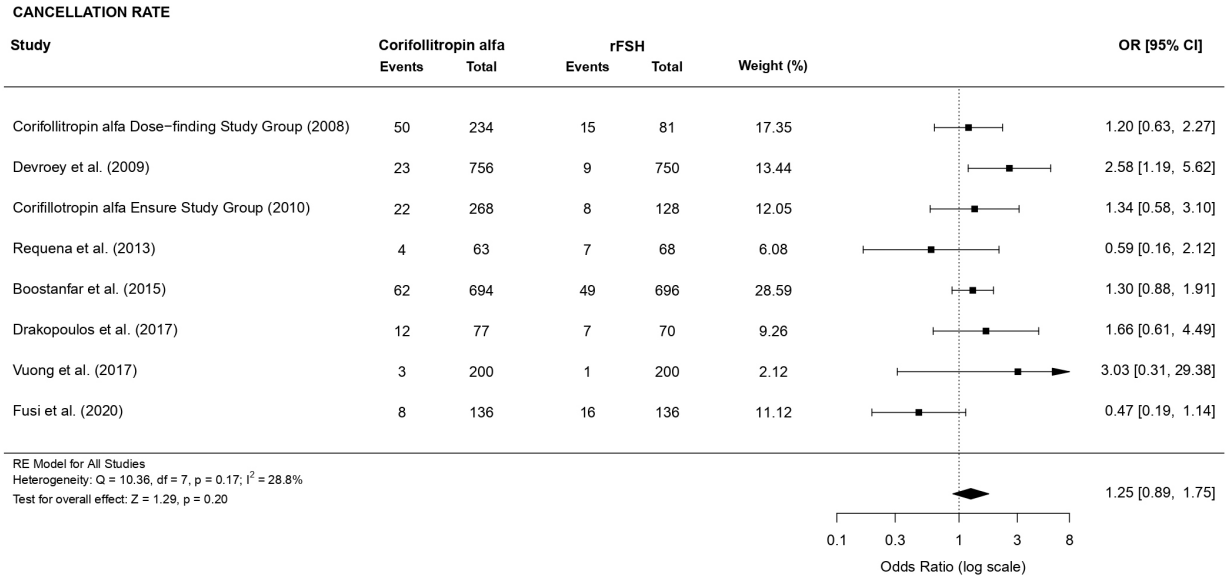


**Fig. 14. Forest plot of the cycle cancellation rate.**

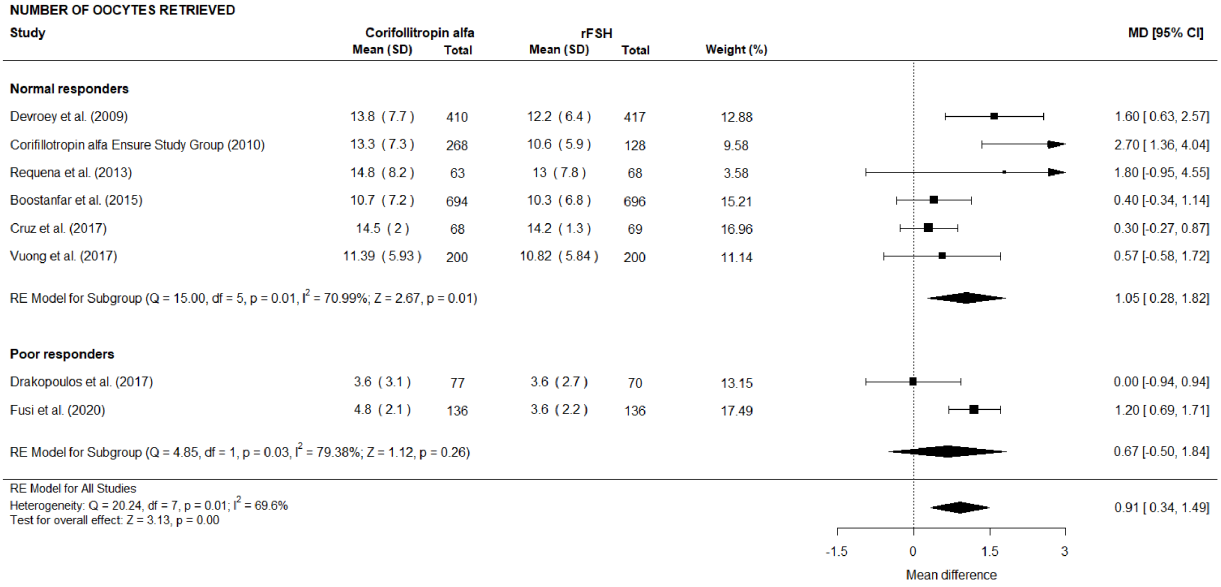


**Fig. 15. Forest plot of number of oocytes retrieved (Subgroup analysis).**

In addition, some RCTs included in the present meta-analysis were carried on considering the ongoing pregnancy rate (defined as presence of at least one fetus with heart activity at least 10 weeks after embryo transfer) as primary outcome instead of the number of oocytes retrieved at ovum pick-up [15,19,20]. No significant differences were noted between the percentage of women getting pregnant following treatment with CFA or rFSH in the studies of Devroey *et al.* [15] and Drakopoulos *et al.* [20]. In addition, Boostanfar *et al.* [19] confirmed the non-inferiority of CFA to daily rFSH with respect to the vital pregnancy rate (defined as the presence of at least one fetus with heart activity assessed at least $\geq$5 weeks after embryo transfer) [19].

It is noteworthy that several studies different from RCTs have been published with the aim to compare the clinical efficacy of CFA and the treatment with daily gonadotropins. The majority of these studies suggested that CFA represents an efficient alternative to daily rFSH formulations [31–33]. Contrarily to these data, Siristatidis *et al.* [34] found that live birth and clinical pregnancy rates were significantly reduced in women treated with CFA compared to those treated with follitropin beta, suggesting that CFA does not represent an equally method of ovarian stimulation compared with follitropin beta [34].

Three of the studies included in the present meta-analysis were carried out on poor responder patients [18,

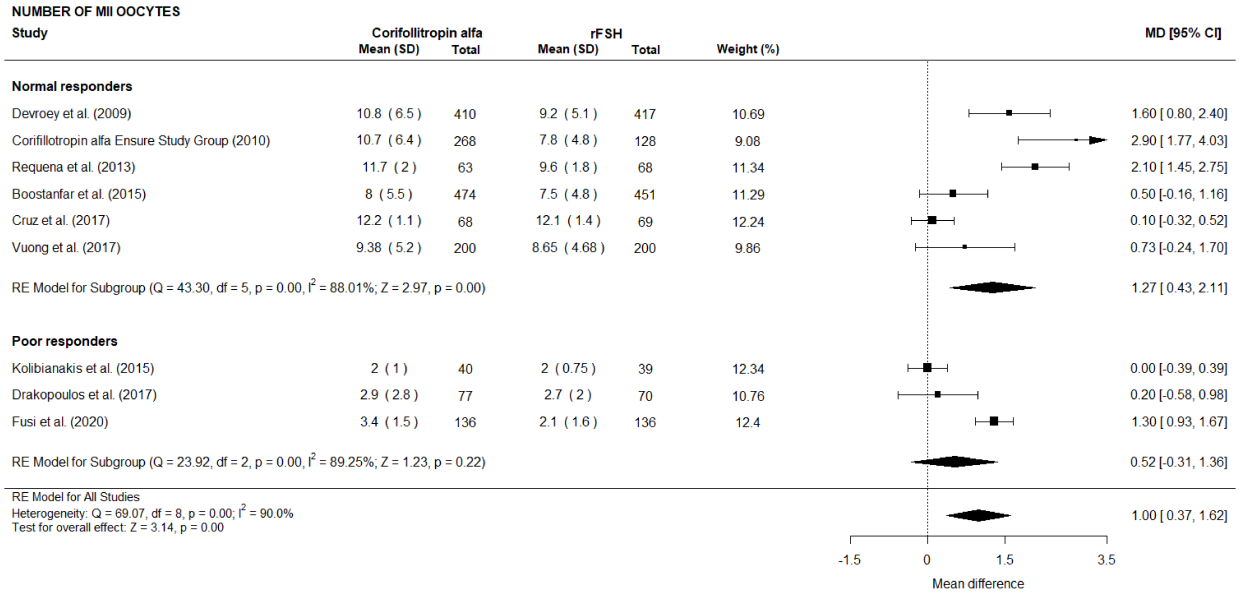


**Fig. 16. Forest plot of number of MII oocytes retrieved (Subgroup analysis).**

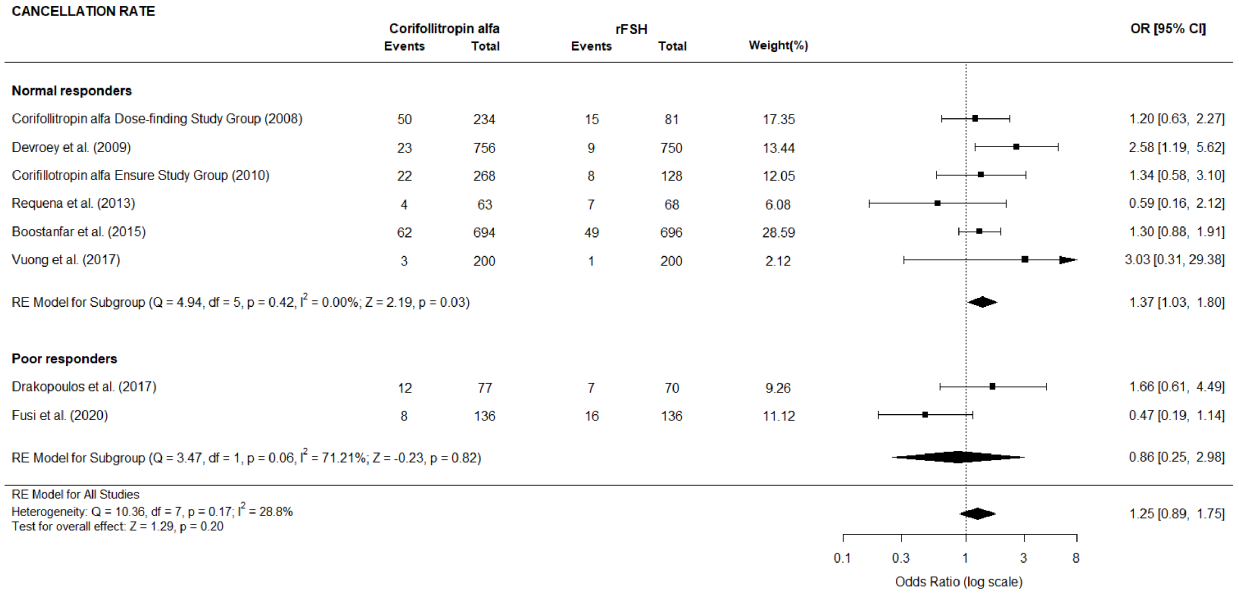


**Fig. 17. Forest plot of the cycle cancellation rate (Subgroup analysis).**

20,24] demonstrating that those treated with CFA showed a higher number of oocytes [24], and higher cryopreserved embryos [20], together with a shorter length of stimulation and reduced suspended treatments [24] compared to those treated with daily rFSH. In the current study, the subgroup analysis performed in order to compare "normal" versus "poor" responders reveals a significantly higher number of oocytes retrieved (MD 1.05, 95% CI [0.28, 1.82], $p = 0.01$), number of MII oocytes (MD 1.27, 95% CI [0.43, 2.11], $p = 0.003$), and cancellation rate (OR 1.37, 95% CI [1.03, 1.80], $p = 0.03$) in the group of normal responders receiving CFA.

In this context, the retrospective study performed by Adrisani *et al.* [35] added significant information in this field [35]. The treatments with CFA and daily gonadotropins resulted comparable in terms of clinical outcomes in poor responders with antral follicle count (AFC) >5. On the contrary, women with AFC ≤5 treated with CFA experienced a lower number of total oocytes, MII oocytes, and total embryos compared to those with AFC ≤5 treated only with daily gonadotropins [35].

Regarding the methodological quality of the trials included in the present meta-analysis, six studies are open label-designed [13,14,17,18,20,24] and three studies are double blind-designed [15,16,19]. A potential selection bias must be recognized since two studies not reported the methods of randomization and allocation [13,23] and in the

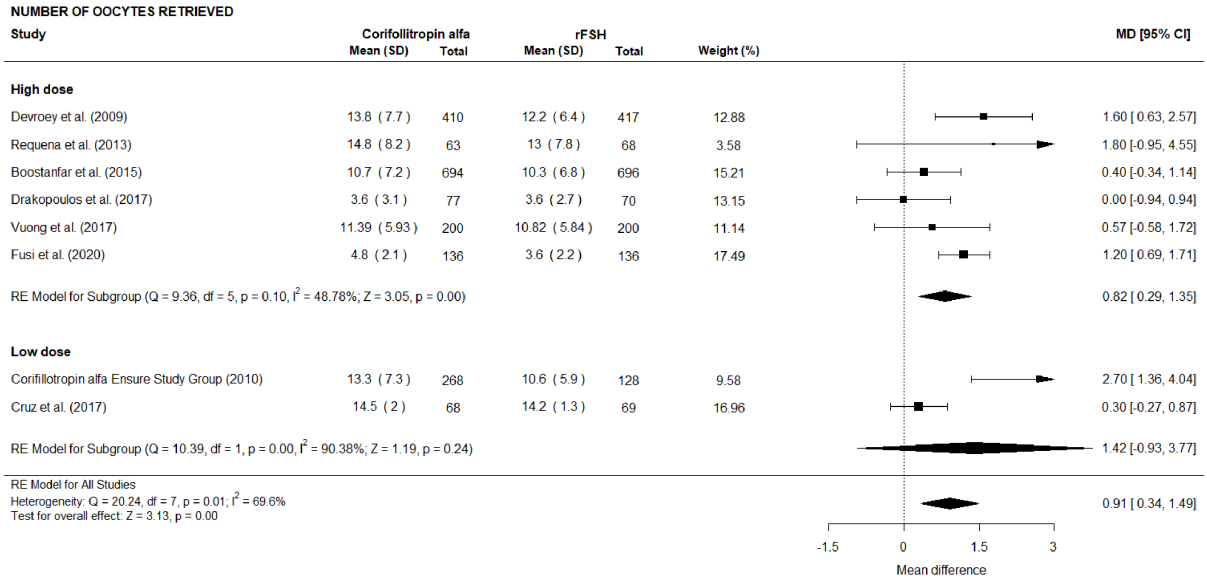


**Fig. 18. Forest plot of the number of oocytes retrieved (Subgroup analysis).**

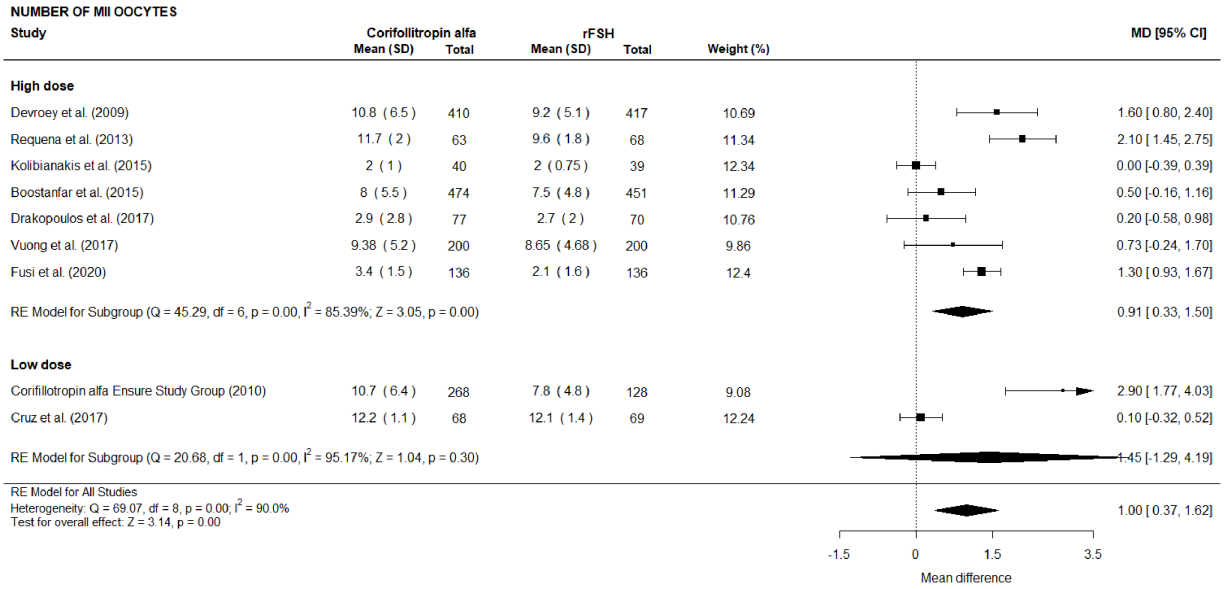


**Fig. 19. Forest plot of the number of MII oocytes (Subgroup analysis).**

study of Requena *et al.* [17] patients were assigned to each protocol directly by investigators. In addition, not all the studies detailed the blinding of participant and personnels and no study was assessor-blinded. We have graphically detected the presence of publication bias using both funnel and normal quantile plots. However, since the number of studies, for almost all the outcomes, is less than ten, this latter has been judged more reliable in revealing the presence of publication bias. In addition it was recognized a clinical heterogeneity among the trials about the inclusion criteria of the patients and the ovarian stimulation protocols, with particular regard for the starting dose of daily rFSH. At this purpose, the subgroup analysis highlighted a higher number of both oocytes retrieved (MD 0.82, 95% CI [0.29, 1.35], $p = 0.002$), MII oocytes (MD 0.91, 95% CI [0.33, 1.50], $p = 0.002$), and embryos obtained (MD 0.61, 95% CI [0.45, 0.77], $p < 0.0001$) in patients treated with CFA for the group where daily doses greater than 150 IU of rFSH were given.

The main limitations of the present meta-analysis are related to the existing heterogeneity among the included studies, as represented by discrepancies in COS. In fact, in addition to differences in the starting dose of daily rFSH, two authors (Requena *et al.* [17] and Cruz *et al.* [21]) investigated oocyte donors and assigned an oral contraceptive pill to patients on day 1 or 2 of menses of the previous cycle before starting the assigned stimulation protocol.

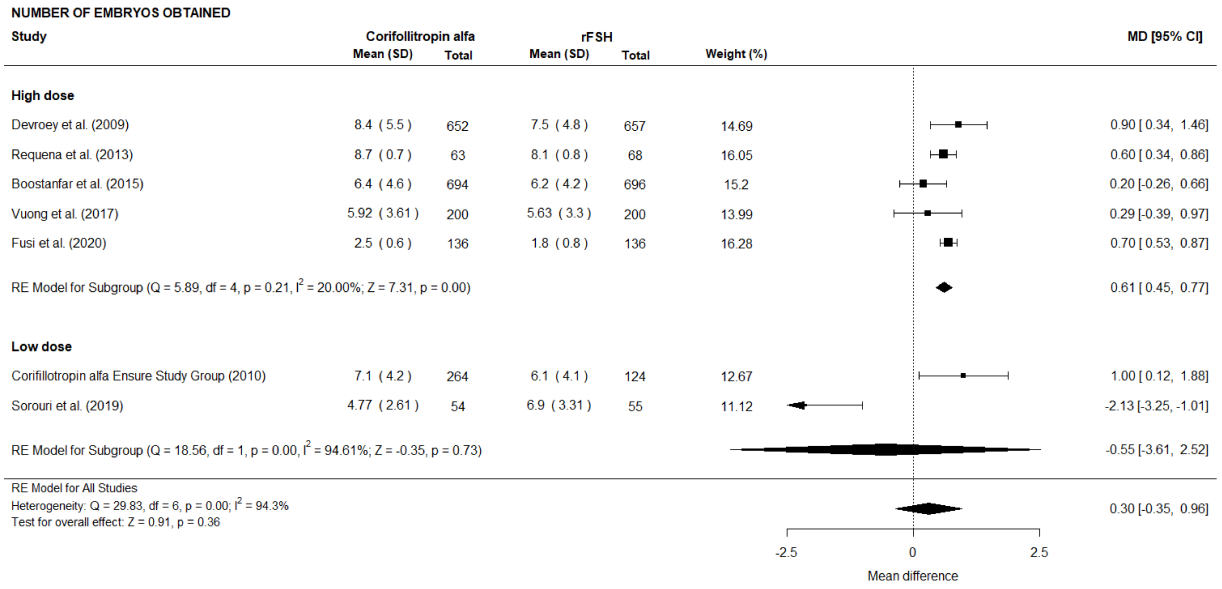


**Fig. 20. Forest plot of the number of embryos obtained (Subgroup analysis).**

In addition, differences in primary endpoints considered, methodological quality and patients characteristics among the studies represent possible sources of bias.

## 5. Conclusions

In view of the EMA statement that recommended to consider the number of oocytes retrieved as the primary endpoint to compare gonadotropins, our study demonstrated that CFA treatment represents an effective method in comparison to daily rFSH. The association between CFA and increased number of retrieved oocytes at ovum pick-up together with a higher number of MII oocyte is possibly due to the capacity of CFA to recruit an increased cohort of developing follicles. However, given the existing heterogeneity between the studies, further comparable RCTs are needed.

## Author Contributions

MCB—conceptualization, methodology, literature search, writing original draft, data curation, formal analysis; SF—conceptualization, methodology, literature search, writing original draft, data curation, formal analysis; MDM—conceptualization, methodology, literature search, writing original draft, writing-review and editing, investigation; GMT—conceptualization, methodology, literature search, writing original draft, writing-review and editing, investigation, supervision. All authors read and approved the final version of the manuscript.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

Not applicable.

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This research received no external funding.


## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5002042.

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