The Association of Thrombophilia and Pregnancy: Six Pregnancies with recurrent fetal deformities: A Case Report

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Abstract

Recurrent pregnancy loss (RPL) can be defined as having two or more pregnancy losses. Fetal death after the 24th week of gestation is defined as stillbirth. In most cases, RPL has now known etiology. Causes may include anatomical defects, infections, and thrombophilia. Thrombophilia has several causes, such as the MTHFR gene mutation leading to hyperhomocysteinemia. Inbreeding and consanguineous marriage may also correlate with a higher incidence of stillbirth. We report a case of a young female who has a multi-factorial RPL.

Keywords: consanguineous marriage; MTHFR c677t Gene; Cytomegalovirus; Thrombophilia; case report

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Introduction

Recurrent pregnancy loss (RPL) affects 1-2% of women in reproductive age. It is defined as experiencing two or more consecutive pregnancy losses [1]. Miscarriage refers to pregnancy loss that occurs before the 24th week of gestation, while stillbirth refers to fetal death that occurs after the 24th week [2]. RPL is idiopathic in 50% of patients. Reasons include thrombophilia, autoimmune illness, infections, genetic diseases, and anatomical anomalies [1, 2, 3]. Consanguineous marriage also carries a significant risk of stillbirth, which is particularly prevalent in developing countries [4]. Several factors contribute to inherited thrombophilia (IT), which may be a cause of RPL, including homozygosity for the methylenetetrahydrofolate reductase (MTHFR) gene and mutations in the prothrombin and factor V Leiden genes [3]. Khalife and Geitani claim that the MTHFR C677T mutation is not related to an increased risk of RPL [3]. However, it may be the cause of RPL, according to other researchers [1-5]. The MTHFR gene, which is found on chromosome 1 [1-5], is linked to an increase in total homocysteine (Hcy) especially in females who consume small amounts of folate. Reduced folate levels in serum, plasma, and red blood cells, as well as a slightly elevated plasma total Hcy concentration, are linked to MTHFR C677T [1]. Many infections, including bacterial infections (bacterial vaginosis, brucellosis, chlamydia trachomatis, etc.) and viral infections (herpes virus, HSV1, HSV2, cytomegalovirus (CMV), etc.), are associated with pregnancy loss [2]. According to in vitro investigations, CMV is linked to placental malfunction, which can result in miscarriage [2]. The prevalence of CMV infection
is higher in low socioeconomic areas and poorer nations [6]. This case can show these factors accompanied together.

Case History/examination

A 30-year-old female presented to the Department of Obstetrics and Gynecology with a family history of thrombophilia. The patient had six pregnancies with recurrent fetal deformities. The first pregnancy was anembryonic, necessitating dilation and curettage to remove the placental tissues. In the second pregnancy, an induction occurred in the sixth month due to many fetal deformities, represented by ascites, pleural effusion, neck cysts, and a hiatal hernia (Fig. 1). In the third pregnancy, anticoagulants were prescribed, and suddenly the fetal heartbeat stopped during the second month. Throughout the fourth pregnancy, Clexane injections and Prednisone 20 mg tablets were taken, and a triple test was done. The calculated risk for trisomy 18 was in the high-risk area. However, this result was considered a statistical approach and has no diagnostic value. The ultrasound (US) examination during the fifth month demonstrated a slight edema in the scalp and the soft tissues of the face, which may express a slight degree of chromosome 18 disorder. During the sixth month, an elongation and edema were seen in the skull. As for the seventh month, there were clear signs of chromosome 18 disorder, fetal ascites, and oligohydramnios. The skull appeared elongated and irregular with severe edema in the soft tissues, which resulted in induction and birth in the seventh month due to the aforementioned deformities (Fig. 2). No anticoagulants were given during the fifth pregnancy, and no edema occurred. There was suspicion regarding the heart’s form. Eventually, the decision was to wait for the fetus’s growth. Unexpectedly, the fetus suddenly died in the sixth month. After confirming the death, labor was induced and the fetus came out naturally. The patient took Aspirin (81 mg/daily) during the last pregnancy, and the fetus grew normally. The amniocyte karyotyping demonstrated a normal male karyotype (XY; 46). However, the same edema returned in the seventh month, and a premature birth occurred. According to a fetus autopsy, signs of fetal CMV infection were found (Fig. 3). The CMV antibody test demonstrated a positive antiglobulin IgG, indicating that the patient had a history of CMV infection. To determine the case’s underlying cause, more tests were conducted. The toxoplasmosis and Rubella blood tests demonstrated high levels of IgG antibodies, indicating past infection or exposure to the Rubella vaccine. In addition, genetic tests demonstrated a heterozygosity with c677t that is associated with reduced MTHFR enzyme activity, which may lead to high homocysteine levels. Furthermore, the results of previous tests have contributed to an increased rate of sudden fetal death in the short term.

Conclusion and Results

This publication highlights the risks of consanguineous marriage during conception. It recommends genetic screening for women with a genetic history, emphasizing the importance of identifying mutations impacting pregnancy. In investigating RPL, viral infections like CMV should be considered, particularly in developing countries. Additionally, blood tests during pregnancy are recommended for the early detection of abnormalities.

Discussion

Recurrent miscarriage (RM) is defined as two or more consecutive pregnancies ending before 24 weeks of gestation or a fetal weight less than 500 g, affects roughly 1-2 % of reproductively active couples (7), and up to 5% of women in reproductive age. RM are clinically visible pregnancies that fail to develop for a variety of reasons, such as chromosomal, genetic, anatomical, immunological, or viral problems (8). Consanguineous marriage was linked to a more than 50% greater risk of stillbirth, according to population-based case-control research (4). A higher incidence of congenital malformations, low birth weight, and other unfavorable perinatal outcomes are linked to inbreeding (4, 8). Thrombophilia has been identified as the primary factor in repeated miscarriages (1, 9). All of the individuals identified as carriers of chromosomal anomalies were younger than 35 years old (8). Our patient is thirty years old, has been consanguineously married for eight years, and has experienced six miscarriages. Our patient’s primary suspected reason was a genetic mutation. Thrombophilia is a common cause of recurrent miscarriage, with an incidence of 40-50%. However, in addition to having thrombophilia, our patient had other associated factors that resulted in recurrent miscarriages.
The rate of births among couples with structural chromosomal abnormalities in the latter is lower than that reported in other research, which indicated up to 45% of live births (7). The MTHFR 677TT polymorphism is a significant genetic risk factor for RPL, especially in Asians (3). In our case, each pregnancy ended in stillbirth. Pregnancy number one was not embryonic (Fig. 1). In addition to dramatically raising the incidence of subsequent miscarriages, hyperhomocysteinemia in pregnant women can lead to preeclampsia, fetal hypotrophy, premature placental abruption, preterm birth, neural tube abnormalities, a cleft palate, and intrauterine fetal mortality (3). During the second pregnancy, many fetal deformities occurred (Fig. 2). Fetal loss is probably more frequent among women who have thrombophilia or exhibit an elevated (often inherited) tendency to clot. Also, there is a proven link between thrombophlebitis diseases such as antiphospholipid antibody syndrome or antithrombin deficiency and fetal loss (9). RM has unclear reasons. However, the fetus has chromosomal abnormalities in about 50% of early miscarriages, such as a structural change or aberrant chromosomal numbers. The chance of miscarriage has been linked to many additional factors. The age of both parents is important since it increases the unfavorable pregnancy outcomes if either parent is 35 or older and if the woman is 42 or older. Additional factors that have been linked to significantly greater risks of miscarriage include ethnic origin, mother’s mental health, very low or very high pre-pregnancy BMI, stress levels, usage of non-steroidal anti-inflammatory medicines, smoking, and alcohol intake (2). The maternal coagulation cascade carefully balances procoagulant and anticoagulant substances throughout pregnancy, a condition that makes blood more susceptible to clotting. Any disturbance in balance (homeostasis) may lead to blood clotting or thrombosis in decidual vessels, which in turn may result in several pregnancy complications such as intrauterine growth retardation, pregnancy-induced hypertension, placental infarction, and even fetal death (9). Differences in stillbirth rates may be due to variations in the frequency of risk factors, such as maternal age, smoking, overweight, and obesity (9). Overall, miscarriage occurred in 25% of 31–36 year-old women (10). In the third pregnancy, an anticoagulant was taken, and suddenly the fetal heartbeat stopped in the second month. Throughout the fourth pregnancy, Clexane injections and Prednisone tablets were taken. More testing was performed to identify the underlying illness’s cause. The couples had tests for karyotyping, biochemical analysis, and genetic mutation research. Inherited thrombophilia (IT) has been discussed as a risk factor for RPL in some studies. Factor V Leiden mutation (FVL G1691A), prothrombin gene mutation (FII G20210A), and homozygosity for the MTHFR C677T deficiency are the most frequent causes, respectively. It has been proven to increase the risk of maternal venous thromboembolism in obstetrics. Despite the research linking RPL and IT, mixed and controversial findings have been found. Additionally, there is a great deal of ambiguity surrounding the usefulness of thrombophilia testing in the normal evaluation of RPL (3). Although it is not a first-line diagnostic method, high-risk patients should be advised to test MTHFR and SNPs (single-nucleotide polymorphisms). Having severe infertility for a very long time, including recurrent miscarriages (9). The key factor causing hyperhomocysteinemia is still a folate deficit. The majority of mild to moderate forms of hyperhomocysteinemia are caused by mutations in the MTHFR gene due to the body’s inability to convert folic acid into methyl folate as a result of the consanguineous marriage mutation. This mutation is a major contributor to an increased risk of miscarriage and the birth of children with Down syndrome (11). The patient suffered from several factors contributing to miscarriage and RPL. These factors are hereditary thrombophilia (hence taking blood thinners during pregnancy) due to MTHFR gene mutations, consanguineous marriage that may lead to higher rates of fetal deformities and premature birth, and infections during pregnancy (specifically viral infections such as CMV (Fig. 3). CMV is the greatest member of the Herpesviridae family, with a diameter of about 200 nm (10). Although mother safety supersedes safety for the developing fetus, changes in the anticoagulant regimen used during pregnancy can eventually reduce risks to the developing fetus while maintaining therapeutic anticoagulant levels in the mother.

**Abbreviations list**

US: Ultrasound

CMV: Cytomegalovirus

MTHFR: Methylene-tetrahydrofolate reductase
RPL: Recurrent pregnancy loss
IT: Inherited Thrombophilia
RM: Recurrent miscarriage
Hcy: Homocysteine

References list


Figure legends

Fig.1: The fetus had several malformations, including a hiatal hernia, ascites in the belly, fluid coming from the side of the chest, and cervical cysts.

Fig.2: Ascites in the fetus’s belly, a reduction in amniotic fluid, the skull appearing elongated and uneven, and significant edema in the soft tissues were all obvious indicators of a chromosome 18 disorder.

Fig.3: The histological examination demonstrated macrocalcification around the ventricles in the head and enlargement of the liver and spleen, which were signs of CMV infection.