Ultrasound-guided hydrosalpinx aspiration during oocyte collection improves pregnancy outcome in IVF: a randomized controlled trial

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BACKGROUND: Hydrosalpinges have adverse effects on IVF outcomes. Salpingectomy is effective in improving outcomes, but it is not always practical or safe. Ultrasound-guided aspiration of hydrosalpinges at oocyte collection is an option for those who develop hydrosalpinges during controlled ovarian stimulation; however, there is no randomized evidence to show whether this practice is effective. METHODS: Between October 1999 and June 2003, consenting women of age ≥39 years with an ultrasound diagnosis of hydrosalpinx were randomized before oocyte collection to transvaginal aspiration of hydrosalpinx under antibiotics cover or no aspiration. Third-party randomization was performed using a computer algorithm, and allocation concealment was achieved with opaque sealed envelopes. Outcomes were biochemical and clinical pregnancies, implantation, spontaneous abortion, ectopic pregnancy and pelvic infection rates. Analysis was by intention to treat. RESULTS: Sixty-six women were recruited to the trial, 32 to the aspiration group and 34 to the no-aspiration group. Aspiration resulted in a greater biochemical pregnancy rate [14/32 (43.8%) versus 7/34 (20.6%), relative risk (RR) = 2.1 (1.02, 4.6), P = 0.04]. Clinical pregnancy rates for aspiration versus control groups were 31.3% (10/32) and 17.6% (6/34), respectively [RR = 1.8 (0.8, 4.3), P = 0.20]. There were no changes in implantation rate or spontaneous abortion risk with aspiration and no differences between the groups in infection or ectopic pregnancy rates. CONCLUSIONS: In women who are identified to have hydrosalpinges during controlled ovarian stimulation during IVF, aspiration of hydrosalpinges during oocyte collection may be effective in improving pregnancy rates (Trial Registration Number: NCT00566956).

Keywords: IVF; hydrosalpinx; aspiration; oocyte collection; pregnancy

Introduction

IVF was first developed to overcome the mechanical obstruction of Fallopian tubes in infertile women (Steptoe and Edwards, 1978). Tubal disease was and still is one of the major indications for IVF treatment. However, patients with severe tubal damage have poor outcome after IVF treatment (Vasquez et al., 1995; Csemiczky et al., 1996). Hydrosalpinx, one of the more severe manifestations of tubal disease, is associated with significantly lower implantation and pregnancy rates when compared with patients who have minimal tubal damage (Strandell et al., 1994; Vandromme et al., 1995; Fleming and Hull, 1996). Additionally, some reports have suggested that spontaneous abortions and ectopic pregnancy rates are increased in those with hydrosalpinges (Andersen et al., 1994; Kassabji et al., 1994; Ng et al., 1997).

A Cochrane review has summarized the randomized trials of laparoscopic salpingectomy on reproductive outcome, showing an increase in the odds of pregnancy, ongoing pregnancy and live birth following laparoscopic salpingectomy prior to IVF (Johnson et al., 2002). However, laparoscopic or open salpingectomy is not always safe or feasible, especially when there are dense pelvic adhesions. Moreover, some studies show that salpingectomy could have a negative effect on the ovarian blood flow and subsequently reduced ovarian response to gonadotrophin stimulation (Lass et al., 1998; Dechaud and Hedon, 2000). On occasions, a clinician may also be faced with the situation of identifying a hydrosalpinx for the first time in the period
before oocyte collection, after IVF treatment had been commenced. In these situations, vaginal aspiration of the hydrosalpinx fluid (HSF) may be an alternative to salpingectomy. Vaginal ultrasound-guided aspiration of HSF is the simplest method of treating hydrosalpinges. However, the literature on this intervention is limited to two small non-randomized retrospective observational studies, which show inconclusive results (Sowter et al., 1997; Van Voorhis et al., 1998). We, therefore, carried out a randomized controlled trial on the effects of ultrasound-guided HSF aspiration of ultrasonically diagnosed hydrosalpinx during oocyte collection on IVF outcome.

Materials and Methods
This is a prospective randomized controlled trial that was conducted in the Assisted Conception Unit (ACU) of Birmingham Women’s Hospital, UK. This study was approved by the South Birmingham Local Research Ethics Committee (LREC reference number 0288). Recruitment started in October 1999 and finished in June 2003. Informed consent was obtained from patients fulfilling the inclusion criteria for the study.

Eligibility and recruitment
Healthy women ≤39 years of age were recruited to the trial if they reached the stage of oocyte collection during IVF or ICSI treatment, and had unilateral or bilateral hydrosalpinges ultrasonically identified during the phase of ovarian stimulation. Patients seen on the ninth day of ovarian stimulation who fulfilled the inclusion criteria had the study explained to them and counselled by doctor. This was supplemented by a patient information leaflet. Explanations of the adverse effect of hydrosalpinx on IVF outcome and the rationale of HSF aspiration, as well as other alternative interventions such as prophylactic salpingectomy, were provided. We also discussed the substantial existing evidence of benefit for salpingectomy and the theoretical possibility of a flare-up of old pelvic infection after aspiration. As there was a long waiting list at Birmingham Women’s Hospital for non-life-threatening surgery, patients who were on the waiting list for salpingectomy were also eligible for our trial.

Randomization
Patients eligible for the trial were randomly allocated before transvaginal oocyte collection to aspiration (intervention) group or no-aspiration (control) group. Randomization was conducted by a third-party administrator using a computer algorithm. Concealment of allocation was achieved by opaque sealed envelopes containing the name of the assigned treatment on a card. Owing to the surgical nature of the interventions, blinding of the participants or clinicians was not possible. As the outcomes were objective measures, we felt it was not necessary to blind the outcome assessor. The study administrator entered the patient’s name, number and assigned treatment on a special study form, which was later given to the doctor to insert in the patient’s notes.

Interventions
For those assigned to the aspiration group, the hydrosalpinx was aspirated after all the oocytes had been collected, under deep sedation. Under ultrasound-guidance, the aspiration needle was inserted into the hydrosalpinx and suction applied until no further fluid could be obtained, and complete drainage was confirmed with transvaginal ultrasound scan (TVS). If there were bilateral hydrosalpinges, the process was performed on both sides, using separate sterile needles on each side to avoid contamination of the contralateral adnexae.

The HSF was sent for microbiological examination for culture and sensitivity. Intra-operatively, the patient was given i.v. augmentin 1.2 g (amoxicillin 1 g, and clavulanic acid 200 mg) and following the procedure the patient was prescribed oral azithromycin 500 mg daily for three days. Those allergic to penicillin were given metronidazole 400 mg thrice daily for 5 days and azithromycin 500 mg daily for 3 days. Patients assigned to the non-aspiration group did not have the hydrosalpinges aspirated. IVF protocols used at the ACU at Birmingham Women’s Hospital have been described in detail elsewhere (Hughes et al., 1992).

Outcomes
The primary outcome measures were biochemical (urinary HCG test performed 14 days after embryo transfer) and clinical (presence of gestational sac by TVS) pregnancy rates per randomized woman. Secondary outcome measures were implantation rate (number of gestational sacs visible on ultrasound divided by the number of embryos transferred), first trimester spontaneous abortions (any pregnancy loss before 12 weeks gestation), pelvic infection (diagnosed as pelvic-abdominal pain and tenderness associated with pyrexia or positive culture of genital swabs) and ectopic pregnancy rates.

Statistical analysis
The pregnancy rate per oocyte collection procedure in tubal disease patients (excluding hydrosalpinx) at the ACU at Birmingham Women’s Hospital varies between 35% and 40%. It is known from the literature that the pregnancy rate is halved in the presence of hydrosalpinx (Camus et al., 1999). Our aim was to evaluate whether TVS aspiration of hydrosalpinges during oocyte collection would restore the pregnancy rate to this level in patients without hydrosalpinges. The null hypothesis was that when compared with no aspiration, transvaginal aspiration of hydrosalpinges during oocyte collection did not improve clinical pregnancy rate.

Assuming that the pregnancy rate in patients with untreated hydrosalpinx is 20%, and the pregnancy rate in those who have the hydrosalpinx aspirated is 40% (doubling), the sample size (two-tailed alpha=0.05; beta=0.2) would be 158 patients or 79 per group. An audit of the eligible patients at the ACU suggested the study could be completed within 3 years. The targeted number of 158 cases was, however, not reached, as several patients opted for salpingectomy, which had been established to be effective in a large multicentre randomised trial (Strandell et al., 1999). Consequently, on the recommendation of the Data Monitoring Committee, the trial was stopped in July 2003, after nearly 4 years of concerted effort at recruitment. At this point, 66 patients had been randomized.

Baseline data and outcome data were separately summarized. For continuous variables, means and SDs, or medians and inter-quartile ranges, were provided as appropriate. Dichotomous outcomes were analysed using either Fisher’s exact test or chi-square. For continuous outcomes, we used t-test or Mann–Whitney U-test as appropriate. The analysis was by intention to treat.

Results
A total of 1220 women were assessed for eligibility to this trial, and 1154 were excluded for reasons given in Fig. 1. Thus, 66 women were randomized, 32 to aspiration group and 34 to the control group. Both groups were comparable in terms of age, aetiology of infertility, stimulation regimen, and number and quality of embryos transferred. Patient and cycle characteristics for both groups are presented in Table I. Of the 66 randomized women, 26 (39%) had hydrosalpinges diagnosed...
during controlled ovarian stimulation and 40 (61%) before the start of the treatment cycle. All randomized patients received their allocated treatment, and none was lost to follow-up or excluded from the analysis.

When rescanned 2–3 days after the aspiration, 3/26 (11.5%) showed the fluid re-accumulation; when scanned 14 days later, 8/26 (30.8%) had fluid re-accumulation. Out of the eight who had re-accumulated hydrosalpinges at 14 days after oocyte collection, three (3/8 = 38%) were pregnant (one biochemical and two clinical pregnancies). Of the other 18 (who did not have re-accumulation), seven (7/18 = 39%) were pregnant (one biochemical and six clinical). Thus, there does not appear to be a poorer prognosis in those with re-accumulation of hydrosalpinges, compared with those who did not, although given the very small samples in these groups, no firm inferences can be made. The aspirated HSF from all women in the aspiration group was sent to microbiology for culture and sensitivity. Out of 32 cases, in one case the HSF culture came back as positive to *Escherichia coli*. However, there were no cases of clinically manifested pelvic infection in both groups.

**Reproductive outcomes**

Biochemical pregnancy, clinical pregnancy, implantation, spontaneous abortion and ectopic pregnancy rates are presented in Table II. The biochemical pregnancy rate was significantly improved in the aspiration group [43.8% versus 20.6%, relative risk = 2.1 (1.02, 4.6) \( P = 0.04 \)]. There was an improvement in the clinical pregnancy and implantation rates, although these results did not reach statistical significance. The spontaneous abortion rate was reduced in the aspiration group but again did not reach statistical significance. There were no ectopic pregnancies in either group.

**Discussion**

As this trial was terminated before the required sample size was reached, the study is underpowered to examine the various trial end-points. Despite this fact, a significant difference in favour of aspiration was noted for the outcome of biochemical pregnancy, and non-significant results favouring aspiration was found for clinical pregnancy and other outcomes such as implantation and spontaneous abortion rates. As there appears to be potentially important imbalance in some prognostic factors between the two arms of the trial, we carried out a sensitivity analysis in which we adjusted for factors for which there are apparent important differences between the two groups (age, number of embryos transferred, cause of infertility, basal FSH and uni- or bi-laterality of the hydrosalpinges) using logistic regression. The findings of the adjusted analysis do not change the conclusions from the crude analysis.

Although the ideal would have been to conduct an adequately powered trial, the reality was that most patients preferred to have salpingectomy (after cancellation of the IVF cycle before oocyte collection), or opted directly to have aspiration of hydrosalpinx at oocyte collection, rather than being randomized to aspiration or no aspiration. To our knowledge, our study is the only randomized study of hydrosalpinx aspiration versus no aspiration, and it is also the largest, compared with the two existing retrospective studies (Sowter et al., 1997; Van Voorhis et al., 1998).

The exact mechanism for the association between hydrosalpinges and poor outcome in patients undergoing IVF is not yet clear. Many theories have been reported, including the embryotoxic effect, endometrial hostility, mechanical washout of embryos (Andersen et al., 1994; Fleming and Hull, 1996; Katz et al., 1996), and even the possibility of the HSF having a negative effect on oocyte development in early follicular recruitment (Freeman et al., 1998).
In the original study protocol, there was no plan to rescan this group of patients to assess for the re-accumulation of HSF following surgical drainage. However, this factor was brought to our attention after we started recruiting patients to the study, and the protocol was amended to take account of this. Twenty-six of the 32 in the aspiration group were rescanned 2–3 days later when patients came for embryo transfer and 14 days later after the oocyte collection when they attended the ACU for pregnancy test. We observed re-accumulation of HSF following surgical drainage in a substantial number of women. Such re-accumulation has been cited by many as to why hydrosalpinx aspiration cannot be expected to be effective. However, our study shows that the aspiration may offer a window of opportunity before which implantation can take place and pregnancy establish before re-accumulation becomes a substantial hindrance to pregnancy. However, our results do indicate that advance aspiration of hydrosalpinges well before oocyte collection are unlikely to be effective given that the hydrosalpinges had re-accumulated in as many as 30% of the aspirated group after 14 days of aspiration. Aboulghar et al. (1990) reported that HSF aspirated during the month before starting IVF did not improve the pregnancy rate significantly, although it led to greater ovarian response to controlled ovarian stimulation and higher numbers of embryos available for transfer.

There was no infectious morbidity associated with vaginal HSF aspiration as none of the 32 women developed acute pelvic inflammatory disease or peritonitis following the procedure. The only patient who had positive HSF culture (for E. coli) remained asymptomatic. It should be noted that all women in the aspirated group received prophylactic antibiotics to avoid a flare up of pelvic infection, whereas those in the control group did not routinely receive antibiotics. This may raise the issue of whether the improvements in outcome in the aspiration group were due to the aspiration or the antibiotics. We believe the results are unlikely to be linked to the antibiotics as there is randomized evidence to suggest antibiotics at oocyte collection or embryo transfer do not improve pregnancy outcome in the general IVF population (Brook et al., 2006). However, a retrospective analysis (Hurst et al., 2001) of 17 women with hydrosalpinges treated with doxycycline reported a high live birth rate of (8/17) 47%, suggesting antibiotics may have an effect in improving outcomes in women with hydrosalpinges, although the weak methods of this study do not allow one to make strong inferences.

In our study protocol, the patients who had aspiration of hydrosalpinges were given i.v. augmentin 1.2 g intra-operatively and oral azithromycin 500 mg daily for 3 days following the procedure. According to the current guidelines, an alternative to azithromycin 500 mg daily for 3 days could be azithromycin 1 g stat.

Contrary to the suggestion by Sowter et al. (1997) that the damage to the aspirated tube would leave the way open for the retrograde passage of transferred embryos which will increase the risk of ectopic pregnancy, our findings did not show any difference between the two groups in the ectopic pregnancy rate, although the intervention and control groups in our study were small and thus may have been underpowered to examine this outcome reliably. We did not have any difficulty aspirating the HSF from any of the patients, at least partly because all our patients underwent deep sedation for oocyte collection.

From this randomized study, we conclude that the ultrasound-guided transvaginal aspiration of HSF during oocyte collection for IVF treatment improves biochemical pregnancy rate, and may improve clinical pregnancy rate while reducing the spontaneous abortion rate. The re-accumulation of the fluid is unlikely to develop rapidly enough to prevent the implantation or pregnancy. We encourage clinicians to consider hydrosalpinx aspiration specifically when the hydrosalpinx diagnosis is made during IVF treatment.

### References


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