Human Reproduction Update, pp. 1–17, 2020
doi:10.1093/humupd/dmz046

human reproduction update

Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis

Yu Zhang[1,2,3,4,†], Chao Zhang[5,†], Jing Shu[2], Jing Guo[2], Hsun-Ming Chang[4], Peter CK Leung[4,*], Jian-Zhong Sheng[6], and Hefeng Huang[1,3,*]

BANDARIAN M.- M.D.

INFERTILITY & IVF FELLOW

IMAM HOSPITAL

Vali-e-Asr Reproductive Health Research Center

TEHRAN UNIVERSITY OF MEDICAL SCIENCE

Introduction

- **Poor ovarian response**
- incidence of POR : 5.6 to 35.1%
- POR may be attributed to
  - advanced maternal age
  - iatrogenic reasons, such as ovarian surgery, pelvic adhesions
  - obesity

Criteria

- To standardize the definition of POR, ESHRE proposed the **Bologna** criteria in 2011

- **POSEIDON** criteria: A novel system to classify infertility patients with 'expected' or 'unexpected' inappropriate ovarian response to exogenous gonadotrophins

- patients with POR

  higher cycle cancelation rates

  lower pregnancy rates per transfer

  lower cumulative pregnancy rates per started cycle

Stimulation regimens and interventions for POR

- Aggressive COS with higher dosages of gonadotrophins:
  associated with a variety of side effects and higher costs
- natural cycle IVF:
  high cancelation rates due to limited number of retrieved oocytes
- Application of adjuvant therapy during COS for POR

Adjuvant or complementary therapy

- Additional treatment used other than GnRH analogs and gonadotrophins containing FSH during the IVF/ICSI cycle

- increasing pregnancy success, especially in women with POR
- Many adjuvant therapies to improve pregnancy outcomes by
  - improving follicular development
  - oocyte maturation
  - embryo quality
  - enhancing endometrial receptivity

Adjuvant agents

- Clomiphene citrate (clomiphene)
- Androgen supplements
  [testosterone and dehydro epiandrosterone (DHEA)]
- Androgen modulating agents (aromatase inhibitors)
- Steroid hormones (oestradiol and progesterone)
- recombinant LH (although it is a gonadotropin)
- Growth hormone (GH)
- Coenzyme Q10 (CoQ10)

Aim

- a systematic review and network meta-analysis
- compare the effectiveness of various adjuvant treatment options, including
  - testosterone, DHEA, letrozole, oestradiol, progesterone, rLH, HCG,
  - clomiphene, GH, CoQ10 and COS protocols

- Bologna standards limit the inclusion criteria for POR patients in the meta-analysis

Methods

- Search was performed using standard databases;
  PubMed, Embase and the Cochrane Central Register of Controlled Trials
- previously published Cochrane systematic reviews on COS with POR were included
- No language restrictions were applied
- RCTs that compared COS protocols including one or more adjuvant treatments to COS protocols without adjuvant agents or other treatments.

Exclusion criteria

- results that were not obtained in RCTs,
- POR defined only by age
- Failed to report clinical pregnancy outcomes
- adjuvant treatments were used as the only stimulation agents without gonadotropins
- compared different doses or durations of the same treatment
- they co intervened with two or more adjuvant agents in the same group.

Bologna criteria

At least, two of the following three features

- advanced maternal age (>40 years) or any other risk factor for POR;
- a previous POR (≤3 oocytes with a conventional stimulation protocol);

- abnormal ovarian reserve test (antral follicle count ≤5–7 follicles or AMH<0.5–1.1 ng/ml)
- Two episodes of POR after maximal stimulation are also sufficient to define a patient as a ‘poor responder’.

- **primary outcome**.
- Clinical pregnancy : gestational sac or a fetal heartbeat using ultrasonography
- **Secondary outcomes**
- number of cumulus-oocyte complexes retrieved
- number of embryos transferred,
- serum oestradiol levels,
- endometrial thickness on the day of HCG administration,
- total dose of gonadotropin required for ovarian stimulation
- global cancelation rate

  - defined as the total canceled cycles without oocyte retrieval or embryo transfer because of POR per woman randomized

Results

- 2677 women with POR in 19 trial were randomized to

  - receive nine different adjuvant agents (testosterone, DHEA, letrozole,

  - oestradiol, rLH, HCG, clomiphene, GH and CoQ10)

- progesterone treatment not be analyzed because no RCT study was available

- 16 trials compared one adjuvant treatment group to one control group
- one study compared two adjuvant interventions
- one study used two different doses of the same adjuvant treatment as subgroups
- one study used two different COS protocols as control groups

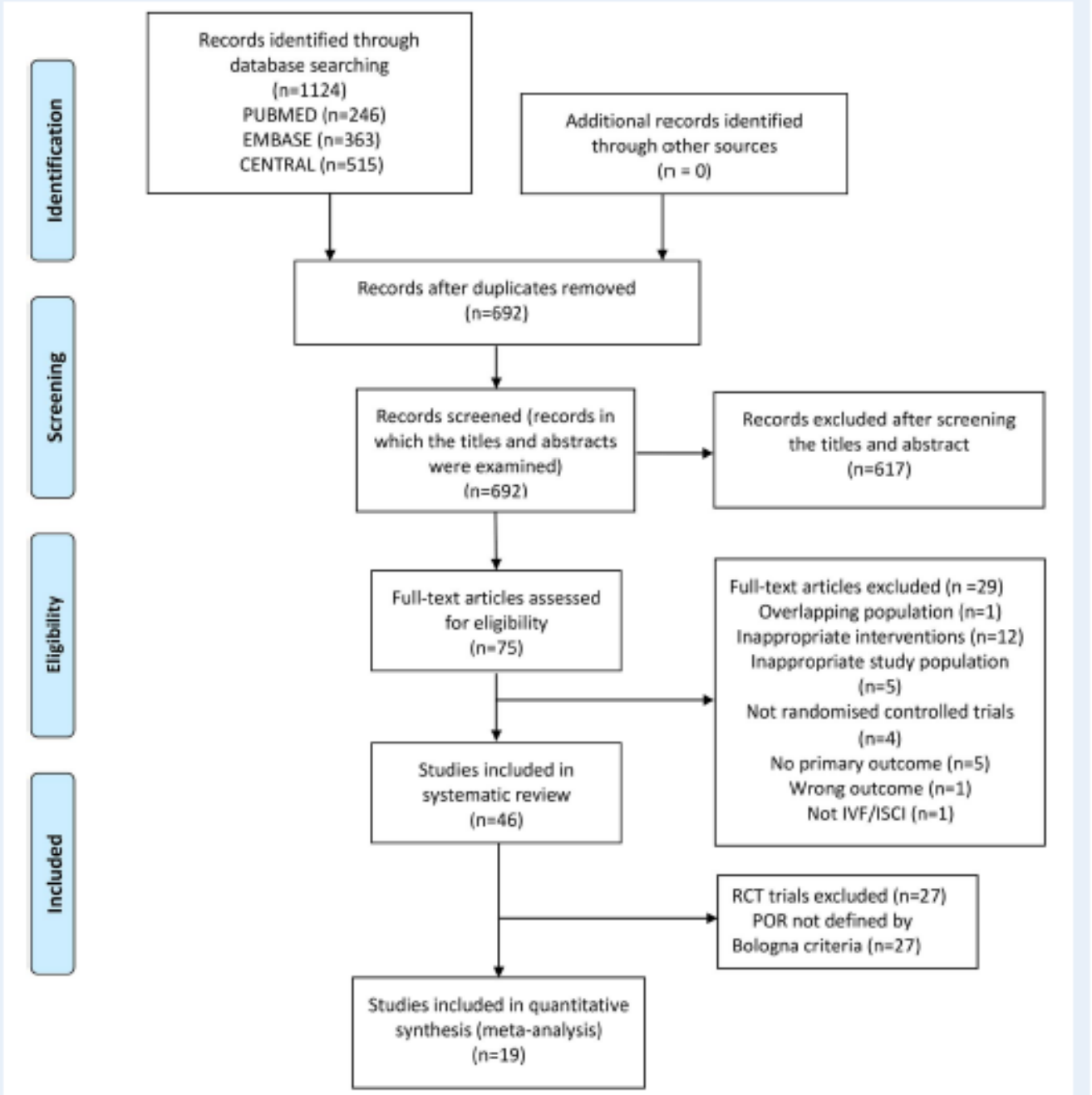

Figure 1 Prisma flow diagram for identification and selection of studies. RCT: randomized controlled trial, POR: poor ovarian response.

Network meta-analysis results

- ***Primary outcome measure***:
- *clinical pregnancy rate*
- DHEA and CoQ10 treatments significantly higher chance of clinical pregnancy

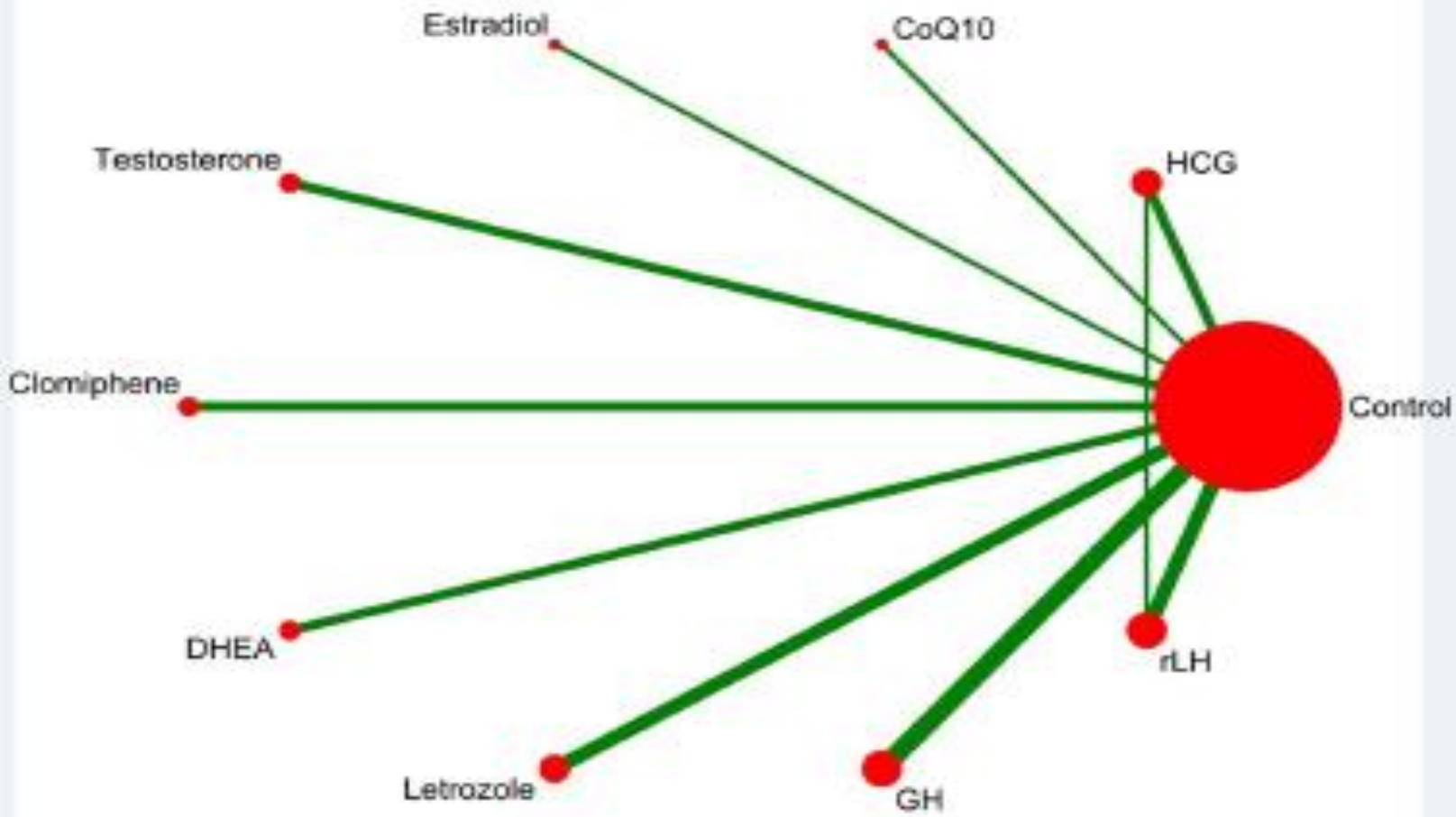

Figure 2 Network plots of eligible comparisons for primary outcomes: clinical pregnancy rate (including 19 studies). The width of the lines is proportional to the number of trials comparing with each pair of treatments, and the size of each node is proportional to the number of studies including the respective adjuvant interventions. Clomiphene: clomiphene citrate, CoQ10: coenzyme Q10, DHEA: dehydroepiandrosterone, rLH: recombinant LH, GH: growth hormone.

Secondary outcome measures

- ***number of oocytes retrieved***
  - 17 studies with a total of 1680 women were included
  - HCG, oestradiol and GH resulted in the highest number of oocytes retrieved

- ***number of embryos transferred***
  - 14 studies with 1527 women were included
  - Testosterone and GH treatments : highest number of embryos VS control

oestradiol levels on the day of HCG administration

- 14 studies with 1460 women were included
- Eight adjuvant treatments were measured with controls
- excluding clomiphene
- **GH** treatment led to the highest oestradiol level on the HCG day compared with controls

Total dosage of gonadotropin required for ovarian stimulation

- 17 studies with 2571 women were included
- Each adjuvant agent treatment : lower dose of gonadotrophin for ovarian stimulation, especially for clomiphene, letrozole and GH

global cancelation rate

- 16 studies with 2402 women were included.
- Eight adjuvant treatments were measured except oestradiol
- CoQ10 treatment was associated with the lowest cancelation rates

Table III A comprehensive sorting table for all the outcomes.

No.	Clinical pregnancy rate	Number of oocytes retrieved	Number of embryos transferred	Oestradiol levels on HCG day	Total dose of Gonadotrophin required (ascending order)	Global cancelation rate (ascending order)
1	DHEA*	HCG*	GH*	GH*	Clomiphene *	CoQ10*
2	CoQ10*	Oestradiol*	Testosterone *	CoQ10	Letrozole*	DHEA
3	HCG	GH*	CoQ10	Testosterone	GH*	HCG
4	Testosterone	CoQ10	HCG	Letrozole	CoQ10	GH
5	GH	DHEA	Oestradiol	HCG	Oestradiol	Letrozole
6	Oestradiol	rLH	DHEA	rLH	DHEA	Control
7	Letrozole	Testosterone	rLH	Control	HCG	rLH
8	Control	Letrozole	Letrozole	Oestradiol	rLH	Clomiphene
9	rLH	Control	Control	DHEA	Testosterone	Testosterone
10	Clomiphene	Clomiphene	Clomiphene	-	Control	-

*With significant difference compared with the control group (multivariate random-effects meta-regression).

Discussion

- The results of study summarized as **three key findings**

- First; all adjuvant treatments used a lower dosage of gonadotropin

- Second, adjuvant treatments, DHEA, CoQ10 and GH

✓ improved the probability of achieving pregnancy

✓ lower cycle cancelation rates in patients with POR

- **Third,** the protocol consisting of co treatment with clomiphene

✓ the lowest probability of resulting in pregnancy,

✓ total dosage of gonadotropin was the most economical

Strengths of the study

- Various induction protocols for ovarian stimulation in POR women
- Analyzed the diversity of POR definitions
- Reported all major outcomes in ART

- Compare the efficacies of a range of interventions

- Allows indirect comparisons of different treatments
- provides a reference for clinical applications that use of combined adjuvant agents in ovulation induction for women with POR

Limitations of the study

- Definition of POR varied among the included studies
- Only 19 RCTs could be included
- A reduced number of included RCTs , limited our evidence

- The protocols interventions and ovarian stimulation also had marked variation in :
  - dosages, timing of initiation, the duration of ovulation stimulation and GnRH analog protocols used.

- Current systematic review : Compared different adjuvant treatments and no (or placebo) treatment

- Did not analyze progestin treatment in this network
- **Porgestin-primed ovarian stimulation**, and freeze-all' strategies
  - a new ovarian stimulation regimen
  - uses progestin's combined with exogenous gonadotropins and
  - triggered by an GnRH agonist or HCG
  - often applied in patients with POR

- No study addressing the overall effect of these adjuvant treatments on the development and health of children delivered

Clinical implications and conclusion

- The present study demonstrates that
- **COS protocol included GH adjuvant was the optimal adjuvant in POR patients** in terms of outcome measures, including

  - the collected oocytes number, embryo number and oestradiol levels on the HCG day
- Did not show improved the pregnancy rate significantly in poor ovarian responders using the Bologna criteria

GH adjuvant

- Adjuvant treatment with GH

✓ significantly reduced the total gonadotropin required in COS.

✓ regulate ovarian function by increasing the production of intra ovarian insulin-like growth factor-1

✓ improved the effects of gonadotropin on granulosa cells

Testosterone and DHEA

- Study results using exogenous androgens (DHEA or transdermal testosterone) had beneficial effects.
- DHEA : best clinical pregnancy rate
- Testosterone : highest number of embryos
- Pretreatment with transdermal DHEA or testosterone :

  -a safe and effective means to increase the concentration

  of intra ovarian androgens
- oestradiol levels on the HCG day were low in the DHEA groups

- clinical pregnancy rate was highest
- cycle cancelation rate was lowest

- A previous meta-analysis review demonstrated that pretreatment with transdermal testosterone, but not DHEA,

- Increased clinical pregnancy and live birth rates

CoQ10

- Addition of CoQ10 may have a beneficial effect on the ovarian response
- Current network meta-analysis :
  - CoQ10 had the lowest cycle cancelation rate
  - Achieved the second highest clinical pregnancy rate
  - The prospects are good for using CoQ10 in the POR population

rLH , HCG

- HCG and rLH increasing the production of endogenous intra ovarian androgens
- HCG obtained the highest number of retrieved oocytes

- **Neither rLH nor HCG** was associated with :

  - Better clinical outcomes
  - Clinical pregnancy rate
  - Number of embryos
  - Cycle cancelation rates

- These results are inconsistent with exogenous androgens (transdermal testosterone and DHEA)

- Interventions have overall differential effects

- Different adjuvant agents act through different molecular mechanisms
- various parameters, are important determinants that affect the efficacy of these interventions
  - types of substances
  - timing of treatment
  - duration of treatment

oestradiol

- Previous studies have proposed : luteal phase oestradiol priming improve the synchronization of the pool of follicles available for COS, resulting in more favorable responses to COS

- In the current network meta-analysis,
- ✓ oestradiol treatment increased the oocyte number significantly

Clomiphene or letrozole

- Mild COS protocols combining clomiphene (or letrozole) with gonadotropin as an effective alternative for conventional COS, in normal responders and POR women

- In some meta-analysis studies
- Mild ovarian stimulation strategy involving clomiphene or letrozole
- pregnancy outcomes similar to those of conventional COS

- Current network meta-analysis : no significant differences compared with the control group

- Co treatment using clomiphene or letrozole with gonadotropin, especially clomiphene
  - the lowest pregnancy rates
  - the lowest oocyte numbers
  - the lowest embryo numbers
  - highest cycle cancelation rates

- Higher dosage of FSH has
- Detrimental effect on egg and oocyte quality
- Increasing the incidence of chromosomally abnormal embryos
- Significantly decreasing live birth rates in sub fertile patients
- May increase the total consumption of ovarian follicles, which is not beneficial for patients with POR
- All adjuvant treatment groups especially **clomiphene, letrozole** and **GH**
  - lower dosage of gonadotropin for ovarian stimulation

- previous studies and our findings suggest **optimal COS protocol for patients with POR :**

- **supplementation with appropriate adjuvant agents** to improve clinical outcomes rather than simply increasing the FSH dosage

Conclusion

- For patients with POR, COS protocols that use adjuvant treatment with **DHEA, CoQ10 and GH produced :**
- better clinical outcomes in terms of pregnancy achievement
- lower dosage of gonadotropin

- Adjuvant treatment using **clomiphene** led to
  - the lowest pregnancy rates,
  - total dosage of gonadotropins was the most Economical

- Mild COS combined with letrozole or clomiphene has no beneficial effect.