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## REVIEW

# Effect of heparin on the outcome of IVF treatment: a systematic review and meta-analysis


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**Abstract** The effect of heparin on IVF outcome has been widely debated in the literature. A systematic review and meta-analysis of the published literature was conducted to evaluate the effect of heparin treatment on IVF outcome. Searches were conducted on MEDLINE, EMBASE, Cochrane Library and Web of Science and identified 10 relevant studies (five observational and five randomized) comprising 1217 and 732 IVF cycles, respectively. The randomized studies included small numbers of women and exhibited high methodological heterogeneity. Meta-analysis of the randomized studies showed no difference in the clinical pregnancy rate (RR 1.23, 95% CI 0.97–1.57), live birth rate (RR 1.27, 95% CI 0.89–1.81) implantation rate (RR 1.39, 95% CI 0.96–2.01) and miscarriage rate (RR 0.77, 95% CI 0.24–2.42) in women receiving heparin compared with placebo during IVF treatment. However, meta-analysis of the observational studies showed a significant increase in the clinical pregnancy rate (RR 1.83, 95% CI 1.04–3.23,  $P = 0.04$ ) and live birth rate (RR 2.64, 95% CI 1.84–3.80,  $P < 0.0001$ ). The role of heparin as an adjuvant therapy during IVF treatment requires further evaluation in adequately powered high-quality randomized studies. 

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**KEYWORDS:** heparin, IVF, observational studies, pregnancy, randomized controlled trials

## Introduction

Embryo implantation is one of the most critical steps in determining the success of an IVF cycle. Implantation is a complex process, which depends on many variables including embryonic, endometrial, anatomical, immunological and endocrinological factors (Edwards, 2006). Most of these factors have not been adequately defined.

Implantation failure in couples undergoing assisted reproduction is common despite the transfer of good quality embryos. Up to 50% of women under the age of 35 years, who receive a blastocyst transfer do not achieve a pregnancy (Khalaf et al., 2008). This would suggest that endometrial receptivity and factors at the endometrial level play a significant role in establishing successful implantation.

Coagulation defects, both congenital and acquired, have been found to be more prevalent in patients with recurrent implantation failure (Qublan et al., 2008; Sher et al., 1998b; Stern et al., 2003). Antiphospholipid antibodies (APA) have been implicated in reproductive failure through implantation failure, recurrent miscarriages (Nelson and Greer, 2008; Rai and Regan, 1997), pregnancy-induced hypertension and intrauterine growth restriction (Polzin et al., 1991).

Consequently, several researchers have evaluated the role of a number of therapeutic interventions including heparin, corticosteroids and aspirin among other approaches to assess their effect on modulating endometrial receptivity and improving IVF outcome (Kutteh et al., 1997; Sher et al., 1998a). It is known that heparin causes modulation of basic physiological processes required for blastocyst adherence, implantation and trophoblast invasion which has the potential to improve pregnancy outcomes (Nelson and Greer, 2008). The heparinoids have been shown to have a regulatory effect on heparin-binding epidermal growth factor and insulin-like growth factors, both of which were reported to have a modulatory role on implantation and trophoblast invasion as well as the early stages of embryo development (Chobotova et al., 2002; Constanica et al., 2002; Stevenson et al., 2005). Apart from its anticoagulant properties, heparin is also thought to exert a beneficial effect on embryo implantation through interactions with adhesion molecules, growth factors, cytokines and enzymes like matrix metalloproteinases (Girardi et al., 2004). Heparin also modulates the decidualization of human endometrial stromal cells through the production of insulin-like growth factor 1 and prolactin (Fluhr et al., 2011).

Heparinoids have been shown to have an immune modulatory effect in addition to their anticoagulant properties through either the E-cadherin system (Erden et al., 2006) or via the heparin-binding epidermal growth factor (Leach et al., 2004) or by the induction of free insulin-like growth factor (Lacey et al., 2002). Adhesion molecules like E-cadherin and growth factors such as heparin-binding epidermal growth factor or free insulin-like growth factor have been reported to play an important role in endometrial receptivity, blastocyst adhesion and trophoblast invasion. Heparin can reduce E-cadherin expression and thereby can modulate and improve trophoblast invasion. Heparin-binding epidermal growth factor is expressed at the time of maximal endometrial receptivity and may play a role in embryo adhesion and embryo implantation (Tamada et al., 1999). Heparin increases the concentrations of both heparin-binding epidermal growth factor and insulin-like growth factor and has been suggested to play an important role in implantation (Nelson and Greer, 2008). These observations have encouraged clinicians to use heparin during the course of IVF treatment. The value of heparin as an adjunct to IVF treatment has been assessed in a number of studies, which have reported conflicting results (Berker et al., 2011; Qublan et al., 2008; Urman et al., 2009). Whilst some studies (Qublan et al., 2008; Sher et al., 1994, 1998a) have suggested a beneficial effect of heparin in recurrent implantation failure, others have found no evidence of benefit (Kutteh et al., 1997; Stern et al., 2003; Urman et al., 2009). Furthermore, the lack of a standardized definition of recurrent implantation failure complicates the interpretation of the evidence published on this topic (El-Toukhy

and Taranissi, 2006). The aim of this systematic review was to evaluate comprehensively the published literature on the use of heparin as an adjunct to improve IVF outcome.

## Materials and methods

### Identification of literature

The following electronic databases were searched: MEDLINE (1950–December 2011), EMBASE (1980–December 2011), Cochrane Central Register of Controlled Trials and Web of Science (1990–December 2011). A *c* subject headings and text words were used to generate two subsets of citations: (i) 'low molecular weight heparin', 'enoxaparin', 'dalteparin', 'tinzaparin', 'parenteral anticoagulants', 'unfractionated heparin', 'fibrinolytic agents', 'heparin sodium', 'fragmin', 'clexane', 'innohep', 'heparinoids', 'danaparoid', 'hirudins', 'bevalirudin and 'lepirudin'; and (ii) 'in-vitro fertilization', 'fertilization *in vitro*', 'intracytoplasmic sperm injection', 'sperm injection intracytoplasmic', 'reproductive techniques assisted', 'embryo transfer' and 'embryo implantation'. The two subsets were combined with 'AND' to generate a subset of citations relevant to the research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. Articles, which were frequently quoted, were used in the Science Citation Index to identify additional citations. Enquires were also made about unpublished studies from researchers in this field. No language restrictions were placed in the searches. The searches were conducted independently by SS and SKS.

### Study selection and outcome measures

Studies were selected if the target population was women undergoing IVF treatment with or without intracytoplasmic sperm injection (ICSI) and the exposure was the use of heparin in the study group and placebo or no intervention in the control group in the presence or absence of thrombophilia. Thrombophilia is a condition where the blood has an inherent tendency to clot (Baglin et al., 2010). Inherited thrombophilias include: factor V Leiden, prothrombin 20210, protein C and S deficiency and antithrombin deficiency (Baglin et al., 2010). Acquired thrombophilias include antiphospholipid syndrome and lupus anticoagulant. Study populations with or without recurrent implantation failures were also included in this review. The primary outcome of interest was the live birth rate (LBR) per IVF cycle. Secondary outcome measures of interest were the clinical pregnancy rate (CPR), implantation (IR) and miscarriage rate (MR). Also recorded were the side effects of heparin use reported in the included studies such as skin bruising or reactions, bleeding episodes or treatment-related thrombocytopenia.

### Data extraction

Studies were selected in a two-stage process. First, the titles and abstracts from the electronic searches were

scrutinized independently by two reviewers (SS and SKS) and full manuscripts of all citations that were likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publications, the most recent or the most complete publication was used. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (HH).

The quality of the randomized controlled trials was assessed using the modified Jadad scale (Jadad et al., 1996). Two reviewers (SS and SKS) completed the quality assessment (Berlin and Rennie, 1999). The Newcastle–Ottawa Quality Assessment Scales for observational studies were implemented (Wells et al., 2000). Items assessed included selection of cases and controls, comparability at baseline and completeness of follow up. An arbitrary score was used based on the assumption of equal weight of all items included in the Newcastle–Ottawa Scale. This was used to provide a quantitative appraisal of overall quality of each observational study. The score ranged from 0 to 9, with a score of either 0 or 1 for each item. From each study, outcome data were extracted in  $2 \times 2$  tables by two reviewers SS and SKS.

### Statistical analysis

Relative risks (RR) and the related confidence intervals (CI) from individual studies were calculated using fixed-effects model (Mantel and Haenszel, 1959) and random-effects models as appropriate (DerSimonian and Laird, 1986). Heterogeneity of the exposure effects was evaluated graphically using forest plots (Lewis and Clarke, 2001) and statistically using the  $I^2$  statistic to quantify heterogeneity across studies (Higgins and Thompson, 2002). Outcome measures were analysed for randomized and observational studies separately. The random-effects model was used to calculate the relative risks if the  $I^2$  statistic was  $>50\%$ . Exploration of the causes of heterogeneity was planned using variation in features of population, exposure and study quality. Sensitivity analyses were performed where possible and appropriate to address the clinical and methodological variations. Publication bias was assessed by funnel plot analysis, using Egger's test to test for asymmetry for the primary outcome of live birth (Egger et al., 1997). Statistical analyses were performed using RevMan 4.2 (Cochrane Collaboration, Oxford, UK).

### Outcome measures

The outcome measures assessed were LBR, CPR, IR and MR. For the purpose of this review, the LBR was defined as the number of live births per randomized woman. A clinical pregnancy was defined as the observation of a pregnancy sac on ultrasound at least 4 weeks after embryo transfer. Miscarriage was defined as any pregnancy loss, including biochemical pregnancies, occurring before 20 weeks of gestation. The IR was defined as the number of gestational sacs observed on scanning divided by the number of embryos transferred. These definitions were used in the included studies in the review.

## Results

The search strategy yielded 594 citations. Of these, 578 studies were excluded as it was clear from the abstract or title that these studies did not address the research question. Of the remaining 16 studies, two were excluded as one was a letter to the editor (Micco et al., 2010) and one was a review article (Nelson and Greer, 2008; Figure 1). The full manuscripts for the remaining 14 articles were obtained and, following scrutiny of these, 10 potentially relevant studies were identified: two studies were excluded (Sher et al., 1998a,b,c) as both the study and control groups received heparin. The third study excluded was an abstract (Stern et al., 2001) as the results were duplicated in Stern et al. (2003). The primary author of Stern et al. (2003) responded and answered queries regarding the study design. The fourth study (Lodigiani et al., 2011) was excluded as the outcomes were reported as per cycle started rather than per woman included in the study.

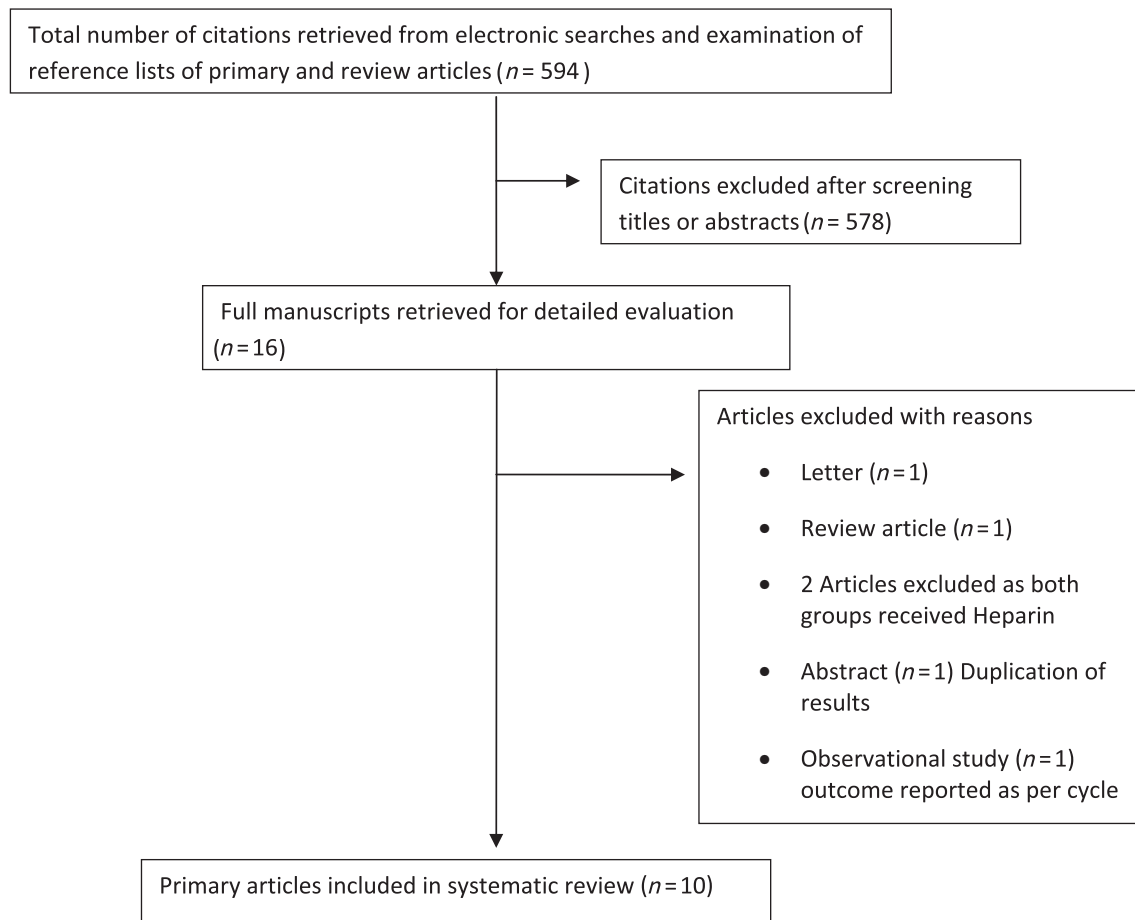
The 10 included studies comprised eight full articles (Berker et al., 2011; Kutteh et al., 1997; Noci et al., 2011; Qublan et al., 2008; Sher et al., 1994, 1998a; Stern et al., 2003; Urman et al., 2009) and two conference abstracts (Perminova et al., 2010; Schenk et al., 1996) and included 1949 IVF cycles. There were five randomized controlled trials and five prospective controlled studies. The main characteristics of the 10 studies and their quality assessment are presented in Tables 1–3.

### Heparin therapy

There was inconsistency in the timing of starting and duration of heparin therapy (Table 1). Four of the studies commenced heparin treatment on the day of the oocyte retrieval and stopped either with a negative pregnancy test or continued up to 9 (Noci et al., 2011), 12 (Berker et al., 2011; Urman et al., 2009) or 13 (Kutteh et al., 1997) weeks of pregnancy. Two trials started heparin treatment on the day of embryo transfer and continued until a positive pregnancy test (Stern et al., 2003) or delivery (Qublan et al., 2008). The remaining four studies commenced heparin treatment on days 1–2 of ovarian stimulation until 10–12 weeks of pregnancy (Perminova et al., 2010; Schenk et al., 1996; Sher et al., 1998a) or 34 weeks of gestation (Sher et al., 1994).

There were considerable differences among the included studies with regards to the type of heparin used (Table 1). Five studies (Berker et al., 2011; Noci et al., 2011; Perminova et al., 2010; Qublan et al., 2008; Urman et al., 2009) used low-molecular-weight heparin (LMWH). Two studies (Sher et al., 1994; Stern et al., 2003) reported the use of unfractionated heparin and three studies (Kutteh et al., 1997; Schenk et al., 1996; Sher et al., 1998a) did not specify the type of heparin used.

With regards to the dose of heparin administered, there was notable variation among the included studies (Table 1). Five studies (Kutteh et al., 1997; Schenk et al., 1996; Sher et al., 1994, 1998a; Stern et al., 2003) administered 5000 IU of heparin subcutaneously twice per day. Two trials (Berker et al., 2011; Qublan et al., 2008) administered 40 mg of heparin per day. The remaining three studies varied in the dosage of administered heparin ranging from 1 mg/kg/day



**Figure 1** The PRISMA flow diagram.

(Urman et al., 2009), 2850 IU/day (Perminova et al., 2010) and 2500 IU/day (Noci et al., 2011).

### Population studied

All the studies included evaluated the role of heparin in women undergoing IVF treatment, although the inclusion criteria varied between the different studies (Table 1). There were only two studies (Berker et al., 2011; Urman et al., 2009) that assessed the effect of heparin on women with unexplained recurrent implantation failures after excluding women with coagulation defects. The other eight studies included women with APA-positive serology. Of these studies, two studies included patients with inherited and acquired thrombophilia (Perminova et al., 2010; Qublan et al., 2008). Noci et al. (2011) was the first randomized trial evaluating the effect of heparin in non-thrombophilic women in their first IVF cycle.

### Quality assessment and publication bias

Individual studies scored well on the Quality Assessment Scale (Table 3). The randomized trials scored between 3/5 and 4/5 on the quality assessment (Jadad et al., 1996). The non-randomized comparative studies scored well on the Newcastle–Ottawa Quality Assessment Scale (Table 2): two

studies scored 8/9, two studies scored 7/9 and one study scored 6/9. Funnel plot analysis for publication and related biases did suggest evidence of bias (Figure 2; Begg's test  $P=0.90$  and Egger's test  $P=0.58$ ), although the analysis of publication bias was limited due to the small number of studies identified in the literature. Side effects of heparin administration were reported in four (Noci et al., 2011; Qublan et al., 2008; Stern et al., 2003; Urman et al., 2009) of the five randomized trials and ranged from minimal bruising at the site of the injection to thrombocytopenia. A single study (Qublan et al., 2008) reported a higher incidence of bleeding (7.1%) in patients who received heparin treatment, although it was the only study where heparin administration was continued until delivery. None of the observational studies reported the side effects of heparin administration.

### Primary outcome: live birth rate

Six studies reported the LBR as an outcome. All five randomized trials ( $n=732$ ) reported the LBR as an outcome. These studies showed no statistical significance in the live birth rate in women receiving heparin treatment compared with controls (RR 1.27, 95% CI 0.89–1.81; Figure 3). Only one observational study reported a statistical significance in the live birth rate in women receiving heparin treatment

Table 1 Characteristics of the studies included in the review.

Study	Type of study	Inclusion criteria	Exclusion criteria	Groups	Outcome measures
Noci et al. (2011)	RCT (n = 153)	First IVF cycle, age <40 years	Coagulation disorders (both acquired and inherited thrombophilia)	Study group received 2500 IU/day dalteparin sodium (from the day of oocyte retrieval to week 9 of pregnancy) and vaginal progesterone (n = 73) Control group received only progesterone (n = 80)	LBR, CPR, IR, MR
Berker et al. (2011)	RCT (n = 219)	Two recurrent implantation failures	Coagulation disorders (both acquired and inherited thrombophilia)	Study group received 40 mg LMWH (from the day of oocyte retrieval to week 12 of pregnancy; n = 110) Control group received no treatment (n = 109)	LBR, CPR, IR, MR
Perminova et al. (2010)	Prospective comparative study (abstract; n = 70)	Infertile with tubal factor, from 1–5 IVF failures and at least one acquired or inherited thrombophilic factor	Infertile women without tubal factor	Study group received 2850 IU LMWH (from day 1 of long protocol to week 12 of pregnancy; n = 60)  Control group (without any thrombophilic factor) received no treatment (n = 10)	IR
Urman et al. (2009)	RCT (n = 150)	(1) History of at least two previously failed fresh embryo transfer cycles  (2) No hormonal, coagulation or immunological disorders detected  (3) Normal uterine cavity, as assessed by hysteroscopy or saline infusion sonography (4) Normal female and male peripheral karyotype	(1) Anticoagulant therapy for other medical reasons  (2) Obvious causes of implantation failure (hydrosalpinx visible on transvaginal ultrasound, fibroids distorting the uterine cavity, the absence of grade-I or grade-II embryos available for transfer) (3) Clinical or laboratory findings of congenital or acquired thrombophilia	Study group received 1 mg/kg/day LMWH (from the day after oocyte retrieval to week 12 of pregnancy (n = 75)  Control group received no treatment (n = 75)	OPR, CPR, LBR, IR, MR
Qublan et al. (2008)	RCT (n = 83)	(1) Age 19–35 years  (2) Three previous IVF failures  (3) Good-quality embryos for transfer (4) Acquired/inherited thrombophilia	(1) Polycystic ovary syndrome, endometriosis, hydrosalpinx, chronic disease (liver, renal, thyroid and thrombocytopenia) (2) Abnormal uterine cavity on the hysterosalpingogram (3) Hormonal treatment  (4) Personal and/or family history of thrombosis  (5) Contraindication for heparin therapy	Study group received 40 mg/day LMWH (from day of embryo transfer to delivery; n = 42) Control group received placebo (0.9% NaCl; n = 41)	CPR, LBR, IR, MR

Stern et al. (2003)	RCT ( <i>n</i> = 127)	Recurrent implantation failure and positive for at least one autoantibody	(1) Abnormal findings on hysteroscopic evaluation of the uterine cavity, osteoporosis  (2) Known haematological/thrombotic disorders including thrombophilia, platelet dysfunction or previous thrombosis	Study group received 5000 IU b.d. unfractionated heparin and aspirin (from day of embryo transfer to week 14 of pregnancy; <i>n</i> = 66) Control group received placebo (0.9% NaCl; <i>n</i> = 61)	LBR, CPR/ cycle
Sher et al. (1998a)	Prospective comparative study ( <i>n</i> = 687)	APA positive	Male infertility, ovum donation and gestational surrogacy	Study group received 5000 IU b.d. heparin and aspirin therapy (from day 2 of ovarian stimulation to week 10 of pregnancy; <i>n</i> = 603) Control group received no treatment ( <i>n</i> = 84)	CPR, LBR, MR
Kutteh et al. (1997)	Prospective comparative study ( <i>n</i> = 191)	(1) First cycle of IVF (<42 years of age)	Two or more prior clinical pregnancy losses (not including ectopic pregnancies), one or more prior stillbirths, thrombocytopenia, allergies to aspirin, a prior history of thromboembolic disorder, a history of osteopenia, osteoporosis or any other bone disorder	Study group received 5000 IU b.d. heparin (from the day of oocyte retrieval to week 13 of pregnancy) and aspirin ( <i>n</i> = 112)	CPR, IR, MR
Schenk et al. (1996)	Prospective comparative study (abstract; <i>n</i> = 75)	(2) APA positive APA positive	None mentioned	Control group received no treatment ( <i>n</i> = 79) Study group received 5000 IU b.d. heparin (from day of oocyte retrieval to week 12 of pregnancy) and aspirin ( <i>n</i> = 35)	CPR, IR, MR
Sher et al. (1994)	Prospective comparative study ( <i>n</i> = 194)	APA positive	None mentioned	Control group received no treatment ( <i>n</i> = 40) Study group received 5000 IU b.d. unfractionated heparin (from day 2 of ovarian stimulation to week 34 of pregnancy) and aspirin treatment ( <i>n</i> = 169) Control group received no treatment ( <i>n</i> = 25)	CPR

*n* = number of women (one cycle per woman included).

APA = antiphospholipid antibodies; CPR = clinical pregnancy rate; IR = implantation rate; LBR = live birth rate; LMWH = low-molecular-weight heparin; MR = miscarriage rate; OPR = ongoing pregnancy rate; RCT = randomized controlled trial.

**Table 2** Appraisal of methodological quality (Newcastle–Ottawa scale) of the observational studies analysed.

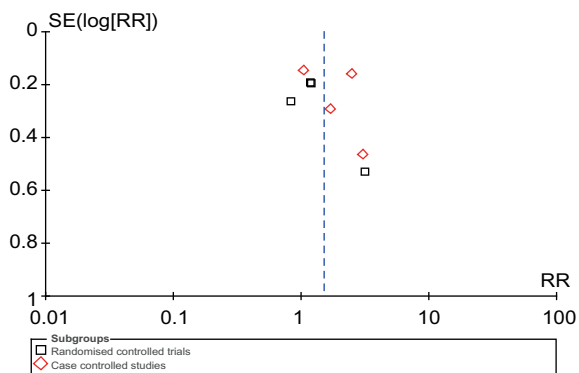
Study	Case cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Comparability by analysis	Outcome assessment	Duration of follow up	Adequacy of follow up	Score
Perminova et al. (2010)	+	+	+	+	+	+	+	–	–	7
Sher et al. (1998a)	+	+	+	+	–	–	+	+	+	7
Kutteh et al. (1997)	+	+	+	+	+	–	+	+	+	8
Schenk et al. (1996)	+	+	+	+	+	–	+	+	+	8
Sher et al. (1994)	+	+	+	+	+	–	+	–	–	6

+ = adequate; – = inadequate/unclear.

**Table 3** Quality of the randomized controlled trials included in the review of the effect of heparin on IVF outcome.

Studies	Study design	Method of randomization	Allocation concealment	Blinding	Intention-to-treat analysis	Follow-up rate (%)
Noci et al. (2011)	RCT	Computer-generated randomization	Yes	Yes	Yes	>95
Berker et al. (2011)	RCT	Assigned consecutively	Not described	No	Not mentioned	>95
Urman et al. (2009)	RCT	Computer-generated randomization	Yes	Yes	Yes	>95
Qublan et al. (2008)	RCT	Table of random numbers	Not described	Yes	Yes	>95
Stern et al. (2003)	RCT	Computer-generated randomization	Not described	Yes	Not mentioned	>95

RCT = randomized controlled trial.



**Figure 2** Funnel plot to assess publication and related biases in the systematic review of heparin in IVF cycles for the outcome of clinical pregnancy.

compared with controls (RR 2.64, 95% CI 1.84–3.80,  $P < 0.00001$ ; **Figure 4**). A sensitivity analysis of the two studies that reported the LBR in women with recurrent implantation failure ( $n = 369$ ) showed no statistically significant difference between the two groups (OR 1.22, 95% CI 0.78–1.9; **Figure 5**).

**Secondary outcomes**

**Clinical pregnancy rate**

Nine studies reported the CPR as an outcome. Analysis of the five randomized trials ( $n = 732$ ) which had reported clinical pregnancy as an outcome showed a trend towards a higher CPR in the heparin group compared with controls, but this trend failed to reach statistical significance (RR 1.23, CI 0.97–1.57; **Figure 6**). Four observational studies reported the CPR and pooling of their results ( $n = 1147$ ) showed a statistically significant increase in the CPR in the heparin group compared with controls (RR 1.83, CI 1.04–3.23,  $P = 0.04$ ; **Figure 7**) Sensitivity analysis of the two studies which included only women with recurrent implantation failure ( $n = 368$ ) showed no difference in the clinical pregnancy outcome between the two groups (OR 1.32, 95% CI 0.86–2.02;  $I^2 = 0\%$ ; **Figure 8**).

**Implantation rate**

Pooling of the results of four randomized trials for the secondary outcome of IR showed no statistical difference in IR

in women receiving heparin (RR 1.39, 95% CI 0.96–2.01; **Figure 9**). There was significant statistical heterogeneity across the four relevant studies ( $I^2 = 61\%$ ). Similarly, pooling the results of the three observational studies showed no statistical difference in IR in women receiving heparin (RR 1.38, 95% CI 0.83–2.29; **Figure 10**). Subgroup analyses of women with recurrent implantation failure did not show a significant improvement in the implantation rate in the group that received heparin (OR 1.22, 95% CI 0.89–1.67;  $I^2 = 0\%$ ; **Figure 11**).

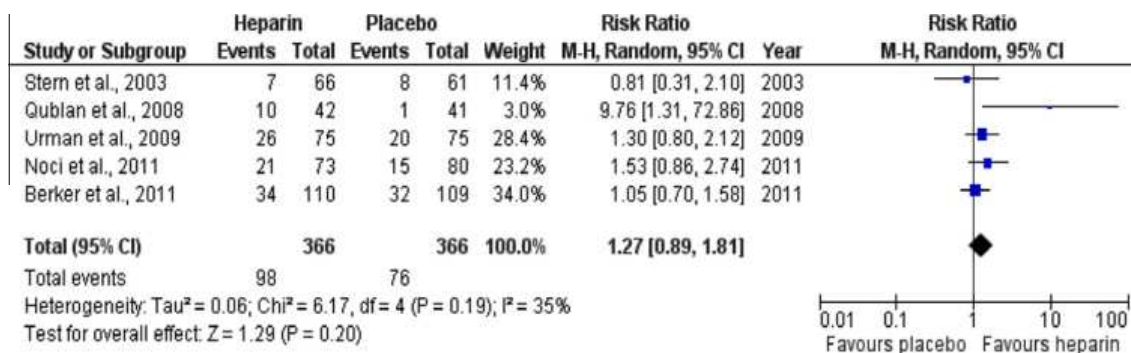
**Miscarriage rate**

Pooling of all the randomized studies that reported miscarriage as an outcome ( $n = 186$ ) showed no difference in miscarriage rate in women receiving heparin, following IVF treatment (RR 0.77, 95% CI 0.24–2.42; **Figure 12**). There was statistical heterogeneity across studies with an  $I^2$  value of 51%. Similarly, pooling all the observational studies showed no difference in miscarriage rate in women receiving heparin, following IVF treatment (RR 0.84, 95% CI 0.49–1.43; **Figure 13**). There was no statistical difference in the miscarriage rate in women with recurrent implantation failure without coagulation defects receiving heparin versus women receiving a placebo (RR 1.03, 95% CI 0.40–2.65; **Figure 14**).

A further subgroup analyses was carried out comparing the LBR and CPR in women with and without thrombophilia. There was no difference in the LBR in women with thrombophilia (RR 2.14, 95% CI 0.81–5.68) or without thrombophilia (RR 1.22, 95% CI 0.93–1.61). There was no difference in the CPR in women with thrombophilia (RR 0.67, 95% CI 0.42–1.08) or without thrombophilia (RR 0.91, 95% CI 0.81–1.02).

**Discussion**

As far as is known, this work is the first comprehensive systematic review of published evidence assessing the role of heparin as an adjuvant therapy during IVF. It provides a quantitative estimate of the relationship between heparin and IVF outcome. It includes both randomized trials (732 cycles) and observational studies (1217 cycles). Analysis of the randomized trials showed that heparin treatment was associated with a nonsignificant trend towards improvement in the CPR, but no improvement in the LBR compared with controls. However, this result should be interpreted with



**Figure 3** The effect of heparin versus placebo on the live birth rate (randomized controlled trials).



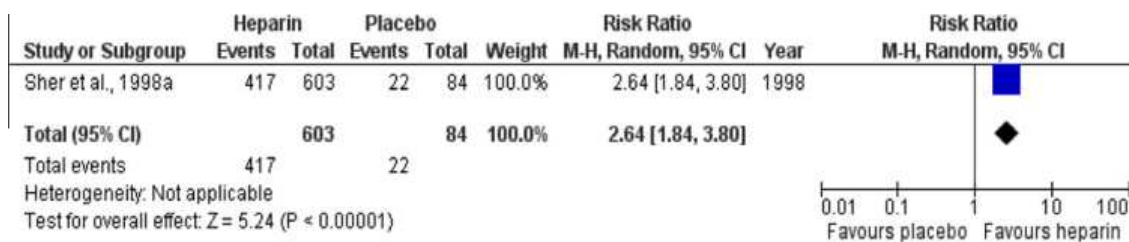


Figure 4 The effect of heparin versus placebo on the live birth rate (observational studies).

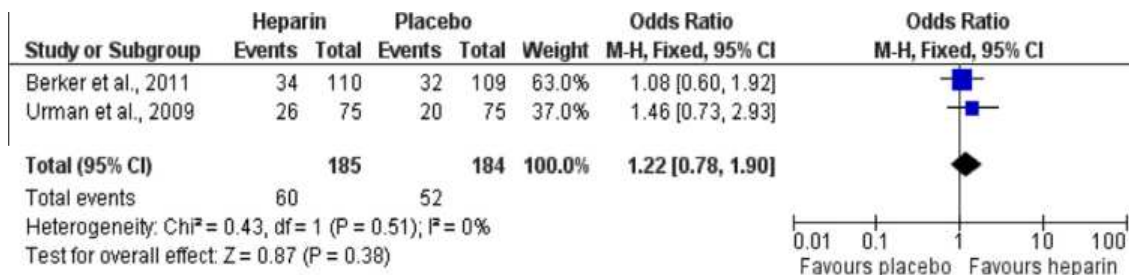


Figure 5 The effect of heparin versus placebo on the live birth rate in women with recurrent implantation failure without coagulation defects.

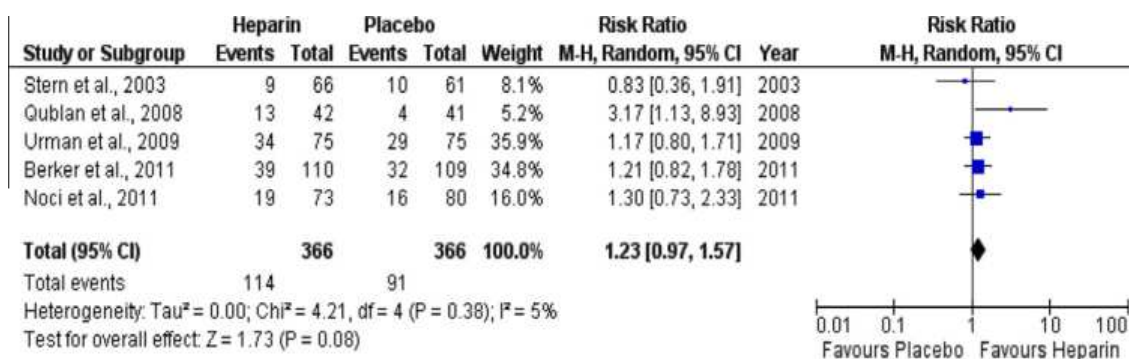


Figure 6 The effect of heparin versus placebo on the clinical pregnancy rate (randomized controlled trials).

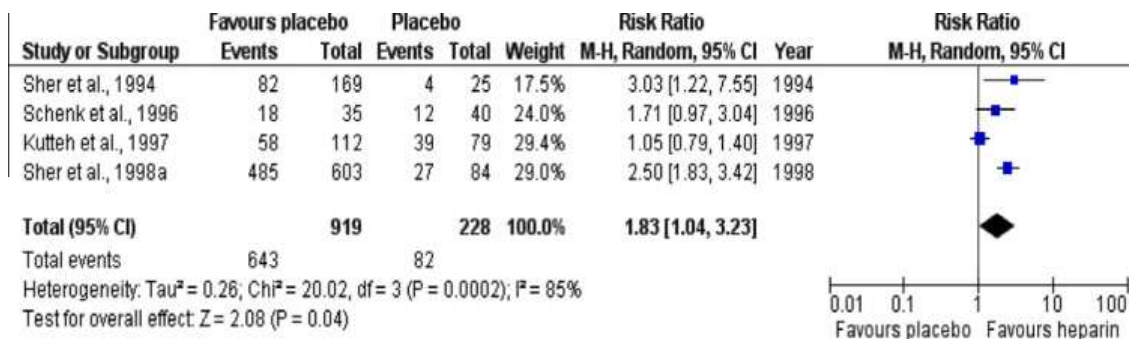


Figure 7 The effect of heparin versus placebo on the clinical pregnancy rate (observational studies).

caution as there was methodological heterogeneity between the trials and the number of patients included in each study was small. Although, the LBR was not statistically significant the apparent positive effect of heparin on LBR is mainly the result of one observational study.

The strength of this review lies in the extensive search strategy and data synthesis methods. Also, authors of the primary studies were contacted for clarification of relevant information. The corresponding author of three randomized trials (Berker et al., 2011; Stern et al., 2003; Urman et al.,

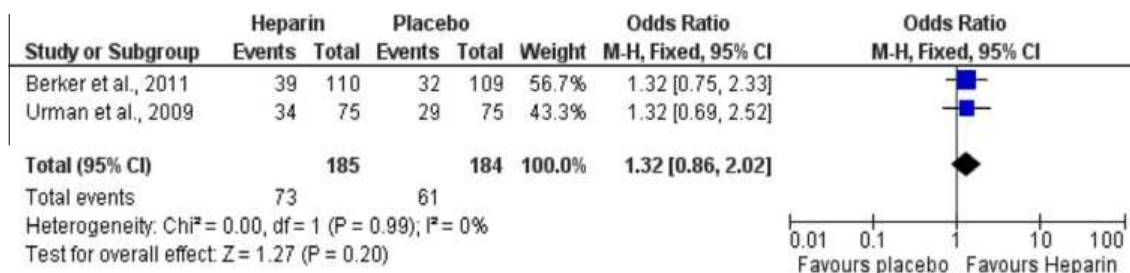


Figure 8 The effect of heparin versus placebo on the clinical pregnancy rate in women with recurrent implantation failure without coagulation defects.

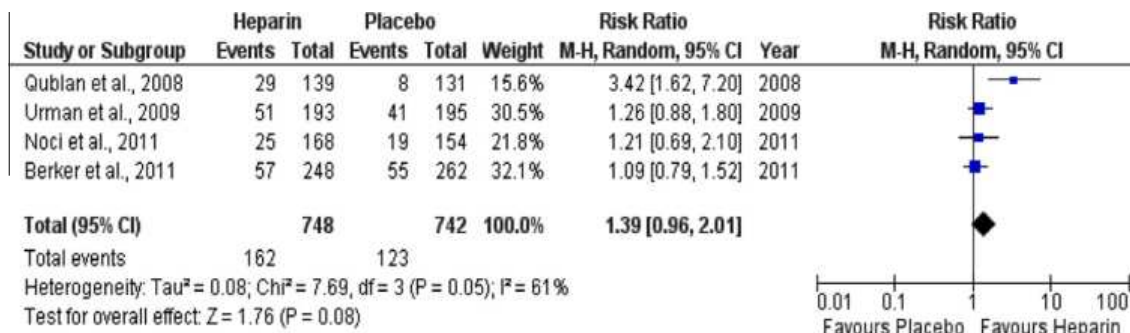


Figure 9 The effect of heparin versus placebo on the implantation rate (randomized controlled trials).



Figure 10 The effect of heparin versus placebo on the implantation rate (observational studies).

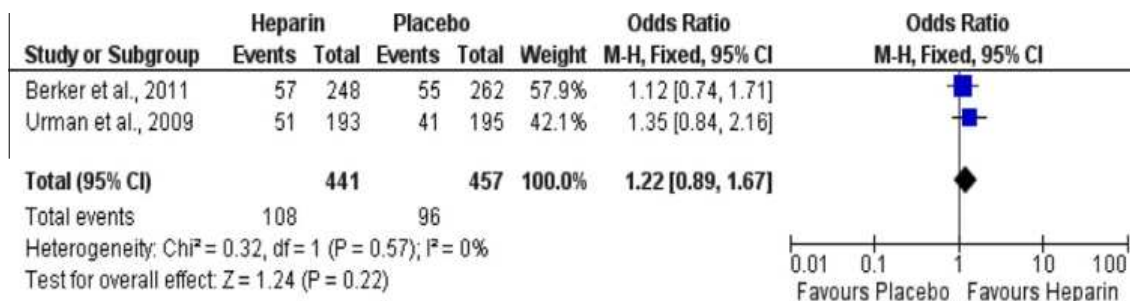


Figure 11 The effect of heparin versus placebo on the implantation rate in women with recurrent implantation failure without coagulation defects.

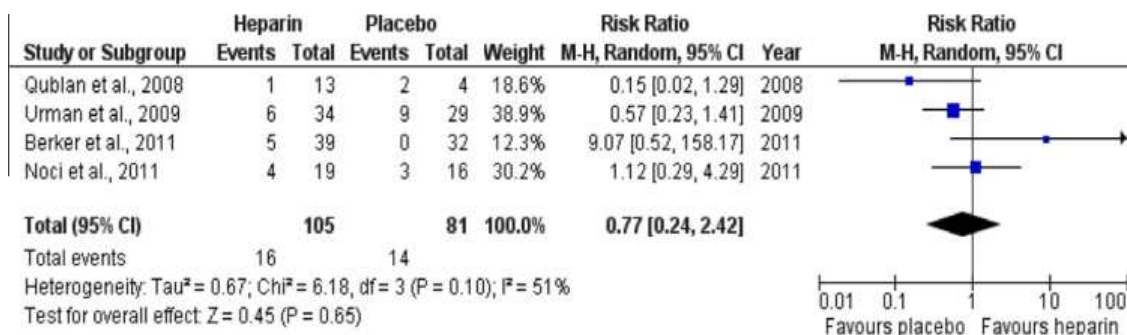


Figure 12 The effect of heparin versus placebo on the miscarriage rate (randomized controlled trials).

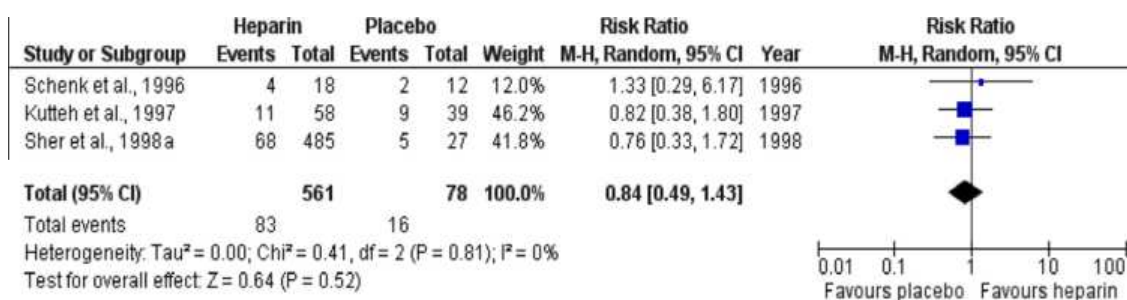


Figure 13 The effect of heparin versus placebo on the miscarriage rate (observational studies).

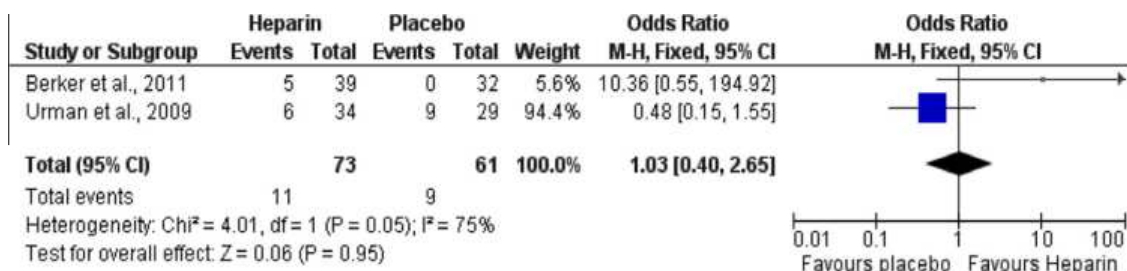


Figure 14 The effect of heparin versus placebo on the miscarriage rate in women with recurrent implantation failure without coagulation defects.

2009) responded and provided us with data which was incorporated into the analysis. The corresponding author of Lodigiani et al. (2011) also responded and was not able to give us the outcome data per woman treated with heparin.

The weaknesses in this review are mainly related to the clinical heterogeneity among the studies. The pooled results of the randomized trials evaluating the role of heparin in assisted conception, were in contrast to those of the observational studies. The reason for the difference could be attributable to the methodological and clinical heterogeneity encountered due to the varied study design, inclusion criteria and the dose and duration of heparin intervention. For example, two studies (Perminova et al., 2010; Qublan et al., 2008) had APA-positive women treated with heparin, five studies (Kutteh et al., 1997; Schenk et al., 1996; Sher et al., 1994, 1998a; Stern et al., 2003) treated APA-positive women with both heparin and aspirin, only

two studies (Berker et al., 2011; Urman et al., 2009) included women with unexplained recurrent implantation failures and one study (Stern et al., 2003) included women with both unexplained recurrent implantation failure and APA positivity. Noci et al. (2011) evaluated the role of heparin in women undergoing their first IVF cycle. Two studies (Kutteh et al., 1997; Stern et al., 2003) showed that treatment with heparin plus low-dose aspirin in women with thrombophilia undergoing IVF treatment did not improve pregnancy rate. In addition, the randomized trials included fewer patients and could therefore suffer from a Type 1 error. Equally, the results of the observational studies could have exaggerated the value of heparin in IVF due to selection bias. This considerable heterogeneity makes it difficult to generate clinical recommendations with regards to the role of heparin as an adjuvant therapy to improve IVF outcomes in the patient group who could benefit from this

treatment such as patients with recurrent implantation failure or those carrying a thrombophilic disorder.

Heparin is an inexpensive and a relatively safe drug as indicated by the side effects profile found in this systematic review. Any theoretical benefit from heparin administration could reflect the role of heparin at the endometrium–embryo interface (Kutteh, 2002). The trials also differed in their methodology as the dose of heparin used in these patients was varied. There is no consistent consensus with regards to the heparin dose used in all the trials. Although, randomized trials minimize the risk of bias, these trials were underpowered.

Furthermore, recommendations regarding optimum dose and duration of heparin therapy are not possible to generate from current evidence in view of the considerable clinical heterogeneity among the studies. Therefore, further studies are warranted to evaluate the role of heparin in IVF treatment. These trials will need to be large randomized trials with well-defined inclusion criteria and should also evaluate the LBR as the primary outcome. The suggested trials could investigate the use of a predefined dose of LMWH and target either the general IVF population or a specific subgroup of patients including those with known thrombophilia or recurrent implantation failure.

In conclusion, this systematic review demonstrates that the role of adjuvant heparin therapy during IVF has not been adequately evaluated by current literature. On the basis of published literature, the group of patients who could benefit from heparin therapy could not be identified with certainty. Specifically, the role of heparin in subfertile women with known thrombophilia and those with unexplained recurrent IVF implantation failure warrants further evaluation with adequately powered randomized studies.

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