# CORRELATION BETWEEN INFERTILITY ETIOLOGY AND FIRST TRIMESTER MISCARRIAGE RATE FOLLOWING INTRACYTOPLASMIC SPERM INJECTION (ICSI).

Thesis
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*Mona Hassan Abd Elshakour*

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AFC** | Antral follicle concentration |
| **APS** | Antiphospholipid syndrome |
| **ASRM** | American society for reproductive medicine |
| **AZF** | Azoospermic factor |
| **CBAVD** | Congenital bilateral absence of vas deference |
| **CF** | Cystic fibrosis |
| **CFTR** | Cystic fibrosis transmmbrane conductance |
| **CL-RI** | Corpus leuteum resistance index |
| **ESC** | Endometrial stromal cells |
| **ESHRE** | European society for human reproduction |
| **FSH** | Follicle stimulating hormone |
| **GIFT** | Gamet intrafallopian transfer |
| **GNRH** | Gonadotrphine releasing hormone |
| **HH** | Hypergonadotrophine hypogonadism |
| **HPG** | Human pituitary gonadotrophine |
| **HMG** | Human menopausal gonadtrophine |
| **IVF** | Invitro fertilization |
| **LH** | leutinizing hormone |
| **MSOME** | Motile sperm organelle morphology examination |
| **PCOs** | Polycystic ovarian syndrome |
| **POF** | Premature ovarian faliure |
| **POI** | Primary ovarian insuffeciancy |
| **PGS** | Pre-implantation genetic screening |

| | |
|---|---|
| **PID** | Pelvic inflammatory disease |
| **RCT** | Randomized controlled (clinical) trial |
| **RPL** | Recurrent pregnancy loss |
| **SGA** | Small for gestational age |
| **SCO** | Sertoli cell only |
| **UI** | Unexplained infertility |
| **uNK** | Uterine natural killer |
| **YCM** | Y chromosome microdeletion |
| **ZIFT** | Zygot intrafallopian transfer |

## Classification of evidence levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g. case reports, case series

4 Expert opinion

## Grades of recommendations

A At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

## Good practice point

✓ Recommended best practice based on the clinical experience of the guideline development group

## Classification of evidence levels

| | |
|---|---|
| Ia | Evidence obtained from meta-analysis of randomised controlled trials. |
| Ib | Evidence obtained from at least one randomised controlled trial. |
| IIa | Evidence obtained from at least one well-designed controlled study without randomisation. |
| IIb | Evidence obtained from at least one other type of well-designed quasi-experimental study. |
| III | Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies. |
| IV | Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities. |

## Grades of recommendations

| | |
|---|---|
| A | Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib) |
| B | Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III) |
| C | Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV) |

## Good practice point

| | |
|---|---|
| ✓ | Recommended best practice based on the clinical experience of the guideline development group. |

# Introduction

Human reproduction is not efficient, with the majority of conceptions being lost very early in gestational life as Implanted embryos may undergo developmental arrest at any point during early gestational life, and spontaneous abortion rates among natural conception are notoriously difficult to measure *(Macklon et al., 2002).*

The incidence of first trimester abortion is estimated to be between 10-20%.However, the true incidence is not well known because many abortions occur before pregnancy is clinically recognized *(Philippe et al., 2003b).*

The introduction of intra cytoplasmic sperm injection (ICSI) in 1992 revolutionized the management of failure of invitro fertilization and in case of severs male factor infertility with high success rate *(Gwendolyn et al., 2005).*

Most IVF programs see that about 70-85% eggs injected using ICSI have become fertilized, we call that fertilization rate which is different from the pregnancy success rate *(Speroff and Fritz, 2005).*

There are no solid data to compare the incidence of miscarriage in spontaneous versus ART pregnancies but it is generally accepted that the incidence is slightly higher after ART. The main reason for higher incidence is the age of the patients, which on average is 3-5 years higher than that of a fertile population at time of a first pregnancy. Indeed, studies on the risk of spontaneous miscarriage indicate that maternal age is an important risk factor *(Andersen et al., 2000).*

Pregnancies achieved by intracytoplasmic sperm injection (ICSI) are at higher risk for obstetrical and prenatal complication than spontaneous pregnancies and also surveillance during pregnancy should be considered. *(Gaudoin et al., 2003).*

It remains unclear if these increased risks are attributable to the underling infertility cause, characteristics of infertile couples or use of assisted reproductive technique *(Allen et al., 2006).*

Several studies have assessed miscarriage rate in intracytoplasmic sperm injection (ICSI) and documented in groups of patients with specific aetiology *(Wang et al., 2004).*

Data from a previous study indicated that the rate of first trimester pregnancy loss was 18.8%.the underling cause of infertility was male factor in 18.9%, unexplained infertility in 18.1%, tubal factor in 17.5%, endometriosis in 23.9% and PCO in 24 % *(Mustafa and Ulun, 2005).*

Conceivably, an increased rate of pregnancy loss may indicate an abnormal outcome related to ICSI as a technique. However, miscarriage rates have not been extensively assessed in a general infertile population (regardless of male factor) undergoing assisted reproduction treatment with ICSI. It is therefore important to document the survival rate of implanted gestations following ICSI and to compare these rates relative to underlying etiology of infertility *(Mustafa and Ulun, 2005).*

# Aim of the work

To assess the association between underling etiology of infertility and first trimester miscarriage rate among women who will undergoing ICSI.

# *First trimester miscarriage*

**Risk factors for first trimester miscarriage according to royal college** guideline,which was first published in 1998 and then in 2003:

*1- Epidemiological factors.*

2- *Antiphospholipid syndrome*.

*3- Genetic factors.*

a- Parental chromosomal rearrangment.

b- Embryonic chromosomal abnormalities.

*4- Anatomic factors.*

*5- Endocrine factors.*

*6- Immune factors.*

*7- Infective factors.*

*8- Inherted thrombophilic defects.*

### *1- Epidemiological factors*

Maternal age and number of previous miscarriages are two independent risk factors for a further miscarriage. Advancing maternal age is associated with a decline in both the number and quality of the remaining oocytes *(Nybo Anderson et al., 2000).*

Previous reproductive history is an independent predictor of future pregnancy outcome.The risk of a further miscarriage increases after each successive pregnancy loss, reaching approximately 40% after three consecutive pregnancy losses, and the prognosis worsens with increasing maternal age *(Nybo Anderson et al., 2000).*

A previous live birth does not preclude a woman developing recurrent miscarriage *(Clifford et al., 1997).*

The evidence on the effect of environmental risk factors is based mainly on data studying women with sporadic rather than recurrent miscarriage. The results are conflicting and biased by difficulties in controlling for confounding factors and the inaccuracy of data on exposure and the measurement of toxin dose.Maternal cigarette smoking and caffeine consumption have been associated with an increased risk of spontaneous miscarriage in a dose-dependent manner. However, current evidence is insufficient to confirm this association *(Peck et al., 2010).* Heavy alcohol consumption is toxic to the embryo and the fetus.Even moderate consumption of five or more units per week may increase the risk of sporadic miscarriage *(Kesmodel et al., 2002).*Working with or using video display terminals does not increase the risk of miscarriage *(Marcus et al., 2000).*The evidence on the effect of anaesthetic gases for theatre workers is conflicting *(McGregor, 2000).*

Recent retrospective studies have reported that obesity increases the risk of both sporadic and recurrent Miscarriage *(Metwally et al., 2010).*

### *2- Antiphospholipid syndrome*

Antiphospholipid syndrome is the most important treatable cause of recurrent miscarriage.Antiphospholipid syndrome refers to the association between antiphospholipid antibodies – lupus anticoagulant, anticardiolipin antibodies and anti-B2 glycoprotein-I antibodies – and adverse pregnancy outcome or vascular thrombosis *(Miyakis et al., 2006).*

Adverse pregnancy outcomes include:
_ three or more consecutive miscarriages before 10 weeks of gestation
_ one or more morphologically normal fetal losses after the 10th week of gestation

_ one or more preterm births before the 34th week of gestation owing to placental disease *(Bose et al., 2005).*

The mechanisms by which antiphospholipid antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation *(Bose et al., 2005).* Activation of complement pathways at the maternal–fetal interface resulting in a local inflammatory response *(Salmon et al., 2003)* and, in later pregnancy, thrombosis of the uteroplacental vasculature *(Peaceman and Rehnberg, 1993)* In vitro studies have shown that the effect of antiphospholipid antibodies on trophoblast function and complement activation is reversed by heparin *(Girardi et al., 2004).*

Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage *(Rai et al, 1995).* By comparison, the prevalence of antiphospholipid antibodies in women with a low-risk obstetric history is less than 2% *(Pattison et al., 1993).*

In women with recurrent miscarriage associated with antiphospholipid antibodies, the live birth rate in pregnancies with no pharmacological intervention has been reported to be as low as 10% *(Rai et al., 1995).*

***3-Genetic factors***

**a- Parental chromosomal rearrangements**

In approximately 2–5% of couples with recurrent miscarriage, one of the partners carries a balanced structural chromosomal anomaly:most commonly a balanced reciprocal or Robertsonian translocation *(Franssen et al., 2006).*

Although carriers of a balanced translocation are usually phenotypically normal, their pregnancies are at increased risk of miscarriage and may result in a live birth with multiple congenital malformation and/or mental disability secondary to an unbalanced chromosomal arrangement *(Franssen et al., 2006).*