Difficult embryo transfers and assisted reproductive outcomes: a systematic review and meta-analysis

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**Introduction**

Assisted reproductive techniques (ART) are widely used for the treatment of subfertility. Various protocols exist but they frequently involve the recruitment of multiple follicles through controlled ovarian hyperstimulation and manipulation of gametes prior to the replacement of one or more embryos. Clinical pregnancy and live birth rates per cycle started remain relatively low, at approximately 30-40% and 20-30% respectively \(^1\)\(^2\). This may be partially explained by the implantation rate - or the chance of an embryo be detected as a gestational sac a few weeks after transference - which remain around 15-20% \(^2\). Although this can be partially circumvented by maximized ovarian hyperstimulation and multiple embryo transfer, these strategies are associated with the main problems of ART: multiple pregnancy and ovarian hyperstimulation syndrome \(^3\).

Implantation is, however, a complex process and, as yet, one not fully understood \(^4\)\(^5\) but aside from the quality of the embryos replaced and the receptivity of the endometrium, the embryo transfer itself may have an impact \(^6\). Embryo transfer involves the placement of one or more embryos into the uterus in such a way as to maximize the chance of implantation. The procedure has changed very little since the first description in 1984 \(^7\). Typically, it is carried out in the dorsal lithotomy position. The cervix is first visualized with the aid of a speculum and cleaned in a variety of ways before a specialized transfer catheter is passed through the external cervical os and into the uterus as gently as possible. The embryo or embryos are then deposited by putting pressure on the attached syringe and the catheter withdrawn. Over the past 10-15 years there has been increasing interest in the technical aspects of embryo transfer \(^6\), which theoretically could interfere with implantation in a positive or, more likely, negative way.
Common sense suggests difficult transfers should be avoided as they are likely to reduce the chance of implantation and subsequent pregnancy rates. The evidence is unclear, however, as whilst several studies support this concept \(^8-10\) others do not \(^11, 12\). Systematic reviews have considered the relative merits of ultrasound-guidance \(^13\) and the use of particular embryo transfer catheters \(^14\) but none are yet evaluate the impact of a difficult embryo transfer on ART outcomes.

The objective of this review is to evaluate whether the difficult embryo transfer, the need for additional maneuvers/instrumentation or the presence of blood in the catheter after the transference interfere with the main ART outcomes: live birth, clinical pregnancy and miscarriage.

**Methods**

**Eligibility criteria**

Inclusion criteria is any type of study that reported original data regarding clinical pregnancy, miscarriage or live birth after ART, separating these outcomes by the ease of transfer, the need for additional maneuvers/instrumentation, or the presence of blood in the catheter used for the embryo transfer. Case reports and case studies where the sample size was < 10 will be excluded due to the high risk of bias. Studies that do not report per woman data (but only per cycle) will be excluded to avoid unit of analysis error which is particularly important in our review, since it is expected that difficult transfers are more likely to be unsuccessful and therefore more likely to be repeated leading to bias. There will be no limitation on language, publication date, or publication status.

**Information sources and search**
We will search the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) Database of Abstracts of Reviews of Effects (DARE), Medical Literature Analysis and Retrieval System Online (MEDLINE), Embase, PsycINFO; Cumulative Index to Nursing and Allied Health Literature (CINAHL); and Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS). We will not impose any limitation regarding language, publication date, or publication status.

**Search terms**

We will use the following search terms, adjusting for each database when necessary: ((difficult$) or (eas$) or (prolonged) or ($traumatic$) or (tenaculum) or (volsellum) or (sheath) or (mandrill) or (stylet) or ((blood$) and (catheter$))) and ((embryo$) or (blastocyst$)) and ((transfer$) or (deposition) or (placement)).

**Study selection**

Two independent reviewers (JP and WPM) will scan the retrieved titles and abstracts selecting and excluding those that clearly do not meet the eligibility criteria; disagreements between reviewers will be resolved by consensus or a third party (NRF). One author (JP) will obtain full copy of all potentially relevant studies and full articles will then be examined for eligibility independently by two reviewers (JP and WPM). Disagreements between the reviewers will again be resolved by consensus, or when not possible, by consulting a third authors (CON).

**Data collection process**

One review author (JP) will extract the data from included studies using a data extraction form designed and pilot-tested by the authors. One author (WPM) will independently check the extracted data. Disagreements will be resolved by consensus and we will contact the corresponding author of a study in order to resolve any data queries as required. The names
of article authors and titles of the included studies will be juxtaposed seeking for duplicate publication; if any duplicated publication is found we will consider both articles as being part of a unique study.

Data items

We will extract the following data from included studies: study characteristics (design, aims, time period, population, inclusion and exclusion criteria); intervention and setting; IVF and embryo transfer protocols (including use of ultrasound, day of transfer, use of ICSI and cryopreserved oocytes); ease of transfer; need for additional maneuvers/instrumentation; presence of blood in the catheter after embryo transfer; and outcomes of ART: clinical pregnancy, miscarriage and live birth.

Risk of bias in individual studies

Each study will be analyzed by the Newcastle Ottawa scale 15.

Summary measures and analysis

All results will be combined for meta-analysis using Review Manager 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). For dichotomous data we will use the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel risk ratio. We choose to use Mantel-Haenszel methods because they have better statistical properties when there are few events 16. If, for any outcome, we observe a zero cell count or prevalence < 1%, we will use the Peto fixed-effect model because this method was found to be the least biased and most powerful, providing the best confidence interval coverage, in these situations 16. We also prefer the risk ratio (RR) because odds ratio (OR) is the hardest summary statistic to understand and to apply in practice, and many practicing clinicians report difficulties in using them 16 and because there is concern
that routine presentation of the results of systematic reviews as odds ratios will lead to frequent overestimation of the benefits and harms of treatments when the results are applied in clinical practice. We will arbitrary consider a difference as clinically relevant when the change in the risk for a dichotomous outcomes is ≥ 20% (RR ≤ 0.80, or RR ≥ 1.20).

We will present the results separated by the 3 criteria used to define difficult embryo transfer: ease of transfer subjectively assessed by the care provider; need for additional maneuvers/instrumentation during embryo transfer; and presence of blood in the catheter used for embryo transfer. We feel this is important because it is very plausible that the different concepts used to define a difficult embryo transfer can interfere with ART outcomes in different ways. We also plan to combine the results of all studies, only stratifying for the 3 aforementioned criteria. If any study report more than one of the 3 criteria, we will only use data of one criterion to avoid double-counting the same subjects. We will respect the following preference: 1. ease of transfer, 2. need for additional maneuvers/instrumentation, and 3. presence of blood in the catheter.

**Synthesis of results**

We will assess heterogeneity by using I². Substantial heterogeneity (I²>50%) among the studies will be addressed firstly by checking again if data is correct and, secondly, by applying a random-effect model.

**Risk of bias across studies**

We aim to minimize the potential impact of publication and reporting biases by performing a comprehensive search for eligible studies and looking for duplication of data. If 10 or more studies are included in an analysis, a funnel plot will be used to investigate the possibility of small study effects.
Authors’ roles

James Philips: Drafted the protocol and developed the search strategy. Additionally this author will search for trials, obtain copies of full article, select which trials to include, perform data extraction, interpret the analysis, and draft the final review.

Wellington P. Martins: Drafted the protocol and developed the search strategy. Additionally this author will search for trials, select which trials to include, check data extraction, carry out the analysis, interpret the analysis, and draft the final review.

Carolina O. Nastri: Drafted the protocol and developed the search strategy. Additionally this author will interpret the analysis, and draft the final review.

Nicholas J. Raine-Fenning: Drafted the protocol and developed the search strategy. Additionally this author will interpret the analysis, and draft the final review.


References


