Management of brain tumors presenting in pregnancy: a case series and systematic review

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Patients who present with brain tumors during pregnancy require unique imaging and neurosurgical, obstetrical, and anesthetic considerations. Here, we review the literature and discuss the management of patients who present with brain tumors during pregnancy. Between 2009 and 2019, 9 patients were diagnosed at our institution with brain tumors during pregnancy. Clinical information was extracted from the electronic medical records. The median age at presentation was 29 years (range, 25—38 years). The most common symptoms at presentation included headache (n=5), visual changes (n=4), hemiparesis (n=3), and seizures (n=3). The median gestational age at presentation was 20.5 weeks (range, 11—37 weeks). Of note, 8 patients (89%) delivered healthy newborns, and 1 patient terminated her pregnancy. In addition, 5 patients (56%) required neurosurgical procedures during pregnancy (gestational ages, 14—37 weeks) because of disease progression (n=2) or neurologic instability (n=3). There was 1 episode of postneurosurgery morbidity (pulmonary embolism [PE]) and no surgical maternal mortality. The median length of follow-up was 15 months (range, 6—45 months). In cases demonstrating unstable or progressive neurosurgical status past the point of fetal viability, neurosurgical intervention should be considered. The physiological and pharmacodynamic changes of pregnancy substantially affect anesthetic management. Pregnancy termination should be discussed and offered to the patient when aggressive disease necessitates immediate treatment and the fetal gestational age remains previable, although neurologically stable patients may be able to continue the pregnancy to term. Ultimately, pregnant patients with brain tumors require an individualized approach to their care under the guidance of a multidisciplinary team.

Key words: brain tumor, patient management, pregnancy

Introduction

Women who present with brain tumors during their pregnancies require unique imaging and neurosurgical, obstetrical, and anesthetic considerations.[1−3] Nearly every aspect of care is complicated by the presence of an intracranial neoplasm during pregnancy. Diagnostic parameters, surgical timing, method of delivery, and adjuvant treatment modalities are influenced by neurologic symptoms, gestational age, pathology, and overall prognosis.[4,5] Although the risk of developing an intracranial tumor in a pregnant patient is roughly equivalent to the risk in a similar nonpregnant female,[4,6−8] pregnancy does influence the pathophysiology of intracranial tumors.[4,9] Pregnancy-related factors that may increase tumor growth and result in severe, debilitating illness include immunologic tolerance, hormone-mediated growth, and hemodynamic changes.[4,9] In addition, the symptoms of increased intracranial pressure (ICP) caused by brain tumors, including nausea, emesis, and headache, may be confused with symptoms of normal pregnancy or other pregnancy-related conditions, making accurate diagnosis challenging.[1,2] In this communication, we review our case series from 2009 to 2019, highlight several specific cases, provide expert considerations for patient management, and summarize the current literature on the treatment of these patients. These data allow us to suggest updated guidelines for the care of patients presenting with brain tumors in pregnancy.

Methods

We performed a retrospective medical record review of 9 patients who were diagnosed with brain tumors during pregnancy and underwent treatment at our institution between 2009 and 2019. Obstetrical, neurologic, anesthetic, histopathologic, imaging, and follow-up information were extracted from the electronic medical records. This project was conducted with institutional review board (IRB) approval and was exempt from patient consent because the information collected included only preexisting, deidentified data, per the IRB.

A systematic literature review was conducted through the PubMed database. The search query ("brain tumor," OR "brain tumour," OR "intracranial neoplasm," OR "brain metastasis," OR "brain metastases" AND "pregnancy") produced 454 publications. Publications were screened between January 1, 1950, and September 30, 2020, first by title and abstract (Supplemental Figure 1).

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Full-text articles were obtained if they met all of the following inclusion criteria: authors described a case series or cohort of patients diagnosed with brain tumors during pregnancy; the case series or cohort was larger than 2 patients; the full-text article was available in English or English translation. Final review of all 454 results produced 15 publications.

Results

The median age at presentation was 29 years (range, 25−38 years). The median gestational age at presentation was 20.5 weeks (range, 11−37 weeks). Intracranial tumors had a median size of 2.3×2.4 cm in the axial plane (range, 0.48−27 cm^2). The patients' ages, histopathologic diagnoses, presenting symptoms, delivery methods, surgical timings, adjuvant therapies, and clinical outcomes are presented in Table 1. In this series, 8 patients delivered healthy newborns, whereas 1 patient opted to terminate her pregnancy.

There was no surgical maternal mortality at our institution. Postoperative neurologic complications were limited to 1 episode of unilateral paresthesia in the lower extremity and a separate case of cranial nerve (CN) VII dysfunction after resection of a large vestibular schwannoma (currently recovering). Morbidity was limited to 1 case of postoperative PE, treated with anticoagulation.

Of note, 3 patients underwent emergent cesarean deliveries (patient number 3 for increased ICP during preterm labor; patient number 4 for obstetrical concerns, including preeclampsia; and patient number 8 for fetal heart rate (FHR) deceleration following anesthetic induction). Pathology included meningioma (World Health Organization [WHO] grade II, n=1; WHO grade I, n=1), pilocytic astrocytoma (WHO grade I, n=2), diffuse large B-cell lymphoma (n=1), pleomorphic xanthoastrocytoma (WHO grade II, n=1), vestibular schwannoma (WHO grade I, n=1), pituitary adenoma (n=1), and metastatic thyroid cancer (n=1). In addition, 1 patient underwent an awake craniotomy because of the location within the eloquent brain. The most common symptoms at presentation included headache (n=5), visual changes (n=4), hemiparesis (n=3), and seizures (n=3). There was no known fetal complication. There was a relatively high cesarean delivery rate of 75% (n=6 of 8 pregnancies after viability). Neonatal outcomes were universally favorable. In the postoperative period, all mothers were neurologically intact (n=9) and were discharged to rehabilitation. Median length of follow-up was 15 months (range, 6−45 months).

Discussion

Given the infrequency of intracranial neoplasm in pregnancy, there is no level I or II evidence to guide the management of pregnant patients with brain tumors (Table 2). The literature is limited to case series and isolated reports,[10−35] and although several authors have presented different algorithms for the care of these patients,[2−4,9,17,24,27−29,36] none has offered evidence for the superiority of 1 clinical pathway over another. The questions of radiotherapy,[37,38] surgical resection,[3,39] awake craniotomy,[40] general anesthesia,[29,41] and vaginal or cesarean delivery[2,3,23,39] and the use of prophylactic anticonvulsants[4,5,42] have been debated, but little consensus has emerged.

In the following sections, we summarize the current literature and provide expert opinion on the management of patients presenting with brain tumors in pregnancy to highlight the following treatment considerations: imaging, obstetrics, fetal monitoring, anesthesia, neurosurgery, adjuvant treatment, and subsequent monitoring. We discuss 4 cases that illustrate how these considerations can be implemented in clinical practice.

Brain imaging and postoperative surveillance

The diagnosis of an intracranial neoplasm requires either computed tomography (CT) or magnetic resonance imaging (MRI).[2] MRI is the preferred diagnostic imaging tool for characterization of brain tumors in general but is of added importance in pregnant patients[1,2] as it provides the best soft tissue visualization and avoids the ionizing radiation of CT scans.[1,2] In a retrospective cohort study from Canada, exposure to MRI during the first trimester of pregnancy was not significantly associated with an increased risk of fetal or early childhood harm.[43] Additional studies did not find harmful effects on the fetus from prenatal MRI exposure in the second or third trimesters of pregnancy in patients scanned at 1.5 Tesla,[44,45] or are there published human studies demonstrating increased tissue heating or acoustic injury afflicting the fetus.[43−45] Therefore, the American College of Obstetricians and Gynecologists (ACOG) states that MRI is not associated with risk and, in addition to ultrasonography, is the imaging technique of choice in pregnancy.[46] The American College of Radiology (ACR) concluded that no special consideration is recommended for the use of MRI in any trimester of pregnancy.[47] If MRI is needed during pregnancy, internationally accepted guidelines recommend acquiring scans using magnets with field strengths of 3 Tesla or less, as specific absorption rate, a measure of tissue energy deposition, increases with field strength.[48] To date, there are no known or proven risks of MRI in pregnancy at either 1.5 or 3 Tesla, and scanning of the fetus can be performed safely at both of these field strengths.[49]

In gravid patients who require MRI, the use of contrast poses another clinical challenge. Gadolinium-based contrast agents can readily cross the placenta and into the fetus where they are excreted by the fetal kidneys into the amniotic fluid,[1,46] and there is conflicting evidence of their safety and teratogenicity in humans.[2−4,33,43,46] However, noncontrast MRI can limit tumor margin visualization. The ACR Committee on Drugs and Contrast Media and ACOG currently recommend that gadolinium-based contrast agents only be used when expected to significantly improve diagnostic performance and when potential benefits justify unknown risks to the fetus.[46,50]

In this case series, MRI was obtained without contrast during gestation and with contrast in the postpartum period without known adverse effects. Importantly, current available data suggest that it is safe for lactating women who receive

TABLE 1
Patient characteristics, diagnosis, management, and maternal and fetal outcomes

					Gestational age			Obstetrics details				Maternal Outcomes			
Patient number	Age at diagnosis	Histopathologic diagnosis	Presenting symptoms	Tumor size (AP, cm)	At presentation	At surgery	Neurosurgical operation performed	Gestational age at delivery	Delivery method	Apgar scores at 1 and 5 min	Adjuvant therapy	Postoperative	Short-term[a]	Current status[b]	Length of follow-up (mo)
1	25	Diffuse large B-cell lymphoma, not otherwise specified	Headache, diplopia, hemiparesis, seizures	2.3×1.9	11 wk	15 wk 1 d	Stereotactic biopsy	Terminated at 15 wk	N/A	N/A	Methotrexate, rituximab, and temozolomide; anticonvulsants	Neurologically intact[c] with no nausea, vomiting, vision deficits, or focal weakness	Neurologically intact with clinical improvement during chemotherapy	Pancytopenic after chemotherapy. Received transfusion. Clinically and radiographically stable. Preoperative symptoms resolved	8
2	38	Meningioma (WHO grade II)	Headache, seizures, apraxia, vertigo	5.3×3.3	15 wk	10 d after delivery	Embolization and craniotomy	37 wk 4 d	Scheduled cesarean delivery	7, 9	XRT; anticonvulsants	RUE and RLE paresthesia on post-op day 1, otherwise neurologically intact with no nausea, vomiting, vision deficits, or focal weakness	Unilateral decreased proprioception and sensory deficits in her right leg. Continued headaches and cognitive slowing. Stable imaging	Improved proprioception and sensory deficits after XRT. Mild, intermittent headaches. No weakness, seizures, or visual deficits. Stable imaging	15

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TABLE 1
Patient characteristics, diagnosis, management, and maternal and fetal outcomes *(continued)*

					Gestational age			Obstetrics details				Maternal Outcomes			
Patient number	Age at diagnosis	Histopathologic diagnosis	Presenting symptoms	Tumor size (AP, cm)	At presentation	At surgery	Neurosurgical operation performed	Gestational age at delivery	Delivery method	Apgar scores at 1 and 5 min	Adjuvant therapy	Postoperative	Short-term[a]	Current status[b]	Length of follow-up (mo)
3	27	Pilocytic astrocytoma (WHO grade I)	Headache, left arm numbness	0.6×0.8	26 wk	6 mo after cesarean delivery	Ventriculostomy, craniectomy, C1–C2 laminectomy	33 wk 2 d	Emergent cesarean delivery	Unknown	XRT recommended, patient declined	Neurologically intact with no nausea, vomiting, vision deficits, or focal weakness	Progressive visual changes and severe headaches. Imaging revealed increased enhancement and masslike extension of known brain tumor	Suffered a pontine hemorrhage after a fall. Deceased	13
4	21	Pleomorphic xanthoastrocytoma (WHO grade II)	Nausea, emesis, seizure	2.5×2.5	37 wk	4 wk after cesarean delivery	Craniotomy	38 wk 0 d	Emergent cesarean delivery	Unknown	Anticonvulsants	Neurologically intact with no nausea, vomiting, vision deficits, seizures, or focal weakness	Clinically and radiographically stable with resolution of preoperative symptoms	Presented after loss to f/u for 3 y with 4 breakthrough seizures in the previous 12 mo. Radiographically stable. Anticonvulsant medication adjusted. Lost to f/u again	45
5	32	Pilocytic astrocytoma (WHO grade I)	Headache, vertigo, photophobia, nausea, emesis	4.2×5.3	29 wk	29 wk 6 d	Retrosigmoid craniotomy and EVD placement	38 wk 5 d	Scheduled cesarean delivery	9, 9	No	Neurologically intact with no nausea, vomiting, vision deficits, or focal weakness	Repeat craniotomy at 8 mo after delivery	Mild LLE dysesthesia. Clinically and radiographically stable with resolution of preoperative symptoms	18
6	27	Metastatic papillary thyroid cancer	Speech difficulty and progression of previously treated left frontal brain metastasis	2.3×1.5	15 wk	15 wk 4 d	Awake craniotomy	39 wk 1 d	Vaginal	9, 9	Lenvatinib and cabozantinib; SRS	Neurologically intact with no nausea, vomiting, vision deficits, seizures, focal weakness, or speech difficulties	Repeat craniotomy 21 mo. later because of progression of disease	CyberKnife SRS to 8 brain lesions to slow progression of disease. Receiving cabozantinib. No dizziness or seizures	40

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(continued)

TABLE 1

Patient characteristics, diagnosis, management, and maternal and fetal outcomes *(continued)*

					Gestational age			Obstetrics details				Maternal Outcomes			
Patient number	Age at diagnosis	Histopathologic diagnosis	Presenting symptoms	Tumor size (AP, cm)	At presentation	At surgery	Neurosurgical operation performed	Gestational age at delivery	Delivery method	Apgar scores at 1 and 5 min	Adjuvant therapy	Postoperative	Short-term[a]	Current status[b]	Length of follow-up (mo)
7	34	Meningioma (WHO grade I)	Neck stiffness, radiculopathy, severe myelopathy	2.1×2.4	13 wk	14 wk 6 d	Far lateral craniotomy, C1—C2 laminectomy	40 wk 0 d	Vaginal	8, 9	SRS	Mild hemisensory deficits. Otherwise neurologically intact with resolution of preoperative symptoms	Developed nausea, vertigo and unilateral hemiparesis after CyberKnife SRS. Resolved with dexamethasone	Mild hemisensory deficits. Clinically and radiographically stable	45
8	32	Vestibular schwannoma (grade I)	Altered mental status; unilateral hearing loss	3.3× unknown	37 wk	37 wk 2 d and 7 d after cesarean delivery	EVD placement, retrosigmoid craniotomy	37 wk 2 d	Emergent cesarean delivery	6, 9	No	HB5. Large bilateral PEs on postoperative day 8. Anticoagulation. Flat affect though improved compared with preoperatively	HB4. Otherwise neurologically intact	Improving CN VII function. Clinically and radiographically stable with resolution of preoperative symptoms	10
9	27	Pituitary adenoma	Headache, blurry vision, facial numbness	0.85× 1.3	14 wk	18 wk	Transsphenoidal resection	38 wk	Scheduled cesarean delivery	9, 9	No	Neurologically intact with resolution of facial numbness and blurry vision	Neurologically intact	Clinically and radiographically stable	6

All grades are classified according to the WHO standards. Gestational ages are listed in weeks as indicated in the electronic medical records. Days and Apgar scores are included when available.

AP, anterior-posterior; *CN*, cranial nerve; *EVD*, external ventricular drain; *f/u*, follow-up; *LLE*, left lower extremity; *PE*, pulmonary embolism; *RLE*, right lower extremity; *RUE*, right upper extremity; *SRS*, stereotactic radiosurgery; *WHO*, World Health Organization; *XRT*, radiotherapy.

[a] Significant events and status changes between postoperative months 3 and 7; [b] Assessed at time of last follow-up; [c] No acoustic, sensory, musculoskeletal, or other neurologic deficits.

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TABLE 2
Systematic review of case series and patient cohorts with intracranial tumors presenting during pregnancy

Authors	Year	n	Pathology (number of patients)	Gestational age at presentation (wk)	Treatments	Preterm birth[a] (number of patients)	Delivery method	Gestational age at delivery (wk)	Other commence or complications
Haas et al[6]	1986	24	Astrocytoma (9)	4–32	Unknown	Unknown	Vaginal (8)	Unknown	Study primarily used to generate population-based estimate of cases; obstetrician and neurologist considerations not reviewed
			Glioblastoma (6)				Cesarean (3)		
			Ependymoma (1)				Terminated (7)		
			Sarcoma (1)						
			Meningioma (3)						
			Acoustic neuroma (3)						
			Pituitary adenoma (1)						
Roelvink et al[8]	1987	3	Medulloblastoma (1)	14–35	Surgery (3)	1	Cesarean (1)	36–37	No maternal or fetal complications noted
			Astrocytoma (2)				Vaginal (2)		
Nishio et al[15]	1996	6	Pilocytic astrocytoma (1)	20–38	Surgery (4)	1	Cesarean (4)	33–40	No maternal or fetal complications noted
			Pituitary adenoma (1)		Surgery + XRT (1)		Vaginal (2)		
			Ependymoma (1)		Surgery + XRT + chemotherapy (1)				
			Medulloblastoma (1)						
			Anaplastic astrocytoma (1)						
			Meningioma (1)						
Isla et al[16]	1997	6	Meningioma (2)	23–40	Surgery (6)	3	Cesarean (2)	33–40	1 maternal death after emergency craniotomy for hemorrhagic meningioma
			Ependymoma (2)		XRT (1)		Vaginal (3)		
			Astrocytoma (2)				Terminated (1)		

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TABLE 2
Systematic review of case series and patient cohorts with intracranial tumors presenting during pregnancy *(continued)*

Authors	Year	n	Pathology (number of patients)	Gestational age at presentation (wk)	Treatments	Preterm birth[a] (number of patients)	Delivery method	Gestational age at delivery (wk)	Other commence or complications
Tewari et al[17]	2000	8	Anaplastic astrocytoma (3)	26–32	Surgery + XRT (3)	7	Cesarean (8)	28–40	28-wk neonate delivered because of fetal distress; died in the NICU. 4 maternal deaths
			Glioblastoma (4)		Surgery (2)				
			Metastatic breast cancer (1)						
Vougioukas et al[18]	2004	3	Glioblastoma (2)	18–33	Surgery (3)	1	Cesarean (1)	33–38	No maternal or fetal complications noted
			Meningioma (1)				Vaginal (1)		
							Terminated (1)		
Ducray et al[22]	2006	3	Anaplastic oligodendroglioma (1)	12–29	Chemotherapy (1)	2	Cesarean (2)	33–36	No maternal complications noted. Fetal outcomes not discussed
			Glioblastoma (2)		Surgery + XRT + chemotherapy (2)		Terminated (1)		
Johnson et al[23]	2009	9	Glioma (2)	10–31	Surgery (8)	3	Cesarean (4)	26–37+	Emergency cesarean delivery at 26 wk for persistent fetal bradycardia during neurosurgery
			Ependymoma (1)		Surgery + XRT (1)		Vaginal (5)		
			Meningioma (6)						
Lynch et al[24]	2011 (updated in 2017 by Pereira and Lynch[27])	12	Meningioma (3)	16–40	Surgery (11)	Unknown	Cesarean (8)	Unknown	No maternal or fetal complications noted
			Melanoma metastases (1)		Surgery + XRT (1)		Vaginal (3)		
			Astrocytoma (4)				Terminated (1)		
			Epidermoid (1)						
			Chemodectoma (1)						
			Pituitary adenoma (1)						
			Oligodendroglioma (1)						

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TABLE 2
Systematic review of case series and patient cohorts with intracranial tumors presenting during pregnancy *(continued)*

Authors	Year	n	Pathology (number of patients)	Gestational age at presentation (wk)	Treatments	Preterm birth[a] (number of patients)	Delivery method	Gestational age at delivery (wk)	Other commence or complications
Abd-Elsayed et al[29]	2013	5	Glioma (4)	6–36	Surgery (5)	Unknown	Cesarean (4)	Unknown	No fetal mortality. No maternal mortality. 1 post-op PE
			Meningioma (1)				Terminated (1)		
Verheecke et al[30]	2014	27	Glioblastoma (6)	8–35	Surgery (8)	14	Cesarean (16)	30–37+	High fraction of preterm births. 2 maternal deaths
			Astrocytoma (6)		Surgery + XRT (4)		Vaginal (5)		
			Anaplastic astrocytoma (4)		Surgery + XRT + chemotherapy (1)		Terminated (4)		
			Meningioma (2)		Chemotherapy (1)		Deceased (2)		
			Choriocarcinoma (1)		XRT + chemotherapy (1)				
			Medulloblastoma (1)						
			Other (7)						
Yust-Katz et al[33]	2014	12	Astrocytoma (1)	5–30	Surgery (6)	Unknown	Cesarean (7)	Unknown	No fetal mortality. 1 patient underwent preterm cesarean delivery because the fetus developed intrauterine growth restriction
			Anaplastic astrocytoma (3)		Surgery + XRT (1)		Vaginal (3)		
			Anaplastic oligodendroglioma (2)				Terminated (2)		
			Oligodendroglioma (2)						
			Glioblastoma (2)						
			Oligoastrocytoma (2)						
Girault et al[34]	2014	6	Meningioma (2)	14–39	Unknown	3	Vaginal (1)	30–39	2 preterm cesarean deliveries because of brain herniation. 2 maternal deaths. No reported fetal deaths
			Oligodendroglioma (1)				Cesarean (4)		
			Chondroma (1)				Terminated (1)		
			Neurocytoma (1)						
			Glioblastoma (1)						

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TABLE 2
Systematic review of case series and patient cohorts with intracranial tumors presenting during pregnancy *(continued)*

Authors	Year	n	Pathology (number of patients)	Gestational age at presentation (wk)	Treatments	Preterm birth[a] (number of patients)	Delivery method	Gestational age at delivery (wk)	Other commence or complications
Mallari et al[35]	2020	3	Meningioma (3)	14–24	Surgery (3)	0	Unknown	37+	No maternal or fetal complications noted
Rodrigues et al (present paper)	2020	9	Pilocytic astrocytoma (2)	11–37	Surgery (5)	1	Vaginal (2)	33–40	No fetal mortality. No maternal mortality. 1 post-op PE
			Lymphoma (1)		Surgery + chemotherapy (1)		Cesarean (6)		
			Meningioma (2)		Surgery + XRT + chemotherapy (1)		Terminated (1)		
			Pleomorphic xanthoastrocytoma (1)		Surgery + XRT (2)				
			Metastatic thyroid cancer (1)						
			Vestibular schwannoma (1)						
			Pituitary adenoma (1)						
Total	—	136	Astrocytoma (40)	5–40	Surgery (83)	36	Cesarean (70)	26–40	—
			Meningioma (26)		XRT (20)		Vaginal (35)		
			Glioblastoma (23)		Chemotherapy (9)		Terminated (20)		
			Glioma, not otherwise specified (11)						
			Ependymoma (5)						
			Other (31)						

NICU, neonatal intensive care unit; *PE*, pulmonary embolism.

[a] Any birth before 37 weeks' gestation.

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gadolinium-based contrast agents to continue breastfeeding without interruption in the postpartum period.[50]

CT is another method of diagnostic imaging that may be used in the gravid patient. Although CT relies on ionizing radiation, the ACOG and ACR note that the diagnostic benefit to the mother may outweigh any fetal risks, especially in cases of acute processes.[46,51] In addition, the fetal radiation exposure from a head or (0.001−0.01 mGy) is thought to be lower than the exposure threshold (50 mGy) associated with fetal harm at any gestational age.[46] Oral and intravenous (IV) contrast media may be used when expected to significantly augment diagnostic confidence. Oral contrast is not absorbed systemically and poses no fetal threat. Although iodinated IV contrast does cross the placenta, animal studies have found no teratogenic or mutagenic effect, and breastfeeding is permitted to continue without disruption.[46] However, even in the absence of a known harmful effect, contrast is only recommended for use if absolutely critical to diagnosis. Moreover, if CT and MRI are expected to be equivalent for the diagnosis in question, the ACOG recommends the use of MRI as the safer alternative.

Regular surveillance should be considered in patients with known brain tumors, and an interdisciplinary team of physicians should carefully review the need for MRI with or without contrast. The imaging interval should be determined by the underlying pathology and the presence or progression of symptoms.

Obstetrics considerations and fetal monitoring

The primary obstetrical considerations for delivery are the gestational age of the fetus and the mother's prognosis. If the patient is neurologically stable at the time of diagnosis, routine obstetrical care should be continued, including dating and anatomic screening ultrasounds and first- and second-trimester prenatal screening. The consideration of vaginal vs cesarean delivery depends on the residual tumor burden, concern for increased ICP, and other clinical factors. If an emergent neurologic event arises, such as widespread edema, midline shift, change in consciousness, paresis, acute hydrocephalus, or acute total neurologic deficit, urgent neurosurgical intervention may be indicated. In some cases, pregnancy is not compatible with the optimal treatment of the mother. For example, in patient number 1 (Table 1), a stereotactic biopsy confirmed a diffuse large B-cell lymphoma, necessitating termination of the pregnancy to begin high-dose methotrexate therapy, a known teratogen, as soon as possible.

The use of intraoperative fetal monitoring is highly dependent on the gestational age of the fetus in cases where delivery is not a planned component of a neurosurgical intervention. Doppler ultrasound detection of FHR should be performed before and after the procedure if the fetus is previable (<24−26 weeks' gestation). At our institution, FHR monitoring is recommended intra- and postoperatively for nonabdominal procedures once the fetus has reached presumed viability (>24−26 weeks' gestation). FHR monitoring can detect impaired uteroplacental blood flow or fetal oxygenation,[52] and surgical contingency plans should be discussed before any operation with FHR monitoring is conducted. If preterm delivery is a possibility, the neonatology team must counsel the patient regarding gestational age−specific outcomes. FHR monitoring at earlier gestational ages is often challenging and requires an experienced maternal-fetal medicine specialist for interpretation.[52] FHR monitoring must be used cautiously, and FHR-informed interventions should be reserved for only the highest risk circumstances.

The administration of corticosteroids should be considered before a procedure to accelerate fetal lung maturation in the event that a premature delivery becomes necessary. In addition, preoperative steroids may have the added benefit of reducing maternal cerebral edema.[4,29]

In almost all circumstances, we recommend treating the mother with the therapy that would be recommended in the absence of pregnancy and then tailoring the approach to minimize fetal risk.[2] In addition, the patient, her family, and a multidisciplinary team, including neurosurgery, high-risk obstetrics, neonatal medicine, and anesthesia, would ideally assist in the shared decision-making process of obstetrical management and tumor excision timing.

Anesthetic considerations

The physiological and pharmacodynamic changes of pregnancy significantly affect the anesthetic management of gravid patients with intracranial tumors, and any anesthetic plan must be designed to mitigate the undesirable effects of anesthesia on both the mother and fetus.

There are many physiological changes in pregnancy that can alter anesthetic management,[53−55] including increased maternal minute ventilation and oxygen consumption, decreased functional residual capacity, expanded blood volume, decreased systemic vascular resistance, decreased lower esophageal sphincter tone, and nonautoregulated uteroplacental perfusion. Adequate uteroplacental perfusion must be ensured by maintaining maternal blood pressure within 20% of baseline with further guidance from FHR monitoring, and it is generally recommended that pregnant patients beyond 20 weeks' gestation be positioned with left uterine displacement to reduce the risk of aortocaval compression. Both indirect-acting agents (eg, ephedrine) and direct-acting agents (eg, phenylephrine) are appropriate for augmentation of blood pressure, although ephedrine has been associated with neonatal acidosis compared with phenylephrine.

High levels of progesterone and increased beta-endorphin concentrations contribute to the increased sensitivity to and the potential toxicity of analgesics and general and local anesthetics. Furthermore, pregnancy is known to affect the bioavailability, distribution, and clearance of many other drugs used during neurosurgery, including muscle relaxants, antihypertensive agents, and anticoagulants. Because most anesthetic and analgesic agents can cross the placenta, fetal pharmacodynamics must also be considered by the neuroanesthesiologist.

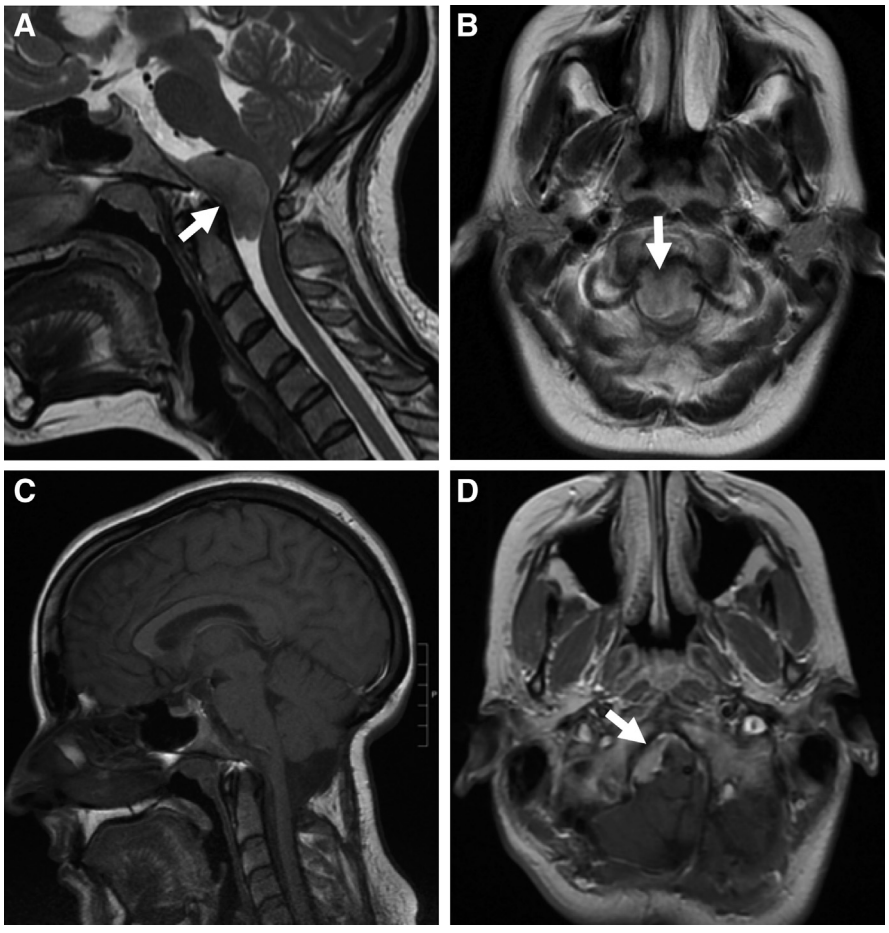
In the pregnant patient with an intracranial tumor, the management of ICP is of great importance. Hyperventilation and osmotic diuresis are therapies frequently employed to decrease ICP.

Hyperventilation should be limited to an arterial carbon dioxide tension of 25 to 30 mm Hg.[56] When hyperventilation is not required, care should be taken to maintain the normal physiological hypocapnia of pregnancy to avoid inadvertent increases in ICP. If necessary, mannitol (0.25−0.5 g/kg) can be administered, although it can accumulate in the fetus and cause electrolyte abnormalities, dehydration, and disturbances in plasma osmolality.[54,56] Loop diuretics should be used only if necessary to avoid electrolyte abnormalities that can affect the fetus.[54]

Generally, the choice of general anesthetic agent is not changed during pregnancy, because no specific agent has demonstrated superior safety or efficacy. Animal studies have shown anesthetic effects on cell signaling, mitosis, and DNA synthesis; however, no currently used anesthetic agent has been shown to have teratogenic effects in humans. Propofol, barbiturates, volatile anesthetics, nitrous oxide, opioids (including remifentanil), neuromuscular blocking agents, and local anesthetics have all been safely used in pregnancy.[54,57] Despite no evidence of teratogenicity in animal studies, the neuromuscular blockade reversal drug sugammadex (Merck) may be avoided in pregnant patients,[58] as its ability to bind progesterone could theoretically threaten pregnancy and promote miscarriage or preterm labor.

In our series, 1 patient underwent an awake craniotomy, and general anesthesia was used for all other surgical procedures. It is important to note that positioning for both the craniotomy and a possible emergent cesarean delivery must be considered, in addition to the risks of rapid general anesthetic induction and intubation.[40] Ultimately, a thoughtful anesthetic plan that balances both maternal and fetal physiology is needed to optimize safety while minimizing morbidity and mortality.

FIGURE 1
Foramen magnum meningioma



A and **B,** Sagittal (**A**) and axial T2-weighted (**B**) magnetic resonance images showing the spinal cord and brainstem compression (*white arrows*) by the meningioma. **C,** Preoperative sagittal T1-weighted image. **D,** Postoperative axial T1-weighted image with contrast showing small residual tumor (*white arrow*).

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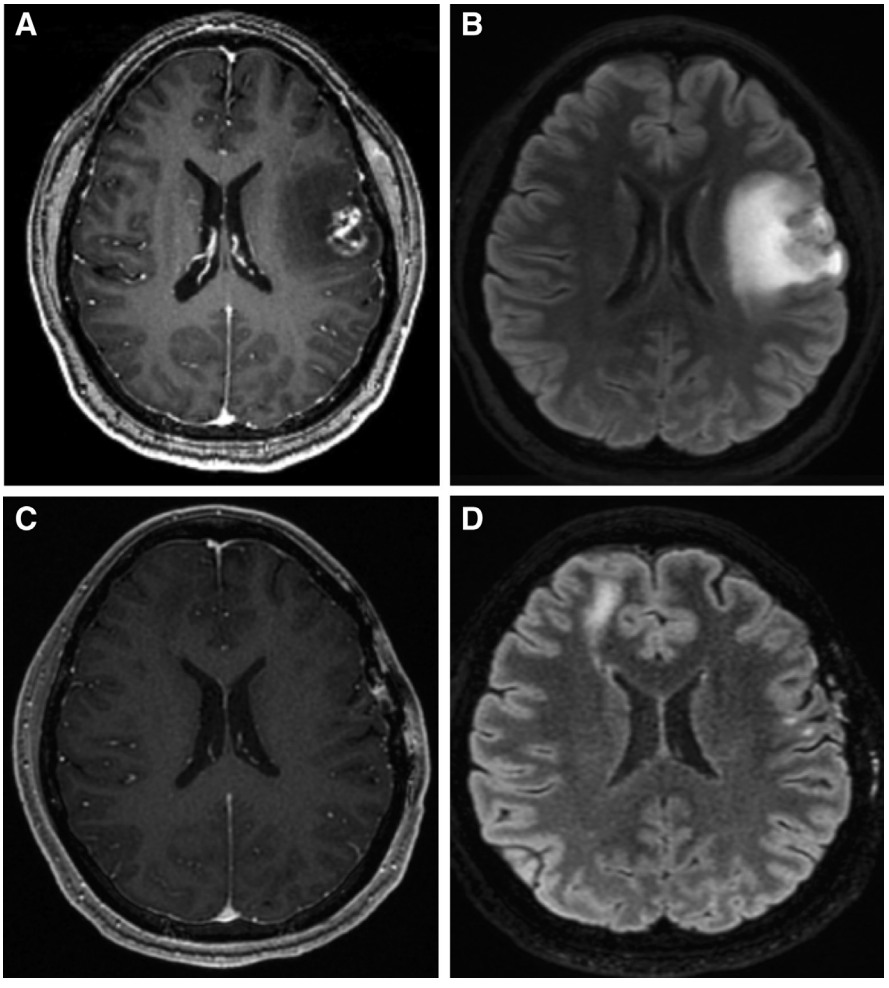
Neurosurgical considerations

Neurosurgical considerations vary by tumor type (eg, benign vs malignant), location (eg, eloquent), size, gestational age, and patient's clinical status. Higher-grade tumors may necessitate more aggressive surgical treatment, as do patients with rapid neurologic deterioration or significant cerebral edema and mass effect. Positioning for tumors in the posterior fossa is complicated by the inability to fully pronate a gravid patient[24]; a lateral or rotated supine position is recommended to avoid aortocaval compression throughout the operation.[5,24] Presentation of a brain tumor in the first or second trimesters of pregnancy is generally more favorable to neurosurgical intervention than at later stages because of the timing of pregnancy-associated hemodynamic changes and fetal development.[4,5,17] If the surgery can be timed, intervention in the second trimester of pregnancy is ideal.[5] For example, patient number 1 presented at 11 weeks, but the stereotactic biopsy was delayed until the 15th week to advance the fetus into the second trimester of pregnancy. In our series, 5 patients underwent surgery during their pregnancies (gestational ages, 14−37 weeks) because of disease progression (n=2) or neurologic instability (n=3).

If the patient is stable and surgical intervention is elective, pharmacologic management (eg, anticonvulsants, dexamethasone) during gestation to delay surgery until the postpartum period should be considered. For example, patient number 2 presented with a WHO

FIGURE 2
Metastatic thyroid cancer



A, Axial T1-weighted magnetic resonance image with contrast showing a left frontal brain metastasis previously treated with radiosurgery (2000 cGy in 1 fraction). **B,** Axial T2-FLAIR image illustrating significant peritumoral edema. **C,** Postoperative axial T1-weighted image with contrast reveals that gross total resection of the tumor was achieved with a dramatic reduction in peritumoral edema (postoperative axial T2-FLAIR image) **(D)**.

FLAIR, fluid-attenuated inversion recovery.

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grade II meningioma during the early second trimester of pregnancy (week 15). Her symptoms were controlled with levetiracetam and prednisone, and she underwent an embolization and craniotomy on postpartum days 10 and 11, respectively.

Presentation in the late second or early third trimester of pregnancy requires complex clinical consideration as the fetus may be periviable or extremely premature. For unstable patients, cesarean delivery under general anesthesia can be followed rapidly by surgical decompression and tumor resection (patient number 8).[4,17] Neurosurgeons may also consider a staged surgical approach that balances operative risk (eg, brainstem resection of an exophytic astrocytoma; patient number 5), prolonged anesthesia, and preterm delivery against a subtotal resection. For example, patient number 5 presented at 29 weeks with severe headache, nausea, and vertigo. She underwent a retrosigmoid craniotomy with concurrent plan for possible emergent cesarean delivery (Supplemental Figure 2) to treat severe obstructive hydrocephalus and debulk the tumor mass. Acute symptoms subsequently resolved and the patient proceeded to term. She then underwent a second craniotomy at postpartum month 8 to completely resect the tumor.

One key surgical consideration is the elevated risk of venous thromboembolism in pregnancy.[59,60] Patient number 8 developed bilateral PE on postoperative day 8 despite a negative preoperative Doppler ultrasound. The role of postoperative anticoagulation for thromboprophylaxis must be weighed against the risk of bleeding at the surgical site. Ultimately, surgical approaches should not be discouraged by a patient's gravidity; a retrospective study of 644 pregnant patients diagnosed with intracranial neoplasms showed no significant association between neurosurgical intervention in the perinatal period and pregnancy complications.[39]

Adjuvant treatment

The treatment of aggressive intracranial cancers may require multiple treatment modalities, including maximal safe resection, fractionated external beam radiotherapy (EBRT), and adjuvant chemotherapy. Maternal health is the primary concern, and thus, the risks of these treatments must be balanced against the need to treat the intracranial tumor.

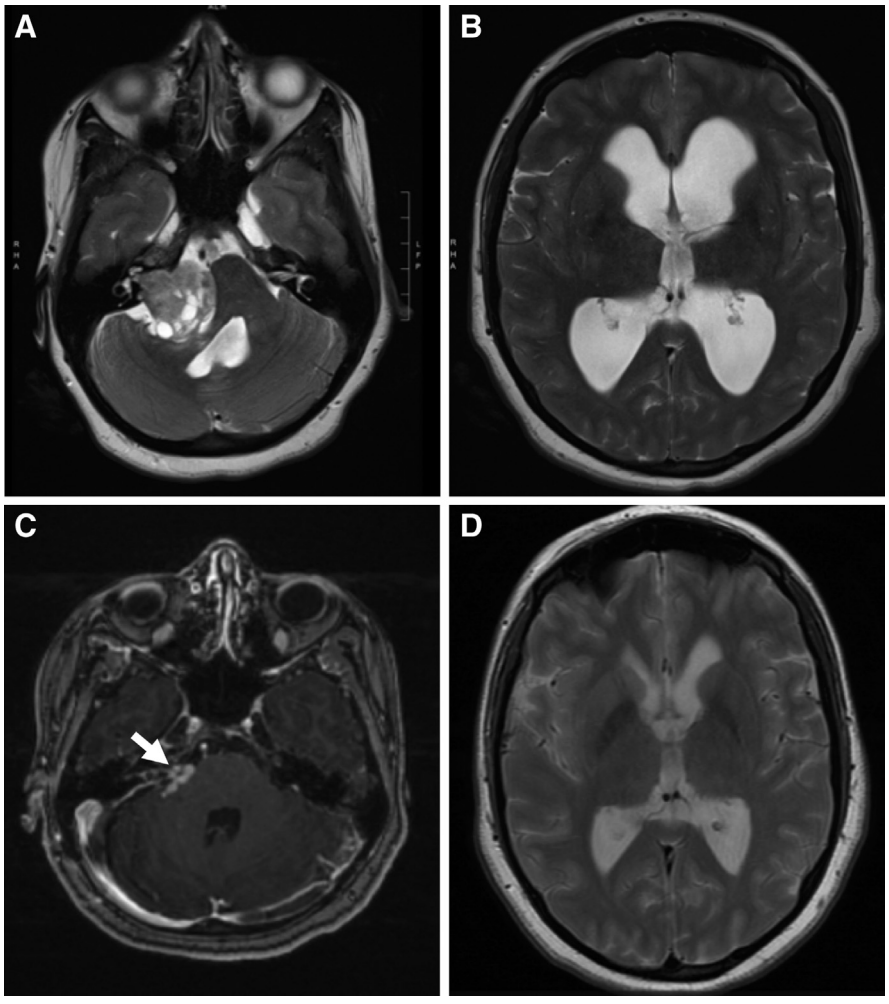
EBRT represents a noninvasive therapy; however, cerebral XRT can scatter to the fetus and, therefore, should be used with extreme caution.[5] Fetal doses above 10 cGy have been associated with congenital malformations and cognitive and developmental delay.[37,38] The use of stereotactic radiosurgery, including CyberKnife (Accuray, Inc, Sunnyvale, CA), is rare in pregnant patients, and its risks in the gravid patient are similar to those of standard XRT regimens.[37,61] XRT should only be used in exceptional cases and only after radiation scatter to the fetus has been calculated by phantom measurements[4,17,62] to ensure fetal doses are within acceptable limits.

Given its systemic delivery and potential teratogenicity, chemotherapy is typically reserved for treating high-grade or

recurrent tumors in gravid patients. Fetal effects may include congenital malformations, potential carcinogenesis, organ toxicity, and growth retardation, especially when delivered in the first trimester of pregnancy.[3,63] The mother may experience stillbirth, spontaneous abortion, and sterility.[63] If chemotherapy is required during the gestational period, the second trimester of pregnancy may be the ideal time for its administration, as organogenesis is largely complete. Procarbazine, often used with high-grade oligodendrogliomas or primary central nervous system (CNS) lymphomas, is worthy of special note, as it readily crosses the placenta and is a potent teratogen and carcinogen.[5,63] Ideally, the patient would undergo initial intervention to debulk the tumor mass and then allow the mother to proceed to term. At that time, adjuvant treatments could be given, if indicated. However, the urgency of chemotherapeutic treatment may supersede the choice of continuing the pregnancy, as with patient number 1 (primary CNS lymphoma).

Some antiepileptic drugs (AEDs) have documented teratogenic effects,[42] but the risk of seizures in pregnant patients may outweigh the risk of the medication, including its potential teratogenicity.[2] Current monotherapy treatment for seizure disorders has demonstrated an acceptable safety profile.[64,65] We recommend the use of AEDs in pregnant patients with repeated seizures, and an anticonvulsant prophylactic drug should be considered in consultation with neurology and epilepsy specialists.

FIGURE 3
Vestibular schwannoma



A, Axial T2-weighted magnetic resonance image showing a large right cerebellopontine angle mass and communicating hydrocephalus (**B**). **C,** Postoperative axial T1-weighted image with contrast showing small postsurgical changes and a residual vestibular schwannoma capsule along the brainstem and peduncle (*white arrow*) and resolved hydrocephalus (axial T2-weighted image) **(D)**.

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Illustrative Case Reports

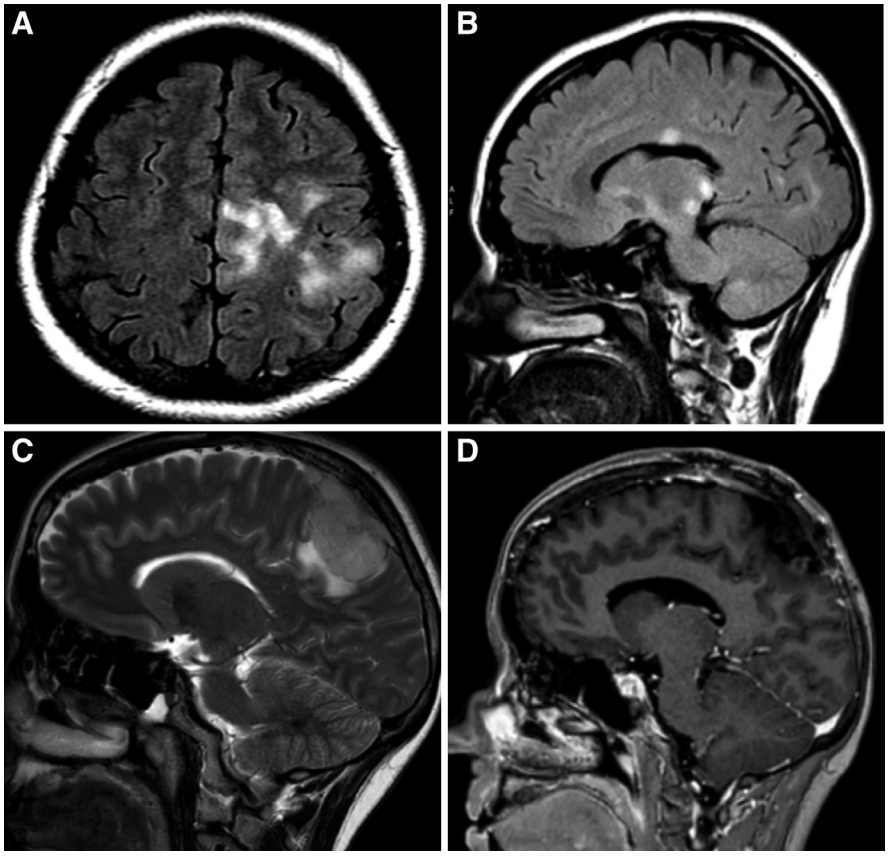
Patient number 7: foramen magnum meningioma

A 34-year-old female presented to the emergency department at 13 weeks' gestation with progressive, radiating neck stiffness, myelopathy, hemibody sensory changes, and weakness. A noncontrast MRI revealed a 2.1×2.4×3.5 cm foramen magnum meningioma (WHO grade I) resulting in severe brainstem and spinal cord compression (Figure 1, A, B, and C). The patient underwent a far lateral craniotomy and C1 and partial C2 laminectomy for the resection of the tumor (Figure 1, D). Pre- and postoperative Doppler ultrasounds revealed a singleton viable intrauterine pregnancy (SVIUP) with grossly normal fluid. The patient had near complete improvement of her preoperative symptoms. She delivered a healthy infant by spontaneous vaginal delivery at 40 weeks' gestation. At postpartum month 4, she underwent CyberKnife radiosurgery to the small residual tumor (25 Gy in 5 fractions). At 4 years follow-up, the patient has recovered all function with only mild hemisensory hot-cold sensation changes and is radiographically stable.

Patient number 6: metastatic thyroid cancer

A 27-year-old female with a history of metastatic papillary thyroid cancer presented at 15 weeks' gestation with speech difficulty and progression of a previously treated left frontal brain metastasis (Figure 2, A and B). The patient underwent an awake craniotomy at that time with gross total resection of the metastatic tumor and radiation-induced cavernoma (Figure 2, C and D). Pre- and postoperative Doppler ultrasounds revealed an SVIUP with grossly normal

FIGURE 4
Diffuse large B-cell lymphoma and grade II meningioma



A and **B**, Axial and sagittal T2-FLAIR magnetic resonance images of the diffuse large B-cell lymphoma. The patient terminated her pregnancy to begin high-dose methotrexate chemotherapy. This is in contrast to patient number 2 (Table 1) with a large grade II meningioma where treatment (surgical resection) could be delayed until after delivery. **C,** Sagittal preoperative T2-weighted image shows patient number 2's meningioma. **D,** Sagittal postoperative T1-weighted image with contrast reveals the postsurgical cavity.

FLAIR, fluid-attenuated inversion recovery.

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fluid, and the patient underwent a spontaneous vaginal birth of a healthy infant at 39 weeks' gestation. She had no postoperative neurologic deficits. At her most recent follow-up (37 months post-op), the patient has remained neurologically intact but has had continued systemic and CNS disease progression.

Patient number 8: vestibular schwannoma

A 32-year-old female presented to the emergency department at 37 weeks' gestation with altered mental status and unilateral hearing loss. Imaging revealed a vestibular schwannoma (WHO grade I) with communicating hydrocephalus (Figure 3, A and B). The patient underwent urgent external ventricular drain (EVD) placement and cesarean delivery. A healthy male infant was delivered and at 7 days after delivery, the patient underwent a right retrosigmoid craniotomy for near-total resection of the tumor (Figure 3, C and D). The patient developed bilateral PEs the day after discontinuation of her EVD (post-op day 8, normal preoperative bilateral lower extremity Doppler ultrasound). At her most recent follow-up (5 months post-op), the patient has had continued recovery of her CN VII function.

Patient number 1: early pregnancy termination to treat diffuse large B-cell lymphoma

A 25-year-old female presented to the emergency department at 11 weeks' gestation with worsening headaches, diplopia, hemiparesis, and seizures. Imaging revealed multiple scattered confluent white matter lesions predominantly involving the left frontoparietal lobe and the corpus callosum (Figure 4, A and B). A stereotactic biopsy at 15 weeks' gestation confirmed a diagnosis of diffuse large B-cell lymphoma. After consultation with the patient, her partner, and the maternal-fetal medicine, neurosurgery, and neuro-oncology teams, the patient decided to terminate her pregnancy and begin high-dose methotrexate chemotherapy. In contrast, patient number 2 had a pathology that did not require urgent intervention and therefore could safely proceed to term (Figure 4, C and D). At the final follow-up (8 months), patient number 1 was clinically and radiographically stable with complete resolution of her preoperative symptoms.

Conclusion

The presentation of a brain tumor during pregnancy requires a multidisciplinary team to plan, coordinate, and implement care. Generally, clinical strategies to ensure the health of the mother will also benefit the fetus. When the timing of intervention is flexible because of clinical stability, neurosurgical intervention would ideally be performed during the second trimester of pregnancy or after delivery. Anesthesia, fetal monitoring, positioning, possible concurrent emergency cesarean delivery, and the need for adjuvant therapy must be carefully integrated into a surgical plan. ■

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