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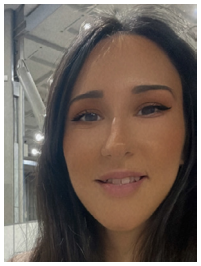
REVIEW

Higher live birth rate following transdermal testosterone pretreatment in poor responders: a systematic review and meta-analysis



BIOGRAPHY

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KEY MESSAGE

Testosterone pretreatment increases both live birth and clinical pregnancy rates in women with poor ovarian response undergoing ovarian stimulation for IVF. These findings confidently highlight the importance of this intervention in women with a poor ovarian response, in whom numerous other interventions do not appear to be beneficial

ABSTRACT

A systematic review and meta-analysis was performed aiming to identify good-quality randomized controlled trials (RCT) evaluating testosterone pretreatment in poor responders. Eight RCTs were analysed, evaluating 797 women. Transdermal testosterone gel was used in all studies, with a dose ranging from 10 to 12.5 mg/day for 10–56 days. The main outcome measure was achievement of pregnancy, expressed as clinical pregnancy or live birth. Testosterone pretreatment was associated with a significantly higher live birth (risk ratio [RR] 2.07, 95% confidence interval [CI] 1.09–3.92) and clinical pregnancy rate (RR 2.25, 95% CI 1.54–3.30), as well as a significant increase in the number of cumulus–oocyte complexes retrieved. Significantly fewer days to complete ovarian stimulation, a lower total dose of gonadotrophins, a lower cancellation rate due to poor ovarian response and a thicker endometrium on the day of triggering of final oocyte maturation were observed. No significant differences were observed in oestradiol concentration, the numbers of follicles ≥17 mm, metaphase II oocytes, two-pronuclear oocytes and embryos transferred, and the proportion of patients with embryo transfer. The current study suggests that the probability of pregnancy is increased in poor responders pretreated with transdermal testosterone who are undergoing ovarian stimulation for IVF.

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Declaration: The authors report no financial or commercial conflicts of interest.

KEYWORDS

Androgens
IVF
Ovarian stimulation
Poor ovarian response
Testosterone pretreatment

INTRODUCTION

A significant proportion of women undergoing ovarian stimulation for IVF, ranging from 9% to 24% (*Kyrou et al., 2009*; *Patrizio et al., 2015*; *Surrey & Schoolcraft, 2000*), show poor ovarian response and are characterized by severely diminished pregnancy rates (*Li et al., 2021*; *Liu et al., 2021*). Among the numerous interventions evaluated in these women, androgen supplementation appears to be associated with an increased probability of live birth (*Jeve and Bhandari, 2016*; *Nagels et al., 2015*; *Noventa et al., 2019*; *Richardson and Jayaprakasan, 2021*).

Androgens have been shown to stimulate the early stages of follicular growth (*Vendola et al., 1998*; *Weil et al., 1998*), and to increase the number of primary, pre-antral and antral follicles (*Hillier and Tetsuka, 1997*; *Weil et al., 1998*; *Weil et al., 1999*) as well as ovarian sensitivity to FSH (*Hillier and De Zwart, 1981*).

Androgen supplementation has so far been evaluated in several randomized controlled trials (RCT) and meta-analysed in seven systematic reviews (*Bosdou et al., 2012*; *González-Comadran et al., 2012*; *Jeve and Bhandari, 2016*; *Noventa et al., 2019*; *Sunkara et al., 2011*; *Zhang et al., 2020*), but no solid conclusions can currently be drawn regarding its effectiveness.

In the latest systematic review and meta-analysis, an increased probability of live birth was present in women undergoing IVF after testosterone pretreatment (*Neves et al., 2022*). However, in that meta-analysis, a literature search did not identify two RCT examining testosterone pretreatment (*Al-Jeborry, 2019*; *Doan et al., 2017*), although it included an RCT with co-intervention (*Fábregues et al., 2009*). Furthermore, no distinction was made between testosterone pretreatment and testosterone administration during ovarian stimulation (*Saharkhiz et al., 2018*). For these reasons, the accuracy and precision of the estimates in that meta-analysis could be significantly improved.

The aim of the current meta-analysis was to evaluate the association between testosterone pretreatment and achievement of pregnancy, expressed as clinical pregnancy or live birth, in poor responders undergoing ovarian stimulation for IVF.

MATERIALS AND METHODS

The current systematic review and meta-analysis was registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42021262098, date of registration 22 August 2021).

Search strategy

A computerized literature search in the MEDLINE, EMBASE, CENTRAL, ISI Web of Science and SCOPUS databases covering the period until July 2022 was performed independently by two reviewers (E.T.K. and J.K.B.), aiming to identify published RCT that evaluated the following research question: does pretreatment with testosterone increase the probability of pregnancy in poor responders undergoing ovarian stimulation with gonadotrophin-releasing hormone (GnRH) analogues and gonadotrophins for IVF? The search terms used are shown in TABLE 1. Various synonyms describing each term were entered as free-text terms in the electronic databases in an attempt to maximize the sensitivity of the search strategy. Additionally, the citation lists of all relevant publications and review articles were hand-searched. No language limitations were applied.

Selection of studies

Criteria for the inclusion/exclusion of studies were established prior to the literature search. Studies had to fulfil the following criteria for eligibility: (i) women characterized as poor responders irrespective of the definition; (ii) testosterone pretreatment in the intervention group irrespective of the dose and protocol used; (iii) ovarian stimulation for IVF using gonadotrophins and GnRH analogues; and (iv) a parallel design using a random allocation of patients in the groups compared. Studies with asymmetrical interventions (co-interventions) were excluded (TABLE 2). Selection of the studies was performed independently by two of the reviewers (E.T.K. and J.K.B.). Any disagreement was resolved by discussion.

Data extraction

Data extraction was performed independently by two of the reviewers (E.T.K. and J.K.B.). The following data were recorded from each of the eligible studies: demographic (citation data, country, study period and number of patients included), methodological (method of randomization, and allocation concealment) and procedural (whether financial support was declared, type of GnRH analogue and protocol used for LH surge inhibition, dose and protocol of the intervention proposed, type and starting dose of gonadotrophin administered for ovarian stimulation, type and dose of medication used for triggering final oocyte maturation, criteria used for triggering final oocyte maturation, type of fertilization, day of embryo transfer, type of luteal support and adverse events associated with the type of intervention) (TABLES 3 and 4). When a study provided data on different protocols of testosterone administration, all the available information was extracted, resulting in multiple datasets.

In the majority of studies, the duration of testosterone pretreatment was 21 days; therefore when studies with protocols of different duration were included, data were extracted to datasets with a similar duration. For example, when a study included groups with different durations of testosterone administration, the group with a duration nearest to 21 days was included in the data extraction. Any disagreement between the two reviewers responsible for the data extraction was resolved by discussion.

Assessment of risk of bias

For the assessment of risk of bias, Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria (risk of bias, inconsistency of the effect, indirectness, imprecision and publication bias) were applied, using GRADEpro GDT in order to assess the quality of the evidence

TABLE 1 SEARCH TERMS USED FOR THE IDENTIFICATION OF ELIGIBLE STUDIES

Intervention	Population	Setting
(testosteron*)	AND [(poor) OR (low) OR (slow) OR (inadequate) OR (suboptimal) OR (decreas*) OR (diminish*)] AND (respon*) OR (reserve)	(in-vitro fertilization) OR (in vitro fertilization) OR (IVF) OR (intracytoplasmic sperm injection) OR (ICSI) OR (IVF/ICSI)

TABLE 2 EXCLUDED STUDIES AND REASONS FOR EXCLUSION

Study	Reason for exclusion
Sipe et al. (1986)	Case report
Balasch et al. (2006)	Prospective, self-controlled trial
Fábregues et al. (2009)	Co-intervention
Sipe et al. (2010)	Prospective, randomized, crossover trial
Saharkhiz et al. (2018)	Testosterone administration during ovarian stimulation
Hassan et al. (2019)	Crossover trial
Erin Ahart et al. (2019)	Prospective, cohort, non-randomized trial
Padmashri et al. (2019)	Not performed in poor responders
Andreeva et al. (2020)	Observational, pilot study

(*GRADEpro, 2022*). The overall quality of the body of evidence was assessed for the primary outcomes included in the meta-analysis. Two authors (E.T.K. and J.K.B.) independently made judgements about the quality of the evidence (high, moderate, low or very low) and any disagreement was resolved by discussion (Supplementary Table I).

Outcomes

The results were interpreted based on an intention-to-treat analysis (defined as the inclusion of all randomized patients). The main outcome measure was the achievement of pregnancy per patient randomized, expressed as clinical pregnancy (evidence of an intrauterine sac with fetal heart activity at 6–8 weeks of gestation) or as live birth. Secondary outcome measures included the following: the duration of gonadotrophin stimulation, total dose of gonadotrophins required for ovarian stimulation, oestradiol concentrations, endometrial thickness and number of follicles ≥17 mm on the day of triggering of final oocyte maturation, cancellation rate due to poor ovarian response, number of cumulus–oocyte complexes (COC) retrieved, number of embryos transferred, number of metaphase II (MII) and two-pronuclear (2pn) oocytes, miscarriage rate and proportion of patients having an embryo transfer. Where information was missing, the study authors were contacted in order to retrieve the relevant data.

Quantitative data synthesis

Estimates for dichotomous data were expressed as the risk ratio (RR) with 95% confidence intervals (CI), using the Mantel–Haenszel approach (*Mantel and Haenszel, 1959*) when using the fixed

TABLE 3 METHODOLOGICAL CHARACTERISTICS OF ELIGIBLE RCT

Authors (year), journal	ITT (*n*)	Per protocol (*n*)	Testosterone pre-treatment	No pre-treatment	Definition of poor ovarian response	Randomization method	Blinding	Primary outcome	Financial support
Massin et al. (2006), *Human Reproduction*	53	49	24	25	Oestradiol <1200 pg/ml on day of HCG and ≤ 5 COC retrieved, and day 3 FSH >12 IU/l, oestradiol >70 pg/ml and inhibin B <45 pg/ml	Computer-generated randomization list	Double blind	COC retrieved	Yes
Kim et al. (2011), *Fertility and Sterility*	110	110	55	55	≤3 COC retrieved despite the use of a high total gonadotrophin dose (>2500 IU)	Computer-generated randomization list	No	Mature oocytes retrieved	Not reported
Kim et al. (2014), *Development and Reproduction*	120	120	30, 30, 30[a]	30	≤3 COC retrieved despite the use of a high total gonadotrophin dose (>2500 IU)	Computer-generated randomization list	No	Mature oocytes retrieved	Not reported
Bosdou et al. (2016), *Human Reproduction*	50	50	26	24	Bologna criteria	Computer-generated randomization list	Single blind	COC retrieved	Partially funded by a scholarship
Doan et al. (2017), *Gynecological Endocrinology*	110	110	55	55	AFC <5–7 follicles or AMH ≤1.26 ng/ml	Not reported	Not reported	Not reported	Not reported
Al-Jeborry (2019), *Annals of Tropical Medicine and Public Health*	132	132	71	61	POSEIDON criteria	Not reported	Not reported	Number of retrieved and mature oocytes and pregnancy rate	No
Hoang et al. (2021), *Reproductive Medicine and Biology*	159	122	42, 38[a]	42	Bologna criteria	Manual lottery	Single	Total number of retrieved mature oocytes	Not reported
Subirá et al. (2021), *Reproductive BioMedicine Online*	63	49	17, 16 [a]	16	Bologna criteria	Computer-generated randomization list	Single	Mature oocytes retrieved	Yes

[a] Testosterone was applied for different durations in different groups of patients.

AFC, antral follicle count; AMH, anti-Müllerian hormone; COC, cumulus–oocyte complex; HCG, human chorionic gonadotrophin; ITT, intention-to-treat; RCT, randomized controlled trial.

TABLE 4 CYCLE CHARACTERISTICS OF ELIGIBLE RCT

Authors (year)	GnRH analogue	Type of analogue protocol	Gonadotrophin type/ starting dose	Gonadotrophin adjustments	Signal for triggering oocyte maturation	Criteria for HCG administration	OPU	Fertilization	Embryo transfer	Type of luteal support	Embryo quality studied	Adverse effects
Massin et al. (2006)	Triptorelin or cetrorelix	Mainly long GnRH agonist but also short GnRH agonist and antagonist (proportions of GnRH analogue protocols were not statistically different between the two arms)	rFSH/300–450 IU	Yes, no further information provided	10,000 IU uHCG	At least three follicles 17 mm in diameter	36 h after HCG	IVF/ICSI	Day 2/3	Micronized progesterone 200 mg/b.i.d. vaginally and 2500 IU HCG at 3, 6 and 9 days after HCG for triggering final oocyte maturation	Not reported	None
Kim et al. (2011)	Cetrorelix 0.25 mg/day	Flexible protocol (when lead follicle reached 13–14 mm in diameter)	r(h)FSH/300IU	Yes, every 3–4 days according to ovarian response	250 mg rHCG	At least one follicle of at least 18 mm in diameter	36 h after HCG	IVF/ICSI	Day 3	Vaginal progesterone gel 90 mg/day	Number of grade 1 and 2 embryos	None
Kim et al. (2014)	Cetrorelix 0.25 mg/day	Flexible protocol (when lead follicle reached 13–14 mm in diameter)	r(h)FSH/300 IU	Yes, every 3–4 days according to ovarian response	250 mg rHCG	At least one follicle of at least 18 mm in diameter	35–36 h after HCG	IVF/ICSI	Day 3	Vaginal progesterone gel 90 mg/day	Number of grade 1 and 2 embryos	None
Bosdou et al. (2016)	Triptorelin 3.75 mg depot, followed by daily injections of triptorelin 0.1 mg, if necessary	Long GnRH agonist protocol	Follitropin alpha/–	Not reported	250 mg rHCG	At least two follicles reached 17 mm in diameter or, if this was not possible, the maximum number of follicles were present	36 h after HCG	ICSI	Day 2	Vaginal micronized progesterone 600 mg/day	Quality of embryos on day 2 of in-vitro culture (top/medium/low)	None
Doan et al. (2017)	Not reported	GnRH antagonist protocol	Not reported	Not reported	5000 or 10,000 IU HCG	At least two follicles of more than 17 mm size	35–40 h after HCG	IVF	Not reported	Not reported	Not reported	Not reported
Al-Jebory et al. (2019)	Cetrotide 0.25 mg/day	Flexible protocol (when lead follicle reached 13–14 mm in diameter)	r(h)FSH/300–4500 IU with or without addition of Menogon 75–150 IU daily	Yes, every few days according to ovarian response/ measuring serial serum oestradiol levels	5000–10,000 IU uHCG	Two or three follicles more than 17–18 mm size	34–35 h after HCG	ICSI	Day 3	Cyclogest progesterone suppository vaginally in dose of 400 mg twice daily	Not reported	Not reported
Hoang et al. (2021)	Cetrotide 0.25 mg/day	GnRH antagonist protocol	rFSH/300 IU	Yes, based on patient's condition and individual ovarian response	6500 IU HCG	At least two follicles reached at least 18 mm	36–37 h after HCG	IVF	Day 3	Micronized progesterone 800 mg/day	Number of good-quality embryos according to Istanbul consensus	Light itching
Subirá et al. (2021)	Not reported	Conventional short antagonist protocol	Human menopausal gonadotrophin/300 IU	No	Not reported	At least one follicle measured over 16 mm	36 h after HCG	ICSI	Day 2 or 3	Not reported	Number of day 3 embryos	None

b.i.d., twice daily; GnRH, gonadotrophin-releasing hormone; HCG, human chorionic gonadotrophin; ICSI, intracytoplasmic sperm injection; OPU, Oocyte pick up; RCT, randomized controlled trials; rFSH, recombinant FSH; r(h)FSH, recombinant (human) FSH; rHCG, recombinant human chorionic gonadotrophin; uHCG, urinary human chorionic gonadotrophin.

effects method, and the DerSimonian and Laird approach (*DerSimonian and Laird, 1986*) when using the random effects method. When the outcome of interest was continuous in nature, the differences were pooled across the studies, resulting in a weighted mean difference (WMD) with 95% CI. The inverse variance method (*Hedges and Olkin, 1985*) and the DerSimonian and Laird method (*DerSimonian and Laird, 1986*) were used when the fixed or random effects method, respectively, was applied.

All results were combined for meta-analysis with STATA/MP Software (Version 14.1; Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, 2011). Study-to-study variation was assessed by using the chi-squared statistic (the hypothesis tested was that the studies were all drawn from the same population, i.e. from a population with the same effect size). A fixed effects model was used where no statistically significant heterogeneity was present (I^2 < 40%), whereas in the presence of statistically significant heterogeneity, a random effects model was applied. Statistical significance was set at a *P*-level of 0.05. The presence of a publication bias was tested using Harbord–Egger's test (*Harbord et al., 2006*).

Qualitative data synthesis

The methodological quality and risk of bias of the studies included in the current systematic review and meta-analysis was assessed using the Risk of Bias (RoB) 2 tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions (*Sterne et al., 2019*). Two authors (E.T.K. and J.K.B.) assessed each study's risk of bias and any disagreement was resolved by discussion (Supplementary Figure I).

RESULTS

Identification of literature

The literature search yielded 2012 publications. After removing 801 duplicates, screening of the remaining publications by title and abstract resulted in 17 studies, further examined in full text, leading finally to eight eligible trials (FIGURE 1).

Systematic review

Eight RCT (*Al-Jeborry, 2019*; *Bosdou et al., 2016*; *Doan et al., 2017*; *Hoang et al., 2021*; *Kim et al., 2011*; *Kim et al., 2014*; *Massin et al., 2006*; *Subirá et al.,*

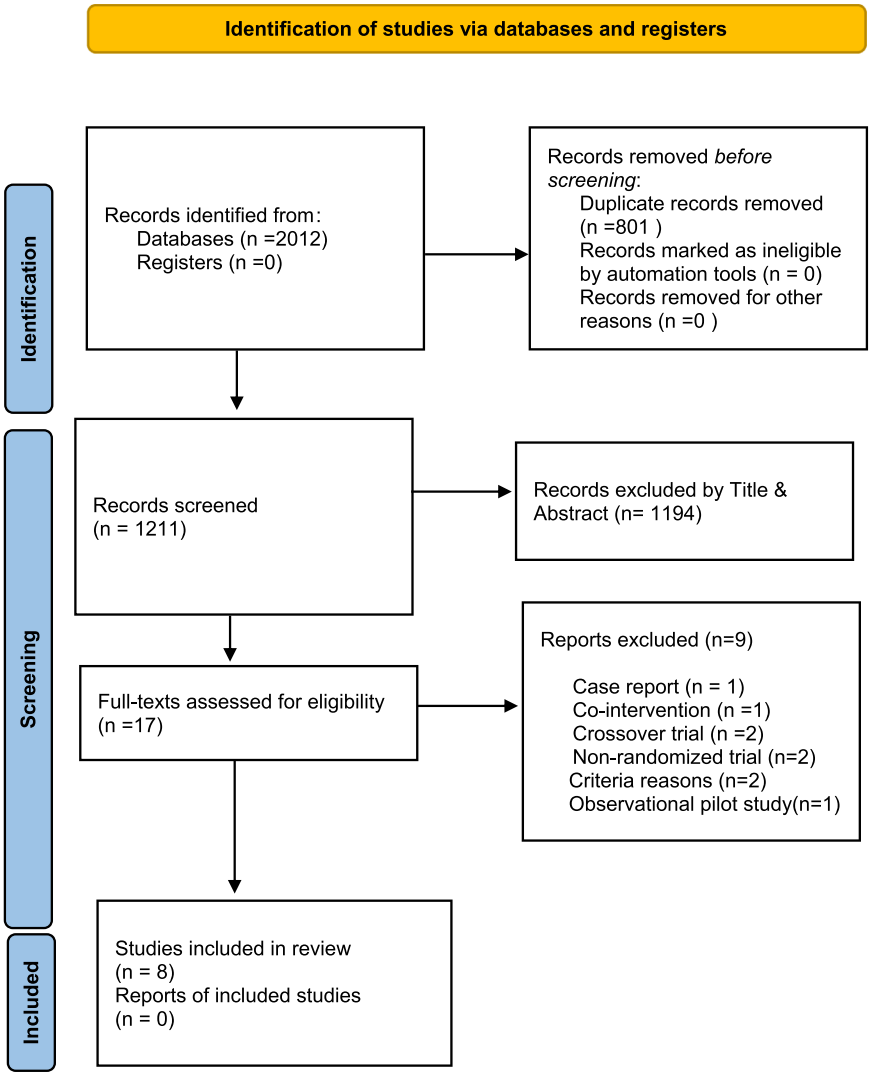

FIGURE 1 PRISMA flow diagram detailing the selection of studies for inclusion.

2021) published between 2006 and 2021 were eligible for the systematic review, including a total of 797 women. The number of included patients ranged from 50 to 132. The characteristics of the studies included in the systematic review are presented in TABLE 3.

The randomization method and allocation concealment were reported in six (Bosdou et al., 2016; Hoang et al., 2021; Kim et al., 2011, 2014; Massin et al., 2006; Subirá et al., 2021) and in three (Hoang et al., 2021; Kim et al., 2011; Kim et al., 2014) out of the eight studies, respectively. The definition of poor ovarian response, as well as the primary outcome, varied among the studies. A power analysis was performed in three studies (Bosdou et al., 2016; Massin et al., 2006; Subirá et al., 2021) and financial support was also declared in three out of the eight studies (Bosdou et al., 2016; Massin et al., 2006; Subirá et al., 2021) (TABLE 3).

To inhibit a premature LH surge, GnRH antagonists were used in six studies (Al-Jeborry, 2019; Doan et al., 2017; Hoang et al., 2021; Kim et al., 2011; Kim et al., 2014; Subirá et al., 2021), whereas in one study a GnRH agonist protocol was applied (Bosdou et al., 2016). In the study by Massin and colleagues (Massin et al., 2006) both GnRH agonists and GnRH antagonists were used (TABLE 4), although the proportions of the different GnRH analogue protocols were not statistically different between the two groups compared.

Ovarian stimulation was performed with using recombinant FSH in six of the studies (Al-Jeborry, 2019; Bosdou et al., 2016; Hoang et al., 2021; Kim et al., 2011, 2014; Massin et al., 2006). Gonadotrophin adjustments were reported in five studies (Al-Jeborry, 2019; Hoang et al., 2021; Kim et al., 2011; Kim et al., 2014; Massin et al., 2006). Human chorionic gonadotrophin (HCG) was used to trigger final oocyte maturation in all the studies, while the criteria for HCG administration and the dose for signalling final oocyte maturation varied across studies (TABLE 4).

The time of oocyte retrieval varied from 35 to 40 h after HCG administration in all studies, whereas in half of them it was performed strictly 36 h after HCG administration (Bosdou et al., 2016; Kim et al., 2011; Massin et al., 2006; Subirá et al., 2021). Fertilization methods included IVF (Doan et al., 2017; Hoang et al., 2021), IVF/intracytoplasmic sperm injection (ICSI) (Kim et al., 2011; Kim et al., 2014; Massin et al., 2006) and ICSI (Al-Jeborry, 2019; Bosdou et al., 2016; Subirá et al., 2021).

Embryo transfers were performed on day 2 or 3 after oocyte retrieval and luteal support varied among the studies, although two studies did not provide details about the type of luteal support used (Doan et al., 2017; Subirá et al., 2021). No systemic or local adverse effects attributed to transdermal testosterone gel were reported (TABLE 4).

Intervention

Regarding the type of intervention performed, pretreatment with transdermal testosterone gel was performed in all studies, with a daily dose ranging from 10 to 12.5 mg/day. The duration of testosterone pretreatment ranged from 10 to 56 days (TABLE 5).

Risk of bias assessment results

Among the eight RCT included in the present systematic review and meta-analysis, all studies (100%) had a low risk of bias on random sequence generation, and three of them (37.5%) had a low risk of bias on allocation concealment; therefore there were some concerns regarding the randomization process for the remaining five studies (62.5%). No study had a high risk of bias on random sequence generation and allocation concealment. Regarding the deviations from the intended outcomes, four studies (50%) were low risk and only one study was high risk (12.5%). Three studies (37.5%) were considered as high risk for missing outcomes and five (62.5%) were low risk. In terms of measurement of the outcomes, two studies (25%) were low risk, one study (12.5%) was considered as creating 'some concerns' and the rest were considered as high risk, according to RoB2. Finally, 7 out of 8 studies (87.5%) were low risk regarding the selection of the reported result.

In conclusion, the current systematic review and meta-analysis included three 'low-risk' studies (37.5%), three studies

TABLE 5 PROTOCOLS USED FOR TESTOSTERONE PRETREATMENT

Authors (year), journal	Testosterone administration			
	Type	Route	Dose	Duration
Massin et al. (2006), *Human Reproduction*	Testosterone gel 1%	Transdermal	10 mg/day	15–20 days
Kim et al. (2011), *Fertility and Sterility*	Testosterone gel 1%	Transdermal	12.5 mg/day	21 days
Kim et al. (2014), *Development and Reproduction*	Testosterone gel 1%	Transdermal	12.5 mg/day	Subgroup a: 14 days Subgroup b: 21 days Subgroup c: 28 days
Bosdou et al. (2016), *Human Reproduction*	Testosterone gel 1%	Transdermal	10 mg/day	21 days
Doan et al. (2017), *Gynecological Endocrinology*	Testosterone gel 1%	Transdermal	12.5 mg/day	From day 6 of previous menstrual period to day 2 of stimulated menstrual period
Al-Jeborry (2019), *Annals of Tropical Medicine and Public Health*	Testosterone gel 1%	Transdermal	10 mg/day	21 days
Hoang et al. (2021), *Reproductive Medicine and Biology*	Testosterone gel 1%	Transdermal	12.5 mg/day	Subgroup a: 28 days Subgroup b: 42 days
Subirá et al. (2021), *Reproductive BioMedicine Online*	Testosterone gel 1%	Transdermal	12.5 mg/day	Subgroup a (long testosterone): 56 days Subgroup b (short testosterone): 10 days

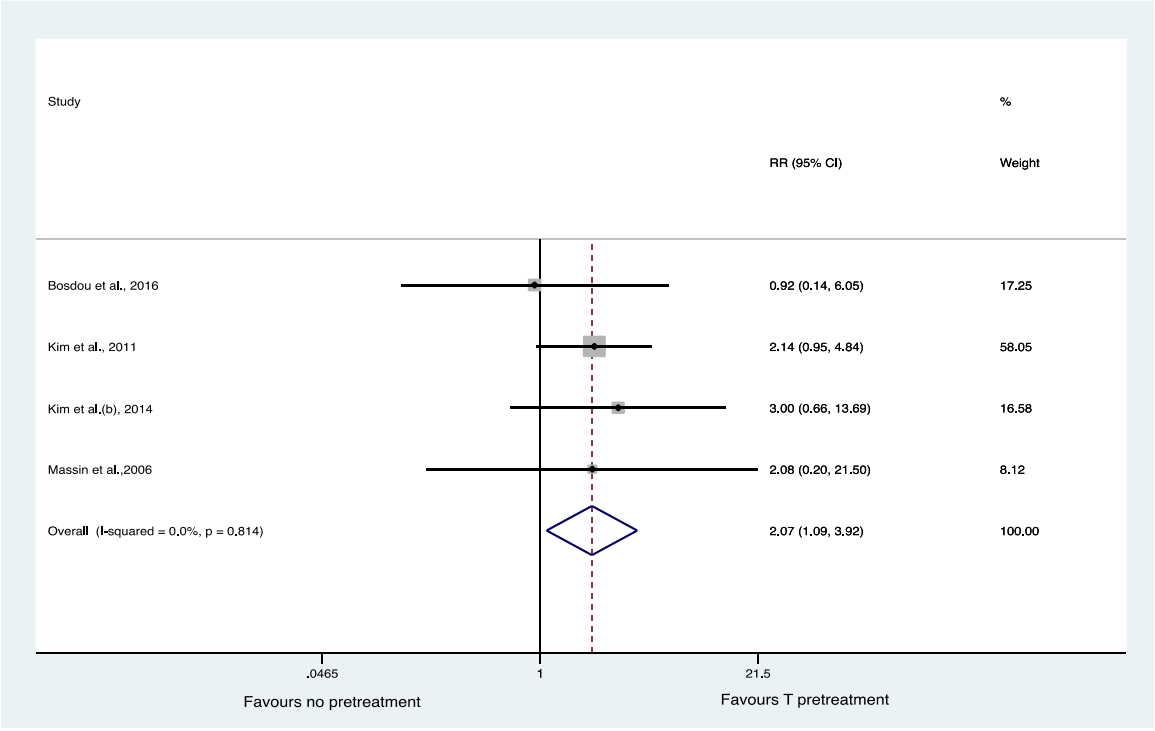

FIGURE 2 Risk ratio (RR) with 95% confidence interval (CI) for live birth in patients with poor ovarian response pretreated or not pretreated with testosterone (T). When the studies were evaluating testosterone pretreatments of different durations, subgroups a–c were created in each study for more precise results. Therefore, a, b or c in brackets next to the study authors represents the particular subgroup from the total sample size evaluating testosterone pretreatment of different durations.

with 'some concerns' (37.5%) and two 'high-risk' studies (25%). Supplementary Table I and Supplementary Figure I show the results obtained from the risk of bias assessment.

Meta-analysis

Primary outcome

The primary outcome was achievement of pregnancy expressed as clinical pregnancy or live birth. The probability of pregnancy was significantly increased in women pretreated with transdermal testosterone compared with those who were not, regarding both live birth (RR 2.07, 95% CI 1.09–3.92; Risk Difference 10%, 95% CI 2–17; fixed effects model I^2 0%, four studies, 333 women) and clinical pregnancy (RR 2.25, 95% CI 1.54–3.30; RD 11%, 95% CI 4–18%; fixed effects model I^2 0%, eight studies, 797 women) (FIGURES 2 AND 3).

Secondary outcomes that improved following testosterone pretreatment (TABLE 6)

Duration of ovarian stimulation

Significantly fewer days were required to complete ovarian stimulation in women pretreated with transdermal testosterone compared with those who were not (WMD –0.81, 95% CI –1.46 to –0.16, random effects model I^2 92%, seven studies, 744 women).

Total dose of gonadotrophins required for ovarian stimulation

A significantly lower total dose of gonadotrophins was required in women pretreated with transdermal testosterone compared with those who were not (WMD –368.8 IU, 95% CI –612.4 to –125.2 IU, random effects model I^2 87%, eight studies, 797 women).

Endometrial thickness on the day of triggering of final oocyte maturation

A significantly thicker endometrium on the day of triggering of final oocyte maturation was present in women pretreated with transdermal testosterone compared with those who were not (WMD 0.83 mm, 95% CI 0.13–1.53 mm, random effects model I^2 77.6%, five studies, 561 women).

Cancellation rate due to poor ovarian response

A significantly lower cancellation rate was present in women pretreated with transdermal testosterone compared with those who were not (RR 0.37, 95% CI 0.20–0.71, fixed effects model I^2 0%, six studies, 681 women).

COC retrieved

Significantly more COC were retrieved in women pretreated with transdermal testosterone compared with women who were not (WMD 0.88, 95% CI 0.22–1.54, random effects model I^2 78.7%, eight studies, 797 women).

Secondary outcomes not significantly different following testosterone pretreatment (Table 6)

Oestradiol concentrations on the day of triggering final oocyte maturation

No significant difference in oestradiol concentrations on the day of triggering of final oocyte maturation was present between women who were pretreated with transdermal testosterone and those who were not (WMD –8.12 pg/ml, 95% CI –118.2 to 101.96 pg/ml, fixed effects model I^2 0%, four studies, 394 women).

Number of follicles ≥17 mm on the day of triggering final oocyte maturation

No difference in the number of follicles ≥17 mm on the day of triggering of final oocyte maturation was present between

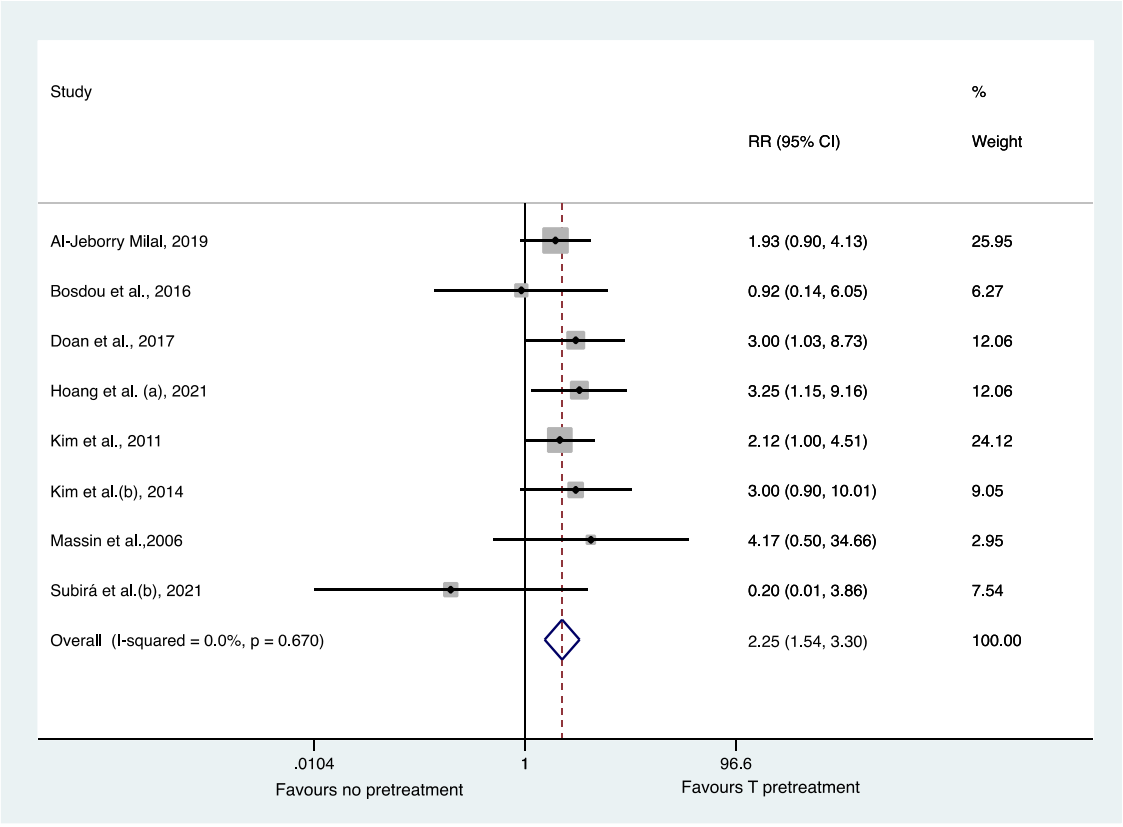

FIGURE 3 Risk ratio (RR) with 95% confidence interval (CI) for clinical pregnancy in patients with poor ovarian response pre-treated or not pretreated with testosterone (T). When the studies were evaluating testosterone pretreatments of different durations, subgroups a–c were created in each study for more precise results. Therefore, a, b or c in brackets next to the study authors represents the particular subgroup from the total sample size evaluating testosterone pretreatment of different durations.

women pretreated with transdermal testosterone and those who were not (WMD 0.82, 95% CI −0.11 to 1.74, random effects model I^2 85.7%, five studies, 386 women).

MII oocytes

No difference in the number of MII oocytes was present between women pretreated with transdermal testosterone and those who were not (WMD 0.48, 95% CI −0.16 to 1.13, fixed effects model I^2 0%, three studies, 245 women).

2pn oocytes

No difference in the number of 2pn oocytes was present between women pretreated with transdermal testosterone and those who were not (WMD 0.49, 95% CI −0.11 to 1.10, random effects model I^2 80.3%, seven studies, 665 women).

Embryos transferred

No significant difference in the number of embryos transferred was present between women pretreated with transdermal testosterone and those who were not (WMD 0.21, 95% CI −0.07 to 0.49, random effects model I^2 70.5%, eight studies, 797 women).

Miscarriage

A significant difference in the probability of miscarriage was present between women pretreated with transdermal testosterone and those who were not (RR 1.12, 95% CI 0.30–4.22, fixed effects model I^2 0%, three studies, 202 women).

Proportion of patients with embryo transfer

No significant difference in the proportion of women with embryo transfer was present between those who were pretreated with transdermal testosterone and those who were not (RR 1.00, 95% CI 0.96–1.04, fixed effects model I^2 15.9%, eight studies, 797 women).

DISCUSSION

The present systematic review and meta-analysis summarizes the best available evidence regarding testosterone pretreatment in poor responders undergoing ovarian stimulation for IVF, using gonadotrophins and GnRH analogues. Pretreatment with transdermal testosterone significantly improved the probability of live birth, as well as that of clinical pregnancy. This was accompanied by a significant increase in the number of COC retrieved and in endometrial thickness on the day of triggering of final oocyte maturation. Concomitantly, testosterone pretreatment significantly decreased the duration of ovarian stimulation, the total dose of gonadotrophins required for ovarian stimulation and the probability of cycle cancellation.

In the present systematic review and meta-analysis the administration of testosterone via the percutaneous route appears to be safe, as no adverse effects following transdermal testosterone administration were reported in the studies analysed, with the exception of itching at the application site in one case (*Hoang et al., 2021*). However, the long-term effects of testosterone pretreatment

TABLE 6 SECONDARY OUTCOMES FOLLOWING TESTOSTERONE PRETREATMENT

	Studies	Sample size	Method applied	Effect(95% CI)
Outcomes improved following testosterone pretreatment				
Duration of ovarian stimulation (days)	7	744	Random effects model, I^2: 92%	WMD: −0.81 (−1.46 to −0.16)
Total dose of gonadotrophins required for ovarian stimulation (IU)	8	797	Random effects model, I^2: 87%	WMD: −368.8 (−612.4 to −125.2)
Endometrial thickness on the day of triggering final oocyte maturation (mm)	5	561	Random effects model, I^2: 77.6%	WMD: 0.83 (0.13 to 1.53)
Cancellation rate due to poor ovarian response	6	681	Fixed effects model, I^2: 0%	RR: 0.37 (0.20 to 0.71)
No. of cumulus–oocyte complexes retrieved	8	797	Random effects model, I^2: 78.7%	WMD: 0.88 (0.22 to 1.54)
Outcomes not significantly different following testosterone pretreatment				
Oestradiol concentration on the day of triggering final oocyte maturation (pg/ml)	4	394	Fixed effects model, I^2: 0%	WMD: −8.12 (−118.2 to 101.96)
No. of follicles ≥17 mm on the day of triggering final oocyte maturation	5	386	Random effects model, I^2: 85.7%	WMD: 0.82 (−0.11 to 1.74)
No. of metaphase II oocytes	3	245	Fixed effects model, I^2: 0%	WMD: 0.48(−0.16 to 1.13)
No. of 2pn oocytes	7	665	Random effects model, I^2: 80.3%	WMD: 0.49 (−0.11 to 1.10)
No. of embryos transferred	8	797	Random effects model, I^2: 70.5%	WMD: 0.21 (−0.07 to 0.49)
No. of miscarriages	3	202	Fixed effects model, I^2: 0%	RR: 1.12 (0.30 to 4.22)
Proportion of patients having an embryo transfer	8	797	Fixed effects model, I^2: 15.9%	RR: 1.00 (0.96 to 1.04)

2pn, two-pronuclear; CI, confidence interval; I^2, heterogeneity; RR, risk ratio; WMD, weighted mean difference.

have not currently been studied. Similarly, no data are currently available on children born after testosterone pretreatment.

To the best of the authors' knowledge, this is the largest systematic review and meta-analysis evaluating the effect of testosterone pretreatment in poor responders undergoing IVF, including eight RCT and 797 patients (a 28.1% increase patients compared with the study by Noventa et al. [2019], with 573 patients). Applying strict inclusion criteria, studies with co-intervention or those available only in abstract form were excluded, leading to more precise estimates.

The review is, however, characterized by certain limitations that should be considered when interpreting its findings. The definition of poor ovarian response varied among studies, limiting the extrapolation of the results obtained. Despite the use of the Bologna criteria (*Ferraretti et al., 2011*) in three out of the eight eligible studies, the Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) criteria (*Al-Jeborry, 2019*), as well as arbitrary definitions of poor ovarian response, were also used. In addition, considerable heterogeneity regarding the type, dose and duration of testosterone pretreatment was present in the studies analysed. Thus, although the present study is currently the largest meta-analysis evaluating testosterone pretreatment, additional relevant trials are still necessary and are certainly justified.

The findings of the current meta-analysis are in line with those of previous meta-analyses on the same subject (*Neves et al., 2022*; *Noventa et al., 2019*). However, the increase in the number of patients/studies and the avoidance of methodological flows allows the confident highlighting of the importance of this intervention in patients with poor ovarian response, in whom numerous other interventions do not appear to be beneficial (*Song et al., 2016*; *Zhang et al., 2020*).

The current study suggests that the probability of pregnancy is increased in poor responders pretreated with transdermal testosterone. For each 10 poor responders pretreated with transdermal testosterone, one additional live birth is expected compared with no pretreatment. This is probably attributed to the fact that testosterone pretreatment increases the number of COC retrieved and therefore the probability of pregnancy.

With regard to the pathophysiological role of testosterone, it is known that testosterone and dihydrotestosterone (DHT) are the only bioactive forms that can bind directly to the androgen receptor, whereas the other androgens require conversion to the bioactive hormones in order to become effective (*Walters and Handelsman, 2018*; *Walters et al., 2019*). Observations from in-vivo investigations in primates revealed that testosterone and DHT treatment increased the number pre-antral and antral follicles, and had an overall positive impact on follicle development (*Vendola et al., 1999*; *Vendola et al., 1998*).

Following that, several studies in animals have confirmed the importance of the role of testosterone. In primate

ovaries, testosterone or DHT raises the transcript levels of insulin-like growth 1 (IGF-1) and IGF-1 receptors. Given that IGF-1 reduces follicular apoptosis and is present in the granulosa cells, theca, interstitial cells and oocytes, testosterone may exert a variety of functions on ovarian function through IGF-1, directly influencing the quality of oocytes and generated embryos (*Prizant et al., 2014*).

Furthermore, androgen support is crucial for overall follicle survival as it lowers follicle atresia and granulosa cell apoptosis, and increases granulosa cells proliferation and differentiation. Some of these findings may be explained by how the FSH receptor (FSHR) and androgen receptor interact as research on primates has revealed a significant correlation between FSHR and androgen receptor mRNA levels in granulosa cells (*Franks and Hardy, 2018*; *Sen et al., 2014*). Additionally, it has been demonstrated that testosterone treatment increases FSHR expression throughout the entire follicular development, whereas FSH increases androgen receptor expression in primary follicles (*Fujibe et al., 2019*; *Laird et al., 2017*; *Weil et al., 1999*).

With human data, there has been controversy regarding testosterone administration before assisted reproduction techniques. In 2006, Massin and colleagues were not able to demonstrate any beneficial effect of testosterone administration on ovarian response (*Massin et al., 2006*). However, in 2009, a randomized clinical trial demonstrated that pretreatment with transdermal testosterone decreased the percentage of cycles with a low response in low-responder IVF patients (*Fábregues et al., 2009*). Clinical trials to investigate the effects of testosterone supplementation for poor responders have recently been attempted, but the results have been limited.

Future studies on testosterone pretreatment should in addition focus on its duration of administration, which was evaluated in three studies in the current meta-analysis (*Hoang et al., 2021*; *Kim et al., 2014*; *Subirá et al., 2021*) albeit with controversial results. Moreover, a prerequisite for accurately evaluating testosterone pretreatment is that relevant RCT are performed in well-defined populations of poor responders (*Ferraretti et al., 2011*).

In conclusion, based on the currently available evidence, testosterone pretreatment increases clinical pregnancy and live birth rates in poor responders undergoing ovarian stimulation for IVF.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the following colleagues for providing data for the purposes of this research: Q. H. Hoang (Vietnam), M.T. Le (Vietnam) and J. Subirá (Spain)

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2022.09.022.

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Received 3 July 2022; received in revised form 8 September 2022; accepted 26 September 2022.