Spinal anesthesia for c-section in patients with protein S deficiency: case report and literature review

Anestesia espinal para cesárea en paciente con deficiencia de proteína S: informe de caso y revisión de la literatura

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Abstract

Introduction: Congenital protein S deficiency is a very rare disease in the population. In pregnant women it is associated with spontaneous abortion and fetal death, among other complications.

Case presentation: We present the case of a 32-year-old multigravida with a 36-week pregnancy, with thromboprophylaxis with enoxaparin from the 4th week of gestation and with a diagnosis of thrombophilia—due to functional protein S deficiency—which was intervened with elective c-section under spinal anesthesia. In addition, a review of the relevant literature was conducted.

Discussion: The risk of venous thromboembolism is approximately 4 to 5 times greater during gestation, and the recommendation of thromboprophylaxis in low-risk thrombophilia is based on the presence of associated risk factors. In patients receiving low molecular weight heparin (LMWH) as thromboprophylaxis, an interval of at least 12 hours after the last dose of LMWH before neuropsy and restarting the next dose after at least 4 hours of spinal technique use is recommended.

Conclusion: Neuroaxial techniques should be individualized and receive pre and postpartum thromboprophylaxis. In addition, non-pharmacological thromboprophylaxis measures in the perioperative period should be considered. Spinal anesthesia was effective and safe in this patient.

Resumen

Introducción: La deficiencia congénita de proteína S es una enfermedad muy rara en la población. En gestantes está asociada a aborto espontáneo y muerte fetal, entre otras complicaciones.

Presentación del caso: Presentamos el caso de una multigesta de 32 años con embarazo de 36 semanas, con tromboprofilaxis con enoxaparina desde la semana cuarta de gestación y con diagnóstico de trombofilia —por deficiencia de proteína S funcional—, la cual fue intervenida con cesárea electiva bajo...
anestesia espinal. Además, se realizó revisión de la literatura al respecto.

**Discusión:** El riesgo de tromboembolismo venoso es aproximadamente 4 a 5 veces mayor durante la gestación, y la recomendación de tromboprofilaxis en trombofilias de bajo riesgo se basa en la presencia de factores de riesgo asociados. En pacientes que reciben Heparinas de Bajo Peso Molecular (HBPM) como tromboprofilaxis, se recomienda un intervalo de al menos 12 horas después de la última dosis de HBPM antes de la punción del neuroeje, y reiniciar la siguiente dosis después de al menos 4 horas de uso de la técnica espinal.

**Conclusión:** Las técnicas neuroaxiales deben ser individualizadas y recibir tromboprofilaxis pre y posparto. Además, se deben tener en cuenta las medidas de tromboprofilaxis no farmacológicas en el periodo periorperatorio. La anestesia espinal fue efectiva y segura en esta paciente.

**Introduction**

Protein S is a cofactor dependent on vitamin K and protein C. Protein C acts by inhibiting factors Va and VIIIa of the coagulation cascade. The free fraction of protein S acts as a cofactor of protein C. Moreover the deficiency of both proteins leads to a state of hypercoagulability that is treated with anticoagulation.

Congenital protein S deficiency is an autosomal dominant disease, very rare in the non-gene carrier population, with a frequency of approximately 1 in 700 individuals in the general population, according to extrapolations from a study conducted on more than 9000 donors. The incidence of protein S increases to 3% to 6% in patients with a history of thrombosis or recurrent thrombosis. Also described is a high frequency in Japanese patients, approximately 12.7%. Venous thromboembolism (VTE) develops in 60% to 80% of patients who are heterozygous for protein S deficiency; however, the remaining patients are asymptomatic and some never develop VTE.

Protein S deficiency in pregnant women is associated with miscarriage, fetal death, restriction of fetal intrauterine growth, placental abruption and pregnancy-induced hypertension, and may also induce thrombosis in deciduous vessels and affect placentation through hypercoagulability and inflammation. The changes that occur in the coagulation system during gestation are compensatory mechanisms of hemostasis that should occur after childbirth; the pregnant woman presents a state of physiological hypercoagulability where the concentrations of coagulation factors, such as VII, IX, and X, are increased, as well as fibrinogen levels increase by 50%, to whose changes a decrease in fibrinolytic response is added. However, anticoagulants such as anti-thrombin and protein S decrease and, consequently, pregnancy alters the equilibrium of the coagulation system, which means that both the pregnant and puerperian woman are pre-disposed to developing thrombotic processes.

It should be noted that the greatest risks of developing these problems occur in the first trimester and up to 12 weeks after childbirth. The risk of VTE is approximately 4 to 5 times greater during gestation, with deep vein thrombosis and pulmonary embolism being the most frequent clinical manifestations.

**Case description**

We present the case of a 32-year-old multigravida with a 36-week pregnancy and a diagnosis of thrombophilia: functional protein S deficiency (Table 1) from weeks before current gestation.

The patient was scheduled for category 4 Caesarean section by Lucas et al. She has an obstetric history: 4 incomplete abortions, a gestation at term 4 years ago concluded by C-section (poor presentation), apparently without complications. No history of thromboembolic events. In normal general condition, accessible venous puncture areas, absence of varicose veins in the lower limbs, presence of edema +/++, isochoric photorefractive pupils. Physical examination: Mallampati II score, thyromentonian distance of 6.5 cm, mouth opening greater than 4 cm and mandibular subluxation greater than 0 degrees, adequate cervical movement, central trachea and denture without alterations, palpable sinal process, no scoliosis, and rest of apparently normal.

**Table 1. Laboratory tests.**

| Coagulation                          | Lupus anticoagulant | Anti-thrombin III | Functional protein C | Functional protein S | Immunology                      |
|--------------------------------------|---------------------|-------------------|----------------------|----------------------|--------------------------------|
|                                      | Negative            | 108.2%            | 126.6%               | 58.6%                | Anticardiolipin IgG 1.83U/mL    |
|                                      |                     |                   |                      |                      | Negative <10U/mL               |
|                                      |                     |                   |                      |                      | Anticardiolipin IgM 3.57 MPLU/mL|
|                                      |                     |                   |                      |                      | Negative <7MPLU/mL              |
|                                      |                     |                   |                      |                      | Beta 2 glycoprotein I IgG 1.22U/mL|
|                                      |                     |                   |                      |                      | NV: 0–20U/mL                   |
|                                      |                     |                   |                      |                      | Beta 2 glycoprotein I IgM 7.52U/mL|
|                                      |                     |                   |                      |                      | NV: 0–20U/mL                   |
|                                      |                     |                   |                      |                      | TORCH                           |
|                                      |                     |                   |                      |                      | Negative                        |

IgG = Immunoglobulin G; IgM = Immunoglobulin M; MPL = Immunoglobulin M units; NV = normal values; TORCH = Screening test for toxoplasmosis, rubella, citomegalovirus, herpes and HIV.
Source: Authors.
the post-anesthetic recovery unit with stable vital func-
tions, where she was monitored for 3 hours; during the
post-anesthetic evolution to discharge, according to the
Aldrete scale, she had 10 points, and according to the
Bromage scale, 0 points. She was then moved to the
hospital for subsequent discharge from nosocomial on
the 3rd day. There were no thromboembolic events in the
15 post-operative days.

Discussion

It is recommended that the risk of thromboembolism be
stratified at the beginning of pregnancy, during pre-
anesthetic evaluation, as well as in the immediate intra-
and postpartum period (Table 3).

In relation to low-risk thrombophilia, such as protein S
deficiency, the recommendation for thromboprophylaxis
is based on the presence of associated risk factors. In this
patient the risk was stratified with a score of 3 (1 point
for low-risk thrombophilia, 1 point for elective c-section,
1 point for pregnancy under 36 weeks). In relation to
pharmacological prophylaxis, the agent of choice is low
molecular weight heparin (LMWH) both antenatal and
postnatal, and doses are based on maternal weight. LMWH
is safe during breastfeeding; monitoring of factor Xa as
follow-up is not necessary when used as prophylaxis.
Unfractionated heparins may be useful in the peripartum,
as they have a shorter action time, but their chronic
use generates heparin-induced thrombocytopenia and
osteoporosis.

One of the advantages of LMWH in obstetrics is the
extended half-life and increased bioavailability which is
therefore used once a day as prophylaxis. Patients
receiving heparin prophylaxis may benefit from neuro-
axial techniques; however, their application should be
personalized. In patients receiving LMWH by throm-
 prophylaxis, an interval of 12 hours after the last dose and
24 hours after its use as treatment is recommended,
before the start of a neuroaxial procedure; and restarting
after 4 hours of the use of a spinal technique or removal
of the epidural catheter, in addition to the fact that it should
not be removed within 12 hours after the last dose of
LMWH.

Regardless of the anesthetic technique chosen, priority
should be given to monitoring and avoiding decreased
cardiac output, hypothermia, intraoperative hypovolemia,
and bleeding, as this is associated with increased risk of
thrombosis in patients with protein S deficiency. Postpar-
tum prophylaxis should be maintained for at least 6 weeks
with LMWH.

It was decided to perform the spinal technique on this
patient due to its simplicity, the anesthetic quality and
the small caliber of the needle used. However, at
discharge, consideration should have been given to
continuing with thromboprophylaxis, given the risk of
developing some thromboembolic event during the
puerperal stage.

| Table 2. Pre-surgical tests. |
|-----------------------------|
| Blood count/biochemistry    |
| Hemoglobin                  |
| Partial thromboplastin time |
| Fibrinogen                  |
| Platelets                   |
| Urea                        |
| Creatinine                  |
| Glucose                     |
| Other                       |
| Cardiac Risk Index          |
| Urine test                  |
| Serological (RPR/VDRL)      |

NV = normal values; RPR = rapid plasma reagin; VDRL = venereal disease research laboratory.

The patient was hemodynamically stable before, during
and after the surgical procedure. The birth occurred at
12:43 p.m., with a healthy newborn. Intraoperative bleeding
of 500 mL was quantified. Tramadol 100 mg and meta-
mozole 2 g were administered intravenously 30 minutes
before the end of surgery for the management of
postoperative analgesia. The patient was transferred to
the post-anesthetic recovery unit with stable vital func-

tions, where she was monitored for 3 hours; during the
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puerperal stage.
### Table 3. Risk factors for venous thromboembolism.

| Pre-existing risk factors                                                                 | Check | Score |
|------------------------------------------------------------------------------------------|-------|-------|
| Previous VTE (except a single event related to major surgery)                            |       | 4     |
| Previous VTE caused by major surgery                                                      |       | 3     |
| High-risk thrombophilia                                                                   |       | 3     |
| Comorbidities such as: cancer, heart failure, active systemic lupus erythematosus, inflammatory polyarthritis, nephrotic syndrome, type 1 diabetes mellitus with nephropathy, intravenous drug use |       | 3     |
| Family history of spontaneous or estrogen-related VTE in first-degree relative             |       | 1     |
| Low-risk thrombophilia (no VTE)                                                           |       | 1     |
| Age >35 years                                                                             |       | 1     |
| Obesity (BMI greater than 30 = 1, BMI greater than 40 = 2)                               |       | 1-2   |
| Parity ≥3                                                                                 |       | 1     |
| Smoker                                                                                    |       | 1     |
| Varicose veins (macroscopic)                                                              |       | 1     |
| Obstetric risk factors                                                                    |       |       |
| Pre-eclampsia during pregnancy                                                            |       | 1     |
| In vitro fertilization/assisted reproduction                                               |       | 1     |
| Multiple pregnancy                                                                        |       | 1     |
| Cesarean section in labor                                                                 |       | 2     |
| Elective cesarean section                                                                 |       | 1     |
| Instrumented labor                                                                        |       | 1     |
| Prolonged labor (>24 hours)                                                                |       | 1     |
| Postpartum hemorrhage (transfusion of more than 1L)                                      |       | 1     |
| Preterm pregnancy                                                                         |       | 1     |
| Stillbirth in current pregnancy                                                            |       | 1     |
| Transient risk factors                                                                    |       |       |
| Any surgical procedure during gestation or puerperium, except immediate repair of the perineum, e.g. postpartum sterilization, appendectomy |       | 3     |
| Ovarian hyperstimulation syndrome (in the first trimester)                               |       | 4     |
| Current systemic infection                                                                |       | 1     |
| Prostate and dehydration                                                                  |       | 1     |

Score ≥4 antepartum, consider thromboprophylaxis in the first trimester. Score of 3, consider thromboprophylaxis from 28 weeks gestation. Score ≥2 postpartum, consider thromboprophylaxis 10 days later. Consider thromboprophylaxis in the antenatal period. Prolonged stay (≥3 days) or re-entry during puerperium, consider thromboprophylaxis. For patients at risk of bleeding, the balance between this risk and that of thrombosis should be evaluated by a hematologist with expertise in thrombosis and bleeding in pregnant women.

BMI = Body Mass Index; VTE = venous thromboembolism.

Source: Adapted from Appendix III: “Risk assessment for venous thromboembolism” of the Royal College of Obstetricians & Gynaecologists.™
Conclusion

Hemostasis changes occur in pregnancy, such as hypercoagulability due to increased coagulation factors and reduced fibrinolytic activity. Neuroaxial techniques should be individualized during the surgical procedure and, according to the risk stratification of thromboembolism, antepartum, and postpartum thromboprophylaxis should be applied. Spinal anesthesia was effective and safe for this patient.

Recommendations

Pre-anesthetic evaluation is recommended days before surgery for anesthetic management in pregnant women with protein S deficiency, prior stratification of thromboembolic risk, and according to this, to perform the corresponding thromboprophylaxis, without forgetting the importance of strict hemodynamic monitoring during and after the surgical procedure, as well as the use of non-pharmacological thromboprophylaxis measures in the perioperative period, such as anti-thromboembolic stockings, effective analgesia, early ambulation and avoiding dehydration.

Ethical responsibilities

Protection of humans and animals. The authors state that no human or animal experiments have been carried out for this research.

Confidentiality of data. The authors state that they have followed their workplace protocols on patient data publication.

Right to privacy and informed consent. Authors have obtained informed consent from the patient and/or subjects referred to in the article. This document is held by the author of correspondence.

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Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Patil AD, Sabu J, D’Souza O. Anesthesia management of the parturient with protein S and C deficiency for cesarean section. J Anaesth Crit Care Case Rep 2017;3:14–15.
2. Muhsin Chisti M, Chinta S, Talavera F, et al. Protein S deficiency [Internet]. 2018; Medscape, New York: [cited 2018 Sep 23]. Available from: https://emedicine.medscape.com/article/205582-overview.
3. Soma-Pillay P, Catherine NP, Tolppanen H, et al. Physiological changes in pregnancy. Cardiovasc J Afr 2016;27:89–94.
4. Springel EH, Ramus RM. Thromboembolism in pregnancy [Internet]. 2018; Medscape, New York: [cited September 26, 2018]. Available from: https://emedicine.medscape.com/article/2056380-overview.
5. Royal College of Obstetricians & Gynaecologists. Thrombosis and Embolism during Pregnancy and the Puerperium, Reducing the Risk (Green-top Guideline No. 37a) [Internet]. 2018; Royal College of Obstetricians and Gynaecologists, London: [cited November 23, 2018]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg37a/.
6. Gupta B, Prakash S, Gujral K. Anaesthetic management of the parturient with protein S deficiency and lumboperitoneal shunt. Anaesth Intensive Care 2003;31:3.
7. Shinozaki N, Ebina Y, Deguchi M, et al. Protein S deficiency complicated pregnancy in women with recurrent pregnancy loss. Gynecol Endocrinol 2016;32:672–674.