

<https://doi.org/10.52645/MJHS.2024.1.10>

UDC: 618.5-089.888.61-089.5:616.832-004.2



CASE STUDY



Obstetrical anesthesia for a patient with multiple sclerosis: case report and literature review

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ABSTRACT

Introduction. Multiple sclerosis is an autoimmune disease characterized by chronic inflammation with progressive demyelination and axonal dysfunction. The disease affects about 1 million young adults, 2/3 of which are women of childbearing age, with all patients develop irreversible neurological dysfunction. There is observed a stagnation of the disease during pregnancy, with the return of exacerbations in the postpartum period. Contemporary specialty textbooks neither confirm nor deny the safety of neuraxial anesthesia in patients with central nervous system diseases.

Clinical case. We present the clinical case of a 25-year-old nullipara pregnant (36 weeks and 6 days gestation age), known with relapsing-remitting multiple sclerosis and epilepsy. The woman has relapsing multiple sclerosis symptoms during last 6 days, reason why is urgently consulted by the anesthesiologist for cesarean delivery.

Management and outcome. The article describes the technique of epidural anesthesia for the obstetrical patient with multiple sclerosis and the course of the perianesthetic evolution, including 1-year follow-up after cesarean section.

Discussions. With the aim of avoiding potential influences on the evolution and progression of the disease, clinical judgment and the choice of anesthetic technique (general vs. neuraxial) depends on several factors: vaginal delivery or caesarean section, the presence of contextual clinical modifiers (native or drug-induced coagulopathy, infection), the urgency of the intervention, and the patient's cooperation. In case of parturients with multiple sclerosis, all the risks should be rigorously evaluated: on one hand - the additional risk of general anesthesia (risk of aspiration, potential loss of airway control, critical desaturations) and on the other hand - the risk of hypothetical local anesthetic toxicity in the case of neuraxial techniques.

Conclusion. Neuraxial epidural anesthesia is a safe technique in obstetric patients with multiple sclerosis.

Keywords: multiple sclerosis, epidural anesthesia, cesarian delivery, high-risk pregnancy.

Cite this article: Plămădeală S, Coloman D, Ciubara R, Belii N. Obstetrical anesthesia for a patient with multiple sclerosis: case report and literature review. *Mold J Health Sci.* 2024;11(1):66-71. <https://doi.org/10.52645/MJHS.2024.1.10>

Manuscript received: 25.06.2023

Accepted for publication: 26.02.2024

Published: 20.03.2024

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Given the fact that multiple sclerosis is a rare disease, there are limited studies describing anesthetic techniques for the obstetric patient with this illness. Also, of special interest is the interrelation between the type of anesthesia and episodes of postpartum recurrences.

The research hypothesis

Using epidural analgesia and anesthesia at the minimum effective concentration can minimize any potential risks of local anesthetic to cross into the cerebrospinal fluid, linked to potential worsening of multiple sclerosis.

The novelty added by the manuscript to the already published scientific literature

The article provides anesthesiology and intensive care specialists with an up-to-date literature review of the perianesthetic management in obstetrical patient with multiple sclerosis, following a case of epidural anesthesia for cesarean section delivery in a patient with multiple sclerosis, providing prospectively the evolution of the disease up to 1 year post-anesthesia.

Introduction

Multiple sclerosis (MS) is a chronic multifocal inflammatory autoimmune disease of the central nervous system, which, through demyelination of the white matter, can lead to considerable disability. It is the most common cause of neurological disability in young adults worldwide, with half of those affected living in Europe [1-3].

According to a national neuroepidemiological study, the prevalence of multiple sclerosis in the Republic of Moldova is 21 cases per 100,000 inhabitants, of which 63.5% are female (average age 42.1 ± 11.9 years old) and 36.5% male (average age 40.8 ± 12.8 years old) [2]. The latest data from the Multiple Sclerosis International Federation Atlas (MSIF) reports an increase in the number of people diagnosed with MS as follows: 2.1 million in 2008, 2.3 million in 2013 and 2.8 million in 2020, with an increased prevalence in women, featuring a female/male ratio of 2:1 [4]. The disease onset could happen at any age, but it often occurs in the second or third decade of life, affecting those of reproductive age [1, 5].

The etiology of MS is multifactorial, involving targeting of the genetic predisposition by a series of environmental (temperate zone) and occupational factors. Thus, a six times higher prevalence of MS was found in monozygotic twins compared to dizygotic twins [1, 5]. Indeed, the human leukocyte antigen (HLA) gene cluster, located on chromosome 6p21, has been identified as the most likely locus of genetic predisposition to MS [2].

The clinical course of MS is marked by periodic subacute symptoms (vague or specific), with exacerbations and remissions, with 4 distinguished patterns of disease evolution: relapsing-remitting, secondary progressive, primary progressive, progressive relapsing [1, 3]. The frequency of MS exacerbations is variable, with an average of 0.4 attacks per year. In general, relapses consist of reinstatement of previously observed neurological deficits (bulbar, cerebellar, and pyramidal) [1].

The pathophysiology of MS involves a functional autoimmune imbalance between CD4+ lymphocytes, known as T-helper type 1 (Th1) and T-helper type 2 (Th2). Thus, an exaggerated response of Th1, which secretes pro-inflammatory cytokines (IFN-gamma, IL 2 and TNF-alpha), and an attenuated response of Th2 lymphocytes, responsible for the production of anti-inflammatory cytokines (IL 4, 5, 10, 13) [1]. Penetration of the blood-brain barrier by activated T-helpers leads to edema and chronic inflammation, with demyelination and axonal dysfunction. During pregnancy, humoral immunity takes over cellular immunity, so that in the MS patient, pregnancy can temporarily correct the auto-

immune imbalance between Th1 and Th2. In the postpartum period, with the reversal of hormonal changes, there is a return to the autoimmune balance existing before conception, with the exacerbation of the Th1 immune response and the decrease of the Th2 mediated immune response [1].

Over time, there have always been precautions regarding subarachnoid anesthesia in patients with MS, due to the exposure of demyelinated areas of the spinal cord to local anesthetics, with potential neurotoxic effects [1, 6].

Currently, the specialty literature neither confirms nor refutes the safety of neuraxial anesthesia in patients with central nervous system diseases, nor is the relative safety of spinal anesthesia versus epidural anesthesia/analgesia in patients with MS defined [1, 7, 8].

The purpose of the article is to present the perianesthetic management of the parturient with MS for cesarean delivery and an updated literature review.

Clinical case

Patients' description. Nullipara (first pregnancy, occurred spontaneously, 36 weeks and 6 days gestation age), 25 years old (1.57 m, 85 kg, weight gain during pregnancy 15 kg) is referred by the obstetrician-gynecologist to the preanesthetic consultation for urgent cesarean delivery.

Disease history. At 24 weeks gestational age, the nullipara patient (amenorrhea since 04.05.2022) registers for pregnancy monitoring and childbirth at Medpark International Hospital. The patient was consulted and added to the hospital records, assigned as a "high-risk pregnancy". In recent years, the pregnant woman has been in the records of many other medical specialists: epileptologist, neurologist, ophthalmologist, and traumatologist.

The patient was definitively, clinically, through imaging, diagnosed with relapsing-remitting MS, with a patient disability score of 2.0 points (The Expanded Disability Status Scale, EDSS), and has been registered in the official records of the neurologist since 2015. MS relapses were documented in 2018 and in February and June of 2021, when specific treatments were initiated. At the same time, since 2015 the primipara has been known to have idiopathic epilepsy (chronic treatment with Depakin Chrono® 250 mg in the morning and 500 mg in the evening), the last episode of seizures occurring 2 years ago.

At the 12-week gestational period, she is consulted by an epileptologist, who recommends continuing the anticonvulsant treatment and re-evaluation at the 32-week gestational age. Additionally, the patient is being monitored by the ophthalmologist for astigmatism, partial atrophy of the optic nerve on the right, decreased bilaterally visual acuity, bilateral amblyopia (more on the right side). The trauma-

tologist-orthopedic doctor monitors the patient for grade I-II scoliosis. Patient denies any family history of MS. Occupation: housewife. Balanced diet. Predominantly sedentary lifestyle.

The patient presents to the consultation of the obstetrician-gynecologist at the 30-week gestational age, showing a physiological progression of the pregnancy, all together with remission of the primary disease. At this term, the ophthalmologist documents the decrease of visual distance acuity (RE > LE). Biomicroscopy and fundus examination: normal.

Later, at 36 weeks gestational age the patient complains of left face paresthesias, with an insidious onset over a few days, accompanied by burning left periocular pain, paresthesias of the upper and lower limb on the left. The neurologist indicates the administration of corticosteroids (dexamethasone 4 mg/1 ml once a day) for 7 days, with improvement of symptoms. Thus, the patient is admitted for the completion of the pregnancy related to the exacerbation of MS.

The neurological examination on the day of the caesarean section revealed hypoesthesia of the left hemiface, with trigeminal neuralgia on the left. Overall, the neurological examination was normal: round symmetrical photoreactive pupils (R = L), bilaterally preserved convergence, absent nystagmus. Symmetrical face, Marinescu symptom absent bilaterally, tongue located medially. Weber test without lateralization. Vivid palatal and pharyngeal veil reflexes. Negative Chwostek sign. Normal symmetrical upper limbs osteotendinous reflexes (R = L); of the lower limbs, normal patellar and Achilles reflexes (R = L). Negative stretch marks. Negative meningeal signs. Absent pathological signs. Normotonus. Deep sensitivity preserved. Cerebellar tests done right. Stable Romberg position, heel-knee test within normal limits. Muscle strength 5/5. It is recommended to continue the antiepileptic treatment and monitor the neurological symptoms, and in case of clinical worsening of MS, quantified as deterioration by 0.5 points according to the EDSS, the initiation of pulse therapy with methylprednisolone.

Given that the ongoing pregnancy on the background of MS exacerbation may have the potential to cause fetal distress, the decision was made to deliver the baby by caesarean section, requesting the urgent consultation of the anesthesiologist doctor.

The paraclinical examination. The ultrasound examination in the third trimester of pregnancy (17.01.23) reveals an ongoing monofetal pregnancy, which sonographically corresponds to 38 weeks and 0 days of amenorrhea, with fetal morphology and functional status within normal limits. Posterior-fundal placenta, nonprevia, normal volume of amniotic fluid for the given gestational age. Estimated weight of the fetus 3319±200 gr.

Complete blood count and coagulations tests (17.01.23) within reference range for the patient in the third trimester of pregnancy. Blood group A (II) positive, Kell negative.

Hemodynamics: blood pressure (BP) 110/96 mmHg, sinus rhythm with heart rate (HR) at 81 b/min. Monitoring parameters of the fetal heartbeats within normal limits.

The challenge was determined by the choice of the type of anesthesia for the given clinical case of MS evolution, in an effort to avoid the contribution of the chosen anesthetic technique to a probable deepening of MS relapse. Although few, there are clinical trials describing the safety of both general anesthesia and neuraxial anesthetic techniques for patients with MS [1, 6, 7].

At pre-anesthetic consultation, the patient was categorized as a "patient with a full stomach and potential risk of aspiration" (she had lunch only 3 hours ago), with necessity of a waiting time of 8 hours from the last meal, in order to evacuate the gastric content. However, the caution that the obstetric patient is considered *a priori* "full stomach patients" persisted throughout the perioperative period. According to the American Society of Anesthesiologists (ASA), the patient was assigned with ASA III-E risk, without predictive signs for difficult airways (mouth opening 4 cm; thyro-mentonary distance 6.5 cm; Mallampati II, no nuchal stiffness or limitations of movements in the temporomandibular or cervical flexion-extension joint), without known drug allergy. Overall, a favorable prognosis was issued.

In a sitting position, using sterile technique and under the protection of local anesthesia (infiltration of the skin with lidocaine 2%/ 2 ml), the epidural space was approached at L3-L4 level (one attempt, G 18 Tuohy), median line, by the technique of loss of resistance to 0.9% saline solution. Epidural space located at a distance of 4.0 cm from the skin. Catheter advanced without technical difficulties, secured to the skin at the 9.0 cm mark. Negative aspiration test for reflux of cerebrospinal fluid. Negative test dose (lidocaine 2%/ 3ml + adrenaline 1:200000), absent motor block. Sterile dressing applied. Dorsal recumbence with tilting to the left.

An 11 ml volume of mixture (10 ml ropivacaine 0.75% 10 ml with 1 ml fentanyl 50 mcg) was initially administered, incrementally (in boluses of 5.5 ml each). It was evaluated a symmetric Th10 level (iliac cristae) thermal sensitive block at 9 minutes after administration, with stable hemodynamics (BP 107/ 53 mmHg). For the decompression of the inferior vena cava, the patient was placed on left-lateral tilt of 15° by placing a roll under the right lower back. Later, 3 ml of ropivacaine 0.75% were added in the epidural space, with thermal sensitive block up to Th7 after 5 minutes. At the pain sensitivity test in the presumed area of the incision – patient complained of discomfort, with the decision to add 2 ml of ropivacaine 0.75% and the request from the obstetrical operative team for a waiting time of at least 5 more minutes for the onset of effective epidural anesthesia. Bromage 4 motor block. The incision was made 19 minutes after the administration of the first epidural bolus, with no complaints of pain (numerical rating score (NRS) 0/10) or discomfort.

The patient presented to the operating room with BP 121/52 mmHg and HR 100 b/min. After epidural placement and incremental epidural administration of local anesthetic, there was a tendency to hypotension associated with sympatholysis. The lowest BP value was 103/46 mmHg (at total

epidural volume: 13 ml ropivacaine 0.75% + 1 ml fentanyl 50 mcg, 14 minutes after the first bolus), with a mean BP \geq 65 mmHg and no maternal bradycardia. Intraanesthetic maternal HR varied between 100 and 87 b/min. The patient's highest blood pressure values were recorded upon admission to the operating room and at the time of first cry of the baby (BP 122/53 mmHg). Overall, no vasoactive support was required to maintain hemodynamics. On transfer from operating room to recovery room, BP 116/66 mmHg with HR 86 b/min. In the recovery room, multiparametric monitoring was initiated (including uterine tone and vaginal secretions) for 2 hours. The epidural catheter was removed before discharge from the recovery room to ward. The anticoagulant (enoxaparin 4000U) was administered 8 hours later.

The sensory and motor sensitivity of the right lower limb was restored at 2.5 hours postanesthesia, of the left lower limb restored at 4 hours postanesthesia. NRS was monitored at 2, 6, 12 and 24 hours postoperatively, with variations between 0-3/10 (maximum intensities associated with mobilization).

Discussions

MS symptomatology include vague (headache, fatigue, depression) or specific symptoms: sensory (paresthesias, numbness of the limbs) or motor (partial paralysis of the lower limbs, certain proof of anterior spinal cord horn lesion). Decreased visual acuity, diplopia, nystagmus, and optic nerve papilla abnormalities reflect cranial nerve involvement [7]. MS is a clinical diagnosis, and nuclear magnetic resonance not only assesses disease progression, but can definitively confirm the clinical diagnosis [1, 3, 7], detecting multifocal demyelination even when it is clinically silent [7]. Lumbar puncture and cerebrospinal fluid sampling demonstrate the production of intrathecal immunoglobulins [7, 9]. At the same time, a series of other diseases can coexist with MS or, until the definitive diagnosis of MS; infections, vitamin B12 deficiency, sarcoidosis, vasculitis, spinocerebellar degeneration, or leukodystrophy must be excluded [1]. The patient in current clinical case had a confirmed diagnosis (clinical and imaging), including lumbar puncture, being in the records of the neurologist.

Although there is no specific treatment for MS, there are a number of treatments that modify the course of the disease, slowing down its progression. For example, destructive antibodies detected during periods of exacerbation can be removed by plasmapheresis. In addition, the administration of corticosteroids accelerates recovery [5, 9]. Glatiramer acetate and interferons-beta have the ability to block antigen presentation, reducing relapses. Antineoplastic medication (mitoxantrone) reduces the number of lymphocytes, with the idea of delaying the progression towards the secondary degenerative phase of the disease [5, 9]. From the moment of MS diagnosis establishing, the presented patient has needed to continuously administer anticonvulsant (Depakin) and intermittent corticosteroids at the occurrence of recurrences (4 recurrences during 7 years, pregnancy inclusively).

Regarding the choice of anesthetic technique for obstetrical patients with MS, a rigorous documentation of pre-existing neurological deficits is necessary. Particular attention will be paid to the implications of the respiratory system: the ability to cough, expectorate secretions, and ensure sufficient respiratory volumes [1, 5, 7, 10]. Reduced motor tone, with involvement of the cervical spinal cord can be associated with diaphragmatic paralysis and the necessity of functional respiratory tests [10].

From the point of view of general anesthesia as an option for the patient with MS, the patient has preserved ability to protect her airway through the cough reflex and expectoration of secretions, as well as the achievement of a forced breathing, were analyzed, confirmed, and documented. The exclusion of bulbar involvement was imperative, given the fact that the presented patient had involvement of the cranial nerves (optic (II), trigeminal (V)). At the same time, a difficult airway was not anticipated.

Regardless of the type of anesthesia selected, it is important to mention that the patient with advanced MS may present autonomic nervous system dysfunction, with the need for rigorous monitoring and control of perioperative hemodynamics [1, 11], with poor responsiveness to volume repletion and vasopressors [10].

The patient's chronic medication was also analyzed. Thus, long-term corticosteroid therapy or recent high doses of corticosteroids may require the administration of an additional stress dose of steroids [1, 7, 10]. In the clinical case presented by our team, this was not necessary, postoperatively only 8 mg of dexamethasone (diluted with 0.9% saline solution up to a volume of 20 ml) was administered slowly intravenously, to prolong the analgesic effect of the echo-guided block of transverse abdominal plane. At the same time, long-term corticosteroids' administration may be associated with muscle exhaustion and osteoporosis, which imply increased risks of injuries related to positioning on the operating table [10].

During the preanesthetic clinical examination, our patient did not present spasticity and denied taking baclofen in the past. Baclofen treatment is known to be associated with prolonged muscle weakness after the administration of muscle relaxants used for induction in general anesthesia [1, 7]. At the same time, the presence of spasticity would have required the avoidance of the depolarizing muscle relaxant (succinylcholine) during orotracheal intubation, due to the potential of inducing severe hyperkalemia with lethal risk [1].

Over time, the optimal anesthesia technique for delivery in pregnant women with MS has been a controversial topic. Initially, general anesthesia was considered the safest method [1, 7, 12], with no preference for the molecule (inhaled vs. intravenous), except for nitrous oxide, which, due to vitamin B12 inhibition and potential for myopathy, is avoided [10]. On the contrary, succinylcholine is contraindicated, due to the denervation zones, with increased population of acetylcholine receptors and risk of hyperkalemia. At the same time, the upregulation of acetylcholine recep-

tors creates conditions for resistance to non-depolarizing muscle relaxants, requiring titration of increased doses and mandatory neuromuscular block monitoring. Locoregional techniques were avoided because of the potential neurotoxic effect of local anesthetics linked with perineural administration, neuronal ischemia, or presumed direct trauma [1, 13]. However, neuraxial anesthesia gives the mother the opportunity to see the baby immediately after the delivery and to benefit from clearly superior pain control in the immediate postoperative period.

The literature reports clinical cases where parturient with MS benefited from spinal anesthesia, without MS exacerbation [11, 13]. At the same time, MS can be exacerbated by emotional stress, trauma, surgery, fluid-electrolyte imbalance, fever, or infection [12]. Above all, in order to avoid litigation, in case of finding the pre-existing neurological deficit in a parturient with MS, there still exists a tendency to prioritize general anesthesia [6]. The 2014 consensus recommends that the decision to practice spinal anesthesia for pregnant women with MS should be an individualized decision within the limits of the given contextual clinical case [14].

Regarding neuraxial techniques, the patient was warned about hypothetical technical difficulties related to the presence of grade I-II scoliosis. Taking into account the patient's normosthenic constitution, after lumbar spine inspection and palpation, the degree of suspicion for possible technical difficulties associated with neuraxial approach was reduced, but these, however, could not be totally excluded. Several clinical contextual modifiers were in favor of neuraxial anesthesia: the absence of native coagulopathy, the absence of drug-induced hypocoagulation, the absence of infection at the puncture site, the patient's psychoemotional stability, and cooperation, as well as the "delayed emergency" status of the intervention. In order to avoid the theoretical risk of local anesthetics neurotoxicity on the demyelinated regions of the nerves (located in the subarachnoid space) during spinal anesthesia, epidural anesthesia was chosen. In addition, in the case of epidural anesthesia, the hemodynamic response is milder compared to spinal anesthesia.

To avoid hypothermia, a temperature of 26°C is maintained in the cesarean operating room, with monitoring of patients' temperature. In case of MS, hyperpyrexia, including an increase in body temperature by only 0.5°C may contribute to temporary deterioration of neurological function [10]. Infusions were administered at room temperature, and 1 g of acetaminophen, a drug also known as an antipyretic, was administered intravenously every 6 hours as part of multimodal analgesia.

Regarding the initially asymmetrical restoration of the lower limbs sensitivity, it could be due to the potentially demyelinated sectors on the left hand (the patient previously described an episode of recurrence on the left). On the other hand, the explanation could lie in the lateralization of the epidural catheter.

All pregnant women benefit from mechanical and pharmacological prophylaxis of deep vein thrombosis. Due to

muscle weakness and the prolonged time until first mobilization, pregnant women with MS may have additional risk for deep vein thrombosis. Although the patient from our case had no motor deficit, given the nocturnal intervention, she was assisted out of bed only in the morning.

Pasto's study found no correlation between epidural analgesia or cesarean delivery and postpartum MS recurrences [15]. Therefore, these procedures can be safely applied to MS patients. The same study reports the relationship between postpartum recurrences and significant remote disability, which necessitates the need for postpartum preventive therapies. Moreover, women who reported recurrences of MS also had a higher disability score preconception, as well as episodes of exacerbations in the year preceding the conception of the child.

The PRIMS (Pregnancy and Multiple Sclerosis) European multicenter study monitored 254 women with MS from the gestational period up to 1 year after delivery. Of the 42 women who received epidural analgesia for vaginal childbirth, compared with 180 women with MS who delivered vaginal without analgesia, no differences were found in the prevalence of MS exacerbation [16].

Contacted 1 year after childbirth, our patient reported no recurrence episodes. However, on the recommendation of the neurologist, starting with 3 months after delivery she doubled the anticonvulsant doses.

According to studies, the prevalence of complications in pregnant women with MS does not exceed that observed in healthy obstetrical population. This statement is also valid regarding for the prevalence of complications in newborns, which shows no additional risks such as low birth weight, premature birth, malformations or sudden death of the newborn [1, 13, 17, 18]. Pregnant women with MS need to be rigorously monitored postpartum, having a slightly longer hospital stay, which is not necessarily associated with an increased prevalence of cesarean sections [18]. In addition, a prospective study of 201 women reports modest protective effects of breastfeeding against MS postpartum relapses [19].

Conclusions

The pregnant woman with MS needs multidisciplinary approach: obstetrician, neurologist, anesthesiologist and intensive care specialists.

The preanesthetic examination of the patient with MS should include thorough documentation of preexisting neurological deficits, assessment of respiratory system involvement, autonomic nervous system dysfunction, and analysis of potential MS chronic medication interactions.

The clinical judgment regarding the anesthetic tactics and selection of the drug molecules for delivery will be made through the prism of risks and benefits for each individual parturient, depending on the neurological examination, the clinical background, the anesthesiologist's experience, but also the patient's preference.

Beyond routine monitoring, intraoperative neuromuscular and body temperature monitoring are mandatory for the MS patient.

MS recurrences in the postpartum period do not depend on the anesthetic technique selected or the method of pregnancy solving, correlating more with recurrences in the immediate preconception year.

Authors' contribution

All listed authors have provided a significant contribution to the collecting of material and writing this article. All authors approved the final version of the manuscript.

Informed consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

None declared.

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