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CASE REPORT

Successful Pregnancy Outcome in a Patient with Recurrent Miscarriage Due to PCOS Complicated by Hereditary Protein C Deficiency

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Abstract: On December 28, 2016, a 35-year-old female patient presenting with chest pain and a brief fainting spell was admitted to a hospital in Guangzhou and promptly received thrombectomy and catheter-directed thrombolysis. She had experienced two episodes of explosive thrombosis, with the second occurring in May 2020, triggered by pregnancy. Her diagnoses included polycystic ovary syndrome (PCOS), hereditary Protein C (PC) deficiency resulting from a heterozygous mutation deletion of 572_574 in exon 7, recurrent spontaneous abortion (RSA), as well as PCOS-associated insulin resistance and chronic endometritis. Our regimen comprises dydrogesterone for cycle regulation, rivaroxaban for PC deficiency-related thrombophilia, and metformin, amoxicillin, and omeprazole to manage PCOS-associated insulin resistance and chronic endometritis, with the aim of mitigating their contribution to impaired endometrial receptivity. Following our targeted and persistent treatment, the patient gave birth to a healthy baby in April 2023. It is rare for RSA to be caused by PCOS complicated by hereditary PC deficiency, and there are no international treatment guidelines for such cases. This report adds to the existing body of knowledge regarding the treatment of PCOS complicated by hereditary PC deficiency. For RSA patients, a comprehensive approach considering all contributing factors and individual circumstances is essential. Multi-disciplinary treatment (MDT) is crucial. Moreover, there are currently no international, evidence-based guidelines for the use of combined oral contraceptives (COCs) in PCOS complicated by hereditary thrombophilia, highlighting the urgent need for multicenter clinical studies to establish appropriate management strategies.

Keywords: PCOS, polycystic ovary syndrome, PC deficiency, protein C deficiency, RSA recurrent spontaneous abortion, VT, venous thromboembolism, childbirth

Background

A 35-year-old female patient with recurrent spontaneous abortion (RSA) presented with polycystic ovary syndrome (PCOS) and hereditary protein C (PC) deficiency. In 2022, our team reported this case.[1] The patient had been hospitalized for emergency surgery due to explosive thrombosis in 2016 and experienced an inevitable miscarriage in 2020 after a second episode of multiple thrombosis, leading to a diagnosis of hereditary PC deficiency resulting from a heterozygous mutation deletion of 572_574 in exon 7. PC, a vitamin K-dependent natural anticoagulant protein synthesized in the liver, exhibits anticoagulant, anti-inflammatory, and cytoprotective properties. Previous studies have reported that pregnant women with PC deficiency face a 500- to 1000-fold[2] higher risk of venous thromboembolism (VTE) compared to those with normal levels. More recent research indicates that the absolute risk of pregnancy-associated VTE in women with PC deficiency reaches 7.8%.[3] In addition, PC deficiency has been associated with adverse obstetric outcomes, including RSA, severe preeclampsia, intrauterine growth restriction, placental abruption, and preterm delivery.[4] PCOS impairs fertility and pregnancy outcomes through three core pathological features:

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hyperandrogenemia, anovulation, and insulin resistance. Hyperandrogenemia contributes to endometrial thinning and poor embryo implantation, reducing conception and live birth rates[5,6] while increasing risks of preterm birth and preeclampsia;[7] it may also promote second-trimester loss by increasing cervical insufficiency.[8] PCOS accounts for 70%[9] of anovulatory infertility cases. Anovulation leads to luteal phase defects and endometrial asynchrony, increasing the risk of early miscarriage.[10] Furthermore, hyperandrogenemia and insulin resistance (IR) interact to suppress follicular development and perpetuate anovulation. IR independently compromises oocyte quality and embryonic development, as evidenced by a 2025 retrospective cohort study (n = 1768)[11] showing reduced oocyte maturation, fertilization, and high-quality embryo rates even in normal-weight PCOS patients. In parallel, IR induces vascular endothelial dysfunction and impaired placental remodeling,[12] increasing risks of late miscarriage and obstetric complications. Through these interconnected pathways, PCOS adversely affects reproductive success across all gestational stages.

The combination of all the factors made conception particularly challenging, with a high risk of miscarriage and recurrent thrombosis. However, after persistent treatment and intensive monitoring, she gave birth to a healthy baby in April 2023, and venous thrombosis was well-controlled during follow-up. This case highlights the effective management of this complex condition and provides valuable insights for clinicians facing similar challenges. Written consent was obtained from the patient.

Case Report

The patient (G0P0), with a height of 170 cm, weight of 64 kg, and body mass index (BMI) of 22.14 kg/m^2, presented in 2015 with irregular menstruation, hyperandrogenemia and polycystic ovarian morphology, leading to a diagnosis of PCOS, and subsequent treatment with ethinylestradiol/cyproterone acetate for over one year. In 2016, she was admitted to a local hospital for urgent thrombectomy and catheter-directed thrombolysis due to multiple thromboses. After the procedure, she was placed on warfarin (3 mg daily) for anticoagulation therapy. In 2020, she became pregnant, and low-molecular-weight heparin (LMWH) (enoxaparin sodium, 0.6 mL twice daily) along with aspirin (100 mg daily) was prescribed in a local hospital for anticoagulation. However, she miscarried at 26 weeks.

Two months later, she sought consultation with our medical team and conveyed her wish to conceive. During a follow-up visit to our hospital, laboratory tests showed elevated D-dimer levels (5.63 ng/L, normal range: 0–0.55 ng/L), an APTT of 19.4 seconds (normal range: 23.3–32.5 seconds), and a protein C level of 38% (normal range: 70–130%). High-throughput sequencing of her genomic DNA revealed a heterozygous PROC c.572_574delAGA mutation, confirming her diagnosis of hereditary protein C deficiency. We recommended switching from warfarin to rivaroxaban (10 mg daily). Additionally, dydrogesterone (10 mg daily for 20 days each month) was used to regulate menstruation, and metformin (750 mg twice daily) was prescribed to manage insulin resistance resulting from PCOS. After three months, Doppler ultrasonography showed an old thrombus (3.1 mm wide) in her left popliteal and femoral veins. Blood tests and thromboelastography (TEG) showed no abnormalities in coagulation function, confirming that the thrombi were well-controlled. This treatment strategy continued for 18 months.

In March 2022, following her last menstrual period on March 5, the patient experienced irregular vaginal bleeding that persisted for approximately 10 days. The gestational age was retrospectively estimated to be approximately 5 weeks. Initially, the patient misinterpreted the prolonged bleeding as normal menstruation; however, she sought medical attention after 7 days when the bleeding persisted. At consultation, the urine pregnancy test was negative due to the combined effect of its inherent low sensitivity and the serum hCG pattern, which had already peaked and declined to baseline, indicating the occurrence of a biochemical pregnancy. Despite various hemostatic treatments, bleeding persisted, and a hysteroscopy confirmed chronic endometritis (Figure 1) and a biochemical pregnancy. She was treated with amoxicillin (228.5 mg every 12 hours for 7 days) and ornidazole (250 mg twice daily for 7 days). After 4 months of treatment, her condition improved, making her suitable for pregnancy. On day 3 of the menstrual cycle, letrozole (5 mg daily for 5 days) was prescribed for ovulation stimulation, and LMWH (0.6 mL daily) was used in place of rivaroxaban for anticoagulation.

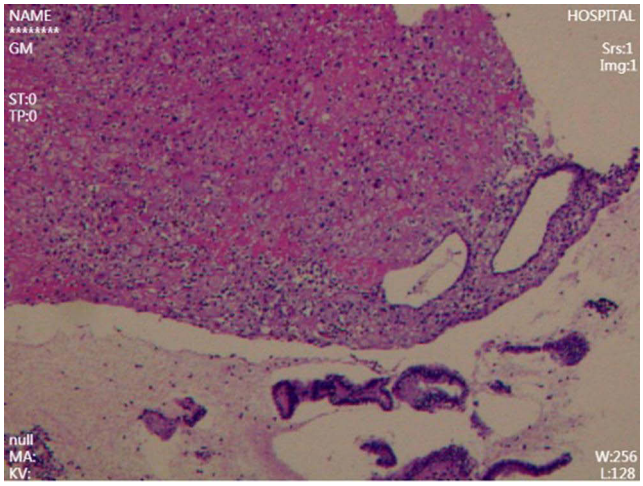

Figure 1 Pathological image of endometrium in March 2022.
Notes: Pathological image and immunohistochemistry of endometrium indicated this female had a biochemical pregnancy and chronic endometritis.

The patient became pregnant following one cycle of ovulation induction, with confirmation of pregnancy by β-HCG on August 19, 2022. Given her medical history, we closely monitored her pregnancy and anticoagulation status. At 15 weeks of gestation, the dosage of LMWH was doubled (0.6 mL twice daily).

Throughout the pregnancy, the patient underwent routine prenatal examinations. Down syndrome screening indicated high risk due to maternal age, but non-invasive DNA tests, the prenatal diagnosis of thalassemia, and TORCH (Toxoplasmosis, Other Agents, Rubella, Cytomegalovirus, Herpes Simplex Virus) tests yielded normal results. The patient adhered to regular venous thrombus monitoring, and ultrasound confirmed stable old thrombi in her left popliteal and femoral veins (3 mm) (Figure 2). At 20 weeks, obstetric examinations showed no complications, and coagulation tests remained stable.

On January 31, 2023, a TEG test revealed satisfactory coagulation values, and Doppler ultrasound confirmed stable venous conditions in her lower extremities. At 37 weeks, another blood test and venous ultrasound (Figure 3) were performed, showing no new thrombus formation, confirming the patient's stable condition. The patient had a vaginal delivery with oxytocin augmentation. (the oxytocin was administered as 2.5 IU in normal saline via IV infusion) and gave birth to a healthy male infant weighing 2.97 kg and measuring 47 cm. Both the mother and the infant were in good

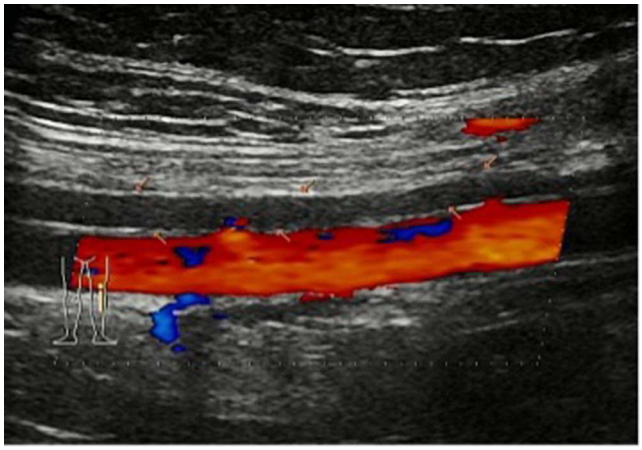

Figure 2 CDFI of the left popliteal-femoral vein on September 24, 2022.
Notes: CDFI revealed a 3-mm, arrow-marked old thrombus in the left popliteal-femoral vein on September 24, 2022.
Abbreviation: CDFI, Color Doppler Flow Imaging.

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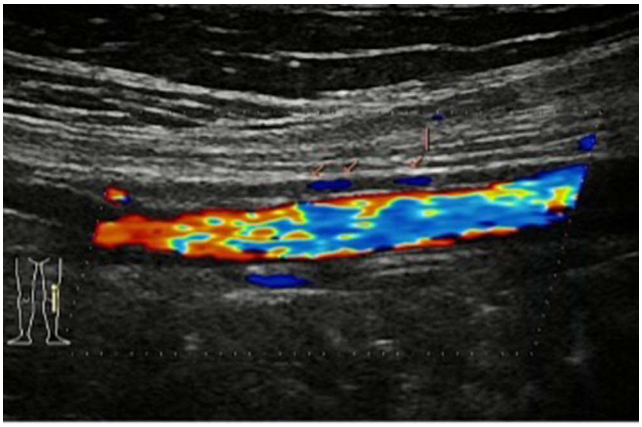

Figure 3 CDFI of the left popliteal-femoral vein on March 30, 2023.
Notes: There was an old thrombus with 1.8mm width indicated by the arrows in the left popliteal-femoral vein, and CDFI was seen in the mentioned-above vein on March 30, 2023.
Abbreviation: CDFI, Color Doppler Flow Imaging.

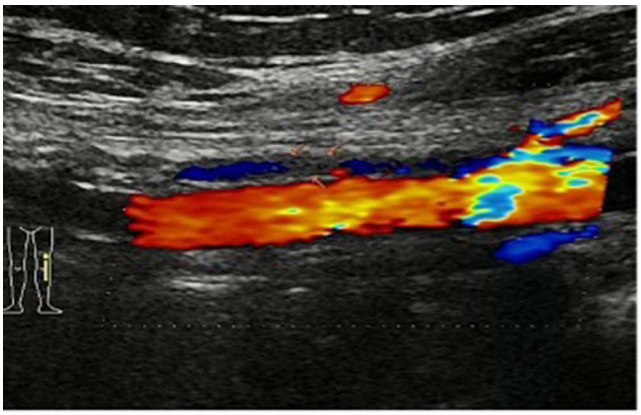

Figure 4 CDFI of the left popliteal-femoral vein on June 7, 2023.
Notes: B-ultrasound indicated that there was an old thrombus with a 1.7mm diameter marked by the arrows in the left popliteal-femoral vein and blood flow signal was detected by CDFI on June 7, 2023.
Abbreviation: CDFI, Color Doppler Flow Imaging.

health. A postpartum venous Doppler ultrasound of the lower extremities revealed that the pre-existing chronic thrombus in the left leg remained stable, with no new thrombus formation.

After delivery, we recommended continuing LMWH (0.6 mL daily) for two months to prevent venous thrombosis. Two months postpartum, ultrasound confirmed an old thrombus (1.7 mm wide) (Figure 4) in her left popliteal and femoral veins, with no recurrence of thromboembolism. Coagulation function and D-dimer levels remained within normal ranges. As of October 2025, the patient's management under our guidance included dydrogesterone (10 mg daily for 10 days monthly) for cycle regulation, metformin (500 mg twice daily) for the management of IR, and rivaroxaban (10 mg daily) for long-term anticoagulation. Following this regimen, she achieved regular menstrual cycles and normal serum insulin levels. Furthermore, monthly lower extremity ultrasounds confirmed thrombotic stability without new clot formation. She elected to use contraception and reported no further pregnancies.

Discussion and Conclusion

RSA is a severe obstetric complication, with an incidence of 1% to 2%.[13] The American Society for Reproductive Medicine (ASRM) defines RSA as two or more clinical pregnancy losses confirmed by ultrasound or histopathology,[14] while the European Society for Human Reproduction and Embryology (ESHRE) defines it as more than two

miscarriages.[13] In China, RSA is defined as two or more consecutive pregnancy losses before 28 weeks of gestation, including biochemical pregnancies. Many factors contribute to RSA, but only about 50% of causes can be identified.[15] These factors include genetic issues, immune factors, endocrine disorders, prethrombotic states (PTS), infections, and uterine abnormalities. Maternal immune dysfunction, PTS, anatomical anomalies, and endocrine imbalances are considered the most significant contributors.[16] PTS, whether hereditary or acquired, provokes placental micro-thrombosis and villous infarction, leading to decidual ischemia and recurrent pregnancy loss.[17] However, the pathogenesis of some RSA cases remains unexplained, known as unexplained recurrent spontaneous abortion (URSA). Recent studies have shown that 50% to 65% of women with RSA have at least one hereditary or acquired hypercoagulability, which can lead to uteroplacental hemodynamic abnormalities and thrombosis, ultimately causing miscarriage.[18] For RSA caused by PCOS complicated by hereditary protein C deficiency, no international treatment guidelines are currently available.

PCOS affects 10% to 13% of women of reproductive age.[19] It is characterized by infertility, irregular menstruation, acne, and hirsutism due to elevated androgens, and it often leads to insulin resistance[20] and obesity. At the molecular level, hyperandrogenism and insulin resistance act synergistically to promote both early and late pregnancy loss through multiple interconnected mechanisms: they drive an endometrial ferroptosis-fibrosis cascade via GPX4 downregulation[21] and TGF-β/Smad activation that compromises receptivity; trigger trophoblast ferroptosis[22] leading to placental insufficiency, late miscarriage, and preterm birth; and sustain chronic inflammation[23] and oxidative stress,[24] which collectively disrupt immune tolerance and impair embryo quality. Obesity, an independent risk factor for RSA, can impair ovum quality and interfere with endometrial function, leading to reduced endometrial receptivity and adverse pregnancy outcomes.[25] Beyond these manifestations, PCOS is also linked to coagulation and fibrinolysis imbalances, predisposing affected women to venous thrombosis,[26] which represents another pathway to RSA.

Endometrial receptivity refers to the state in which the endometrium is prepared for a blastocyst to attach, penetrate, and modify the endometrial interstitial to allow embryo implantation during the nidation window.[27] Chronic endometritis is characterized by the infiltration of endometrial stromal cells, increased secretion of immunoglobulins, and pro-inflammatory cytokines,[28] which can delay the transition to the endometrial secretory phase and promote the formation of polyps. This results in impaired endometrial receptivity and is associated with adverse pregnancy outcomes such as implantation failure, RSA, and premature delivery.[29] Palombo et al[30] suggest that there are differences in endometrial function between PCOS patients and healthy women. PCOS leads to dysregulation of estrogen and progesterone receptors, which increases the risk of endometrial insulin resistance and chronic endometritis. Higher-level evidence from extensive hyperinsulinemic-euglycemic clamp studies confirms that IR as a core and prevalent pathophysiological characteristic of PCOS.[31,32] This holds true even in women with normal body weight, where the prevalence of insulin resistance is significantly higher compared to age- and BMI-matched healthy controls. Furthermore, meta-analyses of these clamp studies demonstrate that women with PCOS exhibit an approximately 27% reduction in whole-body insulin sensitivity relative to healthy control subjects. Recent studies have shown that IR is an independent risk factor for RSA in addition to PCOS and obesity.[33] The mechanism behind this is related to the elevated secretion of androgens, plasminogen activator inhibitor-1, and homocysteine.[34]

In PCOS patients with hereditary PC deficiency, IR and chronic endometritis collectively elevate the risk of RSA through multiple synergistic mechanisms. The inherited PC deficiency establishes a persistent pro-thrombotic state, causing a microvascular occlusion of the maternal-fetal interface.[35] Meanwhile, the characteristic IR and hyperandrogenism of PCOS directly promote endometrial ferroptosis through GPX4 suppression and drive aberrant villous vascular remodeling via TGF-β/Smad activation.[21] This metabolic dysregulation is further exacerbated by chronic endometritis, which amplifies local inflammation through immune cell infiltration and pro-inflammatory cytokine release.[36] All these processes synergistically disrupt both initial implantation and subsequent placental development, ultimately leading to RSA.

Subsequently, warfarin was prescribed for anticoagulation until the first inevitable miscarriage combined with explosive thrombosis in 2020. After this event, high-throughput sequencing (NGS) revealed hereditary PC deficiency resulting from a heterozygous mutation deletion of 572_574 in exon 7. PC, a vitamin K-dependent glycoprotein, exists in the blood as a serine protease precursor and plays a key role in physiological anticoagulation. After binding to the endothelial protein C receptor (EPCR) on vascular endothelial cells, PC is activated by the thrombin–thrombomodulin

complex to form activated protein C (APC).[37] Together with its essential cofactor, protein S, APC inactivates factors FVa and FVIIIa and enhances fibrinolysis, thereby exerting potent anticoagulant activity.[38] Additionally, APC stimulates the release of plasminogen activator, thereby enhancing fibrinolytic activity. Deficiencies in PC are strongly linked to venous thromboembolism VTE.[39–41] Hereditary PC deficiency caused by mutations in the PROC gene is relatively rare compared with acquired forms. The PROC gene, located on chromosome 2q13–14,[42] encodes PC, and the Human Gene Mutation Database currently lists 416 distinct PROC mutations linked to PC deficiency. Genotypically, hereditary PC deficiency is classified into homozygous and heterozygous forms[43] (including simple heterozygous and compound heterozygous). Homozygous and compound heterozygous forms lead to autosomal recessive PC deficiency, often presenting as fulminant neonatal purpura and disseminated intravascular coagulation. Autosomal dominant PC deficiency, with a prevalence of 0.2%-0.5%,[44] is caused by single heterozygous deficiency of PC, and its clinical manifestation is VTE, which most often occurs in the deep veins of the lower limbs and lungs.[37,45] In the Chinese population, the common PROC c.572_574del mutation was shown to confer a 2.84-fold elevation in VTE risk.[46]

In the present case, a heterozygous deletion at positions 572_574 in exon 7 of the PROC gene underlies the hereditary PC deficiency, which in conjunction with PCOS, directly contributed to her first miscarriage and explosive thrombotic event. Additionally, a hypercoagulable state was triggered by COCs (Figure 5). In 2022, a biochemical pregnancy was detected through hysteroscopic pathology, and chronic endometritis was also revealed. The interaction of hereditary PC deficiency, PCOS, insulin resistance, and chronic endometritis led to a second miscarriage. In conclusion, thrombophilia caused by hereditary PC deficiency, PCOS, insulin resistance, and chronic endometritis resulted in RSA in this patient.

She was still eager to become pregnant, so the irregular menstruation and ovulatory dysfunction caused by PCOS were treated actively. Desdrogesterone, which poses a significantly lower risk for thrombosis[47,48] compared to other progestational medications. Given that the patient was in a prethrombotic state due to hereditary PC deficiency and had a higher risk of thrombosis from taking COCs, we selected dydrogesterone (10 mg twice daily, 20 days per month) to regulate her endometrial and menstrual cycles. Moreover, preventing thrombosis was crucial.

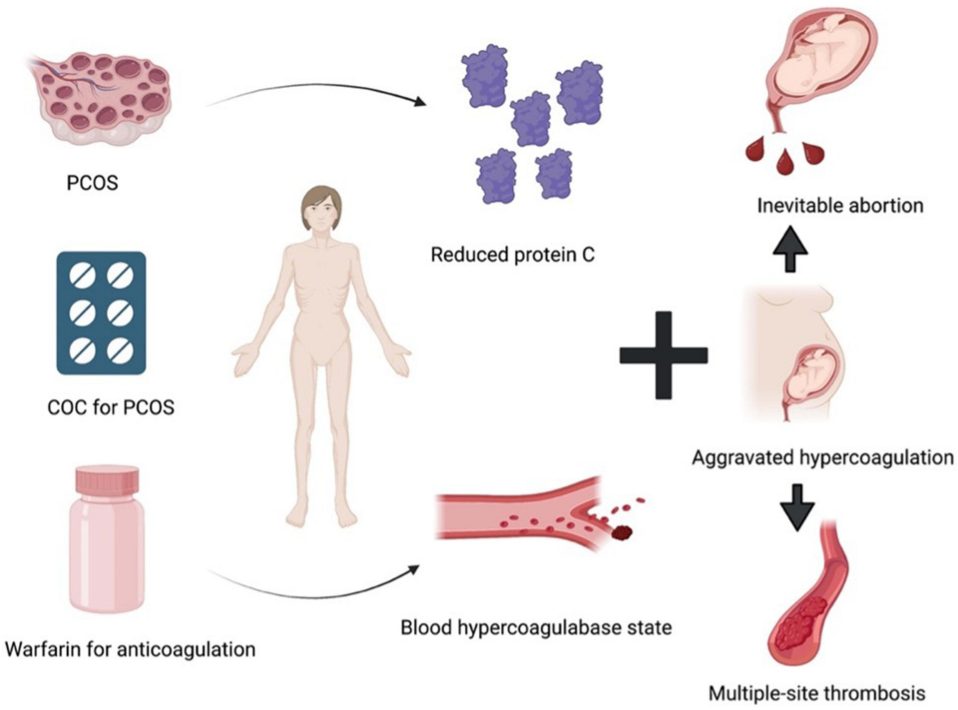

Figure 5 The first treatment before 2020.
Notes: PCOS complicated with genetic PC deficiency was directly responsible for the first-time miscarriage complicated with explosive thrombosis of this female in 2020, and it was stimulated by COC.
Abbreviation: COC, combined oral contraceptives; PC, protein C; PCOS, polycystic ovary syndrome.

Anticoagulation therapy has evolved from traditional agents like warfarin and heparin[49] to newer direct oral anticoagulants, with selection guided by pharmacological profiles and clinical context. Warfarin, the most widely used vitamin K antagonist, introduced in 1954, remains widely-used due to its low cost and manageable monitoring via the International Normalized Ratio. It acts by inhibiting the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X),[50] but concurrently reduces protein C production, requiring 2–3 days to achieve therapeutic effect and 3–5 days[51] to dissipate after discontinuation. In contrast, heparins (unfractionated and low-molecular-weight heparin), some of the earliest isolated anticoagulants,[52] are parenteral mucopolysaccharides that act rapidly and are preferred in pregnancy, malignancy, and perioperative settings.[53] Among newer direct oral anticoagulants, rivaroxaban—approved by the FDA in 2011—inhibits factor Xa directly, thereby reducing thrombin generation without affecting existing thrombin activity. With a half-life of 5–15 hours and a 24-hour pharmacodynamic effect,[54,55] it provides predictable anticoagulation without routine monitoring of blood test[56] and, importantly, does not lower protein C levels.[57] For the present patient, rivaroxaban (10 mg daily) was selected to manage hypercoagulability while avoiding further compromise of protein C activity.

Additionally, the patient had been taking metformin to treat insulin resistance. She was also treated with amoxicillin and ornidazole to manage chronic endometritis, which helped improve endometrial receptivity and reduced the risk of miscarriage.

Letrozole, a nonsteroidal aromatase inhibitor commonly used to stimulate ovulation, was also considered. Although no studies have directly linked aromatase inhibitors to thrombosis, some studies have shown a higher rate of cardiovascular events in patients treated with letrozole.[58] Given that the patient was already on rivaroxaban and her blood clotting indexes were normal, letrozole was used to promote ovulation.

After one cycle of ovulation stimulation, the patient became pregnant. During pregnancy, LMWH, a safer anticoagulant for pregnant women, was used as an alternative to rivaroxaban (Figures 6 and 7). Due to the hypercoagulable

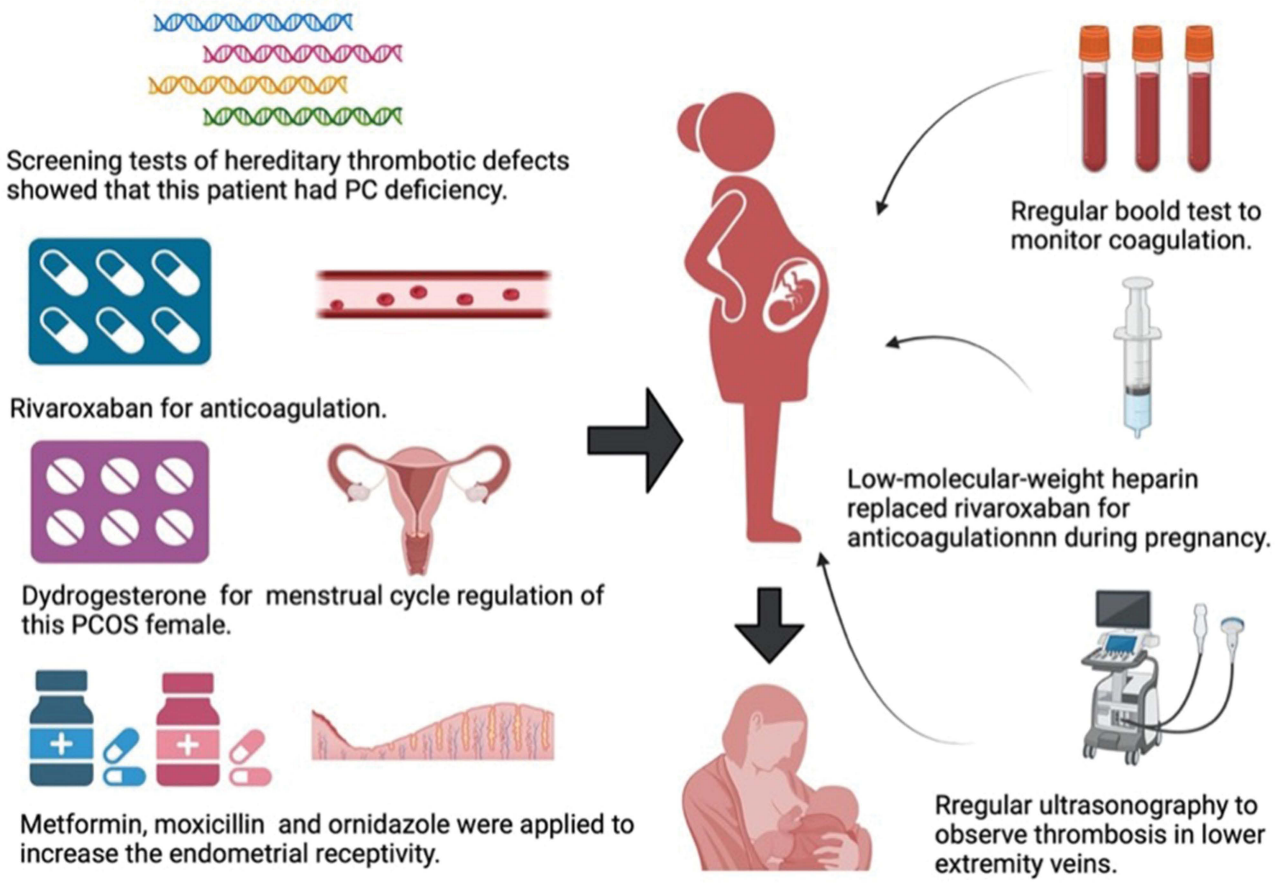

Figure 6 The second treatment after 2020.
Notes: Multi-Disciplinary Treatment was applied on this female, and she finally achieved a successful pregnancy and delivery.

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Figure 7 Summary diagram of the patient's clinical course and intervention.

state during pregnancy, the patient's coagulation indexes were closely monitored, and Doppler ultrasound of the lower extremities was performed regularly. Fetal condition was also monitored using ultrasound to minimize the risk of thrombosis and miscarriage. D-dimer levels were closely observed, as they play a crucial role in diagnosing deep venous thrombosis and estimating the patient's coagulation status.

After delivery, LMWH was recommended as a routine anticoagulation therapy for 8 weeks to prevent thrombosis in this patient, who had a history of multiple thromboses. Regular coagulation tests and ultrasound screenings were also advised.

PCOS complicated with hereditary Protein C deficiency directly caused recurrent miscarriage in this case. Based on our experience, screening tests for hereditary thrombotic defects should be emphasized before prescribing COCs, as these tests are often overlooked. Furthermore, mutations in the PROC gene may increase the risk of venous thromboembolism, so it is important to actively identify the cause and select appropriate medications to prevent thrombosis. Blind use of anticoagulants may cause secondary harm to patients with hereditary thrombotic diseases.

Moreover, dydrogesterone may be a better alternative to COCs for patients at high risk of thrombosis in order to regulate menstruation. Before initiating ovulation stimulation, it is essential to correct any endometrial receptivity issues caused by insulin resistance and chronic endometritis, which are critical to prevent recurrent abortion. For patients with hereditary Protein C deficiency, the use of rivaroxaban before pregnancy can correct coagulation disorders and reduce the risk of thrombosis and miscarriage during pregnancy.

This study reports a patient who achieved a clear diagnosis and received timely intervention. However, it is crucial to acknowledge that similar clinical management pathways often face substantial challenges in resource-limited settings. These challenges not only compromise diagnostic accuracy but also directly constrain therapeutic effectiveness, potentially exacerbating adverse pregnancy outcomes in women with RSA. Many individuals with PCOS and its comorbidities or underlying thrombophilic conditions remain undiagnosed and are often simply categorized as URSA, thereby missing targeted therapy. Furthermore, essential monitoring for high-risk pregnancies including first-trimester serial monitoring of β-hCG and progesterone levels and regular ultrasound assessments, is often not routinely feasible in these regions. Therefore, when interpreting the management strategy described in this case, the limitations of its applicability should be considered and simplified clinical pathways better suited for primary care and resource-constrained regions should be explored.

In conclusion, for RSA patients, all contributing factors and individual circumstances should be carefully considered when formulating a personalized treatment plan. Additionally, a Multi-Disciplinary Team (MDT) approach is essential in managing such complex cases. In this case, a combined approach from gynecological endocrinology, hematology, obstetrics, ultrasound, and internal medicine ultimately led to a successful pregnancy outcome.

Furthermore, the use of COCs in PCOS patients complicated by hereditary thrombophilia requires careful consideration and assessment. Currently, no international evidence-based guidelines address this issue, indicating the urgent need for multicenter clinical studies to develop management strategies for these patients.

Abbreviations

APC, activated protein C; APTT, activated partial thromboplastin time; BMI: body mass index; EPCR: endothelial protein C receptor; HCG, human chorionic gonadotropin; IR: insulin resistance; LMWH, low-molecular-weight heparin; MDT, Multi-Disciplinary Treatment; NGS, high-throughput sequencing; PC, protein C; PCOS, polycystic ovary syndrome; PTS, prethrombotic state; RSA, recurrent spontaneous abortion; TEG, thromboelastogram; URSA: unexplained recurrent spontaneous abortion VTE, venous thromboembolism.

Data Sharing Statement

Data will be made available on request from the corresponding authors.

Ethics Approval and Consent to Participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The studies involving human participants were reviewed and approved by the Guangdong Women and Children Hospital Ethics Committee. Written informed consent was provided by the patient.

Consent for Publication

The case details have been approved for publication by the Guangdong Women and Children Hospital Ethics Committee. Written informed consent was obtained from the patient for publication of her case as well as the accompanying images.

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This paper was presented at the Conference as a poster presentation/conference talk with interim findings. The poster's abstract was published in "Poster Abstracts" in SSRN Journal: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4788745

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships.

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