Management and Pathophysiology of Meningiomas During Pregnancy: literature review and case report

ABSTRACT

Introduction: Intracranial tumors diagnosed during pregnancy can cause complications and aggravation for both pregnant and the baby. Tumors are often confused with the diagnosis of eclampsia, therefore involve cautious analysis. Thus, characteristics such as high blood pressure, seizures, intracranial hypertension increase the level of severity of the tumors in question. Fast and efficient diagnosis is of paramount importance for the best outcomes in cases of intracranial tumors in pregnancy. Case Presentation: A 33-year-old primiparous patient G1P0A0, previously healthy, diagnosed with gestational hypertension, evolved during pregnancy with pre-eclampsia refractory to drug treatment. Computed tomography scan of the skull showed a giant sphenoid wing meningioma. At 38 weeks of gestation, the patient presented with a seizure and was admitted to the maternity ward, the examination of eye fundus showed edema of the papillae. In the week following delivery, the patient underwent cranietomy with total meningioma resection. Methods: We performed a literature review on Medline database using as keywords “meningiomas” and “pregnancy” to carry out our search, and 211 articles were found, with only 6 used in this paper, which were further compared with our case. Conclusion: Meningiomas diagnosed during pregnancy, although rare, require several precautions to preserve mother and baby’s lives. Furthermore, given the gestational period and hormonal changes, tumors undergo changes in their functional and anatomical characteristics. Treatment and diagnosis must be quick and efficient, taking into account the gestation time and tumor location.

Keywords: Cerebral Tumors; Meningiomas; Pregnancy

RESUMO

Introdução: Os tumores intracranianos diagnosticados durante a gravidez podem causar complicações e agravos tanto para a gestante quanto para o bebê. Os tumores costumam ser confundidos com o diagnóstico de eclâmpsia e, portanto, devem ser cautelosamente analisados. Características como hipertensão, convulsões e hipertensão intracraniana aumentam o grau de gravidade dos tumores em questão. O diagnóstico rápido e eficiente é de suma importância para os melhores resultados nos casos de tumores intracranianos na gravidez. Relato do Caso: Uma paciente primípara G1P0A0 de 33 anos, previamente hígida, com diagnóstico de hipertensão gestacional, evoluiu durante a gestação com pré-eclâmpsia refratária ao tratamento medicamentoso. A tomografia computadorizada do crânio mostrou meningioma de asa esfenoidal gigante. Com 38 semanas de gestação, a paciente apresentou convulsão e foi admitida na maternidade, o exame de fundo de olho evidenciou edema de papilas. Na semana seguinte ao parto, a paciente foi submetida a craniectomia com ressecção total de meningioma. Métodos: Realizamos uma revisão da literatura na base de dados MedLine utilizando como palavras-chave “meningiomas” e “gravidez” para realizar nossa busca e encontramos 211 artigos dos quais 6 foram utilizados neste trabalho, e posteriormente comparados nosso caso. Conclusão: Meningiomas diagnosticados durante a gravidez, embora raros, requerem diversos cuidados para que a vida da mãe e do bebê seja preservada. Além disso, dado o período gestacional e
The diagnosis of intracranial tumors during pregnancy has proved to be a challenge, which can generate catastrophic outcome for both the pregnant and the baby, if not treated properly. Such tumors are often confused with the diagnosis of eclampsia. Due to their compressive characteristics they can increase arterial blood pressure, cause seizure, in addition to other signs of intracranial hypertension (IH), such as papilledema, decreased level of consciousness, headache, and others. The main differential diagnosis of refractory eclampsia is intracranial tumors, since under the excess of hormone during the gestational period they tend to grow exponentially. Among these tumors, meningioma is the most frequent in women, the ratio of female to male is 3:2, and such neoplasms express on their surface the hormone receptors for estrogen and progesterone. During the gestational period an intense cellular stimulation occurs increasing the number of tumor cells and consequently their volume.

Meningiomas, first described by Harvey Cushing in 1922, are among the most frequent groups of primary CNS tumors, being more prevalent in female patients aged from 40 to 70 years old. In this way, it is rare a concurrent occurrence in pregnant. Its pathophysiology, still poorly understood, may be related to genetic or extrinsic factors, such as patients exposed to nuclear radiation and heavy metals, smoking and traumatic brain injury.

The clinical signs and symptoms of meningiomas are related to their position in the cranioencephalic space and their capacity to compress structures of the central nervous system and are generally closely adhered to the dura mater. Histologically, a meningioma can be classified in accordance with the World Health Organization's Classification Central Nervous System Tumors (2016). According to the WHO, of the three possible classificatory grades (grades I, II, III) (Figure 1), 15 subtypes can be histologically distinguished. The degrees and classifications of a meningioma are extremely important for comparative indexes, recurrence studies, diagnoses and treatments of patients affected by meningiomas.

Although rare, with 5.6 cases in 100,000 pregnancies, meningiomas can be developed during pregnancy and get worse due to hormonal and physiological changes resulting from pregnancy. Therefore, tumor behavior becomes biologically different and complex, considering the endocrine and vascular mechanisms.

During pregnancy there is a tendency for these excessive hormonal stimuli, and for the growth of meningioma, which may even double its size, causing higher intracranial...
pressure (IP) and, consequently, an increase in mean arterial pressure (MAP), in order to rise to cerebral perfusion pressure (CPP = MAP - IP). During labor and delivery, there is a significant elevation in abdominal and venous pressure, which consequently leads to an increase in IP, aggravating intracranial hypertension (IH) generated by the tumor. In this context, it is essential to the diagnosis of these tumors to be made during the gestational period, preferably in the first trimester of pregnancy. Another issue to be mentioned is the use of spinal anesthesia in these patients, since during the epidural space puncture, a cerebellar herniation can occur leading the patient to death.

In this paper, a comprehensive literature review was carried out on the main evidence of the correct management for patients with meningioma during gestational period. A flowchart was drawn with the treatment and follow-up of these tumors in each trimester of pregnancy, dividing them into supratentorial and skull base meningiomas. In addition, data was correlated to our case report. Besides, in order to synthesize the main theories of meningioma growth and development during pregnancy was also performed another literature review.

The primary objective of this study is to analyze the pathophysiology, treatment and follow-up of meningiomas on pregnant, as well as reviewing the results obtained in the literature, and comparing them with those obtained in our case. A flow diagram was drawn to elucidate the proper management of pregnant who present this type of intracranial tumor, dividing them into first, second and third gestational trimesters, as well as the management for supratentorial and skull base meningiomas.

A literature review on MedLine database was performed using as keywords “meningiomas” and “pregnancy”. In our search 211 articles were found, with only 6 used in this paper. Inclusion criteria of studies were: clinical studies (randomized control trials, retrospective and prospective case-control or case series), systematic reviews, literature reviews and case reports, presenting the clinical/surgical treatment of those patients in the first, second and third gestational trimester, as well as the follow-up until the end of pregnancy, to be published in English, and title showing the aim to present data about the treatment of meningiomas on pregnant.
In addition, we added to the study a literature review about the main pathophysiology of the onset and development of meningiomas during pregnancy, as well as their relationship with the hormones produced in these periods.

**CASE PRESENTATION**

A 33-year-old primiparous patient G1P0A0, previously healthy, diagnosed with gestational hypertension, evolved during pregnancy with pre-eclampsia refractory to drug treatment. In the second trimester, the patient underwent a computed tomography scan of the skull presenting a giant sphenoid wing meningioma (Figure 2). After diagnosis we chose to maintain the clinical follow-up, without surgery at that moment. At 38 weeks of gestation, the patient presented with a seizure and was admitted to the maternity ward, the eye fundus examination showed edema of the papillae. Magnesium sulfate was then administered and performed a cesarean delivery after stabilization. In the week following delivery, the patient underwent cranietomy with total meningioma resection (Figure 3). The patient is currently without sequelae from surgery. The newborn was under exclusive breastfeeding and with adequate neuropsychomotor development (Figure 4).

**Figure 2.** CT scan showing huge meningioma of sphenoid wing.

**Figure 3.** Post-op CT after meningioma removal.

**Figure 4.** A. Immediately post-op after meningioma removal; B. Late post-op; C. Image showing the patient and her newborn both healthy.
RESULTS

Pathophysiology meningioma in pregnancy

At the beginning of pregnancy, the first four weeks, the secretion of hormones such as progesterone and estrogen is maintained through the ovaries. However, from the tenth week onward, it is the placenta that performs this function1. Other hormones associated with pregnancy, such as hCG, play important roles, such as the subsistence of the corpus luteum, and are essential in the first twenty weeks of pregnancy. In addition, hormones such as FSH and LH are at low levels during pregnancy due to the negative feedback that affects the anterior pituitary. The findings of Boyle-Walsh et al. point out that glycoproteins present in FSH, LH and hCG in vitro cell culture inhibit the proliferation of tumor cells. However, glycoproteins present in the hormones hPL (placental lactogenic hormone) and PRL (prolactin), act by stimulating tumor growth1. The quantity of estrogen receptors (ER), even when present in meningiomas, are lesser in comparison to progesterone (PR) and have no impact on tumor growth and development2.

Regarding vascular changes, pregnancy actively contributes to changes in mechanisms such as hemodynamic balance, increased ejection volume, increased volume of heart rate ejection, plasma volume and red blood cell count, which consequently generates physiological hemodilution with decreased blood viscosity. Blood pressure at rest, in turn, becomes, on average 140/90 mmHg due to the decrease in peripheral resistance of blood vessels1. The formation of peritumoral edema (PE) is present in 60% of intracranial meningiomas, being one of the most serious complications in the treatment and its appearance occurs in a vasogenic way instead of cytotoxic6,7. The vascular endothelial growth factor (VEGF), responsible for the regulation of angiogenesis, vascular permeability and vasculogenesis, is an important factor for the formation and development of PE, once its presence points to greater peritumoral edema, than those with negative (VEGF)2. In conclusion, the vascular endothelial growth factor is secreted by the tumor tissue, which is headed to the peritumoral tissue, inducing an edemogenesis in meningiomas7.

Table 1. Management of Meningioma in Pregnancy.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Tumor Location</th>
<th>Number of patients / Trimester of diagnosis</th>
<th>Results</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td>Gurcay et al., 2018</td>
<td>Parasagittal</td>
<td>(1) First trimester</td>
<td>Pregnancy terminated, the tumor was excised, operated on with bifrontal craniotomy, and surgical excision of the tumor yielded positive results.</td>
<td>When neurological symptoms arise and if an obstetrician would not recommend otherwise, termination of the pregnancy would be more beneficial to the patient, especially if the fetus is younger than 10-12 weeks.</td>
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<td>Priddy et al., 2018</td>
<td>Skull base</td>
<td>(1) First trimester (1) Second Trimester (1) Third Trimester</td>
<td>3 patients managed with surgery at presentation of symptoms. 1 (GA 9w) was managed with surgery + radiation, and had a postoperative spontaneous absorption (GA11w 3d) + without neurological deficits 1 (GA 28w) was managed with (EEA + radiation + zygomatic approach) + postoperative cesarean at 34 weeks, without NB complications + patient maintained neurological deficits 1 (GA18w), was managed with cesarean delivery at 35w without complications + surgery after delivery EEA using inhalation anesthesia + 2 frontal orbitotemporal craniotomy (without deficits).</td>
<td>In urgent management, the consideration of trimester drives the decision to intervene, sometimes with only a difference of a week in gestational age guiding the determination. Continued surveillance, at least until after delivery, may be the best decision for the nonurgent patient, especially if imaging is indeterminate. Pre-term delivery before surgery may be appropriate early in the third trimester if neurologic status continues to deteriorate. Finally, the second trimester is the optimal time for surgery, with the least risk for spontaneous abortion or preterm birth.</td>
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Table 1. Management of Meningioma in Pregnancy (continued).

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<tr>
<th>Author (year)</th>
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<tr>
<td>Zoil et al., 2020</td>
<td>Sellar and parasellar</td>
<td>(3) Third Trimester</td>
<td>All 3 patients were treated post-delivery. 2 patients were treated with EEA surgery, and both outcomes were radical resection, normal pituitary function, and recovery of symptoms. Only 1 patient was treated with proton therapy, and her outcome was stability, and spontaneous regression of the neurological symptom.</td>
<td>In literature, meningiomas resulted in the most common lesions, clinically presenting during pregnancy, followed by prolactinomas. This could be due to the greater propensity of these tumors to increase in size in response to the estrogen progestin drive, and, thus, become symptomatic during gestation, or to their higher prevalence of these neoplasms in the population. The appropriate timing at which performing clinical examination and MRI after symptom onset or patient evaluation cannot be defined a priori, since the severity of symptoms (this the acute or sub-acute presentation) and the evolution of each case are unpredictable. When clinical conditions are stable or slowly progressive, treatment, especially surgery, should be postponed after delivery.</td>
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<tr>
<td>Kumar et al., 2020</td>
<td>Supratentorial</td>
<td>(1) First trimester</td>
<td>1 patient underwent supratentorial craniotomy using awake throughout approach, with intraoperative neurological assessment for contralateral motor functions in both upper &amp; lower limb. The use of Awake Craniotomy in this scenario is logical not only to avoid GA and harmful effects of anesthetic medications, but it also enhances recovery. Post procedure obstetric review ensured fetus viability as evident by fetal heart sounds.</td>
<td>Awake Through (AT) approach is logical and safe in pregnant patients requiring tumor resection during pregnancy. Anaesthetic management includes extensive preoperative psychological preparation and intraoperative use of scalp block. The technique provides hemodynamic stability, facilitates intraoperative neurological monitoring, tumor resection and improving fetal-maternal outcome.</td>
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<td>Lynch et al., 2014</td>
<td>Occipital and parietal</td>
<td>(2) Third Trimester</td>
<td>2 patients at the 3rd trimester of pregnancy. 1 (GA 34 weeks) with location Occipital, was submitted to Subtotal removal and Cesarean section before craniotomy, DHB. 1 patient (GA 30 weeks) with parietal meningioma, was managed with gross total removal, followed by C-section after the surgery, and delivery of a healthy baby.</td>
<td>Treatment should always primarily focus on preserving mother’s life and, secondarily, the life of the embryo. The surgical decision should be tailored to each patient according to the circumstances. Whenever possible, delivery should be performed when the fetus weights 1 kg, calculated by ultrasound, corresponding to the gestational period from 26th to 30th week. Following this period, there is a 90% or greater chance for the infant to be born healthy. If delivery is performed around the 25th week, the fetus has less than 50% chance of survival and before the 22nd week, only 5%. The timing for a neurosurgical intervention and the delivery will depend basically on three factors: severity of neurological symptoms, the gestational age of the embryo and the presumed histology of the tumor.</td>
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<tr>
<td>Sahu et al., 2020</td>
<td>Frontal</td>
<td>(1) Third Trimester</td>
<td>1 patient presenting raised ICP and seizures was managed with elective craniotomy pre-delivery. The postoperative period remained uneventful, and the patient had a full term elective cesarean procedure under general anesthesia with delivery of an alive male, 2.5 kg healthy baby. Six-month follow-up after discharge was uneventful.</td>
<td>Continuous monitoring of both mother and fetus is essential. Fetal heart rate monitoring is believed to be useful for identifying intraoperative conditions leading to impaired uteroplacental blood flow and fetal oxygenation. Neurosurgery during pregnancy mandates a multidisciplinary approach, modification of neuroanesthetic techniques and obstetric practices to accommodate the safety requirements of the mother and fetus.</td>
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Considering all these aspects, along with personal experience and literature review of the management of meningiomas during pregnancy, in case of life-threatening maternal or fetal conditions, the gestation interruption or induced cesarean delivery (depending on gestational age) followed by prompt surgical intervention must be considered. Alternatively, if tumor resection could solve the critical state, as in case of hydrocephalus, intracranial hypertension or optic nerve compression, surgery during pregnancy with fetal intraoperative monitoring can be performed.

No specific guidelines were found to define the optimal delivery method. Spontaneous vaginal delivery, for the uterine contractions and the extreme Valsalva’s maneuver, is associated with an important increase of intracranial pressure, potentially dangerous in patients with SPT or in the early postoperative time for the risk of CSF leak after transsphenoidal surgery.

The papers here reviewed, in summary, pointed to the importance and complexity of the treatment and monitoring of pregnant women with meningioma. According to Gurcay et al. (2018), meningiomas are the most common brain tumors among women, between 40 and 60 years of age. During pregnancy, due to hormonal changes, meningiomas may grow rapidly and generate an increase in symptoms for the affected patient. The hormones that play an active role in these changes are estrogen and progesterone receptors, which, through signal transduction, induce an acceleration of tumor growth. This article presents a case report of a 21-year-old pregnant woman diagnosed with vision loss with a progesterone receptor positive giant meningioma.

In contrast, Priddy et al. (2018) pointed out that neoplasms are rare during pregnancy, but when they occur, the increased plasma volume, accelerated growth due to hormone release and the tumor hypervascularity can generate variable complications and increase the level of severity of such tumors. They discussed the management of symptomatic neoplasms in pregnant patients, maintaining the balance between benefit-risk for both mother and fetus, together with surgical recommendations and indications. The gestational trimester is a determining factor for assessing the need for urgent treatment. The second trimester is the ideal time for surgery due to lower risks of miscarriage and preterm delivery. The first and third trimesters are associated, respectively, with an increased risk of miscarriage and preterm delivery. Induction of preterm delivery, followed by surgery, may be appropriate in the beginning of the third trimester.

Kumar et al. (2020) and Sahu et al. (2020) also highlighted the importance of correct and cautious treatment of meningiomas in pregnant women. Both agreed that managing pregnant patients with meningioma is a challenge for neurosurgeons and neuroanesthesiologists in view of the tumor resection and the guarantee of a safe delivery for the baby and the mother. Kumar et al. (2020) mentioned that the choice between general anesthesia and awake craniotomy (CA) is based on tumor location and the need for intraoperative neurological monitoring. The research is a case report of a 29-year-old pregnant Asian woman diagnosed with right frontal meningioma, highlighting the importance of the agreed approach during Awake Through (AT) in terms of patient acceptance, the maternal-fetal neurological outcome and well-being. Furthermore, there is the successful treatment of gross total meningioma resection in pregnant women using CA. In addition, Sahu et al. (2020) admitted that symptoms such as increased intracranial pressure (ICP) may increase during pregnancy due to hormonal changes, in addition to other clinical manifestations during this period. Surgical intervention is used in the treatment of malignant and progressive diseases. In addition, advances related to fetal and maternal monitoring indeed help physicians during surgical procedures, giving them greater security and support. The article presents a case report of a 25-year-old pregnant woman diagnosed with right partial frontal meningioma.

Zoli et al. (2020) refers to sellar/parasellar tumors (SPTs) and how they become a challenge due to the lack of guidelines for their correct management in pregnant patients. Their study involves the search for data from patients with PTS who became symptomatic during pregnancy in two Italian reference centers, in addition to a systematic review of the literature. In conclusion, SPTs that become symptomatic during pregnancy need a careful follow-up and multidisciplinary treatment. Surgery is suggested in cases of rapid progression, life-threatening or risk of permanent neurological impairment or malignant lesions.
Intracranial meningiomas management during pregnancy continues to be a point of divergence in the literature. Several authors over the years have proposed different treatment schemes for these neoplasms based on gestational age and the signs and symptoms presented by the patients. Based on the review carried out and comparison with our case report outcome, we developed a flow diagram for the proper management of pregnant with these intracranial meningiomas (Figure 6).

**Figure 6.** Flow diagram showing the management of intracranial meningiomas during pregnancy

In the first trimester of pregnancy, when meningiomas are diagnosed, we should perform a thorough neurological examination in order to identify possible signs and symptoms of alarm such as: changes in mental status, visual changes and signs of IP. In case of these signs and symptoms identification, we must proceed to an emergency craniectomy in order to preserve the mother and, if possible, to continue the pregnancy until the term, always keeping in mind to follow-up, and carry out a strict monitoring of the pregnant and her fetus.

In the following semester, the behavior is similar, but in this period, some studies have suggested more prominent tendency for the growth of meningioma, causing us to take greater care in monitoring during this gestational period. In
the third trimester, we can divide the management into two large groups. The first group of patients is between the 26th and 36th week of gestation. In this period if the pregnant presents the signs and symptoms of severity described above, there are two paths. First, to perform the craniectomy for urgent removal of meningioma, due to the risk of maternal life, and the second option is to use corticosteroids for 48 hours for fetal maturation and reduction of cerebral edema, and later performing craniectomy. In the second group the pregnant is of 37 weeks of gestation or more, and must undergo elective cesarean section. After a week, post-delivery craniotomy is performed to remove the meningioma. If the patient shows signs of alarm before the cesarean section, a craniectomy with cesarean delivery should be done at the same time.

In skull base meningiomas there is a totally different approach during pregnancy. They often have surgical unresectability or a longer operative time, and usually approached after delivery by radiosurgery. However, in patients showing tumors in areas with potential risk or even symptomatic patients, a stereotactic biopsy is performed in order to decrease the tumor volume.

**CONCLUSION**

Gestational meningiomas are rare, but sometimes fatal. They have different clinical and evolutionary characteristics in pregnant and non-pregnant patients. Due to the hormonal aspects and vascular changes in pregnancy diagnosis can be done, in most cases, by localization and confirmed by clinical symptoms with careful physical examination and neuroimaging exams such as CT. Although rare, meningioma can be confused with common clinical conditions in pregnant woman, such as the presence of vomiting due to hyperemesis in the initial and eventual pregnancy pre-eclampsia with seizure, headache, visual changes and hypertension, from the second half of pregnancy. In this way, the obstetrician must be aware of cases in which symptomatology persists and/or goes beyond the stage of pregnancy, when usually decreases, or even if the condition is refractory to treatment. The professional has the option to request the help of the neurosurgeon and make a differential diagnosis with tumors brain, especially meningiomas.

Finally, taking into account the symptoms, the location of the meningioma and the gestational period, is recommended the approach to be differentiated and individualized, being possible to carry out the craniectomy with the cesarean delivery or even later, in addition to considering stereotactic biopsy to reduce the tumor volume if surgical access is difficult or unresectability of the tumor.

**REFERENCES**


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