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Hydrosalpinges adversely affect implantation in donor oocyte cycles*

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Hydrosalpinges have been associated with poor in-vitro fertilization (IVF) outcome in some, but not all, studies, perhaps through endometrial effects. To determine whether hydrosalpinges affect IVF outcome via endometrial factors alone, we analysed the results of recipients of donor oocytes with hydrosalpinges, thereby controlling for confounding variables, while isolating the intrauterine environment. We retrospectively analysed 110 patients who underwent 121 donor oocyte cycles in a university-based assisted reproduction programme. Thirteen cycles involving recipients ($n = 10$) with hydrosalpinges were compared to 108 cycles involving recipients ($n = 100$) without hydrosalpinges. Pregnancy, implantation, miscarriage, and ectopic pregnancy rates were compared between women with and without hydrosalpinges. There were no significant differences between the hydrosalpinx and no hydrosalpinx groups with respect to donor age, recipient age, or number or grade of embryos transferred. Patients with a hydrosalpinx had significantly lower embryo implantation rates (7.1 versus 19.3%, $P < 0.05$) and significantly higher miscarriage (75.0 versus 14.9%, $P < 0.05$) and ectopic pregnancy rates (33.3 versus 0.0%, $P < 0.05$) than normal controls. We conclude that the presence of a hydrosalpinx adversely affects early pregnancy events by altering the intrauterine environment.

Key words: hydrosalpinx/implantation/in-vitro fertilization/oocyte donation

Introduction

Several studies have shown an association between the presence of a hydrosalpinx and poor in-vitro fertilization (IVF) outcome (Andersen *et al.*, 1994; Kassabji *et al.*, 1994; Strandell *et al.*, 1994; Vandromme *et al.*, 1995; Katz *et al.*, 1996; Fleming and Hull, 1996; Blazer *et al.*, 1997). Akman *et al.* demonstrated a similar effect in cryopreserved embryos as well (Akman *et al.*, 1996). Various theories have been proposed to explain this phenomenon. Sharara *et al.* suggested that chronic endometritis due to the same organism that caused the hydrosalpinx (i.e. *Chlamydia trachomatis*) leads to altered endometrial receptivity (Sharara *et al.*, 1996). Others proposed that the initial infection permanently damaged the endometrium (Strandell *et al.*, 1994). Mansour *et al.* postulated that reflux of fluid into the endometrial cavity could hinder implantation (Mansour *et al.*, 1991). Retrograde spillage may also be embryotoxic (Mukherjee *et al.*, 1996) or alter endometrial receptivity (Meyer *et al.*, 1997). Alternatively, ovarian stimulation increases the fluid volume within the Fallopian tube (Mansour *et al.*, 1991). Natural cycle IVF may decrease the fluid volume within the Fallopian tube and improve IVF success rates (Lindheim *et al.*, 1997). Furthermore, hydrosalpinges may secrete cytokines that adversely affect pregnancy outcome (Grifo *et al.*, 1989; Toth *et al.*, 1992), through reflux of fluid, or via haematogenous or lymphatic routes.

Prior studies examining the effect of hydrosalpinges on IVF cycles have employed autologous oocytes. Using a donor oocyte model we sought to control for confounding variables, such as ovarian and uterine senescence, male factor, embryo quality and number, and the ovarian stimulation protocol with its effect on the endometrium. In this manner we effectively isolated the intrauterine environment so as to analyse early implantation events more accurately.

Materials and methods

A retrospective analysis of cycles ($n = 13$) was performed in 10 patients with hydrosalpinges and normal semen analyses undergoing IVF with donated oocytes in a university-based assisted reproductive programme. The presence of a hydrosalpinx was determined using either transvaginal ultrasonography or hysterosalpingography. These patients were then compared to others undergoing IVF with donated oocytes without hydrosalpinges and normal semen analyses ($n = 100$; 108 cycles).

Oocyte donors underwent ovarian stimulation with follicle stimulating hormone (FSH) and were monitored by transvaginal ultrasound and serum oestradiol concentrations (Sauer, 1995). When the follicles reached 18–20 mm, human chorionic gonadotrophin (HCG) was given to trigger ovulation. Thirty-six hours later follicles were aspirated transvaginally under ultrasound guidance. The oocytes were then incubated with spermatozoa. Fertilization was documented, and resulting embryos were transcervically transferred after 2 or 3 days to the recipient's uterus. Recipients were carefully synchronized with the donors to ensure the endometrium was appropriately primed for implantation. Synchronization was achieved with exogenous oestrogen and progesterone supplementation. Nine and 12 days after embryo transfer the patient was tested for pregnancy with serum HCG.

The two study groups were analysed for donor and recipient age, number and grade of embryos transferred. Measured out-

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Table I. Results of donor oocyte in in-vitro fertilization cycles

	Hydrosalpinx	No hydrosalpinx
Number of patients	10	100
Number of embryo transfers	13	108
Pregnancy rate/embryo transfer (%)	46.2 (6/13)	45.4 (49/108)
Implantation rate/embryo transferred[a] (%)	7.1 (4/56)	19.3 (87/452)
Ongoing pregnancy rate/embryo[a] (%)	1.8 (1/56)	16.4 (74/452)
Ongoing pregnancy rate/embryo transfer[a] (%)	7.7 (1/13)	39.8 (43/108)
Ectopic rate/pregnancy[a] (%)	33.3 (2/6)	0.0 (0/87)
Miscarriage rate/implantation event[a] (%)	75.0 (3/4)	14.9 (13/87)

[a]P value < 0.05.

comes included gross pregnancy rates (a positive β-HCG) and ongoing pregnancy rates (a documented fetal heart rate), as well as implantation, miscarriage, and ectopic pregnancy rates. The embryo implantation rate included only known intrauterine pregnancies. The ongoing pregnancy rate included only intrauterine pregnancies progressing beyond 12 weeks gestational age.

Statistics were performed with the SPSS statistical package. χ^2 and Fisher's *t*-test were used. Significance was defined as a P value < 0.05.

Results

Results are shown in Table I. The hydrosalpinx group had a gross pregnancy rate similar to the group without hydrosalpinges. However, the implantation rate per embryo transferred in the hydrosalpinx group was significantly lower ($P < 0.05$) than the group without hydrosalpinges. Furthermore, the ectopic pregnancy rate and the miscarriage rate were significantly higher ($P < 0.05$) in women with hydrosalpinges. The ongoing pregnancy rate per embryo was significantly lower ($P < 0.05$) in those with hydrosalpinges as was the ongoing pregnancy rate per cycle. There were no significant differences between patients with hydrosalpinges and without hydrosalpinges related to donor age, recipient age, or number or grade of embryos transferred.

Discussion

In reviewing the data it is apparent that outcomes of donor oocyte cycles are negatively affected by the presence of a hydrosalpinx in the recipient. The initial pregnancy rates of the two groups studied were similar. However, women with hydrosalpinges had more ectopic pregnancies ($P < 0.05$), more miscarriages ($P < 0.05$), and a lower ongoing pregnancy rate ($P < 0.05$). All of these observations lessened the overall delivery rate of these patients, principally as a result of increased pregnancy wastage.

This study is unique in using a donor oocyte model to focus on the intrauterine environment. This model allows the dissociation of the donor's gametogenesis and steroidogenesis from the recipient's inherent endometrial receptivity and has been employed before to study isolated parameters that affect IVF outcome such as male factor (Gallardo *et al.*, 1996) and ovarian and uterine senescence (Sauer, 1997). Because extrauterine factors were controlled for in this study, the adverse events appear to be mediated through alterations of the recipient's intrauterine environment.

The early survival of embryos and their ability to express HCG does not appear to be impaired in our study. In fact the presence of two ectopic gestations in the hydrosalpinx group underscores the notion that the tubal fluid itself is not embryotoxic. Deleterious effects are most apparent after weeks of observation, not days, which may reflect chronic endometrial changes rather than acute embryotoxic causes.

In the past we encountered few recipients with hydrosalpinges. More recently the indications for donor IVF have been expanded to include poor responders (Remohi *et al.*, 1993) and failed IVF (Burton *et al.*, 1993). Thus, we are noting a larger percentage of hydrosalpinges in this population.

This study confirms the deleterious effects of hydrosalpinges on IVF pregnancy rates. This effect is noted after weeks and suggests a chronic rather than acute process, which may reflect a chronic alteration of the endometrium rather than an embryotoxic effect of the tubal fluid. In our practice, patients are offered salpingectomy to remove the source of the noxious fluid. Although Shelton *et al.* (Shelton *et al.*, 1996) have reported improved IVF outcome after salpingectomy, this approach still awaits controlled randomized trials to prove efficacy. Simply removing diseased Fallopian tubes may not reverse the chronic endometrial changes that lead to this phenomenon. Freeman *et al.* (Freeman *et al.*, 1998) also noted an improvement in pregnancy outcome after salpingectomy, although a significant impairment of implantation remained. In addition, embryos that were not transferred were at greater risk of growth arrest and degeneration, suggesting a deleterious effect of the hydrosalpinx on the ovary as well. One possible alternative to salpingectomy is aspiration of the hydrosalpinx prior to IVF, which has shown benefit in some small series of patients (Russell *et al.*, 1991; Van Voorhis *et al.*, 1998).

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