An Increased Number of Replaced Embryos Counteracts the Adverse Effect of Hydrosalpinges on IVF/ET Outcome

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Purpose: The relationship between the number of replaced embryos and the outcome of IVF-ET in patients with hydrosalpinges was investigated in a retrospective, nonrandomized study performed at a governmental IVF center.

Methods: One hundred patients undergoing 161 IVF cycles ending in embryo transfer were studied. Previously diagnosed hydrosalpinges were evident on transvaginal sonography in 48 cycles in 26 patients (group I) and not evident in 15 cycles in 10 patients (group II). The control group included 98 cycles in 64 patients with tubal lesions other than hydrosalpinx. Pregnancy and implantation rates were the main outcome measures.

Results: Replacement of three or fewer embryos was associated with significantly lower implantation rates in group I compared to controls. Despite the difference in the rank of IVF trial within the same group, significantly lower implantation rates were found when four or fewer embryos were replaced in the control group and not in group I.

Conclusion: An increased number of replaced embryos counteracts the adverse effect of hydrosalpinges on IVF/ET outcome.

KEY WORDS: in vitro fertilization; infertility; hydrosalpinx; embryo transfer; implantation rate.

INTRODUCTION

Tubal-factor infertility is one of the classical indications for in vitro fertilization/embryo transfer (IVF/

ET) treatment. Tubal factor is not an entity per se but, rather, a heterogeneous group with different anatomical, pathologic, and etiologic factors. Recent retrospective studies suggest that the presence of unilateral or bilateral hydrosalpinx has an adverse effect on implantation and pregnancy rates following IVF/ET therapy (1–5). The mechanism for this negative influence on IVF/ET outcome is not yet fully understood. Simultaneous endometrial damage during the acute-phase damage of the tubes (1,2), with a role for *Chlamydia trachomatis* infection, was suggested (3). The most accepted explanation is that the tubal fluid, drained into the uterine cavity, may hinder implantation (6) through toxic (1,3,7), mechanical, or dilutional (3) effects. Therefore, tubal ligation, salpingostomy (1), or salpingectomy (2–5,7) was suggested to be performed prior to IVF therapy.

Many factors are known to influence success after IVF, such as the age of the patient (8,9), the rank of the IVF trial (9), and the number of replaced embryos (10,11). We conducted a retrospective analysis of the IVF/ET results in our unit for women with known tubal-factor infertility to investigate the relation between the number of replaced embryos and the outcome of IVF/ET in patients with a unilateral or bilateral hydrosalpinx.

MATERIALS AND METHODS

The records of all patients undergoing IVF/ET therapy at the Infertility/IVF Center, King Fahd Specialist Hospital, El-Qassim, Saudi Arabia, between January 1993 and November 1996 were retrospectively analyzed. After exclusion of couples with severe male factor, endometriosis, and previous surgical treatment of hydrosalpinges in women <40 years old, there remained records of 100 women with definite tubal

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lesion. In these patients 161 treatment cycles ending in embryo transfer were scrutinized. The tubal lesions for these women were diagnosed by both hysterosalpingography and laparoscopy or laparotomy, with 36 of them diagnosed to have uni- or bilateral hydrosalpinges.

On transvaginal sonography (TVS), the demonstration of uni- or bilateral hydrosalpinges on basal examination on day 2 of the cycle or their development during ovulation induction (12) was recorded. A hydrosalpinx was defined as an echo-free tubular or fusiform cystic structure located adjacent to the ovary, along with other criteria as discussed by Tessler *et al.* (13). The study cycles were divided into three groups.

Group I: 48 cycles in 26 patients with hydrosalpinges evident, at least once, on TVS.

Group II: 15 cycles in 10 patients with hydrosalpinges, not evident on any occasion on repeated TVS.

Group III (control group): 98 cycles in 64 patients with tubal lesions other than hydrosalpinges.

The stimulation protocols used were either long-term buserelin (LTB) or short-term buserelin (STB) and human menopausal gonadotrophin (hMG). Standard IVF techniques were used in all cases. A maximum of five embryos was replaced. Clinical pregnancy was defined as the presence of a gestational sac on ultrasound or by documenting trophoblastic tissue in pathology specimens from abortions or ectopic pregnancies. The presence of ectopic pregnancy or the loss of a clinical pregnancy before 12 weeks was considered an early pregnancy loss. Ongoing pregnancy was defined as reaching a gestational duration of >12 weeks. The implantation rate was calculated as the ratio between implanted and transferred embryos, taking into consideration the number of intrauterine gestational sacs and assuming the implantation of one embryo in the case of ectopic pregnancy.

Statistical analysis was performed using Student's *t* test and the Mann-Whitney *U* test as appropriate. A *P* value of ≤ 0.05 was considered significant.

RESULTS

The three groups were comparable in terms of age, rank of trial, induction protocols, and number of hMG ampoules used (Table I). Compared to the other groups, group I had significantly higher numbers of retrieved oocytes and replaced embryos. However, the implantation and clinical pregnancy rates were lower, with no statistical significance. All pregnancies were intrauterine, with only one heterotopic pregnancy (2.4%) in

group III, ending in abortion and salpingectomy. Also, three pregnancies ended in midtrimester abortion in group III.

The transfer of more than three embryos in groups I and III was associated with a significantly higher rank of IVF trial (Table II). On transfer of three or fewer embryos, group I had lower clinical and ongoing implantation rates compared to the controls. Also, the multiple pregnancy rate was lower and the difference approached statistical significance ($P = 0.084$). In group III, the transfer of more than three embryos was associated with significantly lower implantation rates. On the other hand, the transfer of more than three embryos group I was associated with a similar clinical pregnancy rate, with insignificantly increased, rather than decreased, rates of ongoing and multiple pregnancies and clinical and ongoing implantations.

DISCUSSION

Reviewing our data as a whole, we failed to find any significant adverse effect of hydrosalpinges on IVF/ET outcome, which contradicts the findings of other studies (2–5). This is not likely explained by confounding factors, which were comparable to those of other reports, including the sample size (1,3,5), the long acquisition time for patients (3–5), and the use of more than one stimulation protocol (2,4). Despite limiting the number of replaced embryos to a maximum of three in some studies (1,5), the numbers of replaced embryos in all study groups in different reports were found to be comparable (1–5). On the contrary, a significantly increased number of embryos was replaced in patients with hydrosalpinx evident on TVS in the present study. This may be attributed partially to the increased number of retrieved oocytes in this group of patients, also observed by other investigators (3). The finding of more cycles ending in replacing four or more embryos in this group might have been responsible for counteracting the unfavorable conditions for the implantation process. Supporting this assumption is the finding that, on replacement of three or fewer embryos, the presence of a hydrosalpinx on TVS, despite being associated with better ovarian responsiveness, with more retrieved oocytes and replaced embryos, was associated with significantly lower clinical and ongoing implantation rates compared to those of controls. This was also associated with a reduction in the multiple pregnancy rate. In this group, the implantation rate was approximately one-third that of the controls, which agrees with the find-

Table I. Outcome of IVF Cycles^a

	Group I (hydrosalpinx evident on TVS)	Group II (hydrosalpinx not evident on TVS)	Group III (controls)
No. of patients	26	10	64
No. of transfers	48	15	98
Age ^b	31.3 ± 3.9	29.9 ± 3.8	32.1 ± 5.3
Rank of trial ^b	1.96 ± 1.03*	1.4 ± 0.63*	1.93 ± 1.83
STB stimulation protocol ^c	13/48 (27.1)	3/15 (20)	23/98 (23.5)
No. of hMG ampoules ^b	37.3 ± 10.9	37.7 ± 18.3	38.3 ± 12
No. of retrieved oocytes/cycle ^b	10 ± 3.8 ^{a,b}	7 ± 3.6 ^a	7.6 ± 4.6 ^b
No. of embryos/transfer ^b	3.7 ± 0.7 ^{c,d}	2.8 ± 1.3 ^c	3.1 ± 1 ^d
Replacement of ≥4 embryos ^c	30/48 (62.5) ^{b,e}	5/15 (33.3) ^e	35/98 (35.7) ^b
Clinical pregnancy rate/ET ^c	10/48 (20)	6/15 (40)	26/98 (26.5)
Early pregnancy loss ^c	3/10 (30)	3/6 (50)	5/26 (19.2)
Ongoing pregnancy rate ^c	7/10 (70)	3/6 (50)	21/26 (80.8)
Rate of multiple pregnancy ^c	3/10 (30)	1/6 (16.7)	10/26 (38.5)
Per-embryo clinical implantation rate ^c	14/179 (7.8)**	7/42 (16.7)**	38/303 (12.5)
Per-embryo ongoing implantation rate ^c	11/179 (6.2)	4/42 (9.5)	32/303 (10.6)

^a Values within rows with the same superscript are significantly different at $P < 0.01$ (a), 0.005 (b), 0.001 (c), 0.001 (d), and 0.05 (e).

^b Values are means ± SD.

^c Values in parentheses are percentages.

* $P = 0.0524$.

** $P = 0.079$.

ings of other investigators (2–4) reporting a similar reduction in implantation rates (2.93 to 4.21%, compared to 10.27 to 11.53% in the controls). In contrast, we found no difference in the pregnancy rate, in agreement with the findings of one other study (5). However, other investigators (1–4) reported a significant decrease in pregnancy rates (10.1 to 19.2%, versus 23 to 37% in the controls).

Different confounding variables could have created the bias in the results in the present study. However,

the nature of such studies truly makes randomization impossible, which negates the value of a prospective study design. The study groups might be influenced by the availability of embryos and the patients' choice, with those with a higher rank of IVF trial being more willing to accept replacement of more embryos (11). It is our policy to replace four or five embryos in the older patient group or those with a history of failed implantation after a previous IVF/ET attempt. In the control group, transfer of more than three embryos

Table II. Effect of Number of Embryos Replaced on IVF/ET Outcome^a

	Group I (hydrosalpinx on TVS)		Group III (controls)	
	Subgroup A (≤3 embryos transferred)	Subgroup B (≥4 embryos transferred)	Subgroup A (≤3 embryos transferred)	Subgroup B (≥4 embryos transferred)
No. of transfers	18	30	63	35
Age ^b	30.8 ± 3.8	31.4 ± 4.2	31.5 ± 5.5	33.2 ± 4.7
Rank of trial ^b	1.56 ± 0.92 ^a	2.2 ± 1.03 ^a	1.6 ± 1.36 ^b	2.51 ± 2.38 ^b
No. of embryos/transfer ^b	2.94 ± 0.24 ^{c,d}	4.2 ± 0.41 ^d	2.47 ± 0.67 ^{k,k}	4.2 ± 0.41 ^e
Clinical pregnancy rate/ET ^c	4/18 (22.2)	6/30 (20)	19/63 (30.2)	7/35 (20)
Early pregnancy loss ^c	2/4 (50)	1/6 (16.7)	3/19 (15.8)	2/7 (28.6)
Ongoing pregnancy rate ^c	2/4 (50)	5/6 (83.3)	16/19 (84.2)	5/7 (71.4)
Rate of multiple pregnancy ^c	0/4 (0)**	3/6 (50)*	9/19 (47.4)**	1/7 (14.3)
Per-embryo clinical implantation rate ^c	5/53 (7.5) ^a	10/126 (7.9)	30/156 (19.2) ^{a,d}	8/147 (5.4) ^d
Per-embryo ongoing implantation rate ^c	2/53 (3.8) ^b	9/126 (7.1)	26/156 (16.7) ^{b,d}	6/147 (4.1) ^d

^a Values within rows with the same superscript are significantly different at $P < 0.05$ (a), 0.02 (b), 0.01 (c), 0.001 (d), and 0.001 (e).

^b Values are means ± SD.

^c Values in parentheses are percentages.

* $P = 0.109$.

** $P = 0.084$.

failed to counteract the adverse effect of these two factors on implantation rates. On the contrary, pregnancy and implantation rates were not lowered on replacement of more than three embryos in patients with hydrosalpinges evident on TVS. Actually, these findings were not expected in view of the expected additional adverse effect of hydrosalpinx (1–5). These findings strengthen our theory that an increased number of replaced embryos counteracts the adverse effect of hydrosalpinx on IVF/ET outcome. In fact, transfer of more embryos was also recently suggested to improve success rates in patients with unexplained repeated IVF failure (11).

An increased incidence of pregnancy loss in association with hydrosalpinx was reported, due mainly to biochemical pregnancies (3). Confirming the findings of other investigators (4,5), we found no difference in the early pregnancy loss. Also, there was no increase in the incidence of ectopic pregnancies, in agreement with other studies (2–4).

The presence of persistent tubal distention appears to be crucial in exerting an adverse effect on IVF/ET outcome. In the present study, the transfer of fewer embryos in the patients with hydrosalpinges not evident on TVS was associated with pregnancy and implantation rates comparable to those of the controls. This agrees with the findings of Strandell et al. (1), who found that an adverse effect on IVF outcome was present only in cases with marked persistent distention of the hydrosalpinges. Moreover, the significant decrease in IVF therapy outcome observed by us and other investigators (2–4) was found only in patients with hydrosalpinges evident on ultrasonography. In fact, considering all patients with hydrosalpinges as one group (5,14,15) might have been responsible for the failure to recognize any adverse effect on IVF pregnancy outcome in some of these studies (14,15).

Various surgical approaches were suggested to normalize IVF/ET pregnancy rates for this group of patients (1–5,7). The suggestion that salpingectomy results in a reduction of ovarian vascularization with stimulation and formation of follicular cysts (1) is denied by other investigators (3). Moreover, a recent study showed that bilateral salpingectomy has no detrimental effect on the ovarian response or the outcome of therapy (16). The role of sonographically guided puncture before stimulation for IVF (17,18) needs to be evaluated. Our results show that an increased number of replaced embryos might be beneficial in counteracting the adverse effect of hydrosalpinx on IVF/ET outcome. The implantation and pregnancy rates might be improved through increased chances of embryos to

escape the mechanical, dilutional, or even toxic effect of the tubal fluid drained into the uterine cavity.

A potential hazard of multiple embryo replacement is the expected increase in multiple pregnancy rates. In the present study, replacement of more embryos in patients with hydrosalpinges on TVS was associated with an overall multiple pregnancy rate of 30%, two sets of twins and one triplet, of 10 pregnancies, compared to 7.3%, only three sets of twins, of a total of 41 pregnancies reported in three studies (3–5). So it appears that the presence of hydrosalpinges on TVS is associated with lower prospects of becoming pregnant or of having a multiple pregnancy. Patients with repeated unexplained IVF seem to have similar prospects. Replacement of more embryos in these patients was associated with an increased pregnancy rate, with a slight increase in the rate of multifetal pregnancy (11). Twin gestations are usually adequately managed and fetal wastage remains low compared to high-order multiple gestations. The need for flexibility in the number of replaced embryos and a compromise between the highest possible pregnancy rate and the lowest frequency of high-risk, high-order multiple pregnancies is evident (10,11,19). The presence of hydrosalpinx on TVS appears to be one of these exceptional circumstances (19) where the transfer of four or more embryos may be justified to optimize IVF-ET outcome. Reviewing the data of other investigators with larger series of IVF cycles seems worthwhile to allow elaboration of this assumption. Proved to be of value, an increased number of replaced embryos in patients with hydrosalpinges might offer an optional alternative to surgical measures with their known hazards.

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