بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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Hereditary Thrombophilia in Recurrent IVF Failure

Thesis

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By

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INTRODUCTION

The predominant part of IVF cycles results in embryo transfer, but only about one third of all cycles reach clinically achieved pregnancy. This is evidence that most embryos failed in an early stage of pregnancy achievement. Recurrent implantation failure after IVF procedures emphasize the clinical importance of this crucial step in assisted reproductive technology. Repeated unsuccessful IVF attempts force efforts to investigate the firm mechanism of the implantation and to find approach to increase pregnancy outcome success ***(Petar et al., 2012).***

Plenty of factors have been recognized to affect either success, or failure rate of IVF embryo transfer. Maternal side factors include age, parity, hormonal levels before stimulation, antral follicles count, endometrial thickness and quality of transformed endometrium. Other factors, having functions in coagulation and fibrinolysis cascades, were found to be connected with the transformation processes in the endometrium during the implantation. In relation with that, the alteration of the functional activity of blood coagulation factors could influence blastocyst acceptance in the endometrium. One proposed cause for implantation failure could be maternal thrombophilias ***(Qublan et al., 2005).***

Pregnancy itself alters the hemostatic system into a hypercoagulable state, which increases throughout pregnancy and is maximal around term. Most notably there is a significant change to coagulation, with increased factor VII, VIII, X and von Willebrand factor activity and marked increases in fibrinogen ***(Szecsi et al., 2010).*** Thrombin generation markers such as prothrombin F1 and 2 and thrombin-antithrombin (TAT) complexes are also increased ***(Sarig et al., 2011).*** There is also a marked decrease in anticoagulant activity including reduced protein S levels and acquired activated protein C resistance. Fibrinolytic activity is also reduced with plasminogen activator inhibitor type 1 (PAI-1) levels increased by five-fold and increases in placentally-derived plasminogen activator inhibitor type 2 (PAI-2), particularly during the third trimester ***(McLean et al., 2012).***

These changes in the hemostatic system can predispose both the mother and fetus to complications during the pregnancy. The risks of are inherently higher in women with acquired or inherited thrombophilia. However, at present routine screening for these disorders is not routinely recommended in the absence of venous thromboembolism. Further, the value of screening those with pregnancy complications is uncertain. In addition, some of the tests themselves are imprecise. Pregnancy and the postpartum state as well as intercurrent illness, in addition to the clinical implications of both positive and negative results are often

misunderstood. Due to the growing pregnant population and successful artificial reproductive technologies, many women are now older and have more medical complications when embarking on pregnancy, hence testing for heritable thrombophilias in women with previous pregnancy complications is becoming increasingly common as a practice despite these limitations ***(Simcox et al., 2015).***

Aim of the Work

The aim of this study is to evaluate the effect of congenital thrombophilia on embryo implantation in an IVF cycle as to make proper management leading to increase IVF success rate.

Chapter 1

IN VITRO FERTILIZATION FAILURE

About one-third of women undergoing IVF and embryo transfer will achieve an ongoing pregnancy. Thus, failure to achieve pregnancy implies failure of the pregnancy at implantation or at a time shortly thereafter. Several factors have been recognized to affect either success or failure rate of IVF–embryo transfer. Such factors include age, parity, previously successful pregnancy, basal hormonal levels, number of antral follicles before stimulation, endometrial thickness, embryo grading, position and length of uterus and technique of embryo transfer ***(Qublan et al., 2005).***

Repeated IVF failure represents an enormous emotional and in some countries financial burden for the patient. Despite the strong desire to become a parent, 50% of infertile couples do not seek treatment, and 50%-60% of couples drop out of treatment after failing two or three IVF cycles ***(Olivius et al., 2004).***

Various definitions of recurrent implantation failure (RIF) exist, but one expert proposed pathologic implantation failure be defined as failure of three IVF cycles in which one or two high-grade quality embryos were transferred to the patient in each cycle or after two failures in oocyte donor recipients ***(Simon and Laufer, 2012).***

The process of implantation depends on the communication between the embryo and the endometrium, which produces numerous factors and signals required for successful implantation and pregnancy outcome after IVF. Despite great investigative effort, this process largely remained an enigmatous '*black box*'. Patient care, follicular recruitment, oocyte quality and aspiration, embryo quality culture, and cryopreservation have greatly improved since the emergence of IVF more than three decades ago. Despite a significant increase in IVF success rates, the implantation of the transferred embryos still remains the major success limiting factor ***(Shufaro and Schenker, 2011).***

TYPES OF RECURRENT IMPLANTATION FAILURE

In some cases, RIF can be defined as a unique condition due to unidentified abnormalities or damage of the endometrium which would not even allow the initial steps of embryo implantation (apposition, attachment). If that is the case, the endometrium and its ability to provide, in a timely restricted manner, an environment suitable for embryo implantation should be regarded as a crucial factor ***(Salker et al., 2010; Teklenburg et al., 2010).***

Nevertheless, another alternative would be the existence of a combined deficiency of both the embryo and the endometrium which would transform the cross-talk between the mother and the embryo in an ineffective or unsynchronized

way. This would create a total blockade or disarrangement of the sophisticated cascade of molecular signaling needed in both embryo and endometrium for successful implantation and pregnancy. The immunological relationship between mother and conceptus still remains a mystery, although the recent advances in molecular biology have lightened a lot of parameters that participate in feto-maternal cross-talk during implantation ***(Timeva et al., 2014).***

The following classification of RIF was suggested to allow taking correct therapeutic approaches for these patients ***(Timeva et al., 2014).***

I. Multifactorial RIF (wide variety of reasons for RIF):

a. Maternal anatomic factors, including congenital uterine abnormalities, endometrial polyps, uterine fibroids, adhesions, hydrosalpinges, endometriosis, etc.

b. Male factors, when severe oligoasthenozoospermia was diagnosed or increased sperm DNA fragmentation

c. Genetic abnormalities, where embryos with good morphology have aneuploidy

d. Hormonal or metabolic disorders (uncontrolled diabetes, thyroid disease, variations in the prolactin level, etc.)

e. Infections