

Article

Assessment of endocervical and endometrial damage inflicted by embryo transfer trial: a hysteroscopic evaluation



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Abstract

The aim was to assess the endocervical and endometrial damage inflicted by embryo transfer trial using office hysteroscopy. Seventy-five consecutive infertile women who underwent office hysteroscopy were enrolled. Hysteroscopy was performed immediately after embryo transfer trial. The relationship between clinical perception of easiness of transfer, presence of blood on the catheter, degree of endocervical and endometrial damage was examined. In the difficult transfer group, minor and moderate endocervical lesions were noted in 35% and 24% of the cases, respectively. The respective figures for the easy transfer group were 19% and 3% ($P > .05$). There was a statistically significant concordance between the perceived difficulty of transfer and degree of endometrial damage ($P < 0.05$). Of interest, in the easy transfer group, 32% of the patients had minor, 3% moderate and 65% no endometrial damage. The respective figures were 42%, 29% and 29% in the difficult transfer group. There was blood on the catheter in 25%, 56% and 71% of the easy, moderate and difficult transfer groups, respectively. There was a statistically significant concordance between the perceived difficulty of embryo transfer and presence of blood on the catheter ($P < 0.05$). These results suggest that clinical perception of difficulty of transfer and the presence of blood on the catheter are directly associated with endometrial disruption.

Keywords: assisted reproduction, embryo transfer, endometrial damage, endometrium, hysteroscopy

Introduction

Embryo transfer is the final and most crucial step in IVF (Schoolcraft *et al.*, 2001). A traumatic embryo transfer technique inflicting minimal or no damage to the endometrium is essential to increase the success rate after IVF. Several factors that may affect the success of embryo transfer include the catheter type used (Wood *et al.*, 2000; Abou-Setta, 2006), catheter loading (Meldrum *et al.*, 1987), vigorous cervical flushing (McNamee and Carwile, 1998), aspiration of cervical mucus (Mansour *et al.*, 1994), performing a trial transfer (Mansour *et al.*, 1990), catheter tip placement (Waterstone *et al.*, 1991), ultrasonographic guidance (Wood *et al.*, 2000), easiness of

transfer (Englert *et al.*, 1986; Lass *et al.*, 1999) and presence of blood and/or mucus on the catheter (Mansour, 1990; Goudas *et al.*, 1998). The presence of complicated networks of cytokines and their overlapping biological activities may also affect pregnancy and implantation rates (Urman *et al.*, 2005; Laird *et al.*, 2006).

Clinical perception of difficulty of embryo transfer is a commonly used marker for the optimum performance of embryo transfer. However, there is controversy about the impact of easiness or difficulty of embryo transfer on subsequent pregnancy rates. Kovacs (1999) surveyed 42 clinicians to assess the relative importance of variables affecting the success of embryo

transfer. The absence of blood on the catheter, avoidance of use of tenaculum, and not touching the fundus were ranked highly as prognostic variables. It has been suggested that the clinician's perception of transfer difficulty was the most important variable of all (Lass *et al.*, 1999). Inferior pregnancy rates have also been reported with difficult embryo transfer in other studies (Englert *et al.*, 1986; Mansour *et al.*, 1990). However, no such significant detrimental effect with difficult embryo transfer has also been noted (Tur-Kaspa *et al.*, 1998; De Placido *et al.*, 2002; Silberstein *et al.*, 2004).

An atraumatic embryo transfer should be associated with no or minimal damage to the endometrium. As Schoolcraft *et al.* (2001) noted, in order to differentiate a traumatic embryo transfer from an atraumatic one, the degree of trauma to the endometrium should be directly assessed during the actual procedure. To date, this has been assessed indirectly by measures such as quoting the difficulty encountered by the clinician and the presence of blood and/or mucus on the catheter. Direct visual assessment of the endocervix and endometrium by office hysteroscopy immediately after an embryo transfer trial may offer a unique insight into the effect of difficulty of embryo transfer on endocervical and endometrial integrity. However, there is paucity of data on direct assessment by hysteroscopy of endocervical and endometrial lesions inflicted by embryo transfer.

In this study, we evaluated the detrimental affect of difficulty of embryo transfer on the endocervix and endometrium as assessed by office hysteroscopy immediately after an embryo transfer trial.

Materials and methods

A total of 81 consecutive patients undergoing office hysteroscopy before IVF were included. The exclusion criteria were the presence of any type of endocervical or intrauterine pathology, including endocervical or endometrial polyp, uterine septum, intrauterine synechiae and submucous myomas, detected by hysterosalpingography and transvaginal ultrasonography.

Informed consent was obtained from all patients. The study protocol was approved by the Institutional Review Board. Embryo transfer trials were performed during days 6–12 after the onset of menses by a single clinician using the same care and technique as a normal embryo transfer. To summarize, following introduction of the speculum to the vagina, the cervical external os was wiped and flushed with saline and cervical mucus was aspirated by means of a mucus aspiration catheter. Patients experiencing cervical bleeding as a result of the traumatic effects of mucus aspiration were excluded from the study. A trial Wallace embryo transfer catheter (TT1816N; Sims Portex Ltd, Hythe, Kent, UK) was, thereafter, introduced into the uterine cavity up to 6 cm from the external cervical os while the bladder was full and without ultrasonography. Ultrasonographic guidance for embryo transfer is not used on a routine basis, so ultrasonography was not employed in this study.

The degree of difficulty encountered during embryo transfer was assessed according to the following subjective scale. The passing of a soft inner catheter directly through the cervical

canal to the endometrial cavity was evaluated as an 'easy' transfer. Use of a positioned outer rigid sheath to negotiate the cervical canal was graded as 'moderately difficult'. The need for the use of a malleable stylette was graded as 'difficult'. Use of the tenaculum was avoided in all patients.

Office hysteroscopy was performed immediately after the embryo transfer trial. A rigid 2.9-mm hysteroscope with 30° telescope (Storz GmbH, Tuttlingen, Germany) and saline distension were used. The whole procedure was recorded on a CD-ROM. To exclude any assessment bias, the endocervical and endometrial damage caused by the previous embryo transfer trial procedure was noted by an observer who was not present at the procedure but who studied it on the CD-ROM. The following subjective scale was used for the severity of endocervical and endometrial damage; none, minor (defined as superficial disturbance of mucosa with no bleeding), moderate (disturbance of mucosa with bleeding), and severe (significant disturbance of mucosa and/or significant bleeding/clots) (Murray *et al.*, 2003).

The data were analysed with the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 10.0. The chi-squared test was used for statistical analyses. *P*-values of <0.05 were considered statistically significant.

Results

Six cases were excluded. The reasons for exclusion were severe stenosis requiring dilatation with Hegar dilators ($n = 2$), severe intrauterine synechiae ($n = 1$), endometrial polyp ($n = 2$), and endocervical polyp ($n = 1$). Therefore, a total of 75 cases were included for statistical analysis.

Although there was a trend between the perceived difficulty of transfer and degree of endocervical damage, it did not reach statistical significance (**Table 1**). There was a statistically significant concordance between the perceived difficulty of transfer and degree of endometrial damage (**Table 1**; gamma value = 0.51).

No severe endocervical or endometrial damage was noted in any patient. In the difficult transfer group, minor and moderate endocervical lesions were noted in 35% and 24% of the cases, respectively; the respective figures for the easy transfer group were 19% and 3%.

It is of interest that, in the easy transfer group, 32% of the patients had minor and 3% had moderate endometrial damage; 65% of the cases had no endometrial damage. The respective figures for the difficult transfer group were 42%, 29% and 29%.

There was blood on the catheter in 26%, 56% and 71% of the easy, moderate and difficult transfer groups, respectively (**Table 2**). There was a statistically significant concordance between the perceived difficulty of embryo transfer and presence of blood on the catheter ($P < 0.05$, gamma value = 0.57, **Table 2**).

The association between the presence of blood on the catheter and the site of trauma is given in **Table 3**. In the blood-positive group, isolated endocervical trauma was noted in only one (3%) case; endometrial-only or endometrial and endocervical

Table 1. Difficulty of embryo transfer trial and degree of endocervical and endometrial damage. Values are numbers with percentages in parentheses.

<i>Difficulty of embryo transfer</i>	<i>Degree of endocervical damage</i>			
	<i>None</i>	<i>Minor</i>	<i>Moderate</i>	<i>Total</i>
Easy	24 (78)	6 (19)	1 (3)	31 (100)
Moderate	15 (56)	7 (26)	5 (18)	27 (100)
Difficult	7 (41)	6 (35)	4 (24)	17 (100)

<i>Difficulty of embryo transfer</i>	<i>Degree of endometrial damage</i>			
	<i>None</i>	<i>Minor</i>	<i>Moderate</i>	<i>Total</i>
Easy	20 (65)	10 (32)	1 (3)	31 (100)
Moderate	8 (30)	16 (59)	3 (11)	27 (100)
Difficult	5 (29)	7 (42)	5 (29)	17 (100)

$P = 0.09$ for main cross table (3×3), which includes comparison between degree of endocervical damage and difficulty of embryo transfer trial.
 $P < 0.05$ for main cross table (3×3), which includes comparison between degree of endometrial damage and difficulty of embryo transfer trial.
 Details of cross table which includes endometrial damage and difficulty of embryo transfer trial are given below:
 $P < 0.05$ for cross table (2×2) between easy–moderate degrees of difficulty of embryo transfer trial and none–minor endometrial damage.
 $P < 0.05$ for cross table (2×2) between easy–difficult degrees of difficulty of embryo transfer trial and none–moderate endometrial damage.

Table 2. Difficulty of embryo transfer trial and blood on the catheter. Values are numbers with percentages in parentheses.

<i>Blood</i>	<i>Difficulty of embryo transfer trial</i>		
	<i>Easy</i>	<i>Moderate</i>	<i>Difficult</i>
Negative	23 (75)	12 (44)	5 (29)
Positive	8 (25)	15 (56)	12 (71)
Total	31 (100)	27 (100)	17 (100)

$P < 0.05$ for main cross table (3×2), which includes comparison between presence of blood on the catheter and difficulty of embryo transfer trial (gamma value = 0.57).
 Details of cross table were given below:
 $P < 0.05$ for cross table (2×2) between easy–moderate degrees of difficulty of embryo transfer trial and blood on the catheter.
 $P < 0.05$ for cross table (2×2) between easy–difficult degrees of difficulty of embryo transfer trial and blood on the catheter.

Table 3. The relationship between the presence of blood on the catheter, difficulty of embryo transfer trial and site of trauma. Values are numbers with percentages in parentheses.

	<i>Site of trauma</i>				<i>Total</i>
	<i>Endometrium</i>	<i>Endocervix</i>	<i>Both</i>	<i>None</i>	
<i>Blood^a</i>					
Negative	8 (20)	3 (7)	6 (15)	23 (58)	40 (100)
Positive	9 (26)	1 (3)	19 (54)	6 (17)	35 (100)
<i>Difficulty of embryo transfer^a</i>					
Easy	6 (19)	2 (7)	5 (16)	18 (58)	31 (100)
Moderate	8 (30)	1 (4)	11 (41)	7 (25)	27 (100)
Difficult	3 (18)	1 (6)	9 (52)	4 (24)	17 (100)

^aNon-significant for comparison between endometrium, endocervix and both.

traumas were noted in 26% and 54% of the cases, respectively. It is noteworthy that no injury was found, despite the presence of blood in 6 (17%) cases. In the blood-negative group, no injury was noted in only 58% of the transfers. However, lesions in the endocervix, endometrium, or both were visualized in three (8%), eight (20%) and six (15%) of the transfers.

The association between the perceived difficulty of transfer and the site of trauma was given in **Table 3**. There was no significant association between the difficulty of transfer and the site of trauma, when present.

All 42 endometrial injuries were located either in the anterior or posterior uterine wall, apart from one case in which the site of injury was the fundus.

Discussion

Assessment of the endocervical and endometrial damage has traditionally been done indirectly by measures such as quoting the difficulty cited by the clinician, or the presence of blood and/or mucus on or in the catheter (Goudas *et al.*, 1998; De Placido *et al.*, 2002; Alvero *et al.*, 2003; Silberstein *et al.*, 2004). However, there is paucity of data on the detrimental effect of the clinician's perception of transfer difficulty on endocervical and/or endometrial damage. Direct visual assessment of the endocervix and endometrium by office hysteroscopy immediately after an embryo transfer trial may offer a unique insight into the effect of difficulty of embryo transfer on endocervical and endometrial integrity.

Marconi *et al.* (2003) first reported the endometrial lesions caused by an embryo transfer trial. In this preliminary report, 23 infertile patients underwent a microhysteroscopy immediately after a trial transfer during the post-ovulatory phase. It is of interest that endometrial damage was noted in all transfers using the Tomcat catheter ($n = 5$), Frydman's catheter ($n = 5$) and Frydman's set ($n = 3$), but only noted in two out of 10 transfers using the Wallace catheter. Although the authors described the type of endometrial lesions, they did not grade the severity and or relate this to the difficulty of embryo transfer and the presence of blood on or in the catheter.

In a similar study design, Marikinti *et al.* (2003a) assessed the association between the easiness of transfer and the presence of endocervical and/or endometrial damage. Thirty-four women were included. The inner soft catheter alone was used in 25 (group 1), an outer sheath was needed in six (group 2), and Allis forceps in three (group 3). The use of a stylet was avoided. In group 1, evidence of trauma to the endometrium was noticed in six women; trauma to the endocervix in seven women; and trauma to both endometrium and endocervix in two women; with 10 women experiencing no trauma. In group 2 ($n = 6$), evidence of trauma to the endometrium was noticed in two women; trauma to the endocervix in two women; and trauma to both in the remaining two women. All women in group 3 ($n = 3$) showed trauma to the endocervix only. Use of an outer sheath and/or Allis forceps was associated with bleeding from the cervical mucosa but not from the endometrium. The authors did not notice any endometrial bleeding into the uterine cavity following embryo transfer trial, although there were hysteroscopically visible traumatic lesions in the endometrium

evident in 12 out of 31 cases as follows: subendometrial haemorrhage ($n = 5$); endometrial grooving ($n = 4$); vascular congestion ($n = 2$); perforation of the endometrium ($n = 1$). In all cases where blood was noted on the inside or outside of the catheter, the source was the endocervix.

The same group, in another study, reported a higher incidence of hysteroscopically visible anatomical abnormalities (23 out of 30) in the cervico-uterine canal (angulations, synechiae, false passages, cysts, polyps and hypertrophied endocervical mucosa) and a higher incidence of bleeding from the endocervix following an embryo transfer trial in those women who had a history of difficult embryo transfer (Marikinti *et al.*, 2003b).

Murray *et al.* (2003), similarly assessed by hysteroscopy the presence and severity of endometrial lesions immediately after a trial embryo transfer using a soft catheter in 30 women. The difficulty of embryo transfer was graded as easy, moderately difficult and difficult. Endometrial damage was independently assessed and graded as follows: none, minor, moderate or severe. Of the 24 easy transfers, 54% showed no endometrial damage. However, moderate and severe damage to the endometrium was noted in 29% and 8% of the cases, respectively. Of the six moderately difficult transfers, minor or severe endometrial lesions were noticed in two and two patients, respectively; no lesion was noted in the remaining two patients. The authors concluded, therefore, that there was no clear association between the perceived difficulty of embryo transfer and severity of endometrial damage. It is of interest that no patient required difficult transfer in this series with a limited number of patients. The authors concluded that clinical perception of ease of transfer does not relate well to the degree of endometrial disruption. Limited sample size, absence of any patient requiring difficult transfer, lack of data on endocervical damage and contamination of the catheter with blood are the limitations of this study.

When the embryo transfer catheter is contaminated with blood, it may be helpful to differentiate the source of blood contamination: endocervix, endometrium or both. One may assume that blood contamination resulting from endocervical trauma may be associated with less, if any, detrimental effect on pregnancy success. In contrast to the study by Marikinti *et al.* (2003a), it was noted that when the catheter was contaminated with blood, endometrial lesions were observed in the majority of the cases (28/35), whereas endocervical-only lesion was noted in only one patient (1/35) (Table 3). It should be stressed that using blood contamination to predict endometrial damage is crude, because in the blood-negative transfers, endometrial lesions were still observed in 14 out of 40 cases. In cases where blood was present in the catheter but no lesion was observed it is postulated that since liquid distension media were used very minor bleeding contaminating the catheter may not be noted at subsequent hysteroscopy as a result of the washing effect of the liquid media. Obviously this will not be expected to be the case for moderate or severe damage.

There are three limitations of this study. Performance of the study in the follicular phase is a limiting factor. The frequency and the severity of endocervical/endometrial damage inflicted by embryo transfer may vary depending on when it is performed during the menstrual cycle. However, because a diagnostic hysteroscopy was part of the goal of the study, it was performed

in the late follicular phase. The second limitation is performance of the embryo transfer trial without ultrasonographic guidance. Ultrasonographic guidance may allow visualization of the tip of the catheter in relation to the depth of insertion; however, it still may not avoid injury to the endometrium, which is caused by the impact and friction of the tip of the catheter on the endometrium. The third limitation is the lack of flushing and observing the tip of the catheter under stereomicroscope following the trial embryo transfer. This may have contributed to a failure to notice microscopic contamination and, therefore, disproportionate assessment of the rates of blood contamination and endometrial damage.

It is concluded that clinical perception of difficulty of transfer and the presence of blood on the catheter directly relate to endometrial disruption. However, the impact, if any, of subtle endometrial lesions inflicted during the actual embryo transfer on subsequent implantation rates warrants further studies. Such studies should include ultrasound measurements to further classify the transfers.

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