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Review Article

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Recurrent pregnancy loss resulting in IVF (In Vitro Fertilization) series. Pathophysiologic mapping. A systematic review

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Abstract

Objective: *Assiduous depiction of recurrent pregnancy loss (RPL) in patients after in vitro fertilisation (IVF).*

Material and Method: *Women undergoing IVF treatment who had experienced two or more consecutive pregnancy losses before 20 weeks' gestation with or without a history of implantation failure. Systematic review resulting in specific data bases such as Pub Med and Cochrane data base.*

Results: *Factors associated with RPL after IVF consist mainly genetic origin (approx. 30%) due to aneuploid embryos, followed by thrombophilia and autoimmune factors. Mainly predisposition factors associated with high risk of recurrent miscarriages include obesity, advanced maternal age, anatomic defects of the uterus and endocrine disorders. On the contrary, 10-15% of cases of RPL represent idiopathic origin (Unexplained RPL). The evaluation of preimplantation genetic testing (PGT) remains a controversial entity.*

Conclusion: *The aim of our study is focusing on the pathophysiologic mapping, presented in current literature, concerning RPL after IVF. Although IVF procedures, including assisted hatching, PGT and immunologic therapy have been suggested to improve live birth rates, their efficacy is controversial, since the factors related to RPL after spontaneous abortion or IVF do not reveal any statistic differences. Additionally, assisted reproductive technique (ART) cannot be supported as a treatment intervention for couples with unexplained RPL, due to the lack of adequate clinical studies.*

Keywords: In Vitro Fertilization, Recurrent Pregnancy Loss, Preimplantation Genetic Diagnosis.

Introduction

Infertility consists a public health issue with considerable consequences including emotional and financial distress for many couples requiring assisted reproductive technology (ART). Despite that ART have been widely depicted during the last three decades, significant issue into consideration revealed the increased rate of not full term pregnancies. According to recent conducted studies presented by Human Fertilization and Embryology Authority for the United Kingdom on May 2021 for the fertility treatment programme 2019, live birth rates (LBR) for patients under 35 estimated about 32% per embryo transferred, while for patients aged 43+ when using their own eggs below 5%. In fact, only one in four attempted IVF cycles result in life birth. Recurrent pregnancy loss (RPL), defined as two or more failed pregnancies, prior to 20 weeks from last menstrual period (American Society of Reproductive Medicine), affecting 1-3% of all reproductive age couples [1,2]. A recent meta-analysis confirmed that there were no differences in abnormal findings, concerning the women's evaluation with two or three or more pregnancy losses [3].

Gestation unexpected failure can be classified into many organic and non-organic factors. Frustration, grief and emotional exhaustion of the couple, parental carriers of structural chromosome rearrangement, endocrine disturbances, antiphospholipid antibodies, uterine anomalies or immunologic deregulations.

In cases of complete genetic, anatomic, immunologic and endocrine evaluation, about 50% of couples can be remained undiagnosed, without etiologic identification of PRL, labelling them as idiopathic or unexplained (URPL). Embryo implantation is strongly accompanied with endometrial receptivity. Currently there is no clear evidence explaining if Recurrent Implantation Failure (RIF) should be evaluated and treated as RPL. Although recent molecular studies investigate several surface NK cell markers to identify a baseline inflammatory profile in women with RPL and RIF, they conclude common pathogenic pathway [4]. On the other hand, immunological factors associated with increased risk of RPL, remain controversial [5]. Immunological factors are divided into autoimmune and cellular immune [6]. Autoimmune factors include the reaction of autoantibodies to the embryo presence.

Approximately, 20% of women with RPL have autoimmune abnormalities, particularly antiphospholipid antibodies (APA), as well as anti-DNA antibody, anti-tyro Pero peroxidase antibody (TPO), and anti-thyroglobulin (anti-tg). Cellular immune abnormalities (all immune factors) due to the presence of certain natural killer (NK) cells, CH50 and C3 include the rejection of fetal paternal DNA during embryo implantation, causing miscarriage or implantation failure. Recent reviews concerning current state of immunological risk factors in RPL, consist depiction of autoantibodies, natural killer cells, regulatory T cells, dendritic cells, plasma cells, and human leukocyte antigen system (HLA) sharing as well as treatment options such as corticosteroids, intra lipids, intravenous immunoglobulins, aspirin and heparin [7].

Absence of standardized procedures, detecting immunological disorders and lack of precise recommendations do not improve IVF outcomes. Thrombophilia represent a major cause of RPL, accounting for up to 40%-50% of cases, classifying into acquired or inherited thrombophilia [8, 9]. Antiphospholipid syndrome (APS), represents an acquired thrombophilia status, characterized by presence of antiphospholipid antibodies (APL), including lupus anticoagulant, anti-cardio lipin and anti-beta2-glycoprotein I, recurrent thrombosis and/or gestational loss. According to recent bibliography, prevalence of positive APL varies reporting in up to 14% of patients, presenting with either venous or arterial thrombosis and over 20% of patients with RPL [10].

Unifying mechanism between complement and coagulation pathways remains elusive, supported by limited clinical data [11]. Inherited thrombophilia occurs due to genetic polymorphisms and deficiencies in the production of natural anticoagulants or substances that influence coagulation. These includes prothrombin gene (PT G20210A) mutation, factor V Leiden (FVL) mutation, protein C and protein S deficiency (PSD), ant thrombin III (ATIII) deficiency, and methyltet-rahydrofolate reductase (MTHFR) mutation.

These non-functional proteins seem to influence implantation consisting a known cause of RPL. Current protocols suggest administration of LMWH during IVF in patients diagnosed with thrombophilia [12]. However, the association with RPL remains controversial. Large majority of early pregnancy losses are the consequence of chromosomal abnormalities witch can be either of parental origin or due to de novo mutation of the foetus.

Age-related fertility decline in patients requiring ART, resulting in high proportions of aneuploidy and spontaneous abortions. Preimplantation genetic testing for aneuploidy (PGT-A) is widely performed in IVF, steadily increased over the past decade. Assiduous performance offers important information about potential causes of pregnancy loss and assists in the planning of appropriate investigations and treatment. According to current literature there are insufficient data to support the use of PGT-A in patients with RPL [13].

Material and Method

Aim of our study consists the pathophysiologic depiction of recurrent pregnancy loss resulting in IVF series. This systematic review assiduously reflects the summary of data, gathering from PubMed or Cochrane data base. Our effort is focused on the pathologic paths, in such entities, affecting so many female patients of reproductive age.

Discussion

We must take into consideration, the following suggestion. Is it the LBR outcome increased in couples with RPL undergoing IVF? Embryo morphology is considered a critical factor in LBR.
Additionally, it is well known the adjunction between elevated rates of pregnancy loss and Aneuploidy especially those reported at the first trimester. Embryos from ARTs, e.g. in vitro fertilisation [(IVF), intracytoplasmic sperm injection (ICSI), frozen embryo transfer (FET) cycles are commonly transferred into a uterus at either the cleavage stage (day 2 to 3 after egg collection) or blastocyst stage (day 5 to 6 after egg collection).

In recent literature and clinical practice, we observe a tendency to support the transfer embryos on day 5 or 6, at the blastocysts stage. Blastocyst morphology and the rate of development were found to be significantly associated with euploidy, whereas cleavage stage morphology was not. All disputes for blastocyst transfer reflect firstly the physiologically pre maturation of exposure early-stage embryos at the cleavage stage to the uterine environment and secondly, the blastocyst has undergone a self-selection process, in which only the most viable embryos have survived and developed [14].

According to recent literature, a Cochrane review suggested a higher clinical pregnancy and live birth rates in fresh blastocyst transfer compared to fresh cleavage stage embryo transfer [15]. However, such meta-analysis was performed for infertile rather than RPL patients. Several conducted studies have depicted the relationship between morphology, euploidy and the implantation rate of cleavage stage and blastocyst stage embryos. Implantation rates of good quality, euploid cleavage stage embryos were higher than the poor quality.

Implantation rates were similar for all transferred euploid blastocysts, irrespective of their morphology or the rate of development. A large proportion of morphologically normal day three embryos are chromosomally abnormal, although, aneuploid embryos on day three often fail to reach the blastocyst stage, while the implantation rates were similar for all transferred euploid blastocysts, irrespective of their morphology or the rate of development [16].

Additionally, logistic analysis reveals that none of the parameters

used for conventional blastocyst evaluation (morphology and developmental rate) was predictive of the implantation potential of euploid embryos, although, the implantation potential of euploid embryos was similar, despite different morphologies and developmental rates [17].

Preimplantation genetic screening (PGS) was emerged as one of the most valuable tools to enhance pregnancy success with ART. Preimplantation genetic testing comprises a group of genetic assays used to evaluate embryos before uterine transfer. Preimplantation genetic testing-monogenic is targeted to single gene disorders, and preimplantation genetic testing-aneuploidy (PGT-A) is a broader test that screens for aneuploidy in all chromosomes, including the 22 pairs of autosomes and the sex chromosomes X and Y. Preimplantation genetic testing-structural rearrangements is used to test embryos that are at risk for chromosome gains and losses related to parental structural chromosomal abnormalities (eg, translocations, inversions, deletions, and insertions) [18]. Main purpose of PGT-A in patients with RPL consists the detection of potential fetal chromosomal abnormalities before uterine transfer.

Preimplantation genetic screening (PGS) by blastomer biopsy and fluorescence in situ hybridization analysis (FISH) are no longer recommended according to current literature since it is limited to just a few chromosomes [19]. PGT-A is now expanded to include assessment of all the chromosomes by using trophectoderm biopsy and next-generation sequencing (NGS) in an attempt to detect embryonic aneuploidy in a trophectoderm biopsy obtained at the blastocyst-stage. The current version of PGT-A is claimed to have significantly improved our ability to accurately diagnose embryonic aneuploidies without compromising the embryo's implantation potential [20].

In 2012, ASRM recommends parental karyotype analysis as a balanced reciprocal or a Robertsonian translocation is present in about 2-5% of RPL couples thus could represent a major prognostic factor [21,22]. Additionally, ESHRE does not recommend the routine use of POC genetic analysis. However, it strongly recommended the use of chromosomal microarray (CMA) platforms whenever genetic POC testing is performed, indicating in couples at an increased risk, evidenced by a prior child with congenital abnormalities, offspring with unbalanced chromosomes, or a translocation in POC [23].

Recent studies have presented that parental karyotype for all RPL does not provide any benefit and that there is no overall difference in live birth rate, comparing (PGT) to natural conception in those cases [24,25]. Additionally, there are cases reported on patients experiencing RPL after PGT-A, in which chromosomal reassessment was found to be aneuploid, raising the incidence of false-negative trophectoderm biopsy (TEB) [26].

Another study, raises concern about false-positive TEBs in relative good prognosis patients, who repeatedly underwent IVF cycles without reaching embryo transfers because all embryos were erroneously reported as aneuploid. At the same time, embryos previously reported aneuploid were transferred, resulting in a surprisingly high number of normal live birth and a relatively low miscarriage rates [27].

Thrombophilia have been investigated in patients with repeated implantation failures and RPL because they are strongly associated with alteration of haemostasis and consequently with defects of implantation. Several reasons have been mentioned, relating recurrent IVF failures with presence of thrombophilia and the use of any antithrombotic drugs. Thrombophilia include both point mutations as well as deficiencies in anticoagulant proteins. The most frequent abnormalities represent Factor V Leiden mutation and the prothrombin gene mutation. These mutations occur in 2-5% of the Caucasian population [28].

The Factor V Leiden mutation is caused by the substitution of arginine by glutamine at amino acid position 506.This results in a conformational change in the protein that contributes to activated protein C resistance through disrupting factor VA inactivation [29]. Pregnancy loss in women with thrombophilia can be explained by excessive thrombosis of the placental vessels, placental infarction, and secondary utero placental insufficiency [30].

First trimester RPL is associated with FVL, activated protein C resistance, thus in several studies, Factor V Leiden mutation has been found to be more prevalent in the IVF failure group [31]. Association of inherited or acquired thrombophilia with RPL is scientifically performed.

Although, association of thrombophilia defects with primary sterility has been suggested by several recent studies [32]. Over the past decade, presence of thrombophilia has represented a daily clinical issue, not only as a cause of recurrent IVF failures but also as a debate regarding the potential therapeutic role of antithrombotic treatments, improving the IVF outcome. Administration of LMWH in ART has been extensively studied and proved to be beneficial for patients with RPL with risk factors, such as presence of thrombophilia and anti-phospholipid syndrome.

On the other hand, there is no sufficient literature data to confirm a relation among inherited thrombophilia and pregnancy rate in patients with previous IVF implantation failures. We must always take into consideration the effect of immune cells in cases of RPL, resulting in controversial outcomes. Immunologic deregulation can be a cause of inadequate placental growth and function leading to placental dysfunction, abnormal uterine development, and eventually immune rejection. Presence of autoimmune factors such as antinuclear factor (ANA), anti-DNA antibody, anti thyro Pero peroxidase antibody (TPO), and anti-thyroglobulin (anti-Tg), as well as the elevated NK-cells levels and imbalanced T helper (Th) 1 and Th2 cell reaction can be a cause for adverse IVF outcome and RPL [33,34].

However, trophoblast modulation depicts the expression of major histocompatibility complex I (MHC I) molecules. On the other hand, avoids all recognition by maternal T lymphocytes. Immunotherapy in patients undergoing IVF have been presented in several studies over the years. The most commonly used immune modulators consist, IV use of immunoglobulin, intralipids and lymphocyte immunotherapy, peripheral blood mononuclear cells, subcutaneous administration of TNF-alpha inhibitors, intrauterine infusion of granulocyte colony-stimulating factor and oral administration of glucocorticoids [35-43].

Conclusion

Recurrent pregnancy loss in IVF series, consist a significant clinical entity, affecting a major amount of female patients of reproductive age. Although several studies have been conducted with many controversial outcomes, multidisciplinary approach is mandatory in order to establish an ultimate scope.

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