

# The Associated Benefits of Low Molecular Weight Heparin in Case of *In Vitro* Fertilization-A Systematic Review

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## Almehiyawi *et al.*: Benefit of Low-Molecular-Weight Heparin in *In Vitro* Fertilization

A lack of definitive research exists regarding the application of low molecular weight heparin during pregnancy in connection with *in vitro* fertilization. The objective of this analysis is to determine if low molecular weight heparin enhances the success of pregnancies in women who do not have thrombophilia and are undergoing *in vitro* fertilization treatment. A comprehensive search was conducted across four databases (PubMed/MEDLINE, ScienceDirect, Scopus, and the Cochrane Library) for articles written in English from 2000 to 2020. All research methodologies evaluating the influence of low molecular weight heparin during *in vitro* fertilization on live birth rate, clinical pregnancy rate, and miscarriage rate were included. Individual case reports and studies focusing on women with hereditary or acquired thrombophilia, hormonal, or autoimmune disorders were excluded. Out of 3490 screened studies, 5 studies satisfied the selection requirements (consisting of 4 randomized and 1 observational study). The review encompassed a total of 1006 women, with 520 receiving low-molecular-weight heparin and 486 belonging to the control group. No significant differences were observed between the low molecular weight heparin and control groups in any of the evaluated outcomes (live birth rate, clinical pregnancy rate, miscarriage rate). It is important to note that the duration and dosage of low molecular weight heparin exhibited considerable variation across the studies included. While it may have a potential benefit especially in terms of live birth rate and clinical pregnancy rate, the current evidence doesn't imply a significant influence of low-molecular-weight heparin on *in vitro* fertilization treatment outcomes in terms of successful pregnancy rates for women without thrombophilia. Additional research is needed to evaluate the actual role of low molecular weight heparin as a treatment during *in vitro* fertilization procedures.

**Key words:** Low molecular weight heparin, *in vitro* fertilization, venous thromboembolic events, anticoagulant

Low Molecular Weight Heparin (LMWH) has become the preferred medication in pregnancy cases<sup>[1,2]</sup>. Women who face an increased risk of blood clot development during pregnancy or after childbirth (postpartum) are often administered LMWH. Moreover, the medication is utilized for other purposes, such as improving perinatal term outcomes<sup>[3]</sup> and as a vaginal stimulant to induce labor in pregnancies<sup>[4]</sup>. Systematic evaluations of various studies have demonstrated the safety and efficacy of LMWH use in pregnant women, as it neither crosses the placental barrier nor enters breast milk<sup>[5]</sup>. A study carried out in a Finnish University Hospital investigated the safety

and effectiveness of LMWH during pregnancy and the postpartum period for 180 d following delivery. The study concluded that LMWH is safe for both the mother and fetus during pregnancy. Additionally, the study reported that the risk of postpartum Venous Thromboembolic Events (VTE) was highest in the 1<sup>st</sup> w following delivery and then rapidly decreased, indicating the need for

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careful evaluation of VTE risk in the immediate postpartum phase<sup>[6]</sup>.

The role of LMWH in pregnancy has been examined in various studies, yielding inconsistent outcomes<sup>[7-9]</sup>. A cohort study conducted by Papadakis *et al.*<sup>[10]</sup> revealed that out of 818 pregnant women in Greece who were administered LMWH, 98.7 % experienced live births, with 7 VTE instances recorded antepartum and 10 postpartum. Despite demonstrating the safety and efficacy of LMWH, the study did not provide conclusive evidence for some indications. In contrast, a study involving women with a history of 2 consecutive early miscarriages, 1 late miscarriage, and no inherited thrombophilia found that LMWH did not enhance ongoing pregnancy or live birth rates<sup>[11]</sup>.

*In Vitro* Fertilization (IVF) has become an increasingly popular pregnancy technique. However, post-IVF pregnancy success rates among women remain low, ranging from 20 %-35 %<sup>[12]</sup>. A systematic review by Dentali *et al.*<sup>[13]</sup> suggested that LMWH might boost pregnancy and live birth rates for women undergoing IVF. Furthermore, a case where a woman diagnosed with Deep Vein Thrombosis (DVT) 5 d after IVF was treated with LMWH demonstrated an improvement in symptoms until delivery, with no additional complications arising<sup>[14]</sup>. Serious complications related to IVF treatment can be rare, with ovarian hyperstimulation syndrome being the most prevalent<sup>[15]</sup>. This syndrome may be linked to a higher risk of thromboembolism, which can be fatal. However, there is scarce information in the literature connecting ovarian hyperstimulation syndrome to the development of VTE and arterial thromboembolism. It has been noted that the risk of thromboembolism doubles in pregnant women following IVF<sup>[16]</sup>. Still, limited data is available regarding the actual incidence of thromboembolism and IVF. A Swedish systematic review clarifies that the antepartum risk of VTE doubles in pregnancies post-IVF, which is correlated to an extremely high risk of VTE during the first trimester following ovarian hyperstimulation syndrome. The authors suggest administering LMWH during the first trimester to IVF patients who experience ovarian hyperstimulation syndrome<sup>[17]</sup>. Despite the lack of concrete scientific evidence, the application of LMWH in pregnancy goes beyond VTE management and extends to addressing vascular gestational issues and enhancing IVF pregnancy

outcomes. Nevertheless, uncertainties remain about LMWH usage in IVF pregnancies. This systematic review aimed to determine if LMWH improves pregnancy outcomes for women without thrombophilia undergoing IVF.

We conducted a systematic review of the effects of LMWH on pregnant women undergoing IVF by searching electronic databases including PubMed/MEDLINE, ScienceDirect, Scopus, and the Cochrane Library for studies published from January, 2000 to October, 2020. The search terms used were, 'heparin AND IVF' OR 'heparin AND *In Vitro* Fertilization'. Our systemic review was developed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Our inclusion criteria covered English written randomized controlled trials, observational studies (both prospective and retrospective cohorts), clinical trials, and quasi-randomized studies that evaluated the influence of LMWH on Live Birth Rate (LBR), Clinical Pregnancy Rate (CPR), and Miscarriage Rates (MR) among women undergoing IVF. We excluded single case reports due to their limited statistical validity. Moreover, animal studies, articles without patient data, conference abstracts, review articles, and studies examining females with hereditary or acquired thrombophilia, hormonal, or autoimmune conditions were excluded. The selection process involved screening titles and abstracts to identify relevant articles for this systematic review. Subsequently, all articles were read, tabulated, and assessed by all authors (Table 1).

Control subjects were defined as women who met the inclusion criteria but did not receive LMWH treatment. In this investigation, LBR referred to the number of live births after 24 w of pregnancy. CPR was identified as the confirmation of a viable pregnancy *via* ultrasound 3-4 w following embryo transfer. MR was characterized as pregnancy loss occurring prior to 24 w of gestation. Approval from the Institutional Review Board was not necessary for this research, as it constitutes a secondary analysis. Out of the 3490 studies initially screened, 3466 were excluded based on their title or abstract. The remaining 24 studies were deemed suitable for full-text examination. After eliminating duplicate entries, 5 studies fulfilled the inclusion and exclusion criteria and were incorporated into this review. Fig. 1, displays the flow diagram for the

systematic review process, while Table 1, outlines the features of the included studies.

The initiation and duration of the treatment varied across the studies (Table 1). One study commenced treatment the day following oocyte retrieval, and if the pregnancy test was positive, treatment continued until 12 w of pregnancy<sup>[18]</sup>. If the pregnancy test was negative, the treatment was halted. 2 studies started treatment on the day of oocyte retrieval and discontinued it with a negative pregnancy test or proceeded until either 9 w of pregnancy<sup>[19]</sup> or 12 w of pregnancy<sup>[20]</sup>. One study started treatment on the day of embryo transfer and carried on until the 3<sup>rd</sup> trimester of pregnancy<sup>[21]</sup>. Finally, one study began treatment for the entire cycle, from a day before the stimulation phase until the procedure's result, and if the pregnancy test was positive, treatment persisted until delivery or the pregnancy's conclusion<sup>[22]</sup>.

The type of LMWH employed differed among the included studies with enoxaparin being the most frequently administered LMWH (Table 1). The LMWH dosage received by participants varied as well (Table 1). One study utilized a dosage of 1 mg/kg/d, another administered 40 mg/0.4 ml of LMWH daily, another employed 2500 IU of LMWH per day, yet another used 3500 IU of LMWH daily, and finally, one study applied either 4250 anti-Xa IU/0.4 ml or 6400 anti-Xa IU/0.6 ml/d<sup>[18-22]</sup>. The studies incorporated into this systematic review examined the role of LMWH in women undergoing IVF treatment, though there were variations in the inclusion criteria among these studies (Table 1). Two studies explored the influence of LMWH on IVF treatment outcomes<sup>[19,22]</sup>. One study investigated the role of LMWH in Recurrent Implantation Failure (RIF) and excluded women with clotting disorders<sup>[20]</sup>. Furthermore, one study evaluated LMWH in sub-fertile women with unsuccessful IVF cycles and excluded those with thrombophilia, coagulation, and endocrine disorders<sup>[21]</sup>. The last study assessed the effect of LMWH administration during the luteal phase in patients with failed Intracytoplasmic Sperm Injection (ICSI)<sup>[18]</sup>.

All 5 studies in this review evaluated LBR among the study participants. 4 of these studies were randomized trials<sup>[18-20,22]</sup>. LBRs were not statistically significant in women taking LMWH compared to the control groups. LBRs in LMWH compared to control were 34.7 % vs. 26.7 %,  $p=0.29$ ;

21 % vs. 16 %,  $p=\text{Non-statistically Significant (NS)}$ ; 30.7 % vs. 29.1 %,  $p=\text{NS}$ ; and 18.5 % vs. 20.6 %,  $p=0.757$ , respectively. One observational study also reported LBR as an outcome<sup>[21]</sup>. The LBR outcome in the observational study was also not statistically significant between the 2 groups. LBR was 17.3 % in the LMWH group, compared to 14.4 % in the control group,  $p=0.56$ . Each of the 5 studies in this review reported CPR as an outcome measure. In 4 randomized trials, higher CPR was observed in the LMWH-treated group compared to the control group<sup>[18-20,22]</sup>, but the results did not reach statistical significance. CPR values were 45.3 % vs. 38.7 %,  $p=0.41$ ; 26 % vs. 20 %,  $p=\text{NS}$ ; 34.6 % vs. 33.9 %,  $p=\text{NS}$ ; and 21.5 % vs. 26.7 %,  $p=0.389$  in the LMWH group compared to control group, respectively. One observational study also reported CPR as an outcome<sup>[21]</sup>. The CPR outcomes for this study were not statistically significant between women receiving LMWH and the control group. CPR was 24.8 % in the LMWH group, compared to 20.6 % in the control group,  $p=0.456$ .

Out of the 5 studies, only 3 reported MR as an outcome<sup>[19,21,22]</sup>. In one study,<sup>[19]</sup> a higher MR was observed in the LMWH group (21 %) compared to the control group (19 %),  $p=\text{NS}$ . Conversely, another study<sup>[22]</sup> found a lower MR in the LMWH group (10.3 %) compared to the control group (22.9 %), but the difference was not statistically significant,  $p=0.319$ . The observational study also did not report a statistically significant difference in MR between the LMWH group (11.3 %) and the control group (9.3 %),  $p=0.624$ <sup>[21]</sup>.

In this analysis, we examined whether or not LMWH enhances pregnancy outcomes for women without thrombophilia undergoing IVF. The investigation encompassed four randomized and one observational trial, evaluating the impact of LMWH on LBR, CPR, and MR. The results of our systematic review indicated that, for non-thrombophilic women, LMWH slightly improved LBR and CBR but it did not reach a significant margin compared to control group. The Impact of LMWH on MR was conflicting and also did not reach a statistical significance. To our understanding, only a limited number of studies have explored the effects of LMWH on pregnancy rates for women undergoing IVF. Women with a history of thrombophilia were excluded to determine any potential benefits of LMWH on

outcomes due to its non-anticoagulant properties. This review aimed to assess the implications of LMWH's effectiveness in non-thrombophilic IVF pregnancies. As indicated by multiple studies, LMWH has demonstrated potential benefits. Administering a prophylactic dose of LMWH to non-thrombophilic women undergoing IVF has shown promise in increasing the likelihood of successful embryo transfer, implantation rate, and pregnancy rate<sup>[19]</sup>.

A systematic review by Sennström *et al.*<sup>[17]</sup> indicated that the risk of thromboembolism doubled after IVF due to physiological changes during pregnancy and ovarian stimulation. Dentali *et al.*<sup>[13]</sup> found that LMWH might increase the number of pregnancies and live births in women undergoing IVF. However, a contrasting study suggested that low-dose heparin and/or aspirin as adjunct therapy in non-screened thrombophilic IVF pregnant women did not enhance live birth rates<sup>[23]</sup>. Two controlled studies utilizing LMWH with varying criteria, types, and doses demonstrated similar outcomes, highlighting LMWH's crucial impact on LBR<sup>[19,22]</sup>. In contrast, three controlled studies employed the same inclusion criteria but differed in LMWH type and dose<sup>[18,20,21]</sup>. Berker *et al.*<sup>[20]</sup> could not establish any beneficial effect of LMWH on pregnancy outcomes, including women who experienced RIF. However, Urman *et al.*<sup>[18]</sup> found that LMWH increased live births by 30%. Siristatidis *et al.*<sup>[21]</sup>, which involved women with two or more IVF failure cycles, provided no evidence of LMWH's effect on LBR.

The evaluation of LMWH focused on LBR, CPR, and MR. All 5 studies in this review considered LBR and CPR as outcomes. Nonetheless, none of the studies demonstrated statistical significance. LBR and CPR were higher in the LMWH-treated group than in the control group<sup>[18-21]</sup>. In contrast, Lodigiani *et al.*<sup>[22]</sup> reported lower LBR and CPR in the LMWH-treated group compared to the control group, which may be due to the small sample size and the trials premature conclusion. In the study by Urman *et al.*<sup>[18]</sup>, researchers observed a roughly 30% improvement in LBR following LMWH administration, implying a clinically significant trend. However, the authors reported that LMWH exhibited a non-significant trend toward increased LBR/embryo transfer and clinical pregnancy rate in women experiencing their first IVF cycle<sup>[19]</sup>.

In a meta-analysis, researchers examined the

impact of LMWH on LBRs and Implantation Rates (IRs) in women experiencing RIF while undergoing IVF<sup>[24]</sup>. 2 separate studies assessing LMWH effects in women without coagulation disorders demonstrated significant improvement in LBR with LMWH groups<sup>[18,20]</sup>. The aforementioned meta-analysis study revealed that adding LMWH to IVF/ICSI treatment increased LBR by 79% in women with 3 RIFs. The employment of LMWH did not yield a statistically significant difference in MR. However, only 3 studies in this review reported MR as an outcome<sup>[19,21,22]</sup>, suggesting that more research is necessary to substantiate scientific evidence for using LMWH to reduce MR. Lodigiani *et al.*<sup>[22]</sup> found a lower MR in the LMWH group compared to the control group, while Noci *et al.*<sup>[19]</sup> and Siristatidis *et al.*<sup>[21]</sup> reported higher MR in the LMWH group. These findings align with those of Yang *et al.*<sup>[25]</sup> and Seshadri *et al.*<sup>[26]</sup>, where no difference in miscarriage rates was identified. However, Potdar *et al.*<sup>[24]</sup> observed a 78% reduction in the miscarriage rate for the intervention group.

The most frequently reported side effects of LMWH include pain, redness, bruising, and allergic reactions at the injection site. However, the most significant side effect is bleeding. Among the 4 studies<sup>[18,19,21,22]</sup>, only minor bruising around the LMWH injection sites was reported as a side effect. In another retrospective study involving pregnant women receiving LMWH, side effects were minimal, but some maternal and infant complications were identified<sup>[27]</sup>. The strength of this systematic review lies in its comprehensive search strategy, incorporating all pertinent studies from 2000 to 2020, which resulted in a large number of publications with varying exclusion and inclusion criteria. On the other hand, the limitations stem from clinical variations among the studies. These differences can be attributed to disparate study designs, inclusion criteria, and LMWH dosages. The study's limitations also include the heterogeneity of LMWH administration's start time, duration, and dosage. Consequently, the results should be interpreted cautiously.

In summary, our systematic review demonstrated that the current literature has not adequately evaluated the role of LMWH in women undergoing IVF treatment. Based on the published literature, it is challenging to definitively identify which patients might benefit from LMWH therapy. To

conclusively determine the role of LMWH in non-thrombophilic pregnant women undergoing IVF, large prospective studies are necessary and could draw upon this study's findings. Furthermore,

therapeutic guidelines and essential education on the appropriate use of LMWH should be made available to healthcare professionals.

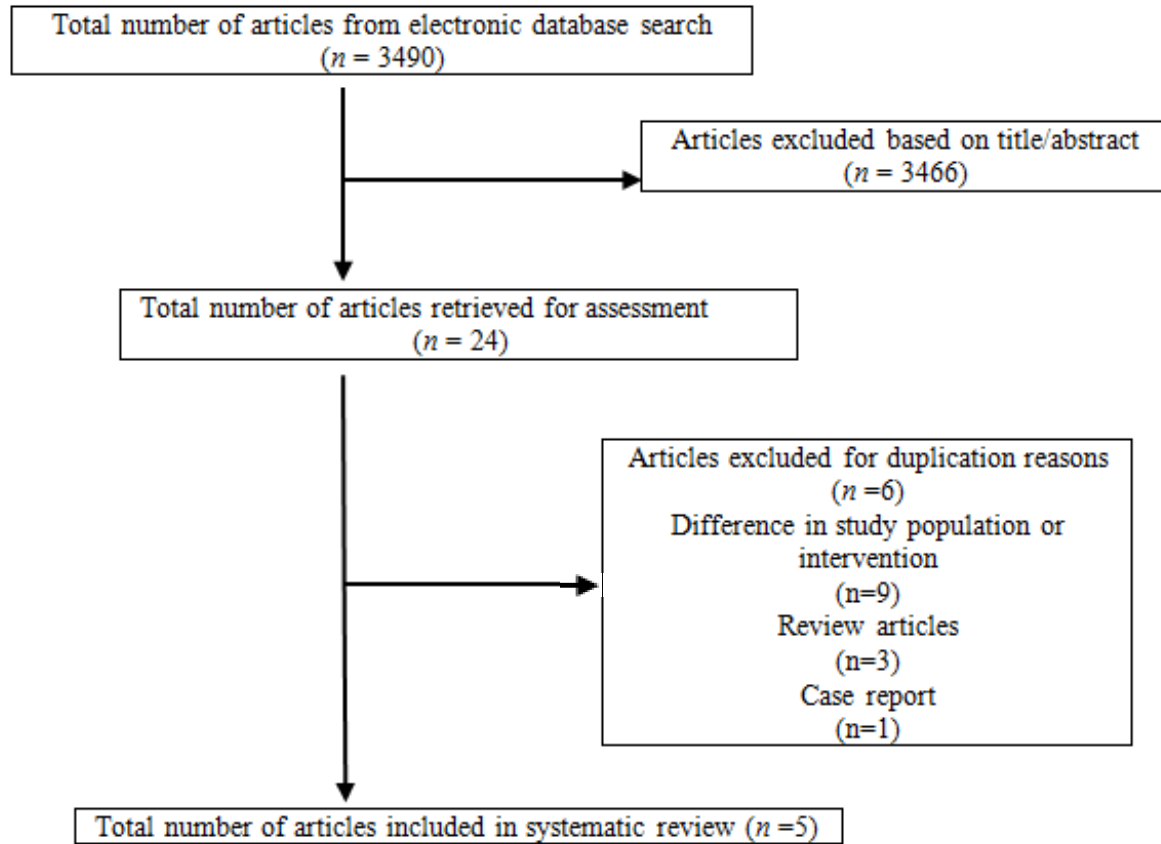


Fig. 1: Systematic review flow diagram

TABLE 1: CHARACTERISTICS OF THE INCLUDED STUDIES

Study	City, country	Duration, age of treated vs. controls	Study design, number of included patients treated vs. controls	Inclusion criteria	Exclusion criteria	Treatment	Outcome measures	Results
Urman <i>et al.</i> <sup>[18]</sup>	Istanbul, Turkey	January 2006 and May 2008, mean age: 34.0±5.0 vs. 34.8±5.8 y	Randomized open-labelled pilot trial, N=150 (75 vs. 75)	Age ≤38 y. ≥2 failed fresh embryo transfer cycles. No hormonal, coagulation or immunological disorders detected. Normal uterine cavity Normal female and male peripheral karyotype	Situations requiring anticoagulant treatment Congenital or acquired thrombophilia	Hormonal treatment, enoxaparin sodium 1 mg/kg/d up to the 12 <sup>th</sup> w of pregnancy if the test was positive	IR, CPR, LBR in treated vs. controls	IR: (24.5 % vs. 19.8 %; p=0.33) CRP: (45.3 % vs. 38.7 %; p=0.41) LBR: (34.7 % vs. 26.7 %; p=0.29)

Noci <i>et al.</i> <sup>[19]</sup>	Pisa, Italy	May 2008 and December 2008, mean age: 34.7±3.6 vs. 35.1±3.1 y	Pilot study, n=153 (73 vs. 80)	Age <40 y. First IVF/ ICSI cycle. No hormonal/ endocrine, coagulation/ haematological immunological disorders detected Absence of chronic diseases Normal uterine cavity. No treatment with LMWH in the previous 3 mo	Not meeting inclusion criteria	Hormonal treatment, dalteparin Sodium 2500 IU/d up to the 9 <sup>th</sup> w of pregnancy if the test was positive	IR, CPR, LBR, MR in treated vs. controls	IR: (15 % vs. 12 %; p=NS) CPR: (26 % vs. 20 %; OR 1.30; 95 % CI 0.58-2.89; p=NS) LBR: (21 % vs. 16 %; OR 1.33; 95 % CI 0.54-3.27; p=NS)
Berker <i>et al.</i> <sup>[20]</sup>	Ankara, Turkey	June 2007 and October 2009, mean age: 31.3±4.9 vs. 31.2±5.0 y	Prospective quasi-randomized, controlled study, n=207 (104 vs. 103)	≥2 consecutive failed cycles of (ICSI-ET) Normal uterine cavity No hormonal or coagulation disorders	Coagulation disorders, situations requiring anticoagulant treatment abnormal uterine cavity	Hormonal treatment, enoxaparin sodium 40 mg/0.4 ml/d up to the 12 <sup>th</sup> w of pregnancy if the test was positive	IR, CPR, LBR, MPR in treated vs. controls	IR CPR LBR MP in treated vs. controls IR: (22.6 % vs. 21.1 %; p=NS) CPR: (34.6 % vs. 33.9 %; p=NS) LBR: (30.7 % vs. 29.1 %; p=NS) MPR: (41.6 % vs. 42.8 %; p=NS)
Siristatidis <i>et al.</i> <sup>[21]</sup>	Athens, Greece	February 2012 to June 2017, median age: 36 (25-40) vs. 35 (22-40) y	Multicentral cohort study, N=230 (133 vs. 97)	Age 25-40 y History of ≥2 failed IVF/ICSI. Body Mass Index (BMI) 35 and 19, basal FSH 12 mIU/ml Poor ovarian response NO coagulation and/or autoimmune disorders primary or secondary subfertility	History of endocrine or metabolic disorders, ovarian cystectomy or oophorectomy, abnormal endometrial cavity and/or receptivity. Hereditary or acquired thrombophilia	Hormonal treatment, enoxaparin sodium 3500 IU/d up to the 3 <sup>rd</sup> trimester of pregnancy if the test was positive	CPR, LBR, MR in treated vs. controls	CPR: (24.8 % vs. 20.6 %; p=0.456) LBR: (17.3 % vs. 14.4 %; p=0.560) MR: (11.3 % vs. 9.3 %; p=0.624)
Lodigiani <i>et al.</i> <sup>[22]</sup>	Milan, Italy	November 2011 to December 2015, age groups: ≤35 y: 36.3 % vs. 37.4 %; 36-38 y: 40.7 % vs. 39.7 %; 39-40 y: 22.9 % vs. 23 %	Prospective randomized controlled trial, N=266 (135 vs. 131)	Age: ≤40 and ≥18 y fresh IVF cycle. Absence of severe thrombophilia no hormonal/autoimmune disorders	Severe thrombophilia, hormonal or autoimmune or haematological disorder, contraindication for heparin chronic treatment with acetylsalicylic acid or steroids	Hormonal treatment, parnaparin sodium 4250 anti-Xa IU/0.4 ml and 6400 anti-Xa IU/0.6 ml for the whole cycle	CPR, LBR, MR in treated vs. controls	CPR: (21.5 % vs. 26.7 %; p=0.389) LBR: (18.5 % vs. 20.6 %; p=0.757) MR: (10.3 % vs. 22.9 %; p=0.319)

**Conflict of interests:**

The authors declared no conflict of interests.

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