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Research Letter

Ultrasound-guided hydrosalpinx aspiration during oocyte retrieval and a mouse embryo assay of hydrosalpinx fluid in a woman with hydrosalpinx and hydrometra during *in vitro* fertilization treatment

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We present a successful pregnancy in a woman with hydrosalpinx and hydrometra after hydrosalpinx aspiration during oocyte collection in the *in vitro* fertilization (IVF) cycle. To our knowledge, this is the first report to combine ultrasound-guided hydrosalpinx aspiration with a mouse embryo assay of hydrosalpinx fluid for selection of appropriate treatment options for women with both hydrosalpinx and hydrometra. This new strategy provides valuable information to clinicians so that a more rational decision can be made to either go ahead with the cycle or to freeze all embryos and consider the possibility of surgical treatment.

A 33-year-old nullipara was involved in our IVF program because of tubal factor infertility. She had received tuboplastic surgery elsewhere for bilateral tubal obstruction 10 years previously. A hysterosalpingogram revealed bilateral tubal obstruction with left hydrosalpinx (Fig. 1A). Before ovarian stimulation, a baseline transvaginal ultrasound revealed no visible hydrosalpinx or any fluid in the uterine cavity. The ovarian stimulation protocol was performed as previously described [1]. Left hydrosalpinx was first recognized from cycle day 7 and had increased in size with ovarian stimulation (Fig. 1B). Serum estradiol levels on the day of human chorionic gonadotropin (hCG) administration and the day of oocyte retrieval were 1832 and 2197 pg/mL, respectively. Endometrial fluid collection was first recognized after hCG administration and reached a maximum diameter of 15 mm at the time of oocyte retrieval (Fig. 1C). Ten oocytes were retrieved transvaginally, and then 12 mL of clear fluid was aspirated from left hydrosalpinx until it collapsed completely. The fluid was cultured and found to be free of bacteria. Fluid was centrifuged at 1000 *g* for 15 min and was then used for the mouse embryo assay, as previously described [1]. The blastocyst development rate on day 3 was used to calculate a blastulation index: Blastulation index = percentage blastocyst development rate of test/percentage blastocyst development rate of the control. A blastulation index of less than 0.5 was considered to be potentially embryotoxic, while an index of 1.0 or higher was consider to be embryotrophic. The blastulation indices of 10, 50, and 100% of hydrosalpinx fluid were 1.37, 1.13, and 1.04, respectively. Analysis of the hydrosalpinx fluid revealed levels of sodium of 135 mmol/L, potassium of 3.6 mmol/L, chloride of 118 mmol/L, calcium of 0.14 mmol/L, glucose of 18 mg/dL, lactate of 2.2 mmol/L, bicarbonate of 28.2 mmol/L, and total protein of 1.6 g/dL; a pH of 7.56; and osmolality of 261 mOsmol/kg. We also analyzed human tubal fluid (HTF) medium, which is utilized routinely in our daily IVF program as control. Analysis of the HTF medium revealed levels of sodium of 138 mmol/L, potassium of 4.1 mmol/L, chloride of 108 mmol/L, calcium of 0.71 mmol/L, glucose of 51 mg/dL, lactate of 10.9 mmol/L, bicarbonate of 21.4 mmol/L, and total protein of 0 g/dL; a pH of 7.42; and osmolality of 269 mOsmol/kg. Transvaginal ultrasound 48 h after oocyte retrieval showed that the endometrial fluid had reduced to 5 mm in diameter (Fig. 1D). In view of decreasing endometrial fluid collection, we decided to perform embryo transfer instead of cryopreservation of all resulting embryos. Four good quality embryos were transferred to the uterine cavity on day 3. An ultrasound was performed 7 days later, which revealed no endometrial fluid collection and hydrosalpinx. A singleton pregnancy was established and the woman vaginally delivered a female baby weighing 3162 g at 39 weeks of gestation.

Hydrosalpinges have adverse effects on IVF outcome. The proposed mechanisms to explain the adverse effects of hydrosalpinges include a direct embryotoxic effect [2],

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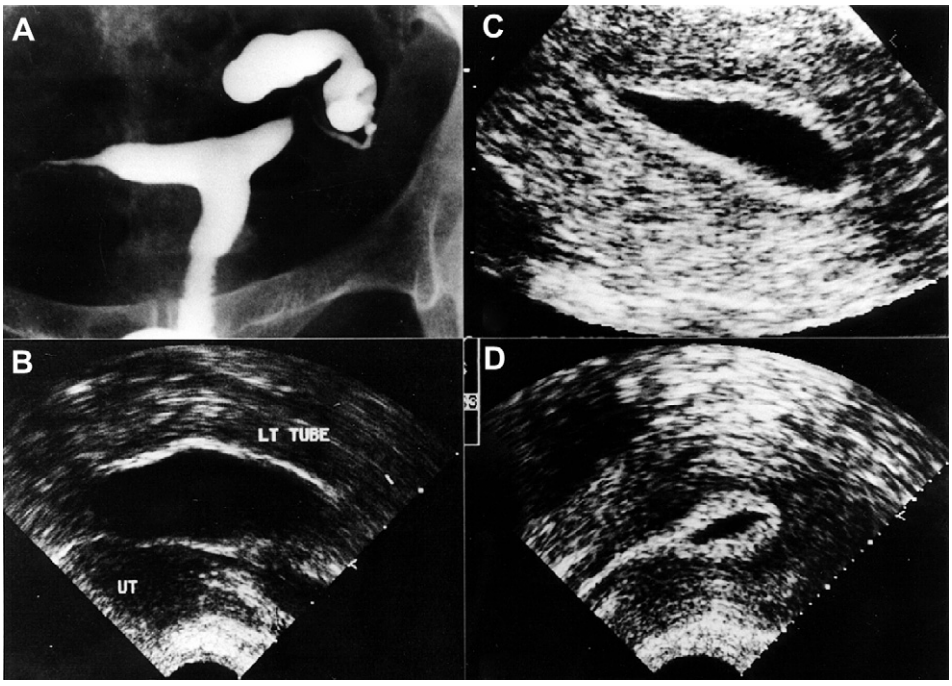

Fig. 1. (A) Hysterosalpingogram shows bilateral obstruction with left hydrosalpinx. (B) Transvaginal ultrasound on cycle day 12 demonstrates enlarging hydrosalpinx. (C) Endometrial fluid collection on the day of oocyte retrieval. (D) Endometrial fluid collection before embryo transfer. Note that endometrial fluid had reduced remarkably after aspiration of hydrosalpingeal fluid.

a decrease in endometrial receptivity [3], and the possibility that tubal fluid might mechanically flush the embryo from the uterus [4].

When hydrosalpinges are presented before IVF treatment is initiated, surgical excision, drainage, or proximal ligation of the hydrosalpinx have been reported to increase the success rate [5]. Table 1 summarizes the published papers of women who developed hydrosalpinx and hydrometra during IVF cycles. The rate of hydrosalpinx with hydrometra varies from 3.1% to 7.8%. [6–9]. Hydrosalpinx patients with documented uterine reflux possibly have the worst prognosis. For these patients, freezing of the resulting embryos followed by surgical correction of hydrosalpinx should be considered [10–12]. A recent study by He et al [13] found that none of the 11 patients with endometrial cavity fluid of 3.5 mm or higher in anterior–posterior diameter on the day of oocyte retrieval conceived. However, even in patients without hydrosalpinx, fluid accumulation can occur in the uterine cavity. Lee et al [14] reported that clinical pregnancy was not compromised if the endometrial cavity fluid was not from hydrosalpinx. Aspiration of uterine fluid seems to be ineffective, because there is a rapid re-accumulation of hydrometra [11].

Table 1
Published papers of women who developed hydrosalpinx and hydrometra during IVF cycles.

Year	Author	Number of patients with hydrosalpinx	Number of patients with hydrosalpinx and hydrometra	Number of clinical pregnancies
1991	Mansour et al [4]	3	3	0
1996	Andersen et al [6]	38	3 (7.8%)	0
1997	Bloechle et al [10]	1	1	0
1997	Sharara et al [12]	2	2	0
2001	Levi et al [9]	71	5 (7.0%)	2*
2002	Chien et al [7]	142	8 (5.6%)	0
2008	Hammadieh et al [8]	32	1 (3.1%)	0
	Total	289	23	2

* Both hydrosalpinx and hydrometra were presented. Endometrial cavity fluid was seen only after the administration of human chorionic gonadotropin.

For women who do not present hydrosalpinx on initial ultrasound, but who do so after ovarian stimulation, the decision making for such condition is more difficult. Ultrasound-guided aspiration of hydrosalpinx at oocyte collection is an option for women who develop hydrosalpinx during controlled ovarian stimulation. A recent randomized controlled study observed that clinical pregnancies occurred in 31.3% (10 of 32) of women after aspiration and 17.6% (6 of 34) of women without aspiration (relative risk = 1.8, $p = 0.2$) [8]. The authors found that the re-accumulation of the fluid is unlikely to develop rapidly enough to prevent the implantation or pregnancy. Aspiration of hydrosalpinx may reduce the endometrial fluid collection by decreasing the reflux of tubal fluid into endometrial cavity. However, recurrence of both hydrosalpinx and hydrometra after transvaginal aspiration of tubal fluid has been reported [10,11]. Recurrence of hydrosalpinx with the development of large hydrometra after aspiration of tubal fluid possibly has the worst prognosis. The clinician should consider freezing the resulting embryos and follow by surgical correction of hydrosalpinx prior to cryotransfer [7,9–12].

Cryopreservation with thaw transfer after salpingectomy or tubal ligation might be a better option for this case if we did not perform hydrosalpinx aspiration and mouse embryo assay

of hydrosalpinx fluid. However, we thought transvaginal aspiration at the time of oocyte retrieval would be the simplest method of treating both hydrosalpinx and hydrometra. Aspiration of hydrosalpinx fluid appears to reduce the amount of endometrial fluid accumulation, which is a favorable prognostic sign for successful implantation.

The mouse embryo assay of hydrosalpinx fluid is a useful tool to test the embryotoxicity of hydrosalpinx fluid [2]. The effect of hydrosalpinx fluid on embryo development and implantation has been examined in several studies and was summarized in a review [15], but findings were not consistent. Five out of eight studies described a toxic effect on mouse embryos at low concentrations of hydrosalpnx fluid, and three studies demonstrated impaired development only in undiluted hydrosalpinx fluid. Our previous study has shown the heterogeneous nature of hydrosalpinx fluid [1]. We demonstrate that the mouse embryo assay of hydrosalpinx fluid may be useful in selection of appropriate treatment options for patients with hydrosalpinx who are undergoing IVF treatment [1]. The present case report further demonstrates that newly formed tubal fluid during ovarian stimulation does not seem to be embryotoxic, and successful implantation could be achieved despite the presence of a small amount of endometrial fluid before embryo transfer. However, detailed follow-up studies are required to ascertain the reliability and feasibility of this proposed strategy.

Cancellation of the treatment cycle or cryopreservation of resulting embryos should only be considered for those patients who developed persistent large hydrometra despite the aspiration of tubal fluid [10,11]; fortunately this is an infrequent condition. In addition, transvaginal aspiration at the time of oocyte collection and sclerotherapy with 98% ethanol can be used as a new alternative treatment option for patients who decide to cancel the current treatment cycle [16].

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