

# Difficult Embryo Transfer: A Systematic Review

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ABSTRACT

We performed a systematic review on the clinical epidemiology and outcome of difficult embryo transfers (ETs) in infertility patients who present with difficult ET. We searched PubMed, ScienceDirect, and Elsevier journals from 1980 to June 2017. We aimed to determine the most successful method resulting in highest pregnancy rates (PRs) in patients with difficult ET. We identified 50 articles, in which 36 were reviewed and 15 were included. Analysis of the data collected showed that the majority of the difficult ETs were caused by cervical stenosis and the most common treatment was cervical dilation. We concluded that cervical dilation was effective at managing difficult ET. Hegar dilators used a minimum of 3 weeks before ET showed to have higher PR.

**KEYWORDS:** Cervical stenosis, difficult embryo transfer, in vitro fertilization, pregnancy rates

## INTRODUCTION

*In vitro* fertilization (IVF) treatment is a procedure known worldwide for its ability to give couples the chance to have a family which they previously thought impossible. It gives hope to thousands of women that they will be able to carry their own child during pregnancy like any other mother. It is estimated that approximately 3.5 million people in the UK will be unable to conceive naturally.<sup>[1]</sup> Around 15–20 million people in India suffer from infertility.<sup>[33]</sup> For these couples, IVF treatment is the next suggested path to aid their conception. With the development of IVF 34 years ago, approximately 12,000 babies are born a year in the UK.<sup>[2]</sup> However, despite this monumental advancement in technology, the figures for the UK in 2009/2010 show a success rate of using fresh embryos of 25.2%.<sup>[2]</sup> The most highly debated and discussed area of fertility medicine is how to improve implantation rates (IRs) and subsequently pregnancy rates (PRs). One of the aspects is improving embryo transfer (ET) technique. Various strategies have been tried to improve ET techniques. Some of these include the use of different types of catheters,<sup>[3]</sup> use of ultrasound guidance during ET,<sup>[4-6]</sup> transferring the embryos into the fallopian tube,<sup>[7]</sup> and use of Hyalurona as a medium glue for transfer.<sup>[8]</sup> A predetermining factor for IRs and PR is whether the ET is successful. A successful ET has been described

as a way to deposit the newly formed embryos into the optimal location of the uterus without causing significant trauma.<sup>[9]</sup> However, some women due to anatomical or physiological reasons present with a “difficult ET.” It is impossible to determine how many women undergo a difficult ET as these data are not often recorded, but studies have shown that 8.4% of patients present with “difficult” ETs.<sup>[10]</sup>

## WHAT MAKES A “DIFFICULT” TRANSFER?

A “difficult” transfer is a subjective description of the ET procedure. There are many different definitions of what qualifies as a difficult transfer, and these differ between practitioners and practices all over the world. It is not possible to have a blanket definition of it, as there are varying opinions on what constitutes a difficult ET. It has been suggested that it can be used in relation to whether it caused discomfort to the patient, whether there was a need for a change in equipment used from the average ET (e.g., change of catheter or use of tenaculum), how long the ET took and if multiple attempts were needed,<sup>[11,12]</sup> or whether there was presence of blood on the catheter.<sup>[9]</sup> In some severe difficult cases,

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cervical dilation may be needed.<sup>[12]</sup> It has been found that the most common causes for a difficult ET are due to the anatomical position of the uterus (whether there is significant anteversion/anteflexion or retroversion/retroflexion) or whether the patient presents with cervical stenosis.<sup>[9,13]</sup> There is also a described “intermediate” difficult transfer, where the initial transfer is met with some resistance. This requires an outer sheath, or stylet or tenaculum to be used to allow the transfer to be completed.<sup>[14]</sup>

There have been many studies that have suggested that the degree of “difficult” experienced correlates to the PR and IR in patients. Some studies have shown that, the easier the transfer, the higher the IR and subsequent pregnancy and live birth (LB) rate.<sup>[14]</sup> Due to these results, there have been many studies done into how to convert a “difficult” ET into an “easy” transfer.<sup>[15-17]</sup> These studies have often placed emphasis on the reduction of cervical stenosis, mentioned later, by procedures such as operative hysteroscopy or the insertion of a Malecot catheter.<sup>[16,18,19]</sup> However, contrary to this, there have been studies done in the past that suggest that there is no correlation between a difficult transfer and a poor PR.<sup>[10]</sup> Both studies do agree that there is a higher rate of miscarriage in those who have multiple attempts on ET.<sup>[10]</sup> When a difficult ET is experienced, there is a risk that there will be a failed transfer. This is mostly caused due to a traumatic deposition of the embryo resulting from a difficult manipulation of the catheter inside the uterus, perhaps stimulating uterine contractions.<sup>[9,20]</sup> Prostaglandins and oxytocin have been found to be released when cervical manipulation occurs and cause uterine contractions.<sup>[9]</sup> These uterine (junctional zone) contractions have been linked to relocating of the embryo once placed in the uterus.<sup>[20]</sup> Other causes of a failed ET are such as embryo damage during the procedure or incorrect placement of the embryo in the uterus (perhaps due to difficulty in locating the optimal position).<sup>[9]</sup>

Therefore, the objective of this review is to systematically examine the literature and identify interventions for difficult ET as well as the success rates. There is a need for this information as there are no definitive guidelines for how to manage a difficult ET patient. The results of this review can be used in the clinical setting to help improve the PRs and also identify gaps in the current knowledge and areas of future research.

## METHODS

### Criteria for study selection in this review

#### Study type

The types of studies included were retrospective study, case reports, case studies, prospective randomized

studies, retrospective case–controlled studies, and retrospective observational studies.

#### Eligibility criteria for inclusion in review

Studies which included women who presented for infertility treatment were known to have or are suspected to have a difficult ET.

#### Intervention

There is no exclusion of interventions for this review. Any technique or procedure can be used on the “difficult ET” patients.

#### Outcome measures

- Interventions used for difficult ET
- Success rates
  - PR of the ET using the specified technique.

### Search methods for identification of studies

#### Electronic searches

We searched literature on PubMed, ScienceDirect, and Elsevier journals from 1980 to June 2017 and National library of India also helped identify the articles. The following search terms were used adjusting for each database as necessary: Difficult embryo transfer, Pregnancy rate, Cervical stenosis, IVF, or *In vitro* fertilisation. Furthermore, references from relevant articles found were followed up and searched. Some reference information was collected from NHS and Human Fertilisation and Embryology Authority.

#### Data collection and analysis

The electronic search results were scrutinized. Full manuscripts of all the articles based on selection criterion were obtained. The articles were numbered to eliminate any replications. The articles were then read and grouped; the abstracts alone in some of these cases were not clear enough to determine whether the article would be applicable, so the full article was read. There were three groups made from this search as follows:

1. Group of articles that were describing difficult ET and were relevant for data collection
2. Group of articles not eligible for data collection but were relevant for background reading and for the discussion and finally
3. Those articles not relevant at all (this included a few French articles, the translated version for which was not found).

For the articles included in Group 1, a table was constructed which helped condense the information found into a comparable scenario. This also helped eliminate any further articles that were not appropriate.

The article searches were crossreferenced and the data were independently extracted and collated. Descriptive analysis based on the data was then done.

## RESULTS

### Results from the search

The electronic database search identified 900 potential articles. Following review of titles and abstracts, 50 articles were selected for review of the full manuscript. Of those, 35 studies were subsequently excluded for reasons which are shown in Figure 1. Fifteen studies met the inclusion criteria and were included in the systematic review. The information from these studies is shown in Table 1.

### Included studies

Fifteen studies were included in this review which comprised two randomized controlled studies, eight case series, and five case reports.

Most of the women patients included in the selected studies belonged to the fourth decade of life and all presented with previous or predicted difficult ETs. The women presented with cervical stenosis/tortuous, multifactorial reasons, endometriosis, or previous difficult ET (no cause described).

### Fertility-related outcomes

Within the studies selected, six of the studies had patients with specific cervical stenosis, two had multifactorial causes for difficult transfer, two had previous difficult ET, and two had previous surgery. With regard to treatment distribution within the selection of articles, five studies used treatment with cervical dilation, two with transmyometrial ET (Towako needle),<sup>[28,30]</sup> two with hysteroscopy, one used laminaria tents, one had blastocyst replacement, and one had a catheter stylet addition.

Cervical stenosis was the most common cause of difficult ET and, of the studies specifically described patients with cervical stenosis, two had cervical dilation, one had laminaria tents, one had an intrafallopian tube transfer, and two had operative hysteroscopy with Foley catheters fitted.

Of the 159 LBs, 77 of them were due to cervical dilation 1–3 months before ET<sup>[22]</sup> and 60 of them were due to the addition of a stylet during difficult ET. Figure 2 depicts the rest of the techniques that provided LB.

Of all the selected studies, five studies used the technique of cervical dilation.<sup>[15-17,21,22]</sup> These studies described different methods of cervical dilatation. They also tested the timing of cervical dilation before the ET. The time frame ranges from 48 h<sup>[21]</sup> to 1–3 months.<sup>[22]</sup> Serhal *et al.* described the use of cervical dilation and hygroscopic rod placement; none of the other articles described the use of these and of the cervical dilation studies, this yielded the highest PR (30/54 patients = 55.6%).<sup>[17]</sup> The

results of the cervical dilation procedures are plotted on a graph, with accordance to their length of time before ET. From the graph [Figure 3], it is easy to see that, the longer the time left after cervical dilation before ET, the greater the PR.

Four studies specified the size of Hegar used for the cervical dilation which ranged from 6.5 to 9. These studies detailed the size of the Hegar dilator used,<sup>[15,21,23,24]</sup> when comparing the PR; the findings of Tews *et al.* had to be excluded as it was only a study with one patient.<sup>[23]</sup> However, a correlation is shown in Figure 4 of the PR against the size of the Hegar dilator.

When analysis of the data was done, only three studies specified that the patient was to be placed in the lithotomy position<sup>[15,21,25]</sup> and the other three studies

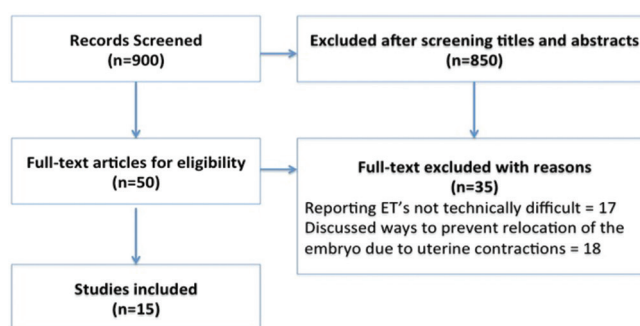


Figure 1: Included studies

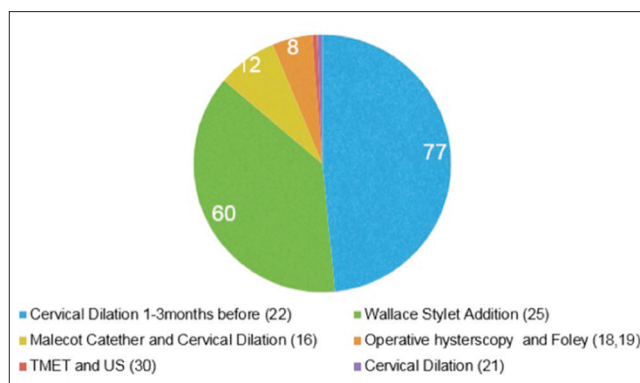


Figure 2: The techniques that provided pregnancy

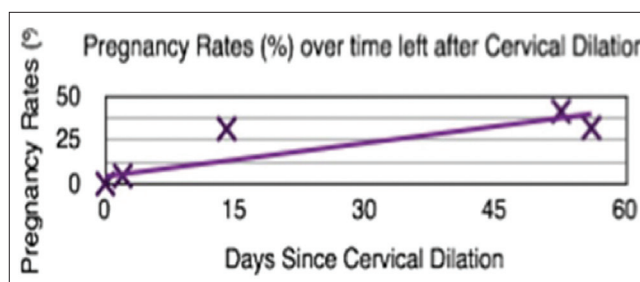


Figure 3: Longer the time interval after cervical dilation before embryo transfer, the greater the pregnancy rate

**Table 1: Included studies**

Author, year, Country	Number of patients	Mean age (years)	Definition of difficult ET	Intervention	Clinical PR
<b>Randomised controlled trial</b>					
Groutz, 1997, Israel	Gp 1 - 20 Gp 2 - 20	Gp 1 - 31.8 Gp 2 - 34.7	Patients with cervical stenosis (as well as patients who failed to conceive after at least three previous IVF-ET cycles)	Gp 1 - Transmyometrial	Gp 1 - 5%
				Gp 2 - Cervical dilators	Gp 2 - 15%
Prapas, 2004, Belgium	Gp 1 - 145 Gp 2 - 138	Gp 1 - 33.16 Gp 2 - 32.48	Difficulty was encountered while introducing the hard Wallace malleable stylet in two previously failed IVF attempts	Gp 1 - Cervical dilatation (Hegar number 9)	Gp 1 - 40%
				Gp 2 - No dilatation	Gp 2 - 24%
<b>Retrospective/prospective case series</b>					
Groutz, 1997, Israel	22	31.6	Not specified	Cervical dilation with Hegar dilators	9%
Abusheikha, 1999, UK	57	-	To be defined as difficult, an ET had to involve one or more of the following: Cervical resistance leading to a prolonged procedure (5 min), the need to use force, or the application of Allis forceps and a metallic guide (stylet) with or without cervical bleeding	Cervical dilatation under general anesthesia after pituitary suppression and before gonadotropin stimulation	32%
Noyes, 1999, USA	Difficult - 67 embryo transfers Extremely difficult - 7 embryo transfers	-	Difficult – Performed with a tomcat catheter requiring cervical manipulation but whose end result was smooth placement of the embryos into the uterine cavity  Extremely difficult – Tomcat catheter was threaded into the cervix with extreme difficulty, with or without cervical dilation, or where frank bleeding from the cervix was seen after the procedure. These transfers were not believed to have a smooth end	-	Difficult - 45% Extremely Difficult - 0%
Yanushpolsky, 2000, USA	36	35.1	Histories of extreme difficulties encountered in entering their endometrial cavities during IUIs, ETs, endometrial biopsies, or papanicolaou smear evaluations	Hysteroscopic evaluation and/or correction of the endocervix, followed by transcervical placement of a Malecot catheter	41.6%
Nielsen, 2002, Denmark	205 embryo transfers	32.1	-	Wallace malleable stylet in combination with an Edwards–Wallace embryo replacement catheter	29.3%
Serhal, 2003, UK	54	36.8	Either failed to conceive after previous difficult embryo transfer or were noted to have a difficult mock embryo transfer	Cervical dilatation with hygroscopic cervical rods (Dilapan-S)	57.7%

Contd...



Table 1: Contd...

Author, year, Country	Number of patients	Mean age (years)	Definition of difficult ET	Intervention	Clinical PR
<b>Retrospective/prospective case series</b>					
Singh, 2012, India	58	31.6	Additional instrumentation was required or firmer catheter was used or required changing of catheter.	-	17.2%
Kava-Baverman, 2017, Spain	547 embryo transfers	38.4	When additional instrumentation, such as a tenaculum or a hysterometer, was required	Use of the outer sheath of the SureView catheter Use of a Wallace malleable stylet (Simcare) Application of a tenaculum Insertion of a hysterometer	27.1%
<b>Case reports</b>					
Glatstein, 1997, USA	2	33.5	Necessitating the use of a cervical tenaculum, dilators, and intracervical lidocaine anesthesia	Laminaria tents	100%
Noyes, 1999, USA	1	29	-	Hysteroscopic cervical canal shaving	100%
Lesny, 1999, UK	1	31	-	Transmyometrial transfer	100%
Jamal, 2009, Canada	1	38	-	Transmyometrial transfer	100%
Tews, 2012, Austria	1	40	-	Intrafallopian transfer	100%

ETs=Embryo transfers, PR=Pregnancy rate, IUIs=Intrauterine insemination, IVF=*In vitro* fertilization

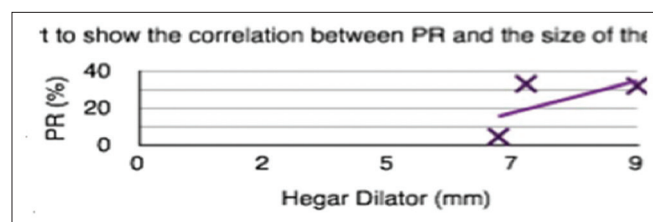


Figure 4: Correlation of the pregnancy rate against the size of the Hegar dilator

suggested that the patient must have a full bladder before the procedure.<sup>[17,22,26]</sup> Seven of the studies performed a mock ET first.<sup>[17-19,21,26-28]</sup>

The list of studies included are summarized in Table 1.

## DISCUSSION

This study provides a comprehensive and a most up-to-date review on the management of difficult ET. There is a correlation between the length of time between cervical dilation and timing of ET as shown in Figure 3. These results show that, the longer the time left between dilation and ET, the higher the success rate. This correlation is supported by Lesny *et al.* that shows

that trauma to the endometrial lining of the uterus can cause failure of the embryo to implant or can cause junctional zone contractions.<sup>[20]</sup> However, a study done by Barash *et al.*, where endometrial samples were taken from the patient just before ET, showed that the LB was double than that of not having the local injury.<sup>[29]</sup> Although this study contradicts the previously found evidence, there is need for more research on when to transfer the embryo after an intrusive procedure to yield the highest PR. During this, there should be the same set of controls within the testing as direct comparison across different studies does not offer the correct control comparison of techniques.

A correlation between the size of the Hegar dilator and the PR is shown in Figure 4. The data suggest that, the larger the dilator, the higher the PR. Significant conclusions cannot be drawn as the studies cannot be directly compared as the procedures were not carried out exactly the same.

Whether a difficult transfer affects the PRs is a theory well disputed within fertility medicine. Tur-Kaspa *et al.* proved that a difficult ET would have no effect on the

PR.<sup>[10]</sup> However, Tomas *et al.* showed that a difficult ET did result in decreased PR.<sup>[14]</sup> A most recent review in 2012 also supported that PR rates were decreased if the transfer was not easy.<sup>[11]</sup> Kava-Baverman *et al.* had supported that PR decreased progressively with the use of additional maneuvers during difficult ET.<sup>[31]</sup> Reduction in PR is also seen with difficult ETs, when blood is present at the catheter tip.<sup>[32]</sup>

This review demonstrates that cervical dilation would be an appropriate treatment for those with difficult ET, due to cervical stenosis. Due to evidence suggesting that easier transfers result in higher IR,<sup>[14]</sup> cervical dilators offer a solution to negotiating the majority of difficult transfers. However, there is also some evidence that some transfers remain difficult even after cervical dilation.<sup>[15]</sup>

The evidence collected shows that for optimal PR, the dilation should be done between 1 and 3 months before the ET. Furthermore, from the data collected on the size of the Hegar dilator, it is seen that that, the larger the dilator, the higher the PR. The Hanks dilator was used only in one study.<sup>[26]</sup> However, it was alongside the use of laminaria tents, so there cannot be a direct comparison between the two dilators. There were inconclusive data to suggest whether the mock ETs performed in some studies<sup>[17-19,21,26,28]</sup> had any effect on the outcomes. Prapas *et al.* did not include a mock ET but did discuss that to help improve IR and PR a mock ET should be done.

The use of hysteroscopy, whether operative, evaluation, or guided in difficult transfer, was used in four of the studies. All of these studies had successful LB ranging from 33.3%<sup>[16]</sup> to 58.3%<sup>[19]</sup> to 100%.<sup>[9,18]</sup> Hysteroscopy was used only in those with cervical stenosis and has shown to be a successful technique for manipulating a difficult ET. The hysteroscopic evaluation can be used alongside cervical dilation and placement of a Malecot catheter,<sup>[16]</sup> which combines the two most successful strategies found within the review; cervical dilation, and the use of hysteroscopy. There has been some debate to how long the Malecot catheter should be kept to improve IR.

From this review, the data suggests that if a difficult ET can be converted into an easy ET, the PR can improve. Cervical dilation has been proven to be able to modify ET to easy transfers in between 64% and 79.5% of patients.<sup>[15-17]</sup> Although it has been suggested that transmyometrial ET (TMET) may be indicated in patients with cervical stenosis,<sup>[24]</sup> research has found that TMET is a traumatic procedure<sup>[15]</sup> that will cause an increase in junctional zone contractions.<sup>[24]</sup> And as previously mentioned, the increase in uterine

contractions can cause an increased risk of displacement of embryo to a suboptimal location, such as the fallopian tubes.<sup>[20,28]</sup>

Ideally, a thorough series of controlled clinical trials between the time of cervical dilation and subsequent ET for those with difficult ET should be done and perhaps a comparative study between the success rates of different size Hegar dilators on patients with difficult ET should be completed. Such studies would help draw definitive conclusions on the management of difficult ETs in infertility patients.

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### Conflicts of interest

There are no conflicts of interest.

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