



## Four Recurrent Miscarriages – Is It a Case of Antiphospholipid Syndrome?

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**Abstract:**

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**Introduction:** Antiphospholipid syndrome (APLS) is usually clinically suspected in antenatal women presented with recurrent miscarriages. Screening is usually conducted, especially for those with persistent, unexplained recurrent miscarriages in the first trimester. However, most patients might not seek medical attention earlier, causing a delay in screening. Nevertheless, it is a dilemma for patients with recurrent miscarriages, especially up to four miscarriages, to be presumed as APLS until proven otherwise. **Case:** We reported a 37-year-old Gravida 5 Para 0+4 at four weeks of amenorrhoea presented with one episode of per vaginal bleeding. APLS and other relevant causative screenings had been performed, and the results were normal. Surprisingly, her pregnancy is still viable and progressing well. **Discussion:** This case proved that recurrent miscarriages on more than three occasions are not always equivalent to antiphospholipid syndrome. The underlying cause can be idiopathic or other causes that have not been investigated yet, including the possibility of a congenital anomaly. **Conclusion:** Suspicion of APLS is warranted and should be verified with the gold standard screening tests. In any case, where the results were normal, further assessments such as uterine evaluation, infectious disease screening, and pathological examination should be considered. Pre-pregnancy screening should be a minimal requirement for all women of reproductive age for the evaluation and prevention of similar outcomes to those of other women.

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**Keywords:** Antiphospholipid syndrome, recurrent miscarriages, suspicion



## Introduction:

Early miscarriages, also known as spontaneous abortions, are a common occurrence in women of childbearing age (Battula et al., 2021). Various factors can contribute to early pregnancy miscarriages, including the mother's age, chromosomal abnormalities, endocrine disorders, thrombophilia, environmental factors, bacterial infections, and viral infections during pregnancy (Musik et al., 2021). Studies have highlighted the potential dangers of viral infections, such as rubella virus, cytomegalovirus, herpes simplex virus, and coxsackievirus B, in causing congenital anomalies and morbidity. The importance of investigating and identifying the causes of early pregnancy miscarriages is crucial for both the mother's future reproductive health and the potential prevention of future miscarriages (Zhu et al., 2023). Immunologic testing plays a crucial role in investigating potential causes of early pregnancy miscarriages. It helps to assess the immune response of the body and identify any underlying autoimmune disorders or immune system abnormalities that may be contributing to recurrent miscarriages (Pontius & Vieth, 2019).

## Case Report:

A 37-year-old Gravida 5 Para 0+4 with four weeks of amenorrhoea came to the primary health clinic for an antenatal booking. All her previous miscarriages ranged from nine weeks to 11 weeks of gestation in 2011, 2013, 2018, and 2021, with no dilatation or curettage done. No investigation was performed previously, as all the incidents occurred in the early trimester without proper antenatal booking and did not require any hospital admission. She only sought medical attention as an outpatient at a private clinic. A bedside pelvic ultrasound revealed an empty uterus without any abnormalities. She also refused further tests, such as assessments for diabetes, autoimmune disease, and infections. Fortunately, she experienced no complications after each miscarriage. The bleeding resolved on its own for several days. She was stable on each occasion without any symptoms of anaemia. She denied any prior history of taking traditional medications, supplements, or traditional massages. She also had no history of trauma. Her risks include advanced maternal age and maternal obesity with a BMI of 36.6kg/m<sup>2</sup>. She has no other significant medical history, no psychosocial stressors and receives good family support. Her blood pressure during the visit was 129/73mmHg. The patient's vital signs were normal and her physical examinations were all unremarkable.

The patient received a scheduled appointment for her gestational diabetes screening (OGTT) and other routine antenatal investigations. Additionally, the plaeed antiphospholipid antibody tests such as a Lupus anticoagulant, an anticardiolipin test, and a beta-2 glycoprotein test were sent to the tertiary centre laboratory. Fortunately, all results came back negative. She was advised to promptly seek immediate medical attention in case of abdominal cramps or vaginal bleeding.

During her follow-up after eight weeks of amenorrhoea, she remained well with no reported incidents of vaginal bleeding or pain. However, it was noted that she had visited the emergency department before her scheduled appointment due to a bout of vaginal bleeding. A pelvic ultrasound conducted during the emergency visit revealed a viable foetus and her cervical os was noted to be closed. She was managed as a threatened miscarriage case and received Duphastone® for one week as supportive treatment. Subsequently, her vaginal bleeding ceased, and her overall condition significantly improved. Her OGTT results were within normal limits. Subsequent follow-up and monthly antenatal checkups were uneventful, with serial ultrasounds indicating normal foetal growth parameters corresponding to gestational age and with adequate amniotic fluid levels. The patient also did not show any signs of anaemia or proteinuria, and her weight gain remained appropriate.

Her most recent follow-up was at 28 weeks of gestation. Her antiphospholipid antibody testing was normal. She remained asymptomatic, and the latest transabdominal revealed normal growth of her foetus without any complications.

## Discussion:

Early pregnancy miscarriages are defined as the loss of a pregnancy before 20 weeks of gestation (Battula et al., 2021). These miscarriages can happen for various reasons, including chromosomal abnormalities in the foetus, hormonal imbalances in the mother, structural abnormalities in the uterus or cervix, and maternal health issues such as chronic diseases or infections (Zhu et al., 2023). To determine the cause of early pregnancy miscarriages, the following investigations and workups should be considered:

1. Medical History and Physical Examination: A detailed medical history of the patient, including previous pregnancies, reproductive history, mental status and emotional burdens, and any known risk

factors, can provide valuable insights into the potential causes of early pregnancy miscarriages (Musik et al., 2021; Zhu et al., 2023).

The physical examination may include assessing the general health of the patient, checking for any signs of infection, and evaluating the condition of the cervix and uterus for any abnormalities.

2. Genetic Testing: Chromosomal abnormalities are a common cause of early pregnancy miscarriages. Genetic testing, such as karyotyping or chromosomal microarray analysis, can be done to evaluate the foetal chromosomes and identify any abnormalities or aneuploidies that may have contributed to the miscarriage (Pontius & Vieth, 2019; Musik et al., 2021; Zhu et al., 2023).

3. Endocrine Evaluation: Hormonal imbalances, such as luteal phase deficiency, can affect the stability of the pregnancy. An endocrine evaluation can be conducted to assess the levels of hormones involved in maintaining a healthy pregnancy, such as progesterone and thyroid hormones (Pontius & Vieth, 2019; Musik et al., 2021; Zhu et al., 2023). However, in our local practice, these assessments are not conducted routinely unless there are clinical signs to suggest the disorder. For our patient, she has no clinical features to suggest any endocrine disorders.

4. Immunological Testing: Some research suggests that an immune response in the mother's body may contribute to early pregnancy miscarriages. Immunological testing, such as antiphospholipid antibody testing or anti-thyroid antibody testing, can be conducted to evaluate the immune response and identify any abnormalities that may be impacting the pregnancy (Musik et al., 2021; Li, Zheng, Zhao, Xu & Wang, 2021; Zhu et al., 2023).

5. Uterine Evaluation: Structural abnormalities of the uterus or cervix can increase the risk of early pregnancy miscarriages. A uterine evaluation can be performed to assess the structure of the uterus and cervix using imaging techniques such as ultrasound, hysteroscopy, or MRI (Pontius & Vieth, 2019; Musik et al., 2021; Zhu et al., 2023). In our local practice, most assessments conducted include cervical thickness measurement, especially in the second trimester for those with recurrent miscarriages that occur in the second trimester. However, in our case, the cervical length was not measured as her previous miscarriages were confined to the first trimester only, in which cervical insufficiency is unlikely.

6. Infectious Disease Screening: Bacterial and viral infections in the genital tract can increase the risk of early pregnancy miscarriages. Screening for infectious diseases, such as rubella, cytomegalovirus, herpes simplex virus, and bacterial infections, can be conducted to ascertain the presence of any infections that might have played a role in the miscarriage (Pontius & Vieth, 2019; Musik et al., 2021). This screening is recommended when patients exhibit symptoms such as vaginal discharges or any indicators of sexually transmitted diseases.

7. Pathological Examination: After a miscarriage, it may be beneficial to perform a pathological examination on the expelled foetal tissue. This can provide valuable information about the cause of the miscarriage, such as chromosomal abnormalities, infections, or structural abnormalities. Given the patient's history of early pregnancy loss, it would be prudent to conduct a thorough investigation to identify any underlying causes that may have contributed to the miscarriage (Pontius & Vieth, 2019; Musik et al., 2021; Arif, Zafar, Ahmed, & Shehzad, 2022). However, these crucial assessments were not conducted in our case previously.

Immunologic testing plays a crucial role in investigating potential causes of early pregnancy miscarriages (Musik et al., 2021; Li, Zheng, Zhao, Xu, & Wang, 2021). It helps to assess the immune response of the body and identify any underlying autoimmune disorders or immune system abnormalities that may be contributing to recurrent miscarriages. The most common immunologic tests used in the investigation of early pregnancy miscarriages include testing for anti-phospholipid antibodies (anti-PL) and anti-phospholipid antibodies (anti-PK). These antibodies have been implicated in early abortions and recurrent miscarriages in certain individuals. In a study conducted on a woman with a history of 13 miscarriages, it was found that reducing her anti-P titre with plasmapheresis prevented the miscarriage of her 14th pregnancy, supporting the proposal that anti-P is the immunologic cause of early abortion in women with Pk or p antigen (Arif, Zafar, Ahmed, & Shehzad, 2022). It is important to note that these tests should be interpreted in conjunction with the patient's clinical history and other investigations, as the exact mechanisms by which these antibodies contribute to miscarriages are not fully understood. In addition to the immunologic testing, it is essential to consider other possible aetiologies of early pregnancy miscarriages (Musik et al., 2021; Arif, Zafar, Ahmed & Shehzad, 2022; Zhu et al., 2023).

In the case of this 37-year-old woman with a history of four previous miscarriages, immunologic testing was considered to assess her immune function and determine if any immunologic factors could be causing or contributing to her recurrent miscarriages. However, the investigations came back with normal results. Consequently, further investigations, such as uterine evaluation and pathological assessment, may provide a better understanding of her recurrent miscarriages. Unfortunately, as her previous miscarriages were not thoroughly investigated, her products of conception could not be examined. This case demonstrated that recurrent miscarriages—even exceeding three occurrences—are not always indicative of antiphospholipid syndrome. The underlying cause may be idiopathic or related to other causes that have yet to be explored, including the possibility of a congenital anomaly. The role of progesterone in recurrent miscarriages is indeed limited. Its role in threatened miscarriage, as experienced by this patient, is only confined to those within the first trimester and should not be given beyond that (Duncan, 2022).

### Conclusion:

Recurrent early pregnancy miscarriages require thorough investigations and comprehensive workups. Suspicion of APLS is warranted and should be verified with the gold standard screening tests. In any case, where the results appear to be normal, additional assessments such as uterine evaluation, infectious disease screening, and pathological examination should be contemplated. Pre-pregnancy screening should be considered as a minimal requirement for all women of reproductive age to facilitate the evaluation and prevention of similar outcomes to those of other women.

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