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Review article

Pregnancy and brain tumors; a systematic review of the literature

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ABSTRACT

The incidence of primary brain tumors during pregnancy is uncommon. The etiology of these can range from different genetic syndromes such as Li Fraumeni, neurofibromatosis type I, and hormonal associated tumors. The number of meningiomas gradually tends to increase during pregnancy, suggesting a relationship between non-malignant meningiomas and hormonal changes. Clinical features are non specific or can be misinterpreted with pregnancy symptoms such as headache, vomiting and dizziness. It is worth mentioning that the symptoms due to intracranial tumors are no different in pregnant compared with non pregnant patients. However, retrospective studies in glioma behavior suggested that both tumor volume and growth, increased during pregnancy. These changes were correlated with clinical worsening and increased frequency of seizures. The diagnosis requires a proper neurologic exploration and the support of imaging studies. Treatment of tumors is very controversial since we look for the preservation of both mother and fetus. In theory, the best therapy for the mother will also be the best therapy for the fetus. During pregnancy, ideally the treatment is symptomatic, to preserve the fetus, and definite treatment may be performed after birth; the latter is not always accomplished since patients may present with impending herniation or a malignant tumor for which immediate management is necessary. We intend to give an updated review in the literature on the adequate treatment of brain tumors during pregnancy and the anesthetic management during the definite treatment. Literature data was obtained from Pubmed using the search terms: "Pregnancy", "Brain", "Tumors". A total of forty-three articles were selected.

1. Introduction

Pregnancy alone generates important physiological changes among women. The presence of an intracranial tumor during pregnancy can be associated with serious complications, such as increased maternal mortality, intrauterine growth restriction, premature delivery, and emergency caesarian delivery [1]. Because of the low prevalence of brain tumors during pregnancy, to our knowledge, no specific management or anesthetic guides are published, so most of the evidence comes from small series, case reports and experts' opinions. We intend to give an updated review in the literature on the adequate treatment of brain tumors during pregnancy and the anesthetic management during the definite treatment (Fig 1).

2. Epidemiology

Incidence rates for primary tumors of the Central Nervous System (CNS) have constantly increased over the last decades [2,3].

According to the CBTRUS (Central Brain Tumor Registry of the United States) the most common tumor site was the meninges representing 36.8% of all tumors in both males and females. Frontal 8.2%), temporal (6.0%), parietal (3.5%), and occipital lobes (1.0%) accounted for 18.7% of all tumors. The cranial nerves and the spinal cord/cauda equina accounted for 10.1% of all tumors. The pituitary

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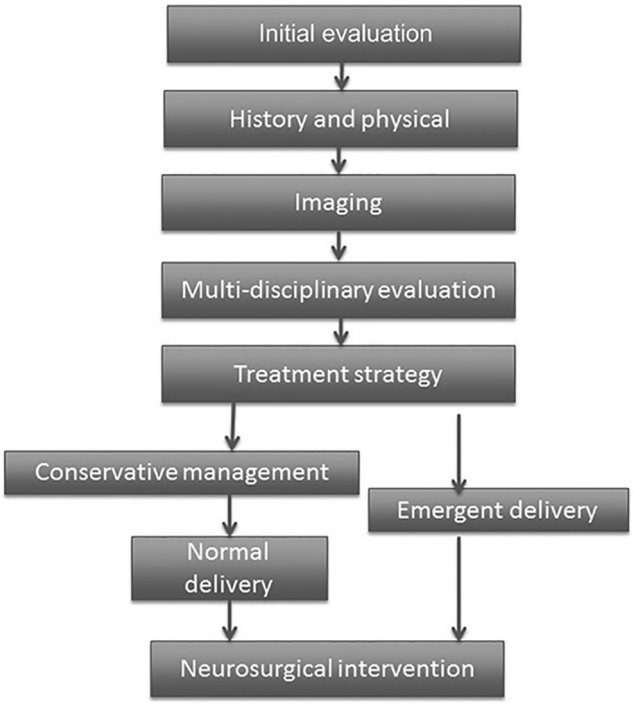

Fig. 1. Intracranial tumors approach in pregnant patients.

and craniopharyngeal duct accounted for 17.5% of all tumors. For malignant tumors, frontal (23.9%), temporal (17.5%), parietal (10.4%), and occipital (2.7%) accounted for 54.5% of tumors. For non malignant tumors, 53.0% of all tumors occurred in the meninges.

The most common of all malignant brain and other CNS tumors was glioblastoma (47.7%). the most common of all non malignant brain and other CNS tumors was meningioma (53.1%) and the most common non malignant nerve sheath tumor (based on multiple sites in the brain and CNS) was vestibular schwannoma.

Overall, 42.0% of all tumors diagnosed between 2011 and 2015 occurred in males (165,148 tumors) and 58.0% in females (227,834 tumors). Approximately 55.4% of the malignant tumors occurred in males (67,210 tumors between 2011 and 2015) and 44.6% in females (54,067 tumors between 2011 and 2015). Approximately 36.0% of the non-malignant tumors occurred in males (97,938 tumors between 2011 and 2015) and 64.0% in females (173,767 tumors between 2011 and 2015) [4].

Primary brain tumors are ranked as the fifth-leading cause of cancer-related death in women aged 20–39 years [5]. However, the occurrence of primary brain tumors during pregnancy is uncommon [6]. The reported incidence of primary malignant brain tumors in pregnant women is slightly lower than the reported in non-pregnant women, which is 2.6 per 100 000 [7]. Interestingly, the frequencies of each brain tumor type appear to be similar for pregnant and non-pregnant women. Nevertheless, the number of meningiomas gradually tends to increase during pregnancy, suggesting a relationship between non-malignant meningiomas and hormonal changes [8]. In fact, meningiomas tend to present more often during the third trimester [9]. In regard to malignant CNS tumors, no increased risk of glioma development during pregnancy has been reported [10]; however, gliomas seem to develop more often in the first two trimesters [8,9]. Retrospective studies in glioma behavior suggested that both tumor volume and growth increased during pregnancy. These changes were correlated with clinical worsening and increased frequency of seizures [11,12]. Moreover, pregnancy is associated with a negative impact on glioma behavior, exacerbating neurological symptoms that may precipitate obstetrical emergencies [13].

Nausea and vomiting are nonspecific symptoms of brain tumors and increased intracranial pressure. Like headaches, these symptoms are common in pregnancy and might be attributed to hyperemesis gravidarum [14]. However, nausea and vomiting are worst during the first trimester in most pregnant women. Therefore, new-onset of nausea and vomiting in the second and third trimester should be closely investigated [15]. On the other hand, for 30% to 50% of patients with brain tumors, an epileptic seizure is the most common clinical sign of a brain tumor [16]. A seizure with a focal onset, with possible generalization, is likely to occur due to a brain tumor. However, it should be noted that seizures, with a generalized onset, arising in the second and third trimester may also be related to eclampsia and should be treated as such.

For low-grade gliomas and meningiomas, surgical resection can be delayed after delivery because such tumors are slow growing and indolent. Steroids and antiepileptic drugs are used if needed. However, due to the hypervolemic state of pregnancy, the peritumoral edema might result in immediate surgical resection, particularly during the late second and third trimester. The latter is usually needed for large tumors with significant mass effect or those with refractory seizure. For high-grade gliomas, the prognosis is poor and neurologic deterioration is faster than other brain tumors. Therefore, surgery should not be postponed for a prolonged length of time. If the fetus is viable, it is reasonable to induce labor or a caesarian delivery. Otherwise, a careful craniotomy could be performed. However, if the patient is in a stable condition, it is recommended to postpone surgery at least until after the first trimester to permit gestational advancement. If there is a clear indication for surgery, the second trimester could be the ideal time because the fetus is too vulnerable during the first, and the risk of intraoperative hemorrhage is increased during the third. Further chemotherapy or radiation therapy should be delayed until after delivery because of the fetal risk [9,10,13,15]. However, the risk to the fetus could be decreased if the radiation therapy is given in the second or third trimester, and by limiting the dose and using abdominal lead shielding [17,18]. Stereotactic surgery could provide a safer method because fetal radiation exposure is nearly zero with such technique. Lastly, for those patients within the third trimester and without need of emergent treatment for a brain tumor, it might be possible to delay treatment until after delivery [15]. In contrast, some authors recommend that complete surgical resection is a favorable prognostic factor and delaying surgery can cause progressive neurologic deterioration and increasing risk of urgent intervention [5]. No differences on progression-free survival and overall survival between pregnant and non-pregnant patients with gliomas have been reported [19,20]. Additional studies suggest that pregnant patients with brain tumors, particularly malignant, have a higher rate of caesarean delivery than their healthy counterpart, as well as serious pregnancy complications, including preterm labor, intrauterine growth restriction, and maternal mortality [21].

Extensive literature about primary brain tumors in association with pregnancy is lacking. Due to the low incidence of primary brain tumors during pregnancy, evidence on management and clinical outcome of these particular patients has been based on few case series and expert opinions only [10].

3. Etiology

In regard to the etiology, the presence of intracranial tumors has been previously reported in patients with Neurofibromatosis type I and Li Fraumeni Syndrome, even in non-pregnant women. Therefore, indicating a possible alteration at the genetic level. On the

other hand, sex hormones have been widely associated with the formation of gliomas and meningiomas. Hormonal contraceptives or hormone replacement therapy have been shown to increase more than 2-fold the risk of exacerbation of symptoms due to brain tumors. Moreover, some specific phases of the menstrual cycle, such as the luteal phase, as well as pregnancy are also associated with worsening symptoms [22]. It is not a coincidence that some intracranial tumors have a higher incidence in women, such as meningiomas, which have a female to male ratio greater than 2:1 [23]. The combination of estrogen and progesterone is a risk factor for developing brain tumors. However, exposure to progesterone alone (2-methoxyestradiol) demonstrated an induction to apoptosis in glioma cells, inhibiting tumor growth in this tumor line. It has been reported that women that gave birth to healthy children show a lower risk of developing glioma when compared to nulliparous patients (OR 0.4). Interestingly, there is a greater impact in women with more than 5 children (OR 0.45) but the evidence is inconclusive and further studies are required [24].

4. Genetics of brain tumors and pregnancy

Breast cancer has been linked to the formation of meningiomas. Particularly polymorphisms of the BRIP1 gene which participate in the repair of the BRCA1 gene [25]. According to the current evidence that demonstrates the existence of a relationship between hormonal factors and the formation of intracranial tumors and considering that during pregnancy a series of complex hormonal changes occur, it is logical to assume a possible relationship between the hormonal changes during pregnancy and intracranial tumors.

5. Clinical features

Since slow-growing tumors are the most common intracranial tumors during pregnancy, one of their principal challenges is the diagnostic approach. Many of the initial symptoms are associated with changes in the dynamics of intracranial pressure, such as headache, vomiting, and dizziness, which are closely related to both pregnancy itself and hypertensive conditions during pregnancy. Therefore, these symptoms might be underdiagnosed or even underestimated [26]. The first diagnosis to rule out in a pregnant woman with new onset of neurological symptoms should be eclampsia. Nonetheless, the semiology of the neurological alteration will allow the physician to distinguish an intracranial tumor pathology from the hypertensive pathology. The main features in hypertension consist in the presence of scotomas, headache described as throbbing or pulsating and bilateral, epigastralgia, and edema associated with albuminuria. Importantly, epigastralgia, edema, and albuminuria are not clinical features of intracranial tumors, which might help to improve the diagnostic presumption. In addition, seizures during pregnancy can be addressed in three different groups: the first one in women diagnosed with seizures prior to gestation; the second one in women with new onset of seizures during pregnancy or the puerperium, in which intracranial tumors could be an etiology; and the third one as the latter, but associated with hypertensive pathologies such as eclampsia and intracranial hemorrhage [27].

It is worth mentioning that the symptomatology of intracranial tumors in the pregnant patient does not vary when compared to non-pregnant patients. Pituitary tumors, such as adenomas, may present visual disturbances more commonly between the 10th and 20th week of gestation. Moreover, tumors at the convexity are characterized by hemiparesis, appearing more frequently between the second and third trimesters. Nevertheless, the symptomatology depends on the location of the lesion and the tumor growth velocity rather than a specific feature of pregnancy [28].

6. Diagnosis

In able to properly diagnose a brain tumor in any patient it is necessary to do a proper physical examinations and to adequately interpret signs and symptoms. The latter, together with the support of imaging studies are necessary to make a precise diagnosis of the pathology and clarify the panorama between the different intracranial diseases that might affect a pregnant patient and dismiss pathologies that might cause similar symptoms. Computed tomography (CT) and magnetic resonance imaging (MRI) provide the greatest number of diagnostic data [26]. MRI is preferred over CT because of its higher image resolution, greater sensitivity, and the absence of radiation. The use of contrast, such as gadolinium for MRI, has not shown any complications different from those that appear in non-pregnant patients. Although contrast is capable to cross the blood–brain barrier (BBB), it has not been associated with any birth defect. Gadolinium is a category C drug established by the United States Food and Drug Administration (FDA), so it can be administered if necessary [29].

7. Treatment

In theory, the best therapy for the mother will also be the best therapy for the fetus. The treatment during pregnancy is mainly symptomatic, that way pregnancy can be carried out normally, and definitive treatment will be postponed ideally after the birth. However, the former is not always achieved due to the mortality risk of certain scenarios that involve the mother. Symptomatic relief may range from medical treatment to ventricular shunts to relieve the increased intracranial pressure (ICP) in several cases.

7.1. Symptomatic treatment

Steroids are the mainstay of medical treatment, improving the vasogenic edema associated with intracranial tumors. It is important to note that steroids benefit the formation of pulmonary surfactant in the embryo in case of premature delivery [15]. An important concern with maternal administration of glucocorticoids during pregnancy is the suppression of the fetal pituitary axis, resulting in neonatal hypoadrenalism. Although, this condition seems to be an extremely rare complication of intrauterine exposure to therapeutic doses of glucocorticoids [31]. Mannitol should be used cautiously during pregnancy due to the risk of compromising fetal circulation. Doses of 0.5–1 g/kg are considered safe [32]. Additionally, antiepileptic treatment is usually needed on a regular basis. Still, many of the antiepileptic drugs are teratogenic since they cross the placenta. In fact, there is an increased risk of major congenital malformations with antiepileptic drugs exposure during the first trimester. Polytherapy contributes to an increased rate of major congenital malformations as compared with monotherapy. The premise is that seizure-associated damage is much greater than the teratogenic risk of the antiepileptic drugs, therefore antiepileptic drugs are used as a treatment when seizures are diagnosed, but are not recommender as prophylaxis [33].

In stable patients with non-life-threatening tumors, such as benign supratentorial tumors without any evidence of increased intracranial pressure, management should be based on obstetric criteria. Pregnancy may be allowed to continue with indication of labor or caesarean section at 34–36 weeks, when the fetus is mature enough to be delivered safely [28,30]. In these cases, neurological examination, routine laboratory studies and surveillance through non-contrast MRI could be of help to monitor patients

until definitive treatment [15]. In regard to the fetus delivery, both vaginal delivery and caesarean section are accepted. An elective caesarean section under spinal epidural anesthesia may be safer for a nulliparous woman, since one-third of women are known to elevate intracranial pressure during vaginal delivery. A multiparous woman might tolerate vaginal delivery without increasing intracranial pressure [28,30]. It is noteworthy to mention that general anesthesia is a preferred option rather than spinal or epidural anesthesia, because a cerebrospinal fluid (CSF) leak can lead to severe neurologic morbidity in the setting of an intracranial tumor lesion [15]. Following delivery, patients must receive definitive treatment based on the same principles as non-pregnant women. On the other hand, in patients with progressive neurological deterioration, impending herniation or malignant tumors, immediate management is necessary, and pregnancy may not be allowed to continue. However, due to modern surgical, anesthetic, and fetal monitoring techniques performing neurosurgical procedures during pregnancy can be safely carried out without any deleterious effect on both the mother and the fetus [28,30,32]. Some authors argue that the treatment may also depend on the timing of presentation. If the patient is in her first trimester, therapeutic abortion may be offered, since surgery, radiation therapy, or chemotherapy, may be too great of a risk for the fetus, and delaying the treatment may be unsafe for the mother. In case a patient needs definitive treatment for the reasons stated above, during the second or third trimester, joint approach should be considered to assess the viability of the fetus, always prioritizing the treatment of the mother.

Literature search reports surgical indications with substantial benefit for life threatening pituitary apoplexy during pregnancy. Visual improvement is the main functional benefit posterior to surgery, as betterment is proportional to the severity of preoperative visual loss. As for endocrine functions (eg, hormoe hypersecretion), surgery is beneficial in CD [41].

7.2. Anesthetic management

Joint management with the maternal-fetal specialist for monitoring during surgery is mandatory. Mother's position can be sitting or lateralized (lateral decubitus or park bench), depending on the location of the tumor. It is important to avoid any position that might reduce the blood flow of the abdominal cava due to fetal risk [15].

When evaluating the suitable anesthetic method for a pregnant patient, it is important to take into account the physiological changes that take place during pregnancy such as pulmonary, cardiovascular, volumetric and gastrointestinal changes, which present additional difficulty when evaluating the patient. These changes are shown in Table 1.

Since pregnant woman must be consider as patients with full stomach it is important to have an adequate perioperative approach. Premedication with antacids, H2-receptor antagonists, and/or metoclopramide for pulmonary aspiration prophylaxis must be considered timely [34]. The monitoring for these surgeries can be invasive or non-invasive depending on the type of lesion and the condition of both the mother and fetus. The electrocardiography, pulse oximetry, capnography, and preferably a trans operative neuromonitoring are recommended, as well as the monitoring of fetal heart rate perioperatively. Taking into account that changes in motility and intra-abdominal pressures start from the 18th to 20th week of gestation, using a rapid intubation sequence is recommended. Nonetheless, changes in ICP should be considered with these types of techniques, as they could worsen intracranial dynamics. The indications that guide which type of anesthesia to used are mainly aimed at neurological protection and avoiding fetal distress. A successful anesthetic management plan is based on the general principles of obstetric and neurosurgical anesthesia.

Table 1
Physiological changes during pregnancy by each trimester and the systemic changes observed.

	First Trimester	Second Trimester	Third Trimester
Pulmonary	Increase in 02 consumption	Increase in alveolar ventilation (25%) Respiratory alkalosis	Increase in alveolar ventilation (70%) Decrease in residual capacity (20%)
Cardiovascular	Increased cardiac output	Decrease in vascular resistance	Decrease venous return (25%) Decrease in cardiac output up to 50%
Circulatory	Expansion of blood volume (30%) Physiologic anemia	Hypercoagulable state (factor VII, VIII, X and XI I)	
Gastrointestinal		Gastric and pyloric anatomy alterations	Lower esophageal sphincter incompetence

It is important to monitor the patient's hemodynamic parameters during surgery to avoid decrease placental blood flow, which could lead to fetal distress. The pressures that are sought to be maintained with adequate hemodynamics are cerebral perfusion pressure (CPP), which depends on the mean arterial pressure (MAP), and placental perfusion pressure. Increased ICP in these cases should be treated with moderate hyperventilation (pCO2: 30–35 mmHg) and the use of low-dose mannitol. However, there is no conclusive evidence regarding these techniques.

Po et al, described that during non-obstetric surgery an effective way to monitor intraoperative fetal heart rate is by ultrasound or cardiotocography, because that way can successfully identify non-reassuring fetal heart that might lead to an emergency intraoperative cesarean delivery [42].

The most commonly used hypnotics in neuroanesthesia are considered to have a neuroprotective profile, such as propofol and thiopental. Thiopental has slight advantages, mainly reducing intracranial pressure. However, propofol infusion pharmacological profile for the anesthesia maintenance suggests that it might be a better option when choosing an induction agent for maintenance during surgery [32]. Currently, it has not been demonstrated that any anesthetic agent has any impact on the fetus. Desflurane, propofol, sufentanil, rocuronium, neostigmine, and atropine are safe to use during pregnancy. Not the case with nitrous oxide, which at high doses and with during a prolonged period of administration inhibits methionine synthase, a necessary enzyme in DNA synthesis. Nevertheless, nitrous oxide at high doses and administered for a prolonged period of time is not used in the clinical practice. Still, it is preferable to avoid its use.

One problem to be taken into account in the anesthetic management of these patients is the placental transfer of drugs, which depends on the solubility and protein binding of the particular drug. The mechanisms underlying placental transfer of drugs are those of cellular transport: simple diffusion, facilitated diffusion, active diffusion, and pinocytosis. Anesthetic agents can be divided into three types: type 1 (e.g. thiopental), where there is a complete placental transfer of the drug and a balance exists between the mother and the fetus; type 2 (e.g. ketamine), where the drug is found in greater quantity in the fetus than in the mother; and type 3 (e.g. succinylcholine), where only a minimum amount of the drug is transmitted to the fetus [35]. Regarding the determination of which anesthetic technique to use, there is no study that makes a recommendation with an adequate level of evidence. The current

recommendations are based on the effects that the drugs might have on the brain and the uterus. TIVA may provide the optimal cerebral hemodynamic state for the injured brain by providing enhanced brain relaxation when compared to a halogenated anesthetic agent [36]. Intravenous anesthetic concentrations are rapidly eliminated from the neonatal circulation; Though it depends on variables such as bolus and perfusion models during the anesthetic procedure, as well as the induction of anesthesia to delivery interval. As an example, the concentration at 1 min of the initial bolus is 5 mcg/ml, however, 20% of the initial concentration is reduced at the time of birth, with clearly different APGAR scores between 1 min and 5 min [37].

A study that compared propofol and thiopental found no significant difference in APGAR scores between these two drugs. However, there was a significant difference in the recovery time of the newborn in the propofol group when compared to the thiopental group at 25 min versus 31 min, respectively ($p = 0.003$) [38]. It is necessary to estimate the exact delivery moment at which the concentrations in both maternal and neonatal blood would be the lowest. In this way, the negative impact in both the mother and the newborn would be less.

In addition, halogenates anesthetics have a direct impact on uterine contractility. Sevoflurane and desflurane inhibit the spontaneous contractility of the uterine muscles of pregnant women, with intensities comparable to halothane. Importantly, their effects are not reversed so easily with the use of oxytocin when anesthetic concentrations are greater than 1 MAC (minimum alveolar concentration). Moreover, a critical role of potassium channels in the regulation of spontaneous myometrial contractility has been reported. In fact, the inhibitory effect of isoflurane on spontaneous myometrial contractility may be mediated through activation of KATP channels [39]. Despite this, the use of higher concentrations of a volatile halogenated agent has become a more common practice, leading to a lower incidence of maternal awareness; per contra, there are concerns about neonatal depression and uterine atony in a dose-dependent manner, particularly when the induction of anesthesia to delivery interval exceeds 8 min [40]. The delivery of the fetus should take place close to a neurosurgical center in case there is a rapid worsening of neurosurgical status of the mother that may require emergency neurosurgical management.

8. Conclusion

Brain tumors during pregnancy are rare. And because there is a lack of guidelines to address these type of patients, physicians must hace a high diagnostic suspicion, since most of the symptoms are non specific or can correlate with pregnancy symptoms. Diagnostic approach requires preferably the uso of contrasted MRI, but in cases of no disposability or low cost approach CT scan can be used without presenting mayor risks to the fetus. When selecting a treatment we need to consider if the mother presents progressive neurological deterioration, impending herniation or malignant tumors which require immediate treatment, or if symptomatic treatment, neurological examination, routine laboratory studies and surveillance through non-contrast MRI can be provided until delivery. Both vaginal delivery and caesarean section are accepted. An elective caesarean section under spinal epidural anesthesia may be safer for a nulliparous woman, since one-third of women are known to elevate intracranial pressure during vaginal delivery. A multiparous woman might tolerate vaginal delivery without increasing intracranial pressure. The definitive treatment is surgery. During primary treatment TIVA is still the best choice of anesthesia for the type of surgery that patients will have to go through and because it is rapidly eliminated from the neonatal circulation.

Literature acquisition methods

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