BIOFLUID SIMULATION OF THE EMBRYO TRANSFER TECHNIQUE

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INTRODUCTION

Embryo transfer (ET) is the last stage of extracorporal fertilization at which embryos generated in the laboratory are returned to the uterus for development of a natural pregnancy. The ET procedure is a mechanical intervention composed of insertion of the catheter into the uterine cavity, injection of the medium that contains the embryos, and removal of the catheter. It is considered to be the major obstacle for embryo implantation, and thus, it is responsible for the low rate of success of IVF procedures (<25%). The anticipated outcome of ET is implantation of the embryo at the fundus (the upper part of the uterus), and it depends on the anatomy and physiological performance of the recipient, the instruments that are used and the manual procedure itself. It was recently suggested that much of the inefficiency associated with the low implantation rate may stem from the currently used ET technique, i.e., catheter type, loading of the catheter, placement of catheter tip and physician skills [1]. In this study we examined the mechanical characteristics of ET by *in vitro* simulations of ET in a simplified laboratory model and by implementing a three-dimensional (3D) computational analysis.

METHODS

In Vitro

The setup for *in vitro* experiments was composed of a uterine model, a computer-operated linear actuator and a video camcoder (Fig. 1). The uterine model was made of two rectangular Perspex boards separated by a rubber pad of 2.5 mm, which has the geometry of the inner cavity of the uterus in the frontal cross-section. The uterine model was positioned in a bath filled with glycerin in order to mimic the viscosity of the uterine fluid. The transferred fluid was simulated by saline colored by 10 mg bromophenol blue dissolved in 10 ml Tris 10 mM PH 8. The catheter was loaded in the following sequence as in the real ET procedure: 1.5 ml air, 3 µl medium, 3 µl air and again 3 µl medium (which usually contain the embryos) and 1 µl air. The catheter was inserted through the narrow opening of the uterine model ("cervix") and the transfer procedure was recorder by the video camcoder. We simulated various locations of the catheter within the uterine cavity: 0.5, 1.5, and 2.5 cm from the fundus. The delivery speed of the transferred matter was controlled by a linear actuator. The piston of the syringe was pushed at various speeds to generate flow rates ranging between 1.6 ml/s to 8 ml/s.

Computational Analysis

The transport phenomenon during an ET procedure was simulated by a thin fluid-filled catheter inserted within a 3D truncated cone of length L with elliptic cross-sections, which represents the intrauterine cavity. The geometry of the tube was defined as follows:

$$\frac{x^2}{a(z)^2}+\frac{y^2}{b(z)^2}=1, \qquad 0\le z\le L$$

where L=5 cm, $a(z)$=0.2+0.04z and $b(z)$=0.75+0.15z are the ellipse constants. The cone was closed at z=L. A rigid catheter of radius r_c=0.05 cm was introduced into the cone with its tip at a distance ℓ=3 cm from the open end of the cone (z=0). The transferred matter was injected at constant speeds of 0.1 and 0.5 cm/s. No-slip and no-penetration conditions were specified on the walls of the cone and the catheter. The continuity and Navier stokes equations for laminar flow of an incompressible fluid with constant viscosity were solved numerically by FLUENT (Fluent Inc., Lebanon, NH).

RESULTS AND DISCUSSION

Numerous mock ET experiments have been conducted by the *in vitro* experimental setup and the dynamic distribution of the transferred matter within the uterine cavity during the injection was analyzed. The final shape of the transferred matter was like a "Mickey mouse" head and composed of two small dye volumes (3 µl) and a big air circle (1.5 ml) (Fig. 2). The two small volumes of air (3 and 1.5 µl) appeared as one small bubble, but most of the time, it was added to the big air bubble. The dye volumes were injected forward, however, as the 1.5 ml air was injected, the dye volumes (i.e., Mickey's "ears") were pushed backward towards the cervix. The goal of ET is to

induce embryo implantation in the fundus, however, the air bubble remained near the fundus while the embryos were transported away from the fundus. The position of the catheter affected the final distribution of the transferred matter only when the catheter was 0.5 cm from the fundus. In this case, the air bubble became elliptic, somewhat squashed and lying along the fundus. Thus, if the embryos "intend" to reach the fundus in order to implant there, the air bubble disturbs since it takes the majority of the fundal surface. When the catheter was far enough from the fundus, the air bubble was circular and the distribution of the dye "ears" was unchanged. When the volume of the air bubbles increased, the transport of the dye volumes towards the cervix increased. Increasing the volume of the dye, increased the size of the "ears", but did not change the position of the air bubble and the direction of transport toward the cervix. As the velocity of injection increased, the "ears" were transported faster towards the cervix.

The 3D simulation of ET revealed the possible trajectories of the embryos (Fig. 3). The particles were transported towards the fundus, then, as they reached the fundus, the stream changed direction towards the cervix. The particles, which left the catheter from its mid-width, hitted the fundus. Particles near the catheter walls did not reach the fundus but entered swirls that turn towards the cervix. Thus, injection at high speeds may accelerate the transport towards the cervix, and thereby, preventing the embryo from implantation in the fundus. The simulation may also explain how embryos may be found in the vagina or on the catheter at the end of the procedure. As the catheter is withdrawn, the embryos may sucked with it.

CONCLUSIONS

The ET process was simulated by *in vitro* experiments and computational analysis within a 3D truncated cone containing a catheter. The computational simulation revealed that the injection of the transferred matter influences the trajectories of the embryos. The *in vitro* simulation showed the contribution of the loaded components in the catheter on the overall transport characteristics. Understanding of the mechanical aspects of ET in the uterus during and after the ET maneuver and the controlling parameters of ET may provide new guidelines for this procedure in order to improve the outcome of IVF.

REFERENCES

1. Schoolcraft,W.B., Surrey,E.S., Gardner,D.K., 2001, "Embryo transfer: technique and variables affecting success. Fertility and Sterility", Vol. 76, pp. 863-870.

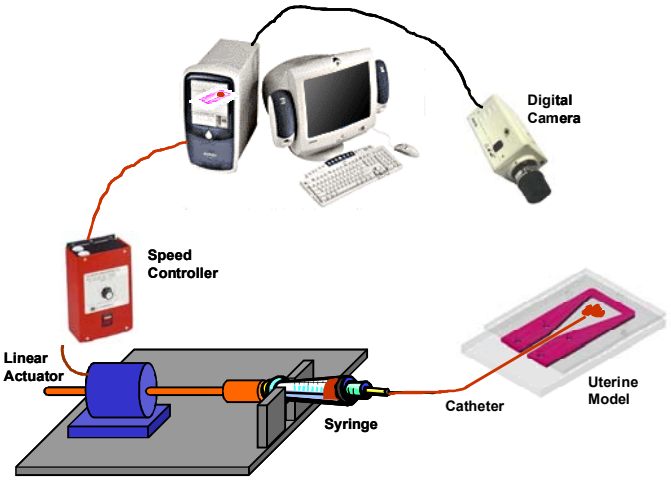


Figure 1. Scheme of setup for in vitro ET experiments.

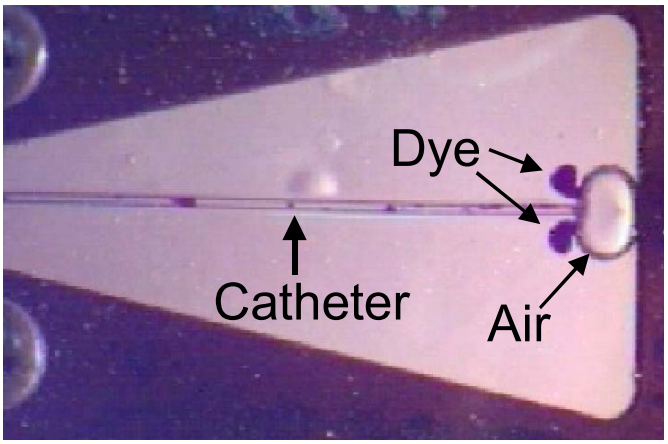
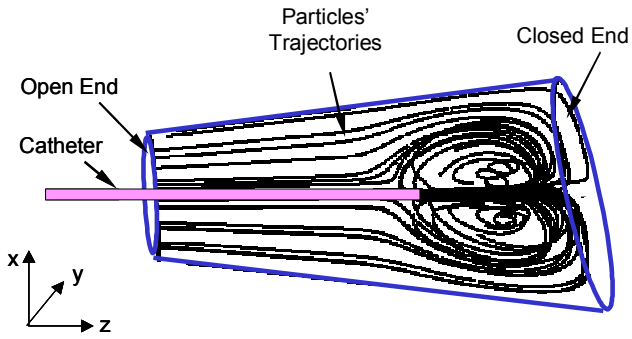


Figure 2. Temporarily distribution of the transferred matter.



Numerical prediction of the trajectories of particles injected at a speed of 1 cm/s.