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Status Epilepticus and Low-Grade Glioma in the Pregnant State: Case Report and Ethical Considerations

Andrew L. Waack[a] Vito M. Lucarelli[a] Amulya Marellapudi[a] Alisa Gega[a] Andrew J. Zillgitt[b] Michael D. Staudt[c, d]

[a]Division of Neurosurgery, Department of Surgery, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA; [b]Department of Neurology, Beaumont Neuroscience Center, Royal Oak, MI, USA; [c]Department of Neurological Surgery, University Hospitals Cleveland Medical Center, Cleveland, OH, USA; [d]Case Western Reserve School of Medicine, Cleveland, OH, USA

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Abstract
Introduction: The pregnant state may cause or exacerbate existing neurological disease. Gliomas appear to be influenced by the physiological changes that occur during pregnancy. The pregnant state may also cause seizures, including status epilepticus. There are currently no defined treatment guidelines to direct clinical decision making, and many of the commonly employed therapies are contraindicated during pregnancy. ***Case Presentation:*** The current article describes the case of a 40-year-old G3P1101 female at 10 weeks' gestation, who sought medical care for recurrent left hemifacial twitching, eventually leading to nonconvulsive status epilepticus. Intubation and sedation were required to achieve seizure cessation. Imaging revealed a lobulated cystic mass in the right parietal lobe, suspicious for low-grade glioma. Despite thorough explanation of the potential risks, the patient adamantly wished to pursue surgical intervention. An uneventful craniotomy was performed for resection of a low-grade glioma. No patient or fetal complications were encountered, and the patient has not had any reported seizures since surgery. ***Discussion:*** Managing complex neurosurgical diseases in pregnant patients provides both clinical and ethical quandaries. We describe the successful management of a patient presenting with status epilepticus caused by an underlying glioma during pregnancy. Although challenging, favorable neurosurgical outcomes are possible during pregnancy.

Correspondence to:
Michael D. Staudt, Michael.Staudt@UHhospitals.org

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Introduction

Neurosurgical conditions during pregnancy can be technically and ethically challenging to treat [1]. Normal physiological changes during pregnancy may cause or exacerbate existing pathologies. For example, there is evidence that the pregnant state can accelerate the growth of central nervous system malignancies through various mechanisms, including effects on hormonal and vascular systems [2–5]. Additionally, seizures can occur in the context of pregnancy, and there have even been rare reports of status epilepticus (SE) during pregnancy reported [6].

There are currently no defined treatment guidelines dictating the management of intracranial neoplasms or SE in the pregnant state. Furthermore, many of the commonly employed medical, radiation, and surgical interventions for these conditions can cause harm to either the mother or the fetus. Anti-seizure medications (ASM) are well-known teratogens, and many chemotherapeutics have been shown to be capable of inducing fetal malformation [6–8]. Surgical intervention is likewise dangerous in the pregnant state and can put both mother and fetus at risk of adverse events [2–4, 9]. We report a case of a patient presenting with SE due to an underlying low-grade glioma (LGG) during pregnancy and describe both the medical and surgical management.

Case Report

A pregnant 40-year-old right-handed G3P1101 female at 10w0d with no significant prior medical history presented with recurrent left hemifacial twitching, which manifested while traveling by flight. Upon landing, she presented to hospital for investigations and was told that imaging demonstrated "an abnormality in the right frontal lobe." She was then discharged on levetiracetam, although without much improvement in her symptoms. These spells were initially spaced out throughout the day, but then began to present every 5 min.

She returned to her home state and was immediately admitted to the hospital. An assessment by neurology identified multiple episodes of halted speech followed by leftward head and chin version and leftward gaze. She remained conscious during these events and could nod her head and occasionally follow commands. These episodes would last 30–45 s and the patient would quickly return to baseline mentation. Continuous electroencephalography demonstrated 101 seizures on the first day of recording, arising from the right hemisphere. Levetiracetam and lacosamide were loaded, with initial improvement; however, 220 seizures were recorded on the second day of admission. Treatment with clobazam was initiated, which proved unsuccessful, and she required intubation and propofol sedation for nonconvulsive SE. Propofol administration resulted in seizure cessation, and she was continued on IV sedation for 48 h prior to weaning. After optimization of her ASM and discontinuation of propofol, the seizures did not recur.

Brain magnetic resonance imaging (MRI) demonstrated a lobulated cystic mass involving the cortex and underlying white matter of the right parietal lobe, suspicious for a low-grade glial neoplasm (Fig. 1a–c). Diffusion tensor imaging was also performed and demonstrated probable inferior and medial displacement of the right superior longitudinal fasciculus with some splaying of the fiber tracts along the medial margin of the mass; medial displacement of the right corticospinal tract and mass effect upon the corpus callosum and cingulate gyrus was also noted (Fig. 1d).

Management options were discussed – it was recommended to defer surgery until after giving birth, as her seizures were controlled and the lesion likely low grade; however, the patient

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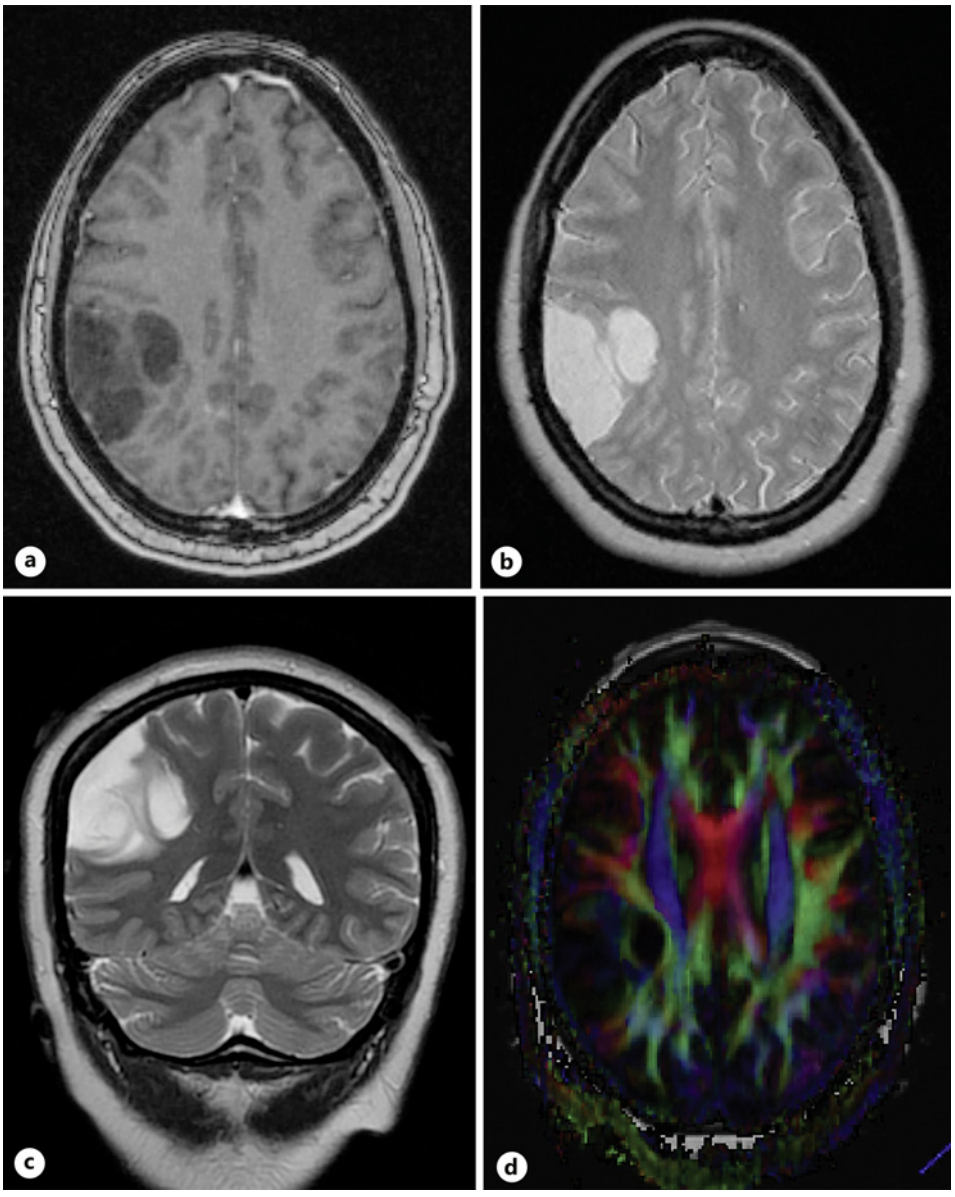

Fig. 1. Preoperative MRI demonstrates a lobulated, cystic mass within the right parietal lobe involving the cortex and the deep white matter, associated with mild mass effect and minimal vasogenic edema. The lesion shows decreased T1 signal without contrast enhancement (**a**) and increased T2 signal (**b**, **c**). The lateral component measures 4.8 × 2.2 cm and medially as 2.2 × 1.4 cm. Global tractography demonstrates probable inferior and medial displacement of the right superior longitudinal fasciculus with some splaying of the fiber tracts along the medial margin of the mass, as well as medial displacement of the right corticospinal tract and mass effect upon the corpus callosum and cingulate (**d**).

adamantly wished to proceed with surgical resection. Following obstetrical clearance, a right parietal craniotomy for tumor resection was planned 2.5 months (22 weeks pregnant) following her admission in SE. Intraoperatively, phase reversal was used to identify the central sulcus immediately anterior to the tumor. Gross total resection was achieved (Fig. 2). Pathology was consistent with a diagnosis of astrocytoma, IDH-mutant, CNS WHO grade 2. After surgery, the patient was maintained on levetiracetam, lacosamide, and clobazam. She remained neurologically intact with no new sensory or motor deficits following surgery.

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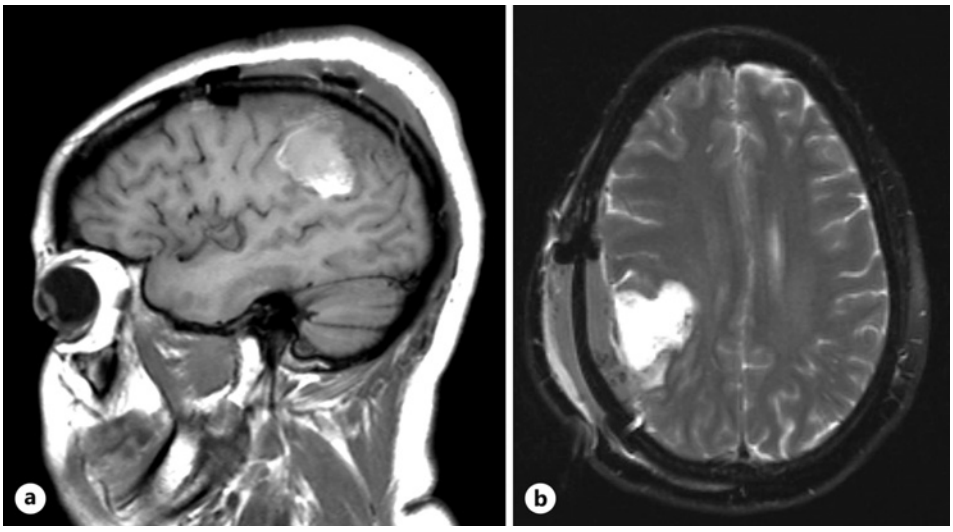

Fig. 2. a, **b** Postoperative MRI demonstrates gross total resection of the right parietal mass with expected postoperative changes.

She gave birth to a healthy child via planned cesarean section due to placenta previa. At a 1.5-year follow-up, the patient continues to be seizure-free and continues on levetiracetam and clobazam. Surveillance imaging has not demonstrated any tumor recurrence. She has been followed by neuro-oncology and continued observation has been favored. The CARE Checklist has been completed by the authors for this case report, attached as online online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539510).

Discussion

Status Epilepticus in Pregnancy

SE is a neurological emergency with a mortality rate between 10 and 15% [8]. Although scarce, there have been reports of SE in pregnancy (SEP); most of these cases can be attributed, directly or indirectly, to the physiological changes encountered during pregnancy [6, 8, 10–12]. For example, eclampsia, cerebral venous thrombosis, posterior reversible encephalopathy syndrome, and increased glomerular filtration rates (which decrease ASM levels in patients with preexisting epilepsy) have all been described in the literature [6]. Additionally, fear of teratogenesis may worsen ASM compliance in women with preexisting epilepsy [12]. Outcomes of SEP are poor: Rajiv and Radhakrishnan [6] demonstrate poor outcomes occurring in 21% of patients, with a 7% maternal mortality rate. Maternal seizures induce fetal hypoxia and acidosis [4]. Prompt and efficacious treatment is paramount to achieving optimal outcomes. However, due to its rarity, there are no established guidelines dictating the treatment of SEP [6, 8]. Rosenow and Mann [8] state that both SE and any identifiable underlying causes of SE should be addressed. Rajiv and Radhakrishnan [6] and Rosenow and Mann [8] both state that SEP should be treated the same as general SE, except for the exclusion of valproate in SEP due to extreme teratogenicity and the use of magnesium sulfate for eclampsia. Thus, benzodiazepines should be utilized as first-line agents, particularly either lorazepam or midazolam [6]. If SE persists, phenytoin, fosphenytoin, phenobarbital, and levetiracetam are all appropriate options [6]. Lastly, cases of refractory SE can be

managed with anesthetics, such as propofol, midazolam, and ketamine [6, 12]. SEP is a unique clinical situation that requires urgent treatment to avoid poor outcomes in both mother and fetus.

Low-Grade Glioma in Pregnancy

LGG has been rarely identified in pregnant patients [2, 5, 9]. Although the connection between pregnancy and LGG has not been fully elucidated, it appears that there is a noncausal relationship between the pregnant state and LGG behavior: pregnancy does not change the *incidence* of LGG, but it has been shown to *accelerate the growth* of existing LGG, and pregnancy does not drastically alter the outcomes of LGG [2–5]. There are several proposed mechanisms responsible for tumor progression during pregnancy, including increased fluid volumes, vascular engorgement, altered hormone levels, immunological tolerance, and steroid-mediated cell growth [2, 3]. Specifically, gliomas have been shown to be sensitive to placental growth factor, vascular endothelial growth factor, insulin-like growth factors 1 and 2, estrogen, and progesterone [2, 5, 9]. Increased peritumoral edema has been noted on imaging during pregnancy [5], and associated seizures have been shown to manifest in 68% of patients, especially during the second and third trimesters [2]. However, LGGs are heterogeneous tumors with various tumor biologies, so the response to the pregnant state is unlikely to be uniform [3].

Like SE, there are no guidelines dictating the management of LGG during pregnancy. First and foremost, maintaining maternal stability is of the utmost importance; there can be no dispute that any urgent, life-threatening maternal issues must be rapidly addressed. Peeters et al. [2] recommend urgent neurosurgical intervention in the first and early second trimesters, and cesarean section followed by neurosurgical intervention in the third trimester in the event of maternal instability. Assuming maternal stability, clinical decision making becomes very difficult, and both maternal and fetal risks must be considered. Treatment algorithms have been proposed by several authors to help guide decision making; however, each case of LGG in pregnancy is unique and should be managed with a multidisciplinary approach guided by informed patient preferences.

There are no clear guidelines for the neurosurgical management of gliomas, low grade or more aggressive, during pregnancy. There are many possible treatment modalities available including chemotherapy, radiotherapy, surgery (including anesthesia), and monitoring with serial imaging. Van Westrhenen et al. [4] note that there is evidence of teratogenicity by chemotherapeutics in animal and epidemiological investigations, with a fourfold increase in teratogenicity with chemotherapy use during pregnancy. The risk of teratogenesis is especially great during the first trimester [7]. For example, in malignant gliomas, procarbazine, lomustine, and vincristine treatment has been shown to cause fetal malformations in one-third of pregnancies, but carmustine wafers are considered safe due to negligible systemic concentrations [7]. Maternal cerebral radiation of malignant glioma may be performed with adequate abdominal shielding, which exposes the fetus to radiation levels considered safe by the American Association of Physics in Medicine [7]; the use of radiotherapy is not uniformly agreed upon, as there are fetal risks associated with maternal cerebral irradiation [4].

Successful resection of a diffuse astrocytoma during pregnancy has been described [9]. As with any glioma, gross total resection is preferred if feasible; however, the pregnant state can promote rapid regrowth in the event of a subtotal resection in either grade II or III glioma [5]. Most authors agree that, if nonemergent surgery is to be performed during pregnancy, the second trimester is the preferred time period, as the embryo is too vulnerable during the first trimester and the risk of hemorrhage is great during the third trimester [4]. If surgery is to be performed, the optimal anesthetic choice is also a matter of debate. Propofol may be superior

to volatile anesthetics during pregnancy, although it may promote uterine relaxation [4, 9]. Nitrous oxide and isoflurane may be teratogenic [4].

If no intervention is to be performed during pregnancy, several authors recommend serial imaging with quantitative assessment to assess tumor progression over the course of pregnancy [2, 4]. Both MRI and computed tomography have been proposed as acceptable modalities, although MRI provides superior tumor resolution and does not subject the patient to radiation. The contrast agent gadolinium is not recommended during pregnancy because it has been shown to be a potent teratogen in animal models [2, 4, 5, 9]. There are several options available for managing pregnancy; termination, premature induction, and carrying to full term have all been described in the literature [2, 4, 5].

The method of delivery should also be considered. Peeters et al. [2] report that about half of patients opt for cesarean section, and half opt for vaginal delivery, and no benefit has been found to cesarean section over vaginal delivery. The coordination of cancer treatment and pregnancy management must be considered. Peeters et al. [2] also reported that only 18% of patients underwent oncological treatment during pregnancy and that 70% of patients initiated therapy soon after delivery. In conclusion, there are many important considerations in the management of LGG during pregnancy, and we agree with Choudhary et al. [1] that, unless there is an acute situation requiring emergent intervention, tumor treatment should be initiated after delivery to minimize iatrogenic risk to the fetus.

Relationship between Status Epilepticus and Low-Grade Glioma

Epilepsy develops in 60–85% of LGG cases, and 15–22% of brain tumor-associated epilepsies will progress to SE [13]. Brain tumor-associated epilepsy development is dependent upon slow tumor growth rates and genetic biomarkers [13]. Advancement to SE depends on tumor grade and location, with higher tumor grades and parietal lobe locations being associated with increased risk of SE [13]. Based on the behavior of LGG during pregnancy (described above), we hypothesize that our described patient had an existing subclinical LGG prior to pregnancy, and that the patient's pregnancy promoted tumor development. Tumor enlargement in the parietal lobe ultimately manifested as SE. The patient's acute SE presentation was managed medically, and subsequent tumor resection resolved the SE impetus. The patient has not had any seizures since surgery.

Ethical Considerations

The management of SE and LGG in pregnant patients involves complex decision making. In diagnoses that can result in neurocognitive decline, it is imperative to assess each aspect of the patient's capacity in an ongoing manner as medical decision-making capacity is dynamic over the course of the disease. The risks and benefits inherent to the maternal treatment strategy must be balanced with possible effects to the fetus and the overall goals of pregnancy. As such, we believe the preferences of the mother and family should guide the goals of clinical treatment; of course, these choices must be made with a solid understanding of the clinical situation, including the disease prognosis, available treatment options, and possible complications of each intervention (including no intervention) to both the mother and the fetus. The treating physicians should fully disclose all pertinent clinical information to help the mother and family arrive at an informed decision. A multidisciplinary team including neurosurgeons, obstetricians, oncologists, and anesthesiologists is necessary for properly guiding patient decision making and carrying out the agreed-upon treatment strategy. Careful preoperative counseling, intraoperative management, and postoperative care are imperative for pregnant women to safely undergo nonobstetric surgeries.

Medical decisions regarding pregnant women require deliberation and collaboration by the patient and treating physicians to optimize care for both the mother and the child.

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Autonomy is the patient's right to make his or her own medical decision regardless of the possible outcomes. While autonomy may be overridden in cases when patients are not cognitively capable of making or expressing their decisions, our patient displayed sufficient capacity to choose her course of treatment. Medical decision-making capacity is a patient's higher order functional capacity referring to the cognitive and emotional ability to make informed decisions related to his or her care [5]. Capacity for healthcare has been described in terms of four criteria: understanding, appreciation, reasoning, and expression of a choice [14, 15]: Understanding is the patient's ability to comprehend the information being relayed regarding his or her condition and the potential risks and benefits of the proposed treatment options and their alternatives; Appreciation involves the ability to apply the relevant information in the context of one's situation; Reasoning refers to evidence that the patient's decisions reflect the ability to reason through consequences and compare options; and Expression of a choice refers to the patient's ability to communicate a decision clearly and consistently.

Importantly, the patient was well informed and clearly understood the general risks, risks specific to the surgical procedure, risk of no treatment, and potential alternatives to treatment. The presented patient satisfied all the requirements necessary for making complex medical decisions, so we respected her decision and proceeded with her preferred choice of treatment.

The case described in this report required both complex medical decision making and care to adhere to ethical principles. The four pillars of medical ethics (autonomy, justice, beneficence, and nonmaleficence) were observed in our case, and the patient was deemed competent to make complex decisions regarding her healthcare. We provided care commiserate with the patient's wishes and achieved a favorable outcome.

Conclusion

We report a case of SE in a pregnant patient with LGG and describe the complex clinical decision making involved. Physiological changes occurring during pregnancy are capable of inducing significant neurological disease. The management of such patients is ethically and clinically challenging; however, favorable neurosurgical outcomes are possible in pregnant patients.

Statement of Ethics

This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images. Ethical approval was not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

Michael D. Staudt is a consultant for Abbott and Boston Scientific, outside the reported work. The other authors have no conflicts of interest to declare.

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Author Contributions

Michael D. Staudt and Andrew J. Zillgitt conceptualized the study. Andrew L. Waack and Vito M. Lucarelli performed the literature review and drafted the manuscript. Amulya Marellapudi and Alisa Gega researched and drafted the ethical considerations. Michael D. Staudt and Andrew J. Zillgitt reviewed and edited the draft. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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