Introduction

Infertility is the central issue in the lives of the individual who suffers from it. It is a source of social and psychological suffering for both men and women and can place great pressure on the relationship within the couple **(Neitherdt et al., 2005)**.

The causes of infertility can be male, female or a combination of both and include ovulatory disorders, tubal disease, endometriosis, chromosomal abnormalities, sperm factors and unexplained infertility. The majority of infertility cases, both male and female factors, are overcome through surgical and medical infertility treatment. Medical treatment options include assisted reproductive techniques (ART) such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and intrauterine insemination (IUI) **(Nazemian, 2011)**.

Successful outcome of ART resulting in implantation is dependent upon good embryo quality with optimal embryo transfer technique and a receptive endometrium. Improvement in these factors will lead to an increase in the success of ART **(Ghanem et al., 2016).**

In vitro fertilization (IVF) has been used over decades as treatment for infertility with different etiologies. Despite the developing technology and advances in the field, implantation failure remains a major problem. Many factors have been proposed including endometrial receptivity, embryo quality and the procedure of embryo transfer (ET) **(Singh et al., 2012)**.

Embryo transfer (ET) is a short, yet the most crucial and critical step that significantly affects the success of the whole process of IVF **(Mains and Voorhis, 2010)**.

Most ET are easy and unforced. Difficulties are, however, encountered in up to 15-20% of cases. Reasons for difficult ET include acute version of flexion angles between the vagina, cervix and the uterine corpus; stenosed internal os; or previous false tract **(Mansour and Aboulghar, 2002)**.

Several strategies have been proposed to overcome difficulty during ET procedure, including performing ET under ultrasound-guidance, instructing the patient to have a full bladder at the time of the procedure, and use of stylet with soft catheter **(Ghaffari et al., 2013)**.

Nevertheless, for a small group of women, ET procedure remains difficult and requires further steps, which

may induce uterine contractions or provoke endocervical or endometrial bleeding; which both might have an adverse impact on successful implantation and the whole IVF outcome **(Garzo, 2006)**.

More interestingly, several prospective and retrospective studies have observed that even women who had successful implantation following difficult ETs might have remote bad outcome, in terms of miscarriage among women who had initially a positive clinical pregnancy outcome **(Tur-Kaspa et al., 1998; Sallam and Agameya, 2014; Ghaffari et al., 2013; Singh et al., 2012; Ghanem et al., 2016; Punhani et al., 2016)**.

The aim of the current study was to assess the association between difficult ET with clinical and ongoing clinical pregnancy outcome**.**

Aim of the work

Study Objective

The aim of the current study is to investigate the clinical and ongoing clinical pregnancy rates in women who experience difficult embryo transfer (ET) after IVF/ICSI cycle.

Study Question

In women who undergo IVF/ICSI, is difficult ET associated with lower clinical and ongoing clinical pregnancy rates?

Study Hypothesis

In women who undergo IVF/ICSI, difficult ET may be associated with lower clinical and ongoing clinical pregnancy rates.

IVF success rates

Fertility is the capacity to produce offspring, and a couple is considered to be infertile if they cannot conceive after 12 months of unprotected intercourse. A more strict definition of infertility is failure to achieve a pregnancy in a 12 month period for patients under 35 years of age and failure to conceive in a 6 month period for the over 35 years **(American Society for Reproductive Medicine, 2008).**

Infertility is the central issue in the lives of the individual who suffers from it. It is a source of social and psychological suffering for both men and women and can place great pressure on the relationship within the couple. For continuation of genesis procreation is human right. Based on the note from UN declaration of human rights Article 16: 1 it is said that men and women of full age, without any limitation due to race, nationality or religion have the right to marry and to find a family **(Neitherdt et al., 2005)**. But unfortunately 1 in 6 couples of any society remains infertile, and 10% of them need the help of assisted reproductive technology **(Mcllveen et al., 2005)**.

The announcement of birth of Luise Brown in July 1978 was not the beginning of the end of in vitro fertilization (IVF),

but an important milestone along the way to what is now an important and internationally recognized treatment option for some infertile couples.

The birth of Luise Brown occurs exactly 100 years after first attempts of in vitro fertilization of mammalian eggs which was made by the embryologist, Schenk in 1878. Since then significant contribution and refinements in the knowledge of reproductive biology and biotechnological science have been adding till date **(Brauer and Schuttman, 2014)**.

The prevalence of infertility worldwide is estimated to be one in seven to one in five (14-20%) couples in their reproductive age. The causes of infertility can be male, female or a combination of both and include ovulatory disorders, tubal disease, endometriosis, chromosomal abnormalities, sperm factors and unexplained infertility. The majority of infertility cases, both male and female factors, are overcome through surgical and medical infertility treatment. Medical treatment options include assisted reproductive techniques (ART) such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and intrauterine insemination (IUI). Infertility treatment has been dramatically advanced in recent years; however, age

related infertility remains as one of the most difficult challenges **(Nazemian, 2011)**.

Age must be taken into account when couples are considering assisted reproductive technology. It is well known for years that the pregnancy rate is inversely related to the age of the female **(American Society for Reproductive Medicine, 2006).**

Some explanations for this include diminished ovarian reserve, increased rate of aneuploidy, decreased frequency of sexual intercourse, diminished desire for childbearing and increased rate of spontaneous abortion. Among infertile women undergoing infertility treatment, advanced maternal age is also associated with lower fertilization rates and higher risk of chromosomal abnormalities. In humans, the age of the oocyte, not the age of the uterus, is the main cause of reproductive failure in IVF and embryo transfer techniques **(Bentov et al., 2010)**

A number of pre-treatment interventions have been proposed in order to maximize the success of in-vitro fertilization (IVF). While this may well be true for some of these, there are others which have been popularized on the basis of relatively poor scientific evidence in support of their

clinical usefulness. Female age has been long recognised as the most important prognostic factor for success; the younger the woman, the higher the chances of live birth after IVF treatment. Other positive predictors of success include a history of previous live birth or pregnancy, short duration of infertility and unexplained infertility which is associated with the better prognosis than other causes **(Nelson et al., 2011)**

Lifestyle factors, such as obesity, smoking and alcohol intake, may also affect the chance of success after IVF treatment. In couples preparing for IVF treatment, these factors are of particular interest as they are potentially modifiable. Two independent systematic reviews have investigated the relationship between obesity and pregnancy outcomes after IVF **(Maheshwari et al., 2007) (Rittenberg et al., 2011)**. Both concluded that women who are overweight or obese (BMI $\geq$ 25) are more likely to miscarry and less likely to achieve pregnancy or live birth after IVF treatment.

In contrast, a systematic review on women undergoing oocyte donation could not demonstrate any difference in pregnancy rates for obese recipients compared to their normal BMI counterparts **(Jungheim et al., 2013),** urging the

authors to suggest that the adverse effect of obesity on IVF success rates may be mediated via oocyte, rather than endometrial quality. The aforementioned findings support research into strategies of weight normalization before starting IVF treatment.

Female smoking can adversely affect virtually every stage of reproductive function, including folliculogenesis, steroidogenesis, embryo transport, endometrial receptivity, myometrial blood flow and contractility **(Dechanet et al., 2011).**

Smokers are also more likely to suffer from diminished ovarian reserve compared to their age-matched counterparts **(Freour et al., 2010)**. Active female smoking halves the chance of clinical pregnancy and live birth and doubles the risk of miscarriage**,** while male smoking can adversely affect semen quality, embryo development and IVF outcome **(Waylen et al., 2009).**

The evidence regarding the potential adverse effect of alcohol intake on IVF success is less conclusive than for smoking. A recent systematic review has reported that both female and male alcohol intake prior to IVF may compromise reproductive outcomes**.** Women who consume a

significant amount of alcohol (at least 4 drinks per week) have a lower chance of live birth after IVF treatment. However, no safe limit of alcohol consumption has yet been proposed during IVF or subsequent pregnancy, which suggests that alcohol intake should be stopped or kept to a minimum **(Nicolau et al., 2014)**.

Ovulatory disorders are one of the most common causes for infertility in women, accounting for 30% of women's infertility. Ovulation is the monthly release of an egg. In some cases, the woman never releases eggs, and in others, the woman does not release eggs during some cycles.

Ovulatory disorders are caused by issues including hormonal problems, damaged or scarred ovaries, premature menopause, and follicle problems **(Hasan et al.,2017).**

Another factor affecting about 25% of infertile couples is poorly functioning fallopian tubes, or tubal disease. It is caused by infections, abdominal diseases, previous surgeries, ectopic pregnancy, and congenital defects. The fallopian tubes can experience a range of issues from mild adhesions to complete blockage, in which case eggs can't, or have trouble being released **(Hasan et al.,2017).**

Endometriosis affects about 10% of all infertile couples. For women with endometriosis, their monthly chance of getting pregnant is reduced to 36% **(Hasan et al., 2017).**

IVF is a multistep process, or cycle, in which eggs are extracted and fertilized with sperm in a lab. Once embryos develop, some are implanted in the woman's uterus (typically 1-3) and if further viable embryos remain, they are stored **(Christiano, 2011)**.

In vitro fertilization may be a treatment option if:

- A woman's fallopian tubes are missing or blocked.
- A woman has severe endometriosis.
- A man has low sperm counts.
- Artificial or intrauterine insemination has not been successful.
- Unexplained infertility has continued for a long time. How long a couple chooses to wait is influenced by the female partner's age and other personal factors.
- A couple wants to test for inherited disorders before embryos are transferred.

(Romito, 2015)

The success of IVF treatment varies by age – yielding 41% pregnancy rate for women under age 35, 32% for women ages 35 to 37, and 23% for those ages 38 to 40. If successful, couples with serious fertility problems can become parents. However, treatments can be costly and can be physically demanding, requiring a regiment of fertility drugs before the start of each cycle **(Christiano, 2011)**. These drug treatments can have serious implications for the mother and baby.

Successful outcome of ART resulting in implantation is dependent upon good embryo quality with optimal embryo transfer technique and a receptive endometrium. Improvement in these factors will lead to an increase in the success of ART **(Ghanem et al., 2016).**

Embryo transfer (ET) is the last step of critically important procedure of in vitro fertilization (IVF) and probably the least successful step in Assisted Reproductive Technology (ART) treatment cascade; though simple in most of the cases, it may pose to be the most difficult in some **(Ghaffari et al., 2013)**. The entire IVF cycle depends on delicate placement of the embryos at the proper location near the middle of the endometrial cavity.

Pregnancy rates will be significantly increased with the following procedures:

1. Trial transfer.

2. Avoiding the initiation of uterine contractility by using soft catheters, gentle manipulation and by avoiding touching the fundus.

3. Removal of cervical mucus, wash and lavage of cervix with culture media.

4. Ultrasound-guided ET with full bladder.

5. Deposition of the embryo 2 cm below the uterine fundus.

6. Examination of catheter following transfer for retained embryos, blood and mucus **(Singh et al., 2012)**.

Slow withdrawal of the embryo transfer catheter, the use of a fibrin sealant, bed rest after embryo transfer, sexual intercourse and routine administration of antibiotics following embryo transfer remained to be studied by randomized clinical trials (RCTs).

The success of in vitro fertilization (IVF) depends on numerous factors such as embryo quality, infertility cause, endometrial receptivity, and the embryo transfer (ET) technique. An ET is the final step in an IVF cycle which,

despite its simplicity, can adversely impact the IVF result. Many investigators have suggested that a meticulous ET technique is essential to IVF success **(Mansour and Aboulghar, 2002)**. Unfortunately, the performance of an ET is not as simple as it appears; poor ET technique accounts for 30% of all IVF failures **(Ghaffari et al., 2013).**

Most ET are easy and do not require the use of force or manipulation. Different attempts have been suggested to prevent technically difficult ET, such as the performance of a dummy ET in order to ascertain the depth and direction of the uterus, ultrasonography-guided ET for correct embryo placement; and instructing the patient to have a full bladder for straightening the uterocervical angle **(Mansour and Aboulghar, 2002)**.

Despite these suggestions, there are a small group of patients for which ET is difficult and accomplished by the use of manipulation, which increases uterine contractions and could affect embryo implantation **(Singh et al., 2012)**.
Because a difficult ET has been shown to cause a significant reduction in pregnancy rate **(Punhani et al., 2016)**, therefore more attention should be focused on this simple, last step of the IVF cycle in order to improve the IVF outcome.

Embryo Transfer

1- Introduction

Since the first successful pregnancy from an in vitro fertilized oocyte in humans almost 30 years ago, significant improvements in the in vitro fertilization (IVF) procedure have been realized.

This first IVF pregnancy used natural cycle monitoring with oocyte recovery during open abdominal surgery. Since then, gonadotropins as well as gonadotropin releasing hormone agonists and antagonists have significantly improved the success rates of IVF by increasing the number of oocytes collected in a single cycle **(Mains and Voorhis, 2010)**.

Improvements in ultrasound technology have facilitated the retrieval of oocytes during an outpatient, trans-vaginal follicle puncture and oocyte aspiration and advancements in our understanding of the developmental requirements of the human embryo have improved our ability to culture embryos in vitro **(Ammar et al., 2013)**.

The procedure of embryo transfer, placing the embryo(s) into the uterine cavity has remained relatively