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Immunothrombosis: The Pathological Basis of Unexplained Recurrent Reproductive Failures

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Abstract

The failure of human reproduction in both natural and assisted cycles of reproduction is currently a major public health problem. In 1975, a hypothesis published in the Lancet entitled “where have all the conceptions gone? concluded that 78% of all conceptions were lost before birth. Unexplained recurrent reproductive failures; the inability to conceive or maintain pregnancy to term in a healthy woman within her reproductive age accounts for 80% of all pregnancy losses and 50% of infertility. In the present review, we describe the concept of immunothrombosis, a major hypothesis in the pathology of unexplained recurrent reproductive failures.

Keywords: Unexplained recurrent miscarriage, Unexplained recurrent implantation failures, Unexplained infertility, Low-grade chronic inflammation, Low-grade intravascular coagulation

INTRODUCTION

Unexplained Recurrent Reproductive Failures (URRF) is a clinical term that broadly defines the inability to conceive or the incapacity to maintain pregnancy to term in a healthy woman during her reproductive age [1 – 3]. It involves three different clinical conditions of infertility namely repeated pre-implantation failures that occurs in a natural reproductive cycle (Unexplained Infertility, UI), repeated implantation failures that occur in assisted reproductive therapy cycles (Unexplained Recurrent Implantation Failures, URIF), and repeated post-implantation failures that occur in a natural reproductive cycle (Unexplained Recurrent Miscarriages, URM) [4, 5]. It accounts for 80% of all cases of reproductive failures and 50% of all cases of infertility [6 – 8].

Types of Unexplained Recurrent Reproductive Failures

- i. **Unexplained Recurrent Implantation Failures:** this refers to repeated failures of embryos to implant in a healthy woman aged less than 40years resulting from a failure of the embryo–endometrial immune tolerance in at least three or more assisted reproductive therapy cycles following the transfer of competent embryos[9,10]. Embryo implantation is a complex process involving apposition, adhesion, and invasion of a competent embryo into a receptive endometrium within a specified period referred

to as the window of implantation[11-13]. It is considered the rate-limiting step in assisted reproductive therapy cycles[14-17].

- ii. **Unexplained Recurrent Miscarriage:** refers to repeated post-implantation failures or expulsion of embryos weighing <500g which is equivalent to approximately <22weeks of gestation in a natural cycle of reproduction due to maternal immunological rejection [6,18-20,]. They may be termed unexplained habitual abortions or unexplained recurrent pregnancy loss. Based on history, unexplained recurrent miscarriage can be either classified as biochemical loss (pregnancy confirmed only by serum HCG), Sac loss(pregnancy confirmed by an ultrasound which shows only a gestational sac with 6 minimal embryonic structures), or fetal loss (loss of fetal heart activity that has been previously confirmed). It can also be classified as first-trimester miscarriages (early pregnancy loss of < 12 weeks gestation) and second-trimester miscarriages (late pregnancy loss of > 12 weeks gestation).
- iii. **Unexplained Infertility:** refers to a condition in which a couple fails to conceive after 1 year of regular unprotected sexual intercourse even though investigations for ovulation, tubal



patency, and semen analysis are normal[21,22]. It could be referred to as unexplained subfertility.

Risk Factors for Unexplained Recurrent Reproductive Failures

There are currently two major hypotheses for the cause of unexplained recurrent reproductive failures:

- i. **Failure of maternal-conceptus crosstalk:** unexplained recurrent reproductive failure is considered a maternal disease involving the failure of alloimmune crosstalk between the mother and the conceptus [23,24]. The intricate crosstalk between the mother and the conceptus in placental mammals creates a potential problem of two genetically distinct individuals having to coexist for the duration of the pregnancy which implies that during pregnancy, the mother's immune system has to tolerate the presence of paternal alloantigens (non-self) from the placenta and/or the fetus [25,26]. In this context, pregnancy is considered a unique immunological challenge which could be compared to the transplantation of a tissue or organ from a donor that is tolerated by the recipient (mother) and not rejected with a failure of tolerance resulting reproductive failure.
- ii. **Inability of scientists to identify subtle reproductive abnormalities:** the scientific assessment of the reproductive process has not been fully established. There are many steps of the reproductive process for which there are no established routine diagnostic tests for its evaluation both in males and females [27]. There are currently no established tests to assess the acrosome reaction and the ability to bind to and penetrate the zona pellucida by spermatozoa. Similarly, limitations also exist for female fertility assessment in which case tubal patency test for female fertility does not assess the characteristic of bidirectional tubal motility which is important for embryo transport[28]. There are equally no tests for the evaluation of the chances for a successful implantation. Sperm defects such as abnormal acrosomes resulting in poor or no zona pellucida binding and defects in acrosome reaction resulting in failure of sperm zona pellucida penetration are possible factors leading to unexplained recurrent reproductive failures[29,30]. Sperm DNA integrity may be a prerequisite for normal fertilization but an otherwise normal semen analysis as per the WHO criteria may include sperm with altered genetic material induced by various factors such as defects in chromatin remodeling at the time of meiotic division, post-testicular oxidative stress, various environmental factors or advanced male age[31,32].

Immunothrombosis and Unexplained Recurrent Reproductive Failures

Immunothrombosis describes the intricate crosstalk between Low-Grade Chronic Inflammation(LGCI) and Low-Grade Intravascular Coagulation(LGIC). Low Intravascular Coagulation and Low-Grade Chronic Inflammation are both pathological states lacking overt inflammation and coagulation but are characterized by continuous and unresolved activation of inflammation and coagulation respectively [33]. Both pathological states triggers an adverse maternal immune response to the deposited sperm cell, zygote, implanting embryo, and/or the fetal allograft[34]. During alloimmune response, inflammatory mediators particularly pro-inflammatory cells induce the activation of coagulation proteins which cause a decrease in natural anticoagulant proteins and a decrease in fibrinolytic activity resulting in a prothrombotic state[34]. The outcome of this is a failure of microvascular circulation which may result to failure of pre-implantation processes of pregnancy, implantation or post-implantation processes, placental abruption, fetal growth restriction, and spontaneous abortion[35].

Conclusion

We hypothesize that modeling of the process of immunothrombosis (low grade chronic inflammation and/or low-grade intravascular coagulation) in patients with unexplained recurrent reproductive failures holds a promise for a better understanding of its pathological basis and targeted therapy.

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