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Case Report,

Predicting Factor of BOH: How to Diagnosed?

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Abstract:

Background: Bad obstetric history (BOH) a common complication pregnancy, defined as 3 consecutive pregnancy losses prior 20 weeks from last menstrual period.
Case Presentation: A 33 years old woman, G4P1A3 hasn't feel fetus movement since 2 weeks ago, didn't experience blood coming out from her vagina or contraction on her stomach. Patient had miscarriage two times. In her first pregnancy, she experienced blood coming out of her vagina, bright red coloured. The ultrasound examination showed no vital signs in fetus and had to terminate her pregnancy with misoprostol.
Conclusion: BOH affecting approximately 15% pregnancies. It is unknown whether miscarriage happened during pregnancy with a normal fetus or not. To diagnose recurrent miscarriage, several steps are taken, namely ensuring that all prerequisite conditions for pregnancy are met, ascertaining the type and cause of recurrent miscarriage, dealing with specific management, empirical therapy, and assisted reproductive technology.

Keywords: Miscarriage, Bad Obstetric History, Misoprostol

Introduction:

The death of an infant in utero or during childbirth has always been a devastating experience for mothers and is a source of concern in clinical practice.(1) Recurrent pregnancy loss is an important global health issue and carries an underappreciated psychological and financial burden for affected couples. Bad obstetric history (BOH) is a common complication of pregnancy, affecting approximately 15% of all clinically recognized pregnancies in the general population.(2)

Recurrent pregnancy loss is defined as the failure of two or more clinically recognized pregnancies before 20–24 weeks of gestation and includes embryonic and fetal losses. Recurrent pregnancy loss can be classified into primary (three abortions in a row with a partner the same without being born before) and secondary (one or more live births) before repeated abortions in sequence).(3) The risk of pregnancy loss increases in women aged 30–35 years and then rises steeply to 33.2% in women aged 40–44 years. Recurrent pregnancy loss can be caused by chromosomal errors, anatomical uterine defects, autoimmune disorders, and endometrial dysfunction. Chromosomal abnormalities are the major recognized genetic causes of any miscarriage, accounting for up to 60% of cases.(1)

Case Presentation:

Mrs. L, 33 years old, G4P1A3 came to ER RSAL Mintohardjo with a chief complaint that she hadn't been feeling the fetus move since 2 weeks ago. She also didn't experience blood coming out from her vagina or contraction on her stomach. The patient had a miscarriage two times in the first and second pregnancy, but in the third, the patient had given birth. In her first pregnancy, she didn't realize that she was pregnant and had a miscarriage at week 9 because she wasn't aware of

it. Before it happened, slight blood came out from her vagina and it had a bright red color. In the second pregnancy, she felt nauseous and vomited. She took a test with a pregnancy test pack by herself and found out that she was pregnant. She also experienced a little blood coming out from her vagina. When she checked it, she was diagnosed with an anembryonic pregnancy and the doctor had to do curettage (in 6 weeks of pregnancy). In the third pregnancy, she gave birth to a baby by cesarean section. It was full-term pregnancy, there was no difficulty at labor, the gender was male with 2,9 kg weight and now he's 3 years old. In the fourth pregnancy, she experienced a little blood coming out from her vagina on October 4, 2022. On October 5, 2022, the amount of blood that came out increased, it was a bright red color, then she went to the polyclinic on October 8, 2022, and had checked with USG. The result was there were no vital signs in her fetus and had to terminate her pregnancy with misoprostol. Due to a lack of financial support, the chromosomal examination was not performed.

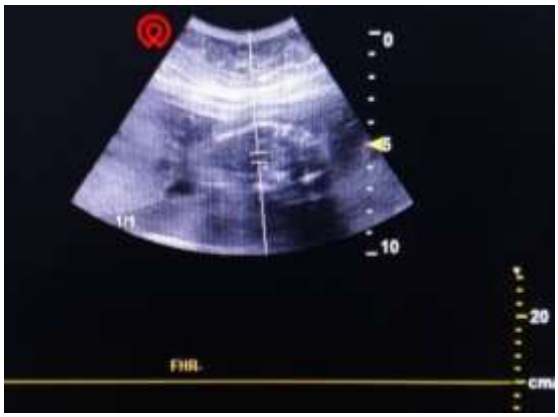

Figure1. Transabdominal ultrasound

Discussion:

Based on the case report above, the patient had three miscarriages which could be caused by several factors. In that case, the patient had experienced recurrent pregnancy loss (RPL). This is explained by the American Society for Reproductive Medicine that RPL is a miscarriage that is more than two or more, both documented by histopathologic or ultrasonography examination.[4]

A complete diagnostic evaluation needs to be done to find the etiology that causes recurrent pregnancy loss. Examinations that can be done include a complete history, including documentation of previous pregnancies, any examinations that have been done in previous abortions, is there evidence of infection or acute or chronic disease, physical or emotional trauma, history of cramps or bleeding in previous abortions, family history of pregnancy loss, and a history of previous gynecological surgery. Next, a follow-up examination is carried out according to the suspected possible etiology. RPL can be caused by age, obesity, and high parity.[3]

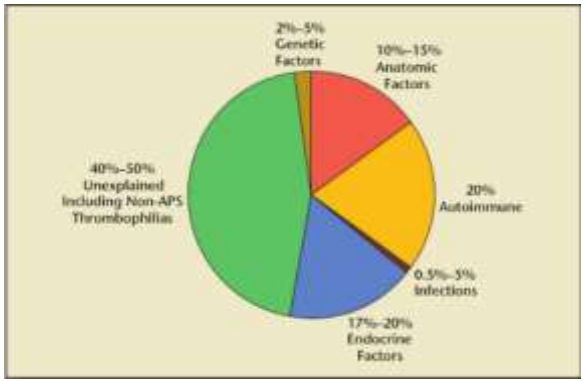

Figure2. Etiology of Recurrent Pregnancy Loss

As can be seen on Figure 2, the anatomic factors have a 10% - 15% risk of RPL.[5] Anatomical factors are uterine factors, which can be categorized as acquired or congenital. Uterine factors that can cause RPL are caused by the presence of intrauterine adhesions, myomas, and endometrial polyps. The appearance of all three can occur at sites where the basal layer of the endometrium has been destroyed. It is caused by frequent curettage, uterine surgery or infection, or birth with complications.[6]

The presence of intrauterine adhesions, which is commonly associated with Asherman's syndrome, has a significant effect on the placental formation and can lead to early miscarriage. The size of intramural uterine fibroids greater than 5 cm and submucosal fibroids of various sizes are also risk factors of RPL. Myomas are known to cause RPL through mechanical and molecular mechanisms. Myoma in the uterus can be located in the submucosa, intramural, or subserosa. Among the three uterine factors, the most common case of RPL is the presence of submucosal myoma and it has been reported that 4.5% of women experience RPL. Other abnormalities, such as the unicornuate uterus, bicornuate uterus, and bicornuate uterus, are associated with an increased risk of RPL.[6,7] Jaslow explained that the abnormalities are caused by abnormal development of the Müllerian ducts.

They are reported to be found in up to 10% of women with RPL.[8]

In addition to uterine factors, other factors that can cause RPL are endometrial factors, where there is a chronic inflammation of the endometrial lining, which is commonly known as chronic endometritis (CE). The prevalence of CE in women who have experienced RPL is 10% - 27%. Endometrial factors are thought to be caused by interference with plasma cell stromal infiltration and changes in the expression of genes involved in implantation leading to RPL, infertility and repeated implantation failure after in vitro fertilization (IVF).[9]

Microbial pathogens such as Toxoplasma, rubella, CMV, and HSV are important causes of infection during pregnancy. This infection often causes mild or asymptomatic infection in the mother.[10] However, infection during pregnancy can cause serious birth defects, intrauterine growth retardation, and fetal death.[11]

On endocrine factors, the percentage risk of RPL is 17% - 20%. Endocrine factors are caused by luteal phase deficiency (LPD), polycystic ovary syndrome (PCOS), diabetes, thyroid disease, and hyperprolactinemia. In LPD, it is suspected that there is insufficient progesterone production by the corpus luteum and inadequate endometrial maturation in the proper formation of the placenta. The diagnosis in this case is the presence of histological development of the endometrium that is persistently delayed for 2 days or more compared to the number of days in the menstrual cycle.[7] Several studies have shown that there is an abnormal increase in luteinizing hormone or androgens, both of which are associated with PCOS, in RPL patients. These abnormalities can cause premature oocyte aging in the endometrium. It is known to contribute to asynchronous maturation. The percentage of women with RPL suffers as much as 40%. Other factors are insulin resistance and hyperinsulinemia, which commonly occur in patients with PCOS and type II diabetes.[7] Another factor that can be associated with an increased risk of pregnancy loss or spontaneous abortion is uncontrolled type I diabetes. It is associated with anti-thyroid antibodies. The investigators explained that untreated hypothyroidism was clearly associated with spontaneous abortion and RPL.[7]

The genetic factor in RPL cases is 2% - 5%. One study said that 50% - 60% of women lost early pregnancy due to chromosomal abnormalities originating from the parents or arising de novo in embryos from parents with normal chromosomes.[12] The most common gene abnormality found from parental gene abnormalities, namely balanced translocation, is reported in 2% - 4% of RPL cases. The abnormalities can be reciprocal (60%), wherein involves the exchange of genetic material from one chromosome to another, or Robertsonian (40%), in which the long arms of two acrocentric chromosomes incorrectly share a centrosome.[13] Other CAs frequently observed are sex chromosome mosaicism, inversion, and ring chromosomes. Additional structural abnormalities include chromosomal inversions and insertions can lead to an abortion. This is known as chromosomal aneuploidy, the most common spontaneous abortion.[14,15] There were about 50% of aborted fetuses had chromosomal abnormalities caused by nondisjunction. As many as 7,3% of mothers with chromosomal abnormalities experienced repeated abortions in the first trimester. The chromosomal abnormality is dominated by X-chromosome mosaicism, followed by reciprocal translocations and Robertsonian translocations. In addition, paternal chromosomes are also involved, where as many as 2.1% of fathers have chromosomal defects with X-chromosome mosaicism and inversion.[15] Generally, mutations in genes used to maintain a pregnancy are known to result in abortion. However, it can cause oxidative stress, thrombophilic, and immunological disorders resulting in RPL. In oxidative stress factors, antioxidant levels in RPL patients are generally lower when compared to patients without RPL, where there are normal levels of antioxidants in whole blood and in plasma, whereas in thrombophilic factors it is explained that there is a coagulation disorder.[15]

Immune factors associated with miscarriage are categorized as autoimmune factors and alloimmune factors. The autoimmune factor that causes RPL is the synthesis of autoantibodies (antiphospholipid antibodies, antinuclear antibodies, antithyroid antibodies). The incidence of RPL is often found, such as an increase in blood viscosity during pregnancy, but the presence of antiphospholipid antibodies in some women causes blood clots in the placental blood vessels thereby reducing blood flow to the baby and can cause miscarriage.[14]

Based on Figure 2, unexplained pregnancy loss factors have 40% - 50% risk of pregnancy loss. Unexplained recurrent pregnancy loss (URPL) is a condition in which no cytogenetics is available when the patient comes to the clinic (which is often the case). In the case of URPL, patients generally will not have additional abnormalities so their routine examination results will be negative. Patients with URPL are healthy patients who are unlucky in pursuing pregnancy and are therefore diagnosed with having URPL because the results of the examination will always be normal. The prognosis for pregnancy in URPL patients is generally excellent without the need for surgical or pharmacological intervention. URPL patients are usually younger, and will have >3 miscarriages (4, 5, or more). The cause of the occurrence of URPI is the egg, sperm, embryo, endometrium, and systemic factors.[16]

In the egg factor, the patient has a poor response to ovarian hyperstimulation, where premature ovarian aging occurs, reducing the quality and quantity of oocytes and requiring donor oocytes. However, the main cause is aneuploidy which can lead to miscarriage in women with increasing maternal age. In the sperm factor, RPL occurs due to DNA fragmentation in sperm. In addition, embryo-endometrium factors are highly correlated with pregnancy loss. This is due to the poor quality of the embryo. In addition, there was an increase in proimplantation cytokine levels which resulted in about 40% of them being super fertile. Excessive fertility also has an effect because it can inhibit the natural selection of healthy embryos and allow the implantation of poor-quality embryos to occur, causing pregnancy loss.[16]

The first thing to do doctors will characterize the type of recurrent pregnancy loss that has happened. This is paramount to determine the priority of checks that will be conducted. The unexplained incidents of recurrent pregnancy loss can only be confirmed if a thorough check has been carried out but no abnormalities are found. Most couples who have had recurrent miscarriages fall into this category. Examinations that are conducted include an ultrasound examination to assess the shape of the uterus and followed by a telescopic examination into the uterus (hysteroscopy), the mother's blood tests to rule out blood clotting disorders, metabolic disorders, reproductive hormone production disorders, infections, and autoimmune diseases, both father and mother's blood tests to rule out chromosome abnormalities, sperm analysis to determine sperm quality.

Ultrasound is used regularly in prenatal care because it can check the health of the fetus in the early stages of pregnancy. Nuchal translucency (NT) is an ultrasound image of the accumulation of subcutaneous fluid behind the fetal neck in the first trimester of pregnancy (1114 weeks gestation). The NT measurement is an excellent and sensitive screening test for fetal chromosomal abnormalities. The etiology of this phenomenon includes heart failure secondary to structural malformations, disruption of the extracellular matrix, and abnormal or delayed development of the lymphatic system. NT is detected in approximately 5% of fetuses during screening. An NT size above the 95th percentile is called an NT increment and the thickness is based on crown-rump length (CRL). CRL was undetectable in 5% of fetuses screened, and the increase in NT thickness was based on CRL. For the minimum CRL (45 mm) and maximum CRL (84 mm) at 11-13 + 6 weeks of gestation, the NT is in the 50-95th percentile.[17]

Non-invasive preterm testing (NIPT) or cell-free DNA tests and non-invasive preterm screening (NIPS) greatly expand the scope of screening tests for fetal chromosomal abnormalities. Specifically for trisomy 21, NIPT is superior to other screening modalities. However, NIPT has limitations and complexities that need to be understood by doctors and their patients.[18]

Nearly half of patients remain without a specific diagnosis when all known and possible causes of RPL are considered. The optimal administration of these patients is often unknown as the pathogenesis of RPL. Progesterone has been shown to be beneficial for lowering the abortion rate of women undergoing at least three streams. Low-dose aspirin (LDA) was also examined as a potential treatment for RPL and was unexplained. The use of pregnancy and pregnancy has been shown to increase the birth rate of women with previous abortions during the 13th week of gestation. In fact, the most effective treatments for patients with unexplained RPL are often the simplest. Prenatal counseling and psychological support. This intervention has been shown to have an 86% success rate for subsequent pregnancies, compared with a 33% success rate for women who were performed without additional antenatal care.[7]

Strategies that can be done in cases of recurrent miscarriage are generally determined by the type of recurrent miscarriage. In the event of an early miscarriage, treatments to increase the quality of the embryo, and strengthen the uterine wall to select formed embryos can be done. The strategy to increase the quality of the embryo is initiated by elevating the quality of sperm by doing sperm selection through the swim-up method which is part of the insemination procedure. This procedure of selecting the sperm that can swim through liquid solutions with different specific weights. The insemination process can be carried out in In vitro fertilization (IVF). If it still does not succeed, then the IVF procedure can also be done, not only to select sperm but also egg cells and embryos. The procedure of selecting sperm for IVF can be done using the intracytoplasmic morphologically selected sperm injection (IMSI) technique. With IMSI, any defects in the sperm can be detected before fertilization. Then, the procedure is continued with an embryo selection with a normal chromosome. This procedure is known as pre-implantation genetic testing aneuploidy or PGT-A in short.

Strategies to treat recurrent miscarriage in early miscarriage are also intended for the uterine wall layer so the selection mechanism for incoming embryos is better. One theory stated that the excessive number of uterine natural killer (uNK) cells results in easy pregnancy, even with an embryo with an abnormal chromosome. Pressing the number of uNK cells in the uterus is expected to improve the process of selection of embryos by the uterine wall. The number of unexplained recurrent miscarriage incidents is quite large. Therefore empiric therapy using certain treatment regimens can be used.

Recurrent miscarriage is a form of fertility disorder. In addition to treatment through medical measures, to increase the chances of pregnancy, it is better for couples to lead a healthy lifestyle. Consume foods with balanced nutrition, maintain ideal body weight before pregnancy, and perform screening measures for an infection that has the potential to trigger any defects during pregnancy such as rubella. Smoking and alcohol intake, as well as the use of drugs without a doctor's supervision, should be avoided during the planning and during pregnancy.

Conclusion:

Recurrent pregnancy loss is the previous adverse fetal outcome in terms of two or more consecutive spontaneous abortions, intrauterine growth retardation, intrauterine growth retardation, stillbirth, premature neonatal death, and/or congenital anomalies. RPL can have a variety of causes, including genetic, endocrine, immunological, infectious diseases, autoimmune diseases, anatomical abnormalities, and unexplained etiologies. The first recommendation when assessing a couple of habitual abortions is to perform a karyotype analysis of the parents and the aborted fetus. It is advisable to test the levels of prolactin, TSH, and anti-thyroid antibodies to rule out some endocrine causes. In pre-pregnant women with unexplained miscarriage, immunological causes should be considered. All prenatal cases of BOH should be screened for TORCH on a regular basis.

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