Protein S Activity in Women with Unexplained Infertility

Thesis

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By

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Esraa Gamal Al Shawadfy

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
AMH	*Anti-mullerian hormone*
APAs	*Anti-phospholipid anti bodies*
APC	*Activated Protein C*
APS	*Antiphosholipid syndrome*
ART	*Assisted Reproductive Technologies*
AT	*Antithrombin*
ATA	*Anti-thyroid antibodies*
C4BP	*C4 - binding protein*
CCCT	*Clomiphene citrate challenge test*
COCs	*Combined Oral Contraception*
DM	*Diabetes mellitus*
DOAC	*Direct Oral Anticoagulants*
DVT	*Deep Venous Thrombosis*
ElISA	*Enzyme-linked immunoassay*
Etc.	*'Et Cetera'.*
E.	*Estrogen*
FPS	*Free Protein S*
FSH	*Follicular-stimulating hormone*
FVL	*Factor V lieden*
GnRH	*Gonadotrophin Releasing Hormone*
HIT	*Heparin Induced Thromboembolism*
HSG	*Hysteosalpingography*
HTN	*Hypertension*
ICSI	*Intracytoplasmic sperm injection*
i.e.	*Id Est*
IF	*Implantation Failure*
IUI	*Intrauterine insemination*
IVF	*In vitro fertilization*
LA	*Lupus anticoagulant*

List of Abbreviations (Cont...)

Abb.	Full term

LH.....*Luteinizing hormone*
LPD.....*Luteal phase defect*
NOAs.....*New Oral Anticoagulants*
P/V.....*Per vaginal*
PAF.....*Platelet activating factor*
PAI-1.....*Plasminogen activator inhibitor-1*
PC.....*Protein C*
PCO.....*Polycystic ovary*
PCT.....*Post Coital Test*
PID.....*Pelvic inflammatory disease*
POF.....*Premature ovarian failure*
P......*Progesterone*
PS.....*Protein S*
RPL.....*Recurrent pregnancy loss*
SLE.....*Systemic lupus erythematosus*
STD.....*Sexually transmitted diseases*
TF.....*Tissue factor*
TFPI.....*Tissue Factor Pathway Inhibitor*
TGA.....*Thrombin Generation Assay*
TSH.....*Thyroid stimulating hormone*
UI.....*Unexplained Infertility*
UK.....*United Kingdom*
USA.....*United States of America*
VT.....*Venous Thrombosis*
VTE.....*Venous Thromboembolism*
WHO.....*World Health Organization*

ABSTRACT

The current study has shown that there was statistically significant difference between the two groups (P value: 0.039) as regard to the percentage of protein S activity, as mean values of protein S in two groups were (98.11±23.86) and (104.22±20.96) respectively**.**

The present study has shown that the number of patients of cases who had decreased protein S activity was (0) zero and its percentage was (0%), while the number and percentage of controls who had decreased protein S activity was 1 (3.33%) and this difference was of statistically not significant (P value: 0. 157).

In conclusion, there was also no statistically significant difference between the two groups regarding protein S activity or incidence of protein S deficiency and The mean of protein S activity percentage (%) in cases is lower than in controls.

Keywords: Platelet activating factor - Premature ovarian failure - Recurrent pregnancy loss

INTRODUCTION

Infertility is a condition in which successful pregnancy has not occurred, despite normal intercourse over 12 months. Approximately, 9 to 18% of normal couples are infertile ***(Aghajanova et al., 2017).***

Studies suggest that 50% of infertility cases are due to a female factor, 20–30% due to a male factor, and the remaining 20–30% are a combination of both ***(Agarwal et al., 2015).***

American Society for Reproductive Medicine committee opinion on the diagnostic evaluation for infertility in women addresses several tests and procedures, starting with a comprehensive medical, reproductive and family history, as well as a thorough physical exam. Subsequently, conducting evaluation should be in a systematic, expeditious and cost-effective manner to identify all relevant factors, with initial emphasis on the least invasive methods for detection of the most common causes of infertility. Diagnostic tests and procedures include evaluation for ovulatory dysfunction, ovarian reserve, cervical factors, uterine abnormalities, tubal disease and peritoneal factors ***(ASRM, 2017).***

In women who have difficulty conceiving, the possible causes of embryo implantation failure have been investigated, both in spontaneous cycles and in induced cycles in assisted

reproduction. Among the various factors that may interfere with the implantation process, thrombophilic factors are considered to prevent fertility.

Over the past ten years, thrombophilias have been identified with increasing frequency in women submitted to repeat treatment cycles of in vitro fertilization (IVF) with failed embryo implantation when compared with fertile women. A study conducted a case-control study analyzing hereditary thrombophilia factors in infertile, fertile and women with failed implantation. That study reported a high frequency of thrombophilia in the subgroup of women with implantation failure. Those authors suggested a negative effect of a state of hypercoagulability on embryo implantation ***(Annichino et al., 2017).***

Thrombophilia seems to be more frequent than expected among the healthy population and could impair implantation in some subgroups of infertile women**.** Thrombophilia is a complex disease process, which clinically expresses as venous thrombosis. The presence of a genetic defect in one of the major contributing components (protein C, protein S, and antithrombin) to thrombophilia can be determined by clinical laboratory assays ***(Marlar et al., 2014).***

Protein S is a vitamin K-dependent protein, unlike the other vitamin K-dependent plasma proteins, Protein S is not a serine protease. Protein S inhibits coagulation by acting as a cofactor for

both tissue factor pathway inhibitor and activated protein C. Therefore, it is not surprising that a deficiency of protein S predisposes to venous thrombosis ***(Mulder et al., 2018).***

The Protein S concentration in normal human plasma is (60–140 IU/dL) ***(Wang et al., 2015).***

In plasma, protein S is present in two forms, a free fraction consisting of 40% of total protein S, which is considered as the active form and the remaining fraction bound to the β-chain of complement component C4-binding protein (C4BP). Even though it is generally accepted that only the free form of protein S has cofactor activity, the protein S fraction bound to C4BP may have some anticoagulant activity ***(Mulder et al., 2018).***

AIM OF THE WORK

Study hypothesis:

In women with unexplained infertility, protein S activity may be low.

Study question:

In women with unexplained infertility, does protein S activity decrease?

This study aims to assess the activity of protein S activity in women with unexplained infertility.

Objectives:

The main objective of this study is:

To determine the prevalence of Protein S activity with unexplained female infertility and to compare its prevalence in fertile women among women attending outpatient clinics at Ain Shams University Maternity Hospital.

Chapter 1

INFERTILITY

Infertility is a condition in which successful pregnancy has not occurred, despite normal intercourse over twelve months. Approximately, 9 to 18% of normal couples are infertile ***(Aghajanova et al., 2017).***

Common causes of infertility include factors of male infertility, female infertility, infertility in couples and unexplained infertility ***(Deroux et al., 2017).***

Female infertility is due to the following definite reasons: Immune infertility, tubal obstruction and ovulatory dysfunction ***(Busnelli et al., 2016).***

Studies suggest that 50% of infertility cases are due to a female factor, 20–30% due to a male factor, and the remaining 20–30% are a combination of both ***(Agarwal et al., 2015).***

Infertility affects one in seven (1: 7) couples, and its rate is on the increase. Ovulatory defects and unexplained causes account for >50% of infertile etiologies ***(Talmor et al., 2015).***

The American Society for Reproductive Medicine considers infertility a disease, rather than a mere quality of life issue. In addition, a recent US Supreme Court opinion expressed that conditions interfering with reproduction should be considered

a disability as defined under the Americans with Disabilities Act since reproduction is a major life activity, which when disturbed, can be severely debilitating ***(Kloss et al., 2015).***

The World Health Organization (WHO) designated the infertility as a disease, and its treatment as one of the fundamental human rights ***(Hajder et al., 2016).***

For healthy couples in their 20s or early 30s, the chance that a woman will become pregnant is about 25–30% in any single menstrual cycle. This percentage decreases rapidly after age 37 years. By age 40 years, a woman's chance of getting pregnant drops to less than 10% per menstrual cycle. A man's fertility also declines with age, but not as predictably ***(ACOG, 2017).***

Secondary infertility is the most common form of female infertility worldwide, often due to reproductive tract infections. The three major factors influencing the spontaneous probability of conception are the time of unwanted non-conception, the age of the female partner and the disease-related infertility ***(Vander et al., 2018).***

Infertility as a complex state and life crisis and sets out the dangers of neglecting the emotional impact of involuntary childlessness and viewing it solely in biological or medical terms.***(RCOG, 2015).***

Infertility counselling in the UK, within the context of fertility treatment includes an explanation of the differences

between the three main types of counselling, implications, support, and therapeutic counselling, and the role of various bodies, including the Counselling Service, Human Fertilization and Embryology Authority and British Infertility Counselling Association ***(RCOG, 2015).***

Counselling plays a major complementary role in providing total patient-centered care by multidisciplinary staff in fertility clinics, emphasizes the review. It also explains that counselling is an amalgam of medicine and mental health, which should be viewed as a continuation of the medical process, where the medical and psychological aspects of infertility treatment are integrated.

At present, the counselling role occupies a unique and diverse position within the infertility field, including that of patient advocate, gatekeeper, researcher and educator, supportive resource to colleagues, confidante and point of liaison.

As reproductive laws continue to develop, these will influence the role of the counselling provider. However, whatever the extent of these changes, counselling practitioners must continue to work within the boundaries of acceptable practice as outlined by their professional body, state the authors. They must also continuously engage in training and professional development, comply with additional available credentialing and be subject to the laws and standards within this specialist field of infertility ***(RCOG, 2015).***