Aspirin and heparin as adjuvants during IVF do not improve live birth rates in unexplained implantation failure

Muhammad A Akhtar a,b, Hanan Eljabu a, James Hopkisson a, Nick Raine-Fenning a, Siobhan Quenby b, Kannamannadiar Jayaprakasan a,c,*

Abstract This study tested the hypothesis that using aspirin and/or heparin as adjuvants in IVF improves the treatment outcome. This retrospective cohort–control study recruited 234 consecutive subjects aged ≤44 years who had previously had one or more unsuccessful IVF cycle. All underwent IVF using conventional protocols. The study group received aspirin and/or heparin post embryo transfer until the day of pregnancy test or until 12 weeks of pregnancy. The control group did not receive adjuvant treatment. The outcome measures were live birth, clinical pregnancy and miscarriage rates. The outcomes were compared by chi-squared test and relative-risk analysis. Analysis was performed in 206 subjects. There was no statistically significant difference in the live birth rate (35.0%, 36/103 versus 47.6%, 49/103), clinical pregnancy rate (40.8%, 42/103 versus 53.4%, 55/103) and miscarriage rate (14.3%, 6/42 versus 10.9%, 6/55) between the study group and the control group. The data in this study show that low-dose aspirin and/or heparin as adjuvant therapies during IVF do not improve live birth rates in an unselected group of subfertile women who have previously had one or more unexplained implantation failure following IVF.

© 2013, Reproductive Healthcare Ltd. Published by Elsevier Ltd. All rights reserved.

KEYWORDS: aspirin, endometrium, heparin, implantation, in-vitro fertilization, pregnancy

Please cite this article in press as: Akhtar, MA et al. Aspirin and heparin as adjuvants during IVF do not improve live birth rates in unexplained implantation failure. Reproductive BioMedicine Online (2013), http://dx.doi.org/10.1016/j.rbmo.2013.02.007
Introduction

Assisted reproduction treatment has provided a successful treatment for subfertile couples. However, its efficacy in terms of the live birth rate has remained relatively constant, showing only gradual improvements over the years (Andersen et al., 2007). The rate-limiting step appears to be embryo implantation, which is a complex process dependent upon many variables, most of which have not been adequately understood. Implantation happens during a time-limited stage called the window of implantation. This involves multiple interactions between the embryo and the endometrium, including trophoblast development, expression of numerous molecules and cytokines that play important part in apposition and interaction and invasion of the embryo into the endometrium.

Failure of implantation in couples undergoing assisted reproduction is a relatively common occurrence despite the transfer of top-quality embryos (Qublan et al., 2006; Stern et al., 2003). The most important cause of recurrent IVF failure is unsuccessful embryo implantation. While over 80% of the couples enrolled in an IVF or intracytoplasmic sperm injection (ICSI) programme reach the phase of embryo transfer, implantation fails to occur in about 60% of women (Martinelli et al., 2003). Implantation failure has been attributed to many factors; however, for most, the causal relationship is not established.

The Cochrane review ‘Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant’ (Empson et al., 2005) suggested that combined unfractionated heparin and aspirin may reduce pregnancy loss by 54%. This finding of a potential reduction in pregnancy loss led to the clinical interpretation that treatment with antithrombotic agents was beneficial to early pregnancy. This meta-analysis was interpreted by many clinicians as suggesting that aspirin and heparin have a similar beneficial effect in women with idiopathic reproductive failure (Empson et al., 2005). However, this interpretation has been put in doubt because a recent blinded randomized controlled trial in women with history of recurrent miscarriage suggested that low-dose aspirin does not decrease the miscarriage rates (Kaandorp et al., 2010).

Prostanoids, primary mediators of inflammatory processes, have an important role in the early events of implantation and artificially induced decidualization (Kennedy et al., 2007). Prostanoids are disregulated in inflammatory-associated disorders of the endometrium (Catalano et al., 2011). Prostaglandin (PG) F2α, a member of the prostanoid bioactive lipid family, is secreted by human endometrium throughout the menstrual cycle and is present in both menstrual fluid and medium of endometrial explants in culture (Milne and Jabbour, 2003). Cyclo-oxygenase (COX) is a rate-limiting enzyme that converts arachidonic acid to PG and exists in two isoforms, COX1 and COX2. PG synthesis catalysed by COX1 is important for localized increased uterine vascular permeability and attachment reaction. PG produced at implantation by COX2 is involved in angiogenesis for the establishment of placenta. The uterine COX1 gene is influenced by ovarian steroids, while the COX2 gene is regulated by the implanting blastocyst during early pregnancy (Chakraborty et al., 1996). Low-dose aspirin acts by inhibiting COX inhibition and platelet aggregation thus reducing vasoconstriction. However, inhibition of COX is detrimental to decidualization, which is an important part of implantation. Aspirin, which suppresses COX, has the potential to interfere with implantation (James et al., 2008). Heparin, beyond its anticoagulant effects, may have a role in the complicated process of implantation (Bohmann, 2011; Fiedler and Wurfel, 2004; Nelson and Greer, 2008). A significant proportion of fertility units in the UK and abroad advise women to take low-dose aspirin and/or heparin following embryo transfer to improve the chance of embryo implantation, particularly in cases of repeated IVF failure. In a worldwide survey of IVF clinics on treatments offered for couples with reproductive failure, in the USA 78% of physicians offered aspirin alone, 47% offered heparin alone and 72% offered both aspirin and heparin, and in Australia 61% of physicians offered aspirin only, 22% offered heparin only and 73% offered both aspirin and heparin (Ghazeeri and Kutteh, 2001).

Several studies have examined the effect of aspirin/heparin on the outcome of assisted reproduction treatment in women with a failed IVF cycle and, despite the heterogeneity of these studies with regard to selection of participants and interventions, the evidence supporting the use of these therapies is still inconsistent (Check et al., 1998; Dirckx et al., 2009; Duvan et al., 2006; Kutteh et al., 1997; Lambers et al., 2009; Moini et al., 2007). The primary aim of this study was to investigate data from a tertiary fertility unit to see if there is any evidence that using low-dose aspirin with or without heparin as adjuvants in IVF treatment in women with history of at least one unexplained implantation failure improves implantation, clinical pregnancy and live birth rates.

Materials and methods

Experimental design

This retrospective cohort—control study was performed at the University of Nottingham’s assisted conception unit (Nottingham University Research and Treatment Unit in Reproduction, NURTURE). This study included subjects undergoing a fresh cycle of IVF or ICSI during the study period of January 2005 to September 2010. All subjects had experienced at least one unsuccessful IVF or ICSI cycle previously despite having had one or two embryo/s transferred. The study group included all subjects who received adjuvant treatment with low-dose aspirin with or without heparin from the day of embryo transfer. The control group was selected from those who did not receive any adjuvant treatment of low-dose aspirin with or without heparin during the study period. All subjects had a pre-treatment 3D transvaginal ultrasound assessment of pelvis and ovarian reserve and a blood test for estimation of their basal FSH and LH concentrations. Subjects were excluded if they were found to have any significant pelvic pathology such as fibroids, hydrosalpinx or uterine anomaly. Subjects were excluded if they were aged < 23 or > 44 years and if they did not reach embryo transfer because of failed fertilization. The participant flow diagram is shown in Figure 1. The study was approved by Institutional Review Board of NURTURE in May 2011 and the process of data extraction was done in consistent with data protection rules.
Adjuvant treatment with aspirin and heparin does not improve IVF outcome

**Figure 1** Flow chart of the study.

**Treatment protocol**

All participants underwent IVF/ICSI using a standard long, short or antagonist protocol depending on ovarian reserve tests and previous treatment response. The long protocol involved down-regulation with gonadotrophin-releasing hormone (GnRH) agonists (500 μg/day buserelin; Suprefact; Aventis Pharma, Kent, UK; or 800 μg/day nafarelin; Synarel; Pharmacia, Milton Keynes, UK) started in the mid-luteal phase of the menstrual cycle 7 days prior to the earliest expected date of menstruation. Two weeks later, following confirmation of pituitary desensitization, defined as an endometrial thickness of <5 mm and no ovarian activity evident on transvaginal ultrasound in association with an oestradiol concentration <200 pmol/l, ovarian stimulation was commenced. The short protocol involved commencing GnRH agonists and ovarian stimulation on day 1 and day 2 of the menstrual cycle respectively. In the antagonist protocol, ovarian stimulation with gonadotrophins was commenced on day 2 of the menstrual cycle with antagonists (0.25 mg of Cetrorelix; Cetrotide; Merck Serono) introduced from day 5 of ovarian stimulation. The starting daily doses of gonadotrophins (recombinant FSH or human menopausal gonadotrophin) were introduced from day 5 of ovarian stimulation with gonadotrophins was commenced on day 2 of the menstrual cycle with antagonists (0.25 mg of Cetrorelix; Cetrotide; Merck Serono) introduced from day 5 of ovarian stimulation. The starting daily doses of gonadotrophins (recombinant FSH or human menopausal gonadotrophin) were 150 IU for women aged less than 30 years, 225 IU for 30-38 years age group or 300 IU for those aged above 38 years, ovarian reserve test and previous treatment outcome.

Subjects were monitored for follicular recruitment and growth by serial transvaginal ultrasound and serum oestradiol measurements from day 5 or 6 of stimulation. Human chorionic gonadotrophin (HCG; 6500 IU Ovitrelle; Merck Serono Pharmaceuticals, Feltham, UK) was administered when there were three follicles measuring ≥18 mm in diameter, and oocyte retrieval was performed 36 h later. Transvaginal ultrasound-guided oocyte retrieval was performed under sedation or general anaesthesia. The oocytes obtained were fertilized by IVF or ICSI dependent on previous seminal fluid analyses and the quality of the spermatozoa obtained on the day of oocyte retrieval. For participants with partners considered to have normal seminal fluid parameters, IVF was performed by incubating collected oocytes in groups of five in a sperm suspension containing 150,000 spermatozoa/mL and the meiotic stage of oocytes assessed by the embryologists 18–20 h post insemination.

For participants having ICSI, the meiotic maturity was assessed after denudation and only mature oocytes were injected with a spermatozoon following its immobilization. Fertilization as determined by the presence of two pronucleoli was assessed at 18–20 h post insemination. A maximum of two embryos were transferred into the uterus 2, 3 or 5 days after oocyte retrieval. Single-embryo transfer was discussed and offered to all participants in line with the study centre’s normal practice. Luteal support using progesterone pessaries (Cyclogest pessaries; Shire Pharmaceuticals, Basingstoke, UK) 400 mg twice a day vaginally was provided from the day of embryo transfer and serum HCG concentration was measured 16 days later to determine the outcome. If the test was positive (HCG >50 IU/l), a transvaginal ultrasound was arranged 3–4 weeks later to confirm the viability of the pregnancy (clinical pregnancy). A repeat ultrasound scan was performed at 12 weeks of gestation to ensure that the pregnancy remained viable (ongoing pregnancy). All pregnant subjects were followed up to know the eventual outcome of their pregnancies. Live birth was defined as a viable infant born after 24 weeks of gestation. Miscarriage rate was calculated as the proportion of clinical pregnancy loss occurring before 24 weeks of gestation.

Subjects in the case group took aspirin (Bayer-Schering Pharma, UK) 75 mg orally per day and/or heparin (clexane; Sanofi-Aventis, Surrey, UK) 20 mg subcutaneously daily from the day of embryo transfer until the day of pregnancy test. Aspirin and/or heparin were continued in pregnant subjects until 12 weeks of pregnancy.

**Statistical analysis**

Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The distribution of the data was checked for normality by the application of the Kolmogorov–Smirnov statistic test. The demographic data and the outcome data of the two groups were compared by Student’s t-test or Mann–Whitney U-test for continuous variables dependent on the statistical distribution of the data. Chi-squared test or Fisher’s Exact text was used for comparing the dichotomous variables. The primary outcome was live birth rate. Secondary outcomes included the miscarriage rate and the clinical and on-going pregnancy rates.

**Results**

The study and control groups had comparable demographic characteristics, markers of ovarian reserve and causes and type of infertility (Table 1), suggesting that the confounding factors thought to influence the outcome of IVF treatment were matched.

The comparison of stimulation characteristics and embryological data are given in Table 2. The only statistically significant differences between the treatment and control groups were the numbers of mature oocytes and fertilized oocytes, favouring the treatment group.

The primary and secondary outcomes are shown in Table 3. The pregnancy and live birth rates were statistically similar between the two groups. However, when absolute values were compared, there was 12.6% difference
in live birth rate favouring the control group, although this difference was not statistically significant.

A subgroup analysis was performed by categorizing the treatment group into low-dose aspirin only, heparin only and both low-dose aspirin and heparin (Table 4). There were no statistical differences in any of the outcome variables compared with the control group. However, there is a non-significant decrease in the clinical pregnancy and live birth rates in the treatment groups. There were no side effects reported specifically related to the use of aspirin and/or heparin (gastrointestinal upset, bleeding tendency, hypersensitivity and congenital anomalies).

**Discussion**

The data in this study indicate that low-dose aspirin and/or heparin as adjuvant treatment during IVF for women who have had at least one previous implantation failure following IVF/ICSI does not offer any advantage in terms of improving the live birth or pregnancy rates. Although the difference was not statistically significant, the live birth rate was 12.6% lower in the treatment group than the control group. While it is difficult to conclude that adjuvant treatment with aspirin and/or heparin is detrimental to implantation following IVF, it certainly does not appear to improve the treatment outcome in an unselected subfertile population in whom the immunological status for thrombophilia and antiphospholipid antibody syndrome are not known. A positive effect of aspirin and/or heparin may potentially have been masked with generalized absence of immune test abnormalities in this study population, but in those with normal or unknown immunological status, treatment may actually reduce success, as the data from this study seem to suggest.

Traditionally, low-dose aspirin is thought to increase uterine blood flow and so improve implantation in early pregnancy. This came from the hypothesis that an adequate uterine blood supply appears to be an important determinant of endometrial receptivity during natural conception and after assisted conception treatment. In theory, use of aspirin in IVF is based on its anti-inflammatory, vasodilatory and platelet aggregation inhibition properties, which postulated that this effect on blood flow will improve success rates (Schisterman et al., 2009). However, low-dose aspirin also inhibits COX enzymes involved in the synthesis of
prostanoids, which are important components of implantation and decidualization; hence inhibiting them may reduce pregnancy rates (James et al., 2008). Raine-Fenning (2008) used quantitative three-dimensional power Doppler angiography at the time of implantation and results showed a fall in endometrial and subendometrial blood flow at the time of implantation in women with unexplained subfertility and controls. Such vascular changes may be associated with local hypoxia and there is evidence to support a beneficial role for this during implantation in humans (Na et al., 2012). Relatively low oxygen values are present around the blastocyst while it implants. So low-dose aspirin as an adjunct to assisted reproduction may increase uterine blood flow, which could potentially result in unsuccessful implantation.

Heparin is also thought to help improving implantation process. Heparin increases various growth factors involved in implantation e.g. insulin-like growth factor-I, interleukins 2 and 6 and heparin-binding epidermal growth factor.

Table 2  Comparison of ovarian stimulation and embryological data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 103)</th>
<th>Treatment group (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long</td>
<td>97 (94.2)</td>
<td>99 (96.1)</td>
</tr>
<tr>
<td>Short</td>
<td>4 (3.9)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Antagonist</td>
<td>2 (1.9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Starting dose (IU)</td>
<td>281.1 ± 85.8 (150–450)</td>
<td>277.0 ± 95.6 (112.5–450)</td>
</tr>
<tr>
<td>Duration of stimulation (days)</td>
<td>10.9 ± 1.3 (9–15)</td>
<td>10.7 ± 1.3 (9–13)</td>
</tr>
<tr>
<td>Total dose used (IU)</td>
<td>3042.9 ± 1046.4</td>
<td>2897.6 ± 1106.1</td>
</tr>
<tr>
<td>Endometrial thickness on the day of HCG (mm)</td>
<td>11.5 ± 1.7 (6.2–16.5)</td>
<td>11.9 ± 2.7 (6–23)</td>
</tr>
<tr>
<td>No. of follicles aspirated</td>
<td>13.8 ± 7.3 (3–40)</td>
<td>15.1 ± 7.6 (3–44)</td>
</tr>
<tr>
<td>Total oocytes retrieved</td>
<td>11.9 ± 9.2 (2–81)</td>
<td>11.9 ± 5.9 (2–34)</td>
</tr>
<tr>
<td>Mature oocytes(^a)</td>
<td>9.1 ± 4.9 (2–23)</td>
<td>10.5 ± 5.2 (1–29)</td>
</tr>
<tr>
<td>Fertilized oocytes(^b)</td>
<td>6.2 ± 4.4 (1–31)</td>
<td>7.6 ± 4.8 (1–29)</td>
</tr>
<tr>
<td>No. of embryo transfers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective single-embryo transfer</td>
<td>13 (12.6)</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Double-embryo transfer</td>
<td>89 (86.4)</td>
<td>91 (88.3)</td>
</tr>
<tr>
<td>Triple-embryo transfer</td>
<td>1 (1.0)</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>Quality of embryo(s) transferred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Top quality</td>
<td>78 (75.7)</td>
<td>72 (69.9)</td>
</tr>
<tr>
<td>Low quality</td>
<td>25 (24.3)</td>
<td>31 (30.1)</td>
</tr>
<tr>
<td>Day of embryo transfer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>55 (53.4)</td>
<td>49 (47.6)</td>
</tr>
<tr>
<td>3</td>
<td>13 (12.6)</td>
<td>10 (9.7)</td>
</tr>
<tr>
<td>5 (blastocyst)</td>
<td>35 (34.0)</td>
<td>44 (42.7)</td>
</tr>
</tbody>
</table>

Values are mean ± SD (range) or n (%).
\(^a\)P = 0.02.
\(^b\)P = 0.01.

Table 3  Comparison of pregnancy outcomes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 103)</th>
<th>Treatment group (n = 103)</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical pregnancy</td>
<td>58 (56.3)</td>
<td>48 (46.6)</td>
<td>0.82 (0.63–1.08)</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>55 (53.4)</td>
<td>42 (40.8)</td>
<td>0.76 (0.56–1.02)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>6 (10.9)</td>
<td>6 (14.3)</td>
<td>1.31 (0.45–3.8)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00 (0.02–49.92)</td>
</tr>
<tr>
<td>On-going pregnancy</td>
<td>49 (47.6)</td>
<td>36 (35.0)</td>
<td>0.73 (0.52–1.02)</td>
</tr>
<tr>
<td>Live birth</td>
<td>49 (47.6)</td>
<td>36 (35.0)</td>
<td>0.73 (0.52–1.02)</td>
</tr>
</tbody>
</table>

Values are n (%) unless otherwise stated. There were no statistically significant differences between the two groups.
enhance interleukin-11-mediated STAT3 activation (Bohlmann, 2011; Fluhr et al., 2010; Nelson and Greer, 2008) thus altering the physiological processes of implantation and trophoblast development. Heparin is also protective against trophoblast apoptosis. There is a Cochrane review (Akhtar et al., 2011) underway which is aimed at evaluating the efficacy of heparin in assisted reproduction.

The literature on the effect of adjuvant therapies with aspirin and/or heparin on IVF treatment is conflicting. While some studies suggested beneficial effects, others reported a lack of improvement with the outcome of IVF treatment. Rubinstein et al. (1999) reported that uterine blood flow, ovarian response, implantation rate and pregnancy rate were significantly improved when participants received 100 mg low-dose aspirin daily. Weckstein et al. (1997) illustrated that using low-dose aspirin among selected women with oocyte donation and thin endometrium improved uterine blood flow and implantation and clinical pregnancy rates. Waldenstrom et al. (2004) reported that using 75 mg aspirin from day of embryo transfer among unselected patients improved the live birth rate (27% versus 23%) but this was not statistically significant. Urman et al. (2000), investigating the effect of low-molecular-weight heparin (LMWH) starting from the luteal phase of the previous cycle among selected group of patients (unexplained recurrent implantation failure with no evidence of thrombophilia), reported that a trend towards improving the implantation and live birth rates. Sher et al. (1994) suggested that there was a higher rate of clinical pregnancies in antiphospholipid antibody-positive women receiving aspirin and heparin. Urman et al. (2009) reported on a randomized pilot study involving 150 women with a history of at least two IVF/ICSI failures without evidence of thrombophilia. The live birth rates in the LMWH and control groups were 34.7% and 26.7% respectively. While there was a lack of statistical significance, the authors reported the relative increase of 30% in live birth rate observed with LMWH may be regarded as a clinically significant trend necessitating further research on the use of empirical LMWH in IVF. They concluded that the lack of statistical significance in their study might have been due to low statistical power associated with the small sample size.

A meta-analysis of 10 randomized controlled studies published in 2008 showed that the clinical pregnancy rate per embryo transfer was significantly high comparing low-dose aspirin with no treatment (relative risk 1.15, 95% CI 1.03–1.27). The authors suggested that more data are needed to resolve the issue of beneficial effects of aspirin. So it was advised that there is no reason to change clinical management and discontinue the use of low-dose aspirin (Ruopp et al., 2008). However, the same group published a review (Schisterman et al., 2009) that reported that conflicting results leave the question of the effects of low-dose aspirin in IVF still unanswered. More trials are required for analysis to have adequate statistical power and until then the data remain unclear. There is not enough data to show that aspirin has a beneficial effect on the outcomes of IVF, but an absence of effect is not adequate grounds to overturn the current clinical practice for those using low-dose aspirin in efforts aimed at achieving success with IVF (Ruopp et al., 2008; Schisterman et al., 2009). Heparin with low-dose aspirin improves pregnancy outcome in patients with antiphospholipid antibody-associated recurrent pregnancy loss to a greater extent than low-dose aspirin alone (Kutteh, 1996; Rai et al., 1997). Low-dose aspirin did not improve pregnancy outcome in women with recurrent miscarriages either with or without detectable antecedent antibodies (Tulppala et al., 1997). A systematic review and meta-analysis of seven randomized controlled trials including 2053 women undergoing IVF (Hornstein et al., 2000) reported that women positive for antiphospholipid antibodies had live birth rate of 49.2%, Clinical pregnancy rate of 57.0% while women negative for antiphospholipid antibodies of live birth rate of 42.9%, clinical pregnancy rate of 46.0%. It concluded that there was no significant association between antiphospholipid abnormalities and either clinical pregnancy (OR 0.99; 95% CI 0.64–1.53) or live birth (OR 1.07; 95% CI 0.66–1.75) in IVF patients. The measurement of antiphospholipid antibodies is not warranted in patients undergoing IVF. A recent retrospective study (Steinivt et al., 2012) reported similar results that thrombophilia screening is not warranted in unexplained reproductive failure as it does not improve outcome.

Table 4 Subgroup analysis of the treatment group, comparing controls with low-dose aspirin only, heparin only and both low-dose aspirin and heparin.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 103)</th>
<th>Aspirin only (n = 43)</th>
<th>Heparin only (n = 18)</th>
<th>Both aspirin and heparin (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>RR (95% CI)</td>
<td>n (%)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Biochemical pregnancy</td>
<td>58 (56.3)</td>
<td>22 (51.2) 0.91 (0.64–1.27)</td>
<td>7 (38.9) 0.69 (0.37–1.2)</td>
<td>19 (45.2) 0.80 (0.55–1.16)</td>
</tr>
<tr>
<td>Clinical pregnancy</td>
<td>55 (53.3)</td>
<td>18 (41.9) 0.78 (0.52–1.16)</td>
<td>7 (38.9) 0.73 (0.39–1.33)</td>
<td>17 (40.5) 0.76 (0.50–1.14)</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>6 (10.9)</td>
<td>2 (11.1) 1.02 (0.23–4.6)</td>
<td>0 (0) 0.54 (0.03–8.7)</td>
<td>4 (23.5) 2.16 (0.69–6.8)</td>
</tr>
<tr>
<td>On-going pregnancy</td>
<td>49 (47.6)</td>
<td>16 (37.2) 0.78 (0.50–1.2)</td>
<td>7 (38.9) 0.82 (0.44–1.50)</td>
<td>13 (31.0) 0.65 (0.39–1.06)</td>
</tr>
<tr>
<td>Live birth</td>
<td>49 (47.6)</td>
<td>16 (37.2) 0.78 (0.50–1.2)</td>
<td>7 (38.9) 0.82 (0.44–1.50)</td>
<td>13 (31.9) 0.65 (0.39–1.06)</td>
</tr>
</tbody>
</table>

No statistically significant differences were found.
Two meta-analyses (Gelbaya et al., 2007; Khairy et al., 2007) and a Cochrane review (Siristatidis et al., 2011) suggested that use of empirical low-dose aspirin for women undergoing in vitro fertilization in order to improve pregnancy outcome cannot be recommended due to lack of evidence. In a recently published update of this Cochrane review (Siristatidis et al., 2012) suggested that there was no evidence of difference in live birth rate (relative risk 0.91, 95% CI 0.72–1.15) and clinical pregnancy rate (relative risk 1.03, 95% CI 0.91–1.17) between treatment and control groups. The authors of the update of Cochrane review recommended that, in order to demonstrate a 10% improvement from the use of aspirin, a sample size of 350 women in each group would be required. A recent published meta-analysis of individual patient data (Groeneveld et al., 2011) of 10 randomized controlled trials suggest that low-dose aspirin does not improve pregnancy rates after IVF: 28.8% clinical pregnancies in the low-dose aspirin group compared with 31.9% in the placebo group (OR 0.86, 95% CI 0.69–1.1) and 23.6% ongoing pregnancies in the aspirin group compared with 26.7% in the placebo group (OR 0.85, 95% CI 0.65–1.1).

There is heterogeneity among these studies, which might explain the most likely reasons behind the varying results. There is a wide variation in the time of commencement of adjunct therapies in relation to embryo transfer, whether the therapy is given alone or in combination with other medications such as immunoglobulin or prednisolone or any other adjuvants. The study populations are also different in these studies, so that some studies were on an unselected population while others selected groups of patients, such as those positive for antiphospholipid syndrome or those who had recurrent miscarriages or recurrent implantation failure with assisted reproduction.

While aspirin is generally safe with no evidence of an overall increase in congenital malformations, aspirin exposure during first trimester of pregnancy could carry an increased risk of gastrochisis or cleft lip and palate in the fetus (Kozer et al., 2002). There is conflicting evidence over empirical low-dose aspirin during first trimester of pregnancy could carry an increased risk of gastroschisis or cleft lip and palate in the fetus (Kozer et al., 2002). There is conflicting evidence over the therapeutic potential of aspirin in the prevention of early miscarriage. Two studies (Nielsen et al., 2001 and Li et al., 2003) reporting increased risk of miscarriage included women taking non-steroidal anti-inflammatory drugs including aspirin rather than only those taking specifically aspirin in the study group, another two studies (Coomarasamy et al., 2003; Dirckx et al., 2009) evaluating women taking aspirin alone reported similar miscarriage rates between the study and control groups. However, certain reports of an increased risk of early trimester miscarriage (Li et al., 2003) and on higher ectopic pregnancy rates (Urman et al., 2000) cause some concern over on periconception use of aspirin and there is need for further evaluation on this issue. However, reassuringly, in the present study, there were no side effects specifically related to the use of aspirin and/or heparin (gastrointestinal upset, bleeding tendency and hypersensitivity). Further, the miscarriage rate was not significantly different between the treatment and control groups, nor was there any reported case of ectopic pregnancy or congenital anomalies.

This study looked at comprehensive data of 5 years at a university teaching hospital in the UK. It is a common practice that clinicians prescribe low-dose aspirin with or without heparin in subsequent IVF cycles with previous failed implantation. The participants in this study were from the general population. The participants were not tested for immunological factors (e.g. antiphospholipid antibodies, lupus anticoagulant) because it is not cost effective to routinely screen every woman after just one implantation failure. However, one of the limitations of the study apart from its retrospective nature is that the sample sizes were small, which may possibly have influenced the ability to detect minor differences in the outcomes. Because this study is also limited to an unselected population with unknown immunological status, a better diagnosis for reasons of implantation failure is required before planning further studies to examine the effect of adjuvant treatment in a selected population of positive and negative test results.

In conclusion, this study revealed that the empirical use of low-dose aspirin and/or heparin as an adjuvant treatment during IVF does not improve live birth rate in an unselected group of subfertile women who had previously had one or more previous implantation failure and had not had immunological screening for thrombophilia and antiphospholipid antibody syndrome. Additionally, in agreement with other studies, there was a non-significant trend towards reducing the clinical pregnancy as well as the live birth rate in the treatment group, which suggests that these adjuvant therapies in vulnerable groups of patients should be stopped unless in a research setting. Couples undergoing IVF are often desperate enough to try any interventions to boost their fertility performance, even without an evidence base. Testing any prescribed pharmacological compound is mandatory so that potential benefits and risks can be clearly presented to both clinicians and patients, and it is fertility units’ ethical responsibility to provide couples with evidence-based treatment.

References


Tulppala, M., Marttunen, M., Söderstrom-Anttila, V., Foudila, T., Allius, K., Palouso, T., Ylikorkala, O., 1997. Low-dose aspirin in...
prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. Hum. Reprod. 2, 1567–1572.


Web references


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

Received 11 October 2012; refereed 6 February 2013; accepted 7 February 2013.