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Case report

Intraoperative monitoring during awake craniotomy for glioblastoma resection in the second trimester of pregnancy. A case report and literature review

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ABSTRACT

Objective: To demonstrate the feasibility and safety of awake craniotomy (AC) with intraoperative neurophysiological monitoring (IONM) for glioblastoma (GB) resection in a pregnant patient, ensuring preservation of neurological functions and fetal well-being.
Methods: A 27-year-old gravida 2, para 1 woman presented at 19.4 weeks of pregnancy with severe headaches and a generalized tonic-clonic seizure. Imaging confirmed a malignant glioma, and an interdisciplinary team opted for AC with IONM to achieve maximal tumor resection while minimizing maternal and fetal risks.
Results: Surgery was performed during the second trimester with successful gross total resection of the tumor. IONM strategies preserved neurological function, and fetal well-being was maintained. Postoperative evaluations showed no complications, and the patient was discharged in improved condition.
Conclusions: AC with IONM is a viable and safe surgical approach for GB resection during pregnancy. Tailoring the surgical plan by considering gestational age, maternal health, and fetal safety is crucial.
Significance: This case highlights the importance of multidisciplinary management in optimizing outcomes for pregnant patients with GB, contributing valuable insights to the limited literature on neurosurgical interventions during pregnancy.

1. Introduction

Gliomas are the most common type of primary brain tumor in adults, accounting for approximately 30 % of all primary tumors (Weller et al., 2015). Among these, glioblastoma (GB) is the most prevalent and aggressive malignant brain tumor (Di et al., 2022). GB during pregnancy is uncommon, and presents unique challenges for patients, families, and healthcare providers (Molina-Botello et al., 2021). Management necessitates balancing potential maternal benefits against fetal risks given the limited evidence on optimal treatment timing and approaches (Jayasekera et al., 2012). Anesthetic considerations for surgery must account for both obstetric and neurosurgical factors (Jayasekera et al.,

Abbreviations: GB, Glioblastomas; AC, Awake craniotomy; OINM, Intraoperative Neurophysiological Monitoring; GTCS, generalized tonic-clonic seizure; MRI, Magnetic Resonance Imaging; IBM, Intraoperative Brain Mapping; BOLD, blood oxygenation level-dependent; fMRI, Functional Magnetic resonance imaging; EBRT, external beam radiation therapy.

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2012). Additionally, managing peritumoral edema and seizures is complicated by potential teratogenic effects of medications. Also, the hormonal changes and increased blood flow associated with pregnancy can potentially accelerate tumor growth, alter pharmacokinetics of anesthetic agents and complicating the clinical management (Guarracino, et al., 2022a; Jayasekera et al., 2012; Molina-Botello, et al., 2021).

Due to the rarity of GB during pregnancy, there are currently no established medical, surgical, or anesthetic management guidelines. Each case requires a tailored, multidisciplinary approach to balance the risks and benefits for both mother and fetus. Ensuring the preservation of neurological functions during pregnancy surgery is essential (Ostrom et al., 2014), especially for the safety of the newborn (Guarracino et al., 2022a).

Awake craniotomy (AC) is a highly specialized neurosurgical approach that enables maximal resection of brain tumors while safeguarding critical functional areas. This technique is particularly advantageous in the management of glioblastomas, which are aggressive primary brain tumors with a predilection for infiltrating eloquent regions of the brain. By facilitating real-time neurological assessment during surgery, AC minimizes the risk of postoperative deficits and enhances the extent of tumor removal. Central to the success of AC is

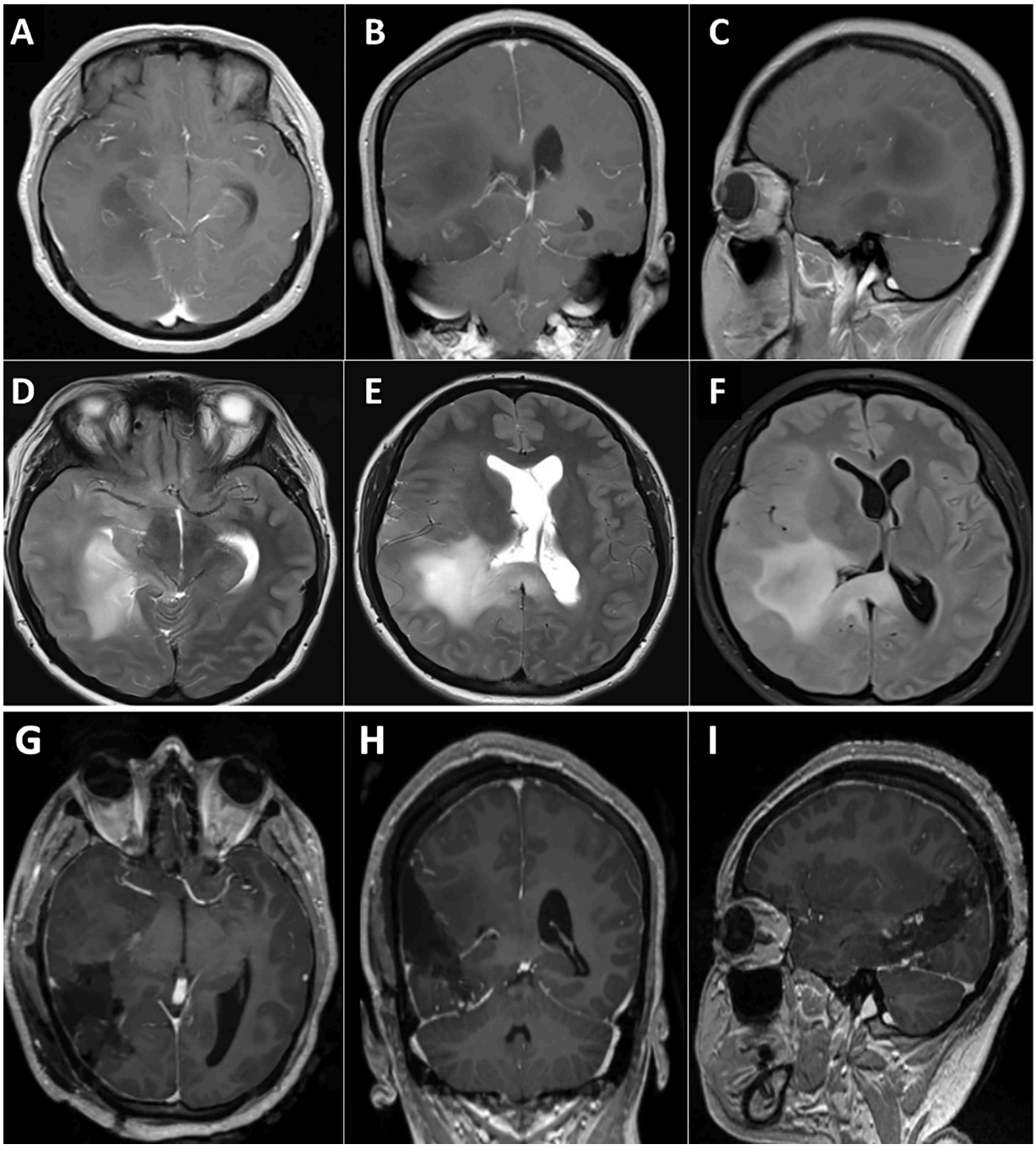

Fig. 1. Pre-surgical brain 1.5 Tesla's MRI. T1WI with gadolinium in axial (**A**), coronal (**B**) and sagittal (**C**) sections, showing a hypointense subcortical lesion the tempo- occipital-parietal junction of the right hemisphere with an area of enhancement at the level of the inferior temporal gyrus, and displacement of adjacent structures. On T2WI (**D** and **E**) and FLAIR sequences (**F**), the lesion is hyperintense and a subcortical extension through the corpus callosum is evident. Post-surgical 1.5 Tesla's brain MRI. T1WI with gadolinium in axial (**G**), coronal (**H**) and sagittal (**I**) sections shows postsurgical changes, without evidence of contrast-enhancing lesions.

intraoperative neurophysiological monitoring (IONM), which provides precise functional mapping and continuous evaluation of motor, sensory, and language pathways. Techniques such as cortical and subcortical stimulation, motor-evoked potentials (MEPs), and electroencephalography (EEG) are integral components of IONM, guiding surgical decision-making and achieving the critical balance between tumor resection and preservation of neurological function and quality of life (Sanai and Berger, 2008; Meng et al., 2016; Gunasekaran et al., 2022). Fortunately, in the hands of experienced practitioners, AC has been shown not to significantly elevate levels of stress, anxiety, or depression. Nevertheless, the potential psychiatric impact of the procedure warrants careful consideration and proactive management (Mofatteh, Mashayekhi, Arfaie, Chen, et al., 2023a)However, its application during pregnancy remains underexplored, with limited reported cases addressing its feasibility and safety in this high-risk context (Gunasekaran, 2022; Oblitas López, 2023; Meng, et al., 2016; Mofatteh et al., 2023b; Mofatteh et al., 2023c; Ostrom, et al., 2014; Sanai and Berger, 2008; Mofatteh, Mashayekhi, Arfaie, Adeleye, *et al.*, 2023a).

This report provides evidence supporting the safety of AC with intraoperative neurophysiological monitoring (IONM) for resecting GB in a pregnant patient, highlighting its potential as a viable option in similar challenging scenarios.

2. Patient

A 27-year-old right-handed female (gravida 2, para 1, abortus 0), previously healthy, with an intrauterine pregnancy at 19.4 weeks of gestation, was transferred to our hospital due to a 6-month history of sudden-onset severe persistent bilateral headache accompanied by a generalized tonic-clonic seizure (GTCS). At admission, the physical examination was normal, with a body mass index of 25, revealing a gravid uterus in the second trimester of gestation and no neurological deficits.

Initial 1.5 T brain Magnetic Resonance Imaging (MRI) demonstrated a right temporo-occipito-parietal lesion suggestive of a malignant supratentorial glioma. Fig. 1 **A-F**. A scalp standard EEG showed a generalized slowing, with focal slowing over the right frontocentral region. She received intravenous 1 g levetiracetam BID and dexamethasone 8 mg IV for 6 days to promote further fetal development under medical surveillance. Fetal Doppler examination before surgery confirmed normal fetal cardiac activity. A multidisciplinary board of neurosurgery, neurology, anesthesiology, and perinatology decided to offer a resection with Intraoperative Brain Mapping (IBM) during an AC guided by IONM.

On the day of surgery, a fetal Doppler examination confirmed normal fetal cardiac activity. The Neuro-anesthesiology team positioned the patient, and under intravenous general anesthesia, a scalpel block with 0.37 % ropivacaine, a functional right radial arterial line, and a high-flow line in the right thoracic extremity was set up. The patient, in the lateral decubitus position, was secured with a Mayfield head holder and pins. Fentanyl 1 ng/ml and dexmedetomidine 0.1 ng/ml IV infusions were used for analgesia, and a propofol 2 ng/ml IV infusion was used for sedation intermittently during portions of the procedure.

A standard navigation-guided craniotomy centered on the tumor was performed under a sleep-awake-sleep anesthesia technique. Dura mater was widely opened in a C-shaped fashion to allow access to the dorsolateral surface of the posterior quadrant of the hemisphere. Fusion of blood oxygenation level-dependent (BOLD) images of language, motor and visual cortex obtained in a previous functional Magnetic Resonance Imaging (fMRI) with the inferior fronto-occipital fascicle, arcuate fascicle, optic radiations and pyramidal tract. These structural images, along with the structural lesion, were identified and marked in the navigation system (BrainLab AG, Munich, Germany) prior to implementing motor, visual, and language tasks using complex multiple tasks to identify functional cortical zones and subcortical connectivity fibers using IBM. Resection was initiated with a subpial technique around the boundaries of the tumor for vascular control minimizing secondary brain edema. IONM strategies were implemented during the procedure to evaluate and compare in real time the functional status of the patient in various stages of the resection.

The IONM procedure was performed with Cadwell IOMAX (Kennewick, WA; USA) system using a subdural cortical electrode 8 contact strip recording for intraoperative electrocorticography and phase reversal protocol for sulcus identification with electrical motor and language cortical and subcortical mapping according to international recommendation using bipolar and monopolar probes (Molina-Botello et al., 2021).

Motor electrical cortical mapping was performed using a multi-pulse technique with cathodal stimulation, square wave pulses with a duration of 0.5 ms, frequency of 250 Hz, and a train of 5 pulses with current intensities ranging from 0 to 5 mA Fig. 2**A**. The handheld ball-tip monopolar probe was used, but no response was obtained, despite the attempt. Several subdermal needle electrodes on the left side of the patient were applied. Two dorsal lateral frontal regions showed positive motor response during cortical stimulation recorded from the left; deltoid, abductor digiti minimi, vastus lateralis, tibialis anterior, and abductor hallucis. Electrical cortical mapping of language was performed with the Penfield technique using a bipolar probe stimulating at 60 Hz from 1-5 mA, which successfully identified expressive and receptive areas. Electrocorticography recordings showed isolated interictal epileptiform discharges around the tumor and no afterdischarges during electrical cortical and subcortical mapping were observed (Sinha et al., 2016; Molina-Botello et al., 2021). During the IONM techniques, a neuropsychologist performed motor, expressive and receptive language and visual tasks to successfully identify eloquent areas, also independently during the resection of the lesion as we previously published (Sandoval-Bonilla, et al., 2022).

After the initial evaluations, the resection of the lesion was carried out with intermittent electrical cortical and subcortical motor, visual and language mapping and neurophysiological active evaluations Fig. 2 **B-C**, and the surgical view revealed a soft greyish lesion. After the safe maximum resection, hemostasis was secured, and the tumor was completely removed. The patient was awake for approximately 2.5 h of the 4-hour procedure, with efforts made to minimize this time while ensuring effective cortical mapping and patient safety. The patient was transported to the recovery room, and a fetal Doppler examination was completed, demonstrating a normal fetal heartbeat.

3. Outcome

The pathological diagnosis was a IDH1 wild-type, MGMT methylated grade 4 GB. Postoperative MRI showed gross total resection and surgical changes with no enhancements Fig. 1 **G-I**. The patient was discharged on the 5th postoperative day with no complications and improvement in her symptomatology.

4. Follow up

The Multidisciplinary Board offered the patient focal cranial radiation with fetal protection through a shielding device, but she declined concurrent treatment. The patient also refused pregnancy termination. Consequently, external beam radiation therapy (EBRT) was deferred until after delivery. Temozolomide was not recommended to avoid potential fetal impairment. She is currently under surveillance with serial non-contrast MRI scans and remains free of tumor progression as the last visit of Neurosurgery Department. The baby was delivered at full term via cesarean section, healthy and without any complications.

5. Discussion

A pregnant woman with a high-grade glioma successfully underwent AC with IONM at 19.4 weeks gestation. Tailoring the approach based on health, fetal status, and gestational age is crucial for optimal outcomes.

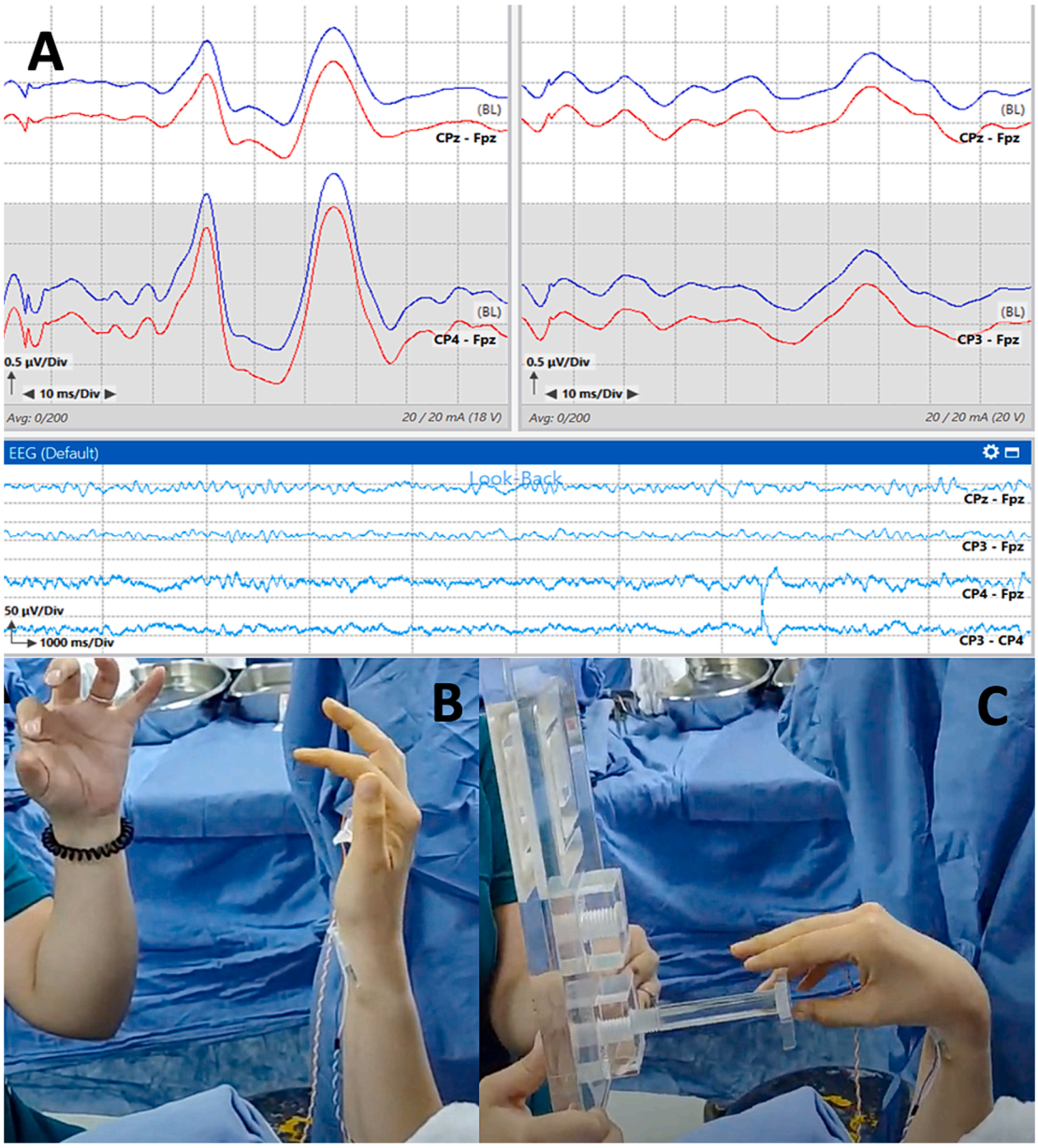

Fig. 2. Demonstration of tests on awake patient. **(A)** Lower limb SSEP and raw scalp EEG. (**B-C**) Motor, fine movement device, language test. (**C**) Conventional tapping motor.

Surgical risk reportedly decreases during the second trimester but individualized treatment plans are necessary due to the lack of standard guidelines (Sinha et al., 2016). Glioma management varies by grade, with monitoring, chemotherapy, and radiation considered, and surgery may be safely performed in select cases during pregnancy. MRI, with cautious use of contrast, is generally safe after the first trimester (SINGH et al., 2020). However, recent research suggests that gadolinium can persist in maternal blood, cord blood, and breastmilk even in subsequent pregnancies after pre-pregnancy exposure (Athiraman, Jebadurai and Tempelhoff, 2017). Another relevant consideration during the medical treatment of GB during the pregnancy is that serum levels of antiseizure medications can fluctuate during pregnancy and should therefore be monitored closely, however, levetiracetam in monotherapy is considered as the first choice as carbamazepine and lamotrigine. Also, the use of corticosteroids is recommended during the second and third trimester of pregnancy avoid the chronic use of dexamethasone (Athiraman, Jebadurai and Tempelhoff, 2017).

In this report we considered: 1) Scheduling surgery during the second trimester. 2) Selection the most appropriate surgical approach based on tumor localization and functionality. 3) Implementing meticulously planned IONM strategy to ensure maternal and fetal safety. 4) Addressing specific anesthetic considerations. Consequently, the decision-making process confronting this diagnosis hinges on the expertise of a multidisciplinary team, with a paramount priority being the preservation of the mother's life.

The decision to proceed with surgical tumor removal is contingent upon the patient's clinical manifestations and overall condition (Gunasekaran et al., 2022). Because of these safety features, appropriate timing for surgical intervention was considered in the second trimester, and an AC IBM was offered Table 1**.** In this case, the mother steadfastly declined pregnancy termination and simultaneous EBRT. While tumor progression hasn't transpired, the potential for uncertainty exists. To avert a second intervention if tumor progression occurs, we recommend focal cranial radiation with a fetal protection shield device for GB treatment during pregnancy. Early EBRT is scheduled post-delivery, followed by conventional temozolomide treatment in this scenario.

Table 1
Case reports of pregnant patients who underwent awake craniectomies for glioma resection guided by IOM.

Variables	Meng L 2016., et al. [10]	Gunasekaran 5A 2022., et al. [3]	Oblitas López S 2023, et al. [14]
Country	San Francisco, USA	Erlangen, Germany	Lima, Perú
Age, years	31	24	33
Weeks of gestation	30	7	18
Tumor type	Anaplastic astrocytoma	Giant cell glioblastoma	Diffuse astrocytoma
Location	Left frontoparietal	Left frontal	Left frontal
Size	7 x 6 x 5 cm	3.0 × 2.5 × 1.8 cm	4.69 x 4.36, x 5.26 cm
Stage	WHO grade III	WHO grade IV	WHO grade II
Symptoms	Word- finding difficulty, dysfluency, right upper monoplegia and right lower extremity paresis.	Generalized tonic-clonic seizures, headache, right leg weakness and numbness, and difficulty with memory and cognition	Generalized tonic- clonic seizures, headache and right hemiparesis
Medication during pregnancy	None	None	None
Obstetric outcomes	Delivery on postoperative day 4 under spinal anesthesia	Cesarean section at 34- weeks	Cesarean section at 37- weeks
Oncological outcomes	Remission, a partial course of radiotherapy and chemotherapy. She received (12 months after resection) hospice care due to the progressively worsening right leg weakness.	Remission, disease free at 1-year	Radiotherapy 66 Gy over 33 fractions in two months and residual tumor of less than 10 mm plus a porencephalic cyst of 32 x 24 x 22 mm
Anesthesia management	Intravenous infusions of propofol (25–60 mcg/kg/min) and remifentanil (0.04–0.14 mcg/kg/min), along with local anesthesia using 0.5 % lidocaine and 0.25 % bupivacaine mixed in a 1:1	Nerve blocks using 2 % lidocaine with 1:100,000 epinephrine and 0.5 % ropivacaine mixed 1:1	Scalp block using xylocaine and bupivacaine mixed 1:1
Treatment	Awake craniotomy, motor mapping and fetal hear rate monitoring	Awake craniotomy, motor mapping and fetal heart rate monitoring	Awake craniotomy, motor mapping and fetal heart rate monitoring.

AC is standard for tumors near eloquent brain areas, in addition, is carried out safely in resource-poor environments (Mofatteh et al., 2023). While associated with benefits like shorter hospital stays and improved survival, its application during pregnancy is underexplored (Sanai and Berger, 2008; Meng et al., 2016). In a systematic review based on 24 studies involving 1450 patients across 13 countries, indicate that AC does not significantly increase stress, anxiety, or depression in most patients when performed by experienced teams. Anxiety was the most frequently assessed psychological outcome, with visual analog scales and self-developed questionnaires being the most used evaluation tools. Despite the generally reassuring results, one study identified younger age as a risk factor for panic attacks, highlighting the need for tailored preoperative and intraoperative psychological support. These results underscore the importance of addressing potential psychiatric stressors in AC patients, emphasizing that while the overall impact appears minimal, the psychological well-being of patients should remain a key consideration in AC protocols (Mofatteh et al., 2023; Mofatteh et al., 2023b).

Considerations include tumor localization, intraoperative neurophysiological monitoring (IONM) needs, and maternal-fetal well-being (Kumar et al., 2020). Anesthetic goals include keeping the patient alert during mapping and resection while providing sedation during opening and closing. Limited literature exists on using this technique in pregnant patients, but a multimodal analgesia approach is common, with drugs like remifentanil/fentanyl, dexmedetomidine, and propofol (Mofatteh et al., 2023). Caution is advised against hyperventilation, which may impact fetal cardiac output, and efforts are made to minimize fetal exposure to anesthetics (Kamata, 2017; Handlogten, et al., 2015; Jayasekera et al., 2012; Guarracino *et al.*, 2022b). Modest hyperventilation with PaCO2 of 25–30 mmHg is recommended because a severe hyperventilation can be deleterious by decreasing the maternal cardiac output and the hypocarbia may impair the fetal oxygen delivery by shifting the oxygen hemoglobin dissociation curve to the left (Weller et al., 2015). Anesthesiologists must consider pregnancy-induced physiological changes and their impact on intracranial pressure and hemodynamics as well. Maintaining adequate uteroplacental perfusion is crucial, avoiding maternal hypotension and hypertension (Weller et al., 2015).

IBM strategies include complex multiple-functional evaluation at the same time with combinations of visual, language and motor tasks. The extension of the resection during a task-related monitoring and no direct cortical-subcortical stimulation (DCS) after the initial conventional DCS-IONM/tasks IBM, previously described was implemented. Also, avoid mannitol and hypocapnia to prevent fetal dehydration and cerebral ischemia respectively during the pregnancy or delivery (Athiraman, Jebadurai and Tempelhoff, 2017).

Additionally, this case highlights the need for a multidisciplinary approach, including neurosurgeons, neuroanesthesiology, perinatologists, and neuropsychologists, to address the complex challenges posed by the coexistence of GB and pregnancy. The timing of surgery in the second trimester was crucial, balancing maternal safety and minimizing risks to fetal development. While immediate surgical and postoperative outcomes were favorable, further research is needed to establish standardized protocols for managing high-grade gliomas during pregnancy (Molina-Botello et al., 2021; Guarracino *et al.*, 2022; Gunasekaran et al., 2022). This case emphasizes the importance of individualized care plans and the judicious use of advanced techniques like IONM and functional brain mapping to optimize both oncological and obstetric outcomes.

6. Limitations

It is a single case report from a single institution, which limits the generalisability of the results. However, the results were compared with those of several authors who have performed safe resections during pregnancy (Gunasekaran, 2022; Kamata, 2017; Handlogten, et al., 2015; Jayasekera et al., 2012; Kumar, et al., 2020; SINGH, P. et al., et al., 2020). In our case, the immediate outcomes for both mother and fetus were favourable, and follow-up is still being maintained to gain a full understanding of the long-term prognosis. This study serves as a milestone demonstrating the safety and efficacy of AC with IONM during pregnancy, which can be replicated in future surgeries, potentially avoiding the risk of pregnancy termination or maternal death due to delayed care.

7. Conclusions

Intraoperative Brain Mapping during AC is the gold standard methodology for a GB resection in eloquent areas. Pregnancy requirements for AC and IONM are essential to preserve the maternal-fetal integrity and to improve oncological outcome. IONM, anesthesical and IBM strategies require to be individualized and the multidisciplinary team can adjust and extend IBM goals to fit every situation that the patient requires during a resection. This is the first report of an AC for GB during the second trimester of pregnancy in Latin America.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' highest academic degrees

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Submission Statements

All authors have reviewed and agree with the contents of the manuscript. Daniel San-Juan, MD, the corresponding author, takes full responsibility for the data, analyses, interpretation, and implementation of the research. Daniel San −Juan MD also had full access to all data; he has the right to publish any and all data separately and distinctly from any sponsor. We certify that the submission (aside from an abstract) is not under review at any other publication. All authors participated in a meaningful way in the preparation of the manuscript.

Ethics form Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article and that this report does not contain any personal information that could lead to their identification.

Authors' contributions

Baryon A. Sandoval-Bonilla: Neurosurgeon, conception, prepare the case history, discussion and critical review.

Isela Valverde Luna: Clinical Neurophysiological staff, critical review Daniel San-Juan: Corresponding Author, conception, prepared the manuscript for submission critical review and writing. Aleida Arritola-Uriarte: Literature review and writing, contributed with the introduction, discussion and prepared the figures and tables. Ricardo García-Iturbide: Neurosurgery team, literature review, and writing and prepared the figures.

Alma Edith Gress Mendoza Neuroanestesiology team, critical review Lorely Cumplido Pulido Neuroanestesiology team, critical review Lizzette Hinojosa González: Neuroanestesiology team, litterature review Maria F. De la Cerda Vargas: Neurosurgery team, literature review Alfredo Lara Bahena: Neurosurgery team, literature review They all wrote the discussion and conclusions and read and approved the manuscript.

Consent

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

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