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Prothrombin Complex Concentrate as a Key Adjunct in Massive Hemorrhage Management in Placenta Accreta Spectrum Disorder: A Case Report

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A B S T R A C T

Placenta accreta spectrum disorder (PASD) is a severe obstetric complication associated with significant hemorrhage risk. This report highlights the successful use of prothrombin complex concentrate (PCC) as part of a multidisciplinary approach to managing a case of massive hemorrhage in PASD. A 36-year-old woman, G3P2002, at 33 weeks gestation, diagnosed with placenta previa totalis and suspected PASD, underwent a planned cesarean hysterectomy. The surgery was complicated by 5200 mL hemorrhage due to placental invasion and bladder injury. Hemodynamic instability was managed with massive transfusion protocol activation, including PCC, tranexamic acid, and packed red blood cells. Intra-abdominal packing was performed for hemostasis, and the bladder injury was repaired. Continued PCC administration in the ICU, along with other supportive measures, resulted in hemorrhage control and stabilization. The patient was successfully extubated and discharged after a second surgery to remove packing. This case emphasizes the vital role of PCC in the multidisciplinary management of massive hemorrhage in PASD. Early recognition of PASD risk factors and prompt intervention, including PCC administration, are crucial for optimal maternal outcomes.

1. Introduction

Placenta accreta spectrum disorder (PASD), a collective term encompassing placenta accreta, increta, and percreta, has emerged as a formidable challenge in modern obstetrics. This spectrum of disorders is characterized by abnormal placental adherence to the uterine wall, where the placenta invades beyond its usual confines into the myometrium (accreta), deep into the myometrium (increta), or even through the uterine wall and into adjacent organs (percreta). This aberrant placentation carries a profound risk of catastrophic obstetric hemorrhage, often necessitating immediate, multidisciplinary intervention to safeguard maternal life. The rising incidence of PASD parallels the global increase in cesarean deliveries. As the uterine scar from a previous cesarean section becomes a vulnerable site for abnormal placental implantation, the more cesarean sections a woman undergoes, the higher her risk for PASD in subsequent pregnancies. This alarming trend has not only escalated the frequency of PASD but also amplified its associated maternal morbidity and mortality rates, making it a leading cause of adverse maternal outcomes worldwide.[1,2]

The intricate pathophysiology underlying PASD involves a complex interplay of defective decidualization and aberrant trophoblast invasion. In

normal pregnancies, the decidua, a specialized endometrial lining, forms a physiological barrier that regulates trophoblast invasion, ensuring that the placenta anchors securely but does not penetrate excessively into the uterine wall. However, in PASD, the decidua is often compromised, either due to scarring from prior surgeries or inherent abnormalities, leading to an unrestrained trophoblast invasion. This breach of the decidual barrier allows the placenta to burrow deeply into the myometrium, ensnaring uterine blood vessels and establishing an intricate network of abnormal vasculature. This abnormal placental vascularity poses a significant challenge during delivery. The intertwined placental and uterine blood vessels resist conventional hemostatic mechanisms, making hemorrhage control exceptionally difficult. Even minor manipulations during placental separation can trigger torrential bleeding, rapidly destabilizing the patient's hemodynamic status and potentially leading to disseminated intravascular coagulation (DIC), multi-organ failure, and death.[3,4]

Early and accurate diagnosis of PASD is paramount for optimal management. While a history of previous cesarean deliveries and the presence of placenta previa on ultrasound raise suspicion, definitive diagnosis often relies on advanced imaging modalities like magnetic resonance imaging (MRI). MRI can provide a detailed assessment of the depth of placental invasion, involvement of adjacent organs, and the presence of aberrant vascularity, all of which inform surgical planning and intraoperative strategies. When PASD is diagnosed, a multidisciplinary team approach is indispensable. Obstetricians, with their expertise in placental disorders and high-risk pregnancies, lead the team. Anesthesiologists are vital for ensuring hemodynamic stability, managing blood products, and providing optimal anesthesia during complex surgeries. Interventional radiologists may perform pre-delivery uterine artery embolization to reduce blood flow to the placenta and potentially mitigate intraoperative blood loss. Urologists are consulted when bladder involvement is suspected or confirmed. Intensive care specialists are critical for postoperative care, especially in cases complicated by massive hemorrhage, coagulopathy, or multi-organ dysfunction.[4,5]

In the face of massive hemorrhage, the cornerstone of PASD management is swift and effective hemorrhage control. Traditional approaches like blood product transfusion and surgical intervention remain essential, but they are often insufficient to address the unique challenges of PASD-related bleeding. The emergence of prothrombin complex concentrate (PCC) as an adjunctive therapy has shown promise in improving hemostasis and reducing transfusion requirements. PCC, containing vitamin K-dependent clotting factors, can rapidly correct coagulopathy and enhance clot formation, potentially bridging the gap between initial hemorrhage control and definitive surgical hemostasis.[6,7] This case report delves into the successful utilization of PCC in a patient with PASD who experienced a massive hemorrhage during a cesarean hysterectomy. By detailing the clinical course, interventions, and outcomes, this report aims to shed light on the potential role of PCC in the multidisciplinary management of this challenging condition.

2. Case Presentation

Mrs. A.B., a 36-year-old woman, gravida 3, para 2 (G3P2002), with a history of two prior cesarean deliveries, presented to our institution at 33 weeks and 2 days gestation with placenta previa totalis and suspected placenta accreta spectrum disorder (PASD). Her prenatal course had been unremarkable until a routine ultrasound at 32 weeks gestation revealed a placenta completely covering the internal cervical os. A subsequent MRI confirmed placenta previa totalis and suggested the presence of placenta accreta, with possible myometrial invasion. Given the high-risk nature of the case, a multidisciplinary team, consisting of obstetricians, anesthesiologists, and

urologists, convened to formulate a comprehensive management plan. The patient's medical history was meticulously reviewed, including her previous cesarean sections, current medications, and allergies. A detailed physical examination was performed, with particular attention to her cardiovascular and respiratory systems. Laboratory tests were ordered to assess her hematologic profile, coagulation status, and baseline liver and kidney function. A repeat MRI was obtained to confirm the diagnosis of PASD and assess the extent of placental invasion. The MRI revealed a placenta accreta index (PAI) score of 9, indicating a high probability (96%) of invasion. Additionally, the estimated fetal weight was 2348 grams, suggesting a viable fetus. Based on these findings, the decision was made to proceed with a planned cesarean hysterectomy at 33 weeks and 2 days gestation. The surgical plan involved a midline laparotomy, followed by a stepwise approach to hysterectomy, with careful dissection of the bladder and ureters to avoid injury. Given the high risk of massive hemorrhage, multiple units of cross-matched blood, fresh frozen plasma (FFP), and cryoprecipitate were reserved. In addition, tranexamic acid, a potent antifibrinolytic agent, was readily available in the operating room.

The patient underwent general anesthesia with endotracheal intubation. Standard monitoring, including electrocardiography, pulse oximetry, invasive arterial blood pressure, and central venous pressure, was established. A large-bore intravenous (IV) line was placed for rapid fluid resuscitation. Upon laparotomy, the uterus was noted to be distended and discolored, with engorged vessels on its surface. The placenta was located anteriorly, completely covering the lower uterine segment. Upon delivery of the infant, massive hemorrhage ensued, with an estimated blood loss of 5200 mL within minutes. The patient's blood pressure plummeted, and her heart rate accelerated. A massive transfusion protocol was immediately activated. The patient received 1 g of tranexamic acid intravenously, followed by a rapid infusion of 8 units of packed red blood cells (PRBC), 5 units of FFP, 4 units of thrombocyte concentrate, and 500 IU of prothrombin complex concentrate (PCC). Despite these measures, hemorrhage control remained elusive. Close inspection revealed a tear in the urinary bladder, likely caused by the invasive placenta. The obstetrician, in collaboration with the urologist, performed intra-abdominal packing to tamponade the bleeding site and sutured the bladder injury. However, the patient's hemodynamic status continued to deteriorate. To support her failing circulation, vasopressors (norepinephrine) and inotropes (dobutamine, epinephrine) were initiated. The patient's blood pressure and heart rate gradually stabilized, but she remained critically ill.

The patient was transferred to the ICU for postoperative management. She was intubated and mechanically ventilated, with continuous monitoring of her vital signs, urine output, and laboratory parameters. Hemostasis function was assessed daily, with close attention to her platelet count, fibrinogen level, prothrombin time (PT), and activated partial thromboplastin time (aPTT). On the first postoperative day in the ICU, the patient received an additional 500 IU of PCC, along with 2 units of PRBC, due to persistent oozing from the surgical site. Her coagulopathy gradually resolved, and her hemoglobin levels stabilized. On the third postoperative day, with stable hemodynamics and satisfactory coagulation parameters, the patient underwent a second laparotomy to remove the intra-abdominal packing and finalize the bladder repair. The surgery was uneventful, and the patient returned to the ICU in stable condition. On the fourth postoperative day, the patient was extubated and demonstrated good neurological function. She was transferred to the general ward on the fifth day and continued to recover uneventfully. On the ninth postoperative day, she was discharged home with instructions for close follow-up.

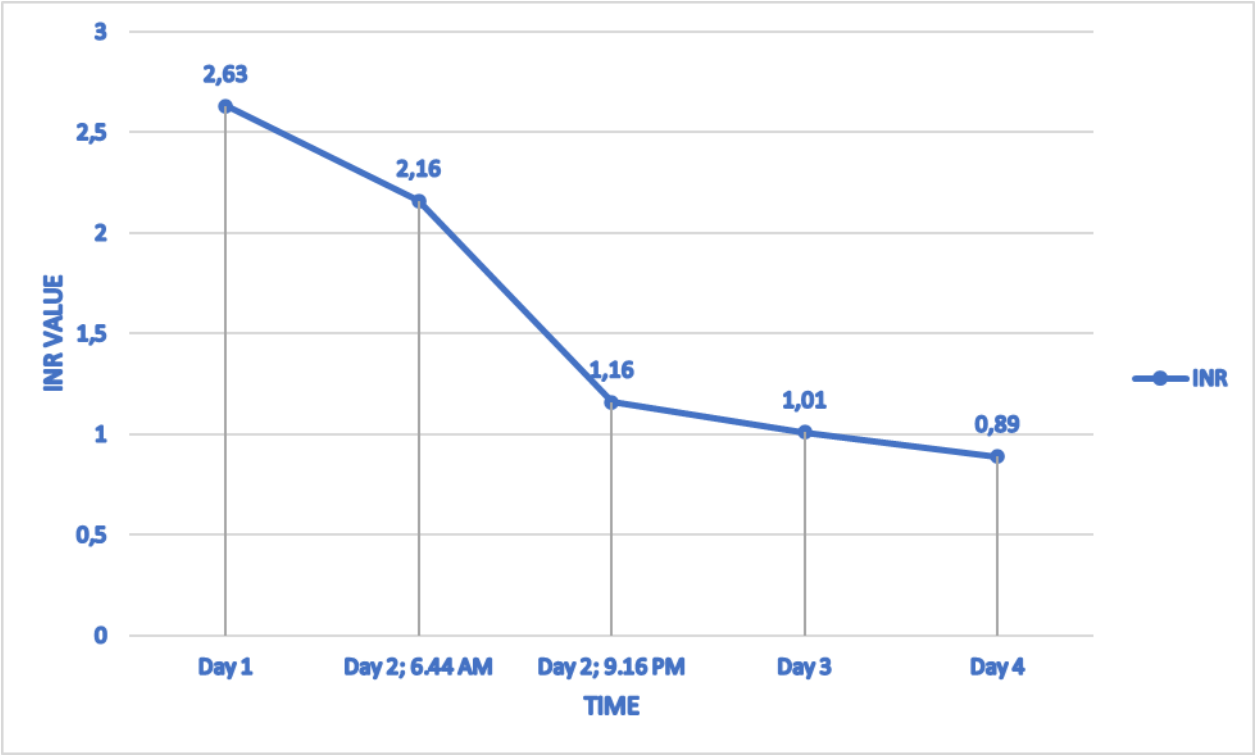

Figure 1. Hemostatic function evaluation with International Normalized Ratio (INR) at ICU.

3. Discussion

Prothrombin complex concentrate (PCC) is a life-saving therapeutic agent derived from pooled human plasma. It is available in various formulations, the most common being the four-factor PCC, which contains vitamin K-dependent clotting factors II (prothrombin), VII, IX, and X. Some preparations also include proteins C and S, which act as natural anticoagulants. This complex cocktail of coagulation factors plays a pivotal role in hemostasis, the intricate process that prevents excessive bleeding after injury. The coagulation cascade is a marvel of biological engineering, a symphony of enzymatic reactions meticulously orchestrated to maintain the delicate balance between bleeding and clotting. This cascade is a safeguard against uncontrolled hemorrhage, ensuring that blood remains fluid within the vasculature but rapidly forms a clot to seal any vascular breach. At its core, the coagulation cascade is a series of sequential activations of zymogens, inactive enzyme precursors, into active enzymes. These enzymes then cleave specific peptide bonds in subsequent zymogens, leading to an amplification cascade that culminates in the generation of thrombin, the master regulator of hemostasis. Thrombin orchestrates the final act of coagulation, converting soluble fibrinogen into insoluble fibrin monomers, which polymerize and crosslink to form a stable clot. Traditionally, the coagulation cascade has been divided into two initiating pathways: the intrinsic pathway and the extrinsic pathway. The intrinsic pathway, triggered by internal factors like collagen exposure, involves the activation of Factor XII, which initiates a cascade leading to Factor X activation. The extrinsic pathway, activated by tissue factor released from damaged tissues, directly activates Factor VII, which in turn activates Factor X. Both pathways converge at the common pathway, where Factor X, in complex with Factor Va, converts prothrombin (Factor II) to thrombin. This seemingly linear cascade is, in reality, a complex network of interactions and feedback loops. Numerous regulatory mechanisms

ensure that the coagulation cascade is tightly controlled, preventing excessive clot formation while maintaining the ability to rapidly seal vascular injuries. These mechanisms include natural anticoagulants like antithrombin and Protein C, which inhibit key enzymes in the cascade, and fibrinolysis, a process that dissolves the clot once the injury has healed. In massive hemorrhage, this delicate balance is thrown into disarray. The rapid and voluminous blood loss triggers a cascade of events that overwhelm the body's hemostatic mechanisms. The consumption of clotting factors, particularly fibrinogen, platelets, and Factors II, V, VII, VIII, IX, X, XI, and XIII, exceeds the rate of their production, leading to a state of coagulopathy. This coagulopathy is further exacerbated by the dilutional effect of fluid resuscitation, which lowers the concentration of remaining clotting factors. The hypothermia, acidosis, and hypocalcemia that often accompany massive hemorrhage can further impair coagulation. This vicious cycle of bleeding and coagulopathy can rapidly spiral out of control, leading to multi-organ failure and death if not promptly addressed.[8-10]

Prothrombin complex concentrate (PCC) emerges as a potent weapon in the fight against coagulopathy and hemorrhage. By rapidly replenishing the depleted clotting factors, PCC acts as a bridge, bypassing the time-consuming process of endogenous synthesis, which is often impaired in the setting of massive hemorrhage. The exogenous administration of PCC provides an immediate influx of Factors II, VII, IX, and X, restoring the balance of the coagulation cascade and promoting thrombin generation and fibrin clot formation. The inclusion of Factor VII in PCC is of particular significance. Factor VII, in complex with tissue factor, can activate the extrinsic pathway independently of other factors. This unique ability allows PCC to circumvent deficiencies in other clotting factors, potentially achieving hemostasis even in the face of complex coagulopathy. In the context of PASD, where placental tissue factor is abundant and the extrinsic pathway is already primed, the administration of PCC can rapidly amplify thrombin generation, leading to a robust and sustained hemostatic response. While PCC's initial development was aimed at the rapid reversal of vitamin K antagonist (VKA) anticoagulation, its clinical applications have broadened significantly due to its unique properties and potential benefits in various bleeding scenarios. In recent years, PCC has emerged as a valuable adjunct in the management of massive hemorrhage across diverse medical specialties, including trauma, surgery, and obstetrics.[10-12]

In the trauma setting, massive hemorrhage is a leading cause of mortality. Traditional approaches like blood product transfusion and surgical hemostasis are often employed, but they may not always achieve adequate hemostasis promptly, especially in the presence of coagulopathy. PCC has gained traction as a potential adjunctive therapy in trauma patients with hemorrhagic shock. Several studies have explored its efficacy and safety in this context. A systematic review and meta-analysis assessed the effects of PCC in trauma patients with hemorrhagic shock. The authors found that PCC, compared to plasma alone, reduced the need for massive transfusion and improved 24-hour survival rates. Another study reported that PCC administration in trauma patients was associated with decreased blood loss, reduced transfusion requirements, and improved clot strength. These findings suggest that PCC may offer a valuable tool for mitigating the coagulopathy of trauma and enhancing hemostasis, ultimately improving patient outcomes. Massive hemorrhage is also a major concern in surgical practice, especially during high-risk procedures like cardiac surgery, liver transplantation, and major orthopedic surgery. In these settings, achieving rapid and effective hemostasis is critical to prevent complications and improve patient outcomes. PCC has been increasingly utilized in surgical settings as a potential adjunctive therapy to control bleeding. A study evaluated the use of PCC in patients

undergoing elective cardiac surgery. The authors found that prophylactic PCC administration reduced intraoperative blood loss and the need for allogeneic blood transfusion. Another study reported that PCC, administered during liver transplantation, was associated with improved coagulation parameters and reduced blood product transfusion requirements. These findings suggest that PCC may offer a safe and effective means of optimizing hemostasis and reducing blood loss in high-risk surgical procedures. In the field of obstetrics, postpartum hemorrhage (PPH) remains a significant cause of maternal morbidity and mortality. While uterotonic agents and blood product transfusion are the mainstays of PPH management, these interventions may not always be sufficient, particularly in cases of underlying coagulopathy or massive hemorrhage. PCC has emerged as a promising adjunctive therapy in obstetrics, particularly in the management of PASD, where the risk of massive hemorrhage is especially high.[13-15]

Several studies have explored the role of PCC in obstetric hemorrhage. A systematic review and meta-analysis evaluated the use of PCC in women with PPH. The study concluded that PCC, compared to FFP, was associated with a significantly lower risk of thromboembolic events and a trend toward reduced blood loss. Another study specifically examined the use of PCC in women with PASD undergoing cesarean hysterectomy. The authors found that PCC, administered as part of a multidisciplinary approach, was associated with reduced blood loss and transfusion requirements compared to historical controls. Furthermore, no thromboembolic events were reported in the PCC group. While these studies are promising, it is important to note that the evidence base for PCC in obstetric hemorrhage is still evolving. Larger, randomized controlled trials are needed to definitively establish the efficacy and safety of PCC in this setting. Additionally, the optimal dose, timing, and route of administration of PCC remain to be determined. The use of PCC in massive hemorrhage is often guided by point-of-care coagulation tests like thromboelastography (TEG) or rotational thromboelastometry (ROTEM). These tests provide real-time information on the patient's coagulation status, including clot formation, clot strength, and fibrinolysis. By identifying specific coagulation deficiencies, these tests can inform personalized PCC dosing and facilitate monitoring of treatment response. For instance, in a patient with prolonged clotting time and reduced clot firmness on TEG/ROTEM, suggesting deficiencies in the extrinsic and common coagulation pathways, PCC can be administered to replenish the deficient factors and improve clot formation. Similarly, in a patient with accelerated clot lysis, PCC may be combined with antifibrinolytic agents like tranexamic acid to prevent clot breakdown and enhance hemostasis.[16-18]

Recent years have witnessed a burgeoning interest in prothrombin complex concentrate (PCC) as a versatile and potentially transformative therapeutic agent in the management of coagulopathy and massive hemorrhage. While its primary role in replenishing depleted clotting factors has been well-established, a wave of new research has illuminated additional benefits that extend beyond simple hemostasis. Massive hemorrhage often necessitates aggressive fluid resuscitation and blood product transfusion. This, however, can lead to dilutional coagulopathy, a condition characterized by the dilution of clotting factors and platelets, further compromising hemostasis. PCC, by replenishing not only the vitamin K-dependent clotting factors but also other essential procoagulant proteins like Factor V and Factor VIII, may effectively mitigate dilutional coagulopathy. This could translate to reduced transfusion requirements, faster hemostasis, and potentially improved outcomes in patients with severe bleeding.[17,18]

Hemorrhage and trauma trigger a complex inflammatory cascade that, while initially protective, can become dysregulated and contribute to organ dysfunction and multi-organ failure. Recent studies

have suggested that PCC may exert anti-inflammatory effects by inhibiting the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). Additionally, PCC may modulate the complement system, a key component of the innate immune response, potentially mitigating the systemic inflammatory response syndrome (SIRS) often associated with severe hemorrhage. The endothelium, the inner lining of blood vessels, plays a crucial role in hemostasis and vascular integrity. In massive hemorrhage, endothelial dysfunction can occur, further compromising blood clotting and contributing to organ damage. Emerging evidence suggests that PCC may improve endothelial function by promoting the release of vasoprotective substances like nitric oxide (NO) and prostacyclin. This endothelial protection could have far-reaching implications, potentially reducing the risk of organ failure and improving long-term outcomes.[18,19]

While the promising potential of PCC has garnered significant attention, several questions remain unanswered, fueling ongoing research in this field. The optimal dose of PCC in different clinical scenarios remains a topic of debate. While some studies suggest early administration, even before significant coagulopathy develops, others advocate for a more conservative approach, reserving PCC for cases of refractory bleeding or documented coagulopathy. Further research is needed to determine the ideal dose and timing of PCC administration for specific patient populations and clinical settings. PCC is typically administered intravenously, but the potential for alternative routes, such as topical application or intraosseous infusion, is being explored. Topical PCC may be particularly useful in controlling localized bleeding, while intraosseous infusion could offer a rapid and effective route in situations where intravenous access is challenging. While short-term safety data on PCC are generally reassuring, concerns remain regarding its potential prothrombotic effects, especially in patients with underlying thrombophilia or cardiovascular disease. Large, randomized controlled trials are needed to rigorously assess the long-term safety of PCC and identify any potential adverse events. The comparative effectiveness of PCC versus other hemostatic agents, such as recombinant activated factor VII (rFVIIa) or fibrinogen concentrate, is an area of active research. Head-to-head trials are needed to determine the most effective and cost-effective approach to hemorrhage control in different clinical scenarios.[18,20]

As research continues to unravel the intricacies of PCC's mechanism of action and clinical applications, its role in modern medicine is poised for significant expansion. The potential for PCC to not only correct coagulopathy but also mitigate dilutional coagulopathy, modulate inflammation, and enhance endothelial function opens up exciting possibilities for its use in a wide range of clinical scenarios, including trauma, surgery, obstetric hemorrhage, and critical care. The development of novel PCC formulations, with enhanced stability, longer shelf life, and potentially lower thrombotic risk, is also on the horizon. These advancements could further expand the accessibility and applicability of PCC, making it a valuable tool in the global fight against hemorrhage-related morbidity and mortality. PCC represents a paradigm shift in the management of coagulopathy and massive hemorrhage. Its rapid onset of action, ability to replenish multiple clotting factors, and potential pleiotropic effects make it a valuable addition to the therapeutic armamentarium. As research continues to elucidate its full potential, PCC is poised to revolutionize hemorrhage management and improve outcomes for countless patients worldwide.[19,20]

4. Conclusion

PASD is a complex and potentially life-threatening obstetric condition that requires a multidisciplinary approach and meticulous planning. The use of PCC, as demonstrated in this case report, shows promise as an adjunctive therapy in the management of massive

hemorrhage associated with PASD. However, further research is needed to determine the optimal dose, timing, and patient selection for PCC administration in this setting.

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