



CLINICAL PRACTICE ARTICLE

**REVISED** A case series discussing the anaesthetic management of pregnant patients with brain tumours [v2; ref status: indexed, <http://f1000r.es/2hn>]

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**Abstract**

Pregnancy may aggravate the natural history of an intracranial tumour, and may even unmask a previously unknown diagnosis. Here we present a series of seven patients who had brain tumours during pregnancy. The aim of this case series is to characterize the current perioperative management and to suggest evidence based guidelines for the anaesthetic management of pregnant females with brain tumours. This is a retrospective study. Information on pregnant patients diagnosed with brain tumours that underwent caesarean section (CS) and/or brain tumour resection from May 2003 through June 2008 was obtained from the Department of General Anaesthesia and the Rose Ella Burkhardt Brain Tumour & Neuro-Oncology Centre (BBTC) at the Cleveland Clinic, OH, USA. The mean age was 34.5 years (range 29-40 years old). Six patients had glioma, two of whom had concomitant craniotomy and CS. Six cases had the tumour in the frontal lobe. Four cases were operated on under general anaesthesia and three underwent awake craniotomy. The neonatal outcomes of the six patients with elective or emergent delivery were six viable infants with normal Apgar scores. Pregnancy was terminated in the 7th patient. In conclusion, good knowledge of the variable anesthetic agents and their effects on the fetus is very important in managing those patients.

**Article Status Summary**

**Referee Responses**

Referees	1	2	3
<b>v1</b> published 21 Mar 2013	 report 1	 report 1	 report 1
<b>v2</b> published 11 Dec 2013 <b>REVISED</b>			 report

- 1 **Michael James Paech**, University of Western Australia Australia
- 2 **Hiroyuki Sumikura**, National Center for Child Health and Development Japan
- 3 **Carolyn Weiniger**, Hadassah-University Medical Center Israel

**Latest Comments**

No Comments Yet

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**REVISED Amendments from Version 1**

In response to the reviewers comments we adjusted the numbers of cases in our results and discussion sections to reflect the effect of anaesthetics used during craniotomy in the pregnant patient only. We also performed some grammar and spelling changes.

We also corrected the order of references to make sure they are exactly corresponding to the text within the manuscript.

**See referee reports**

**Introduction**

Pregnancy may increase the growth of a previously existing intracranial tumour, and can even unmask a previously undiscovered tumour. A previous study that included 8 patients who had been diagnosed antenatally with a malignant brain tumour stated that all had severe neurological manifestations, and six of them had a severe neurological event that lead to premature termination of the pregnancy<sup>1</sup>. It was suggested that immunological tolerance and steroid mediated growth led to this exacerbation during pregnancy<sup>2</sup>.

In a population based study; Haas *et al.* reported that the number of meningiomas, acoustic neuromas, and primary malignant intracranial neoplasms diagnosed during pregnancy was less than expected with the ratio of observed/expected tumours associated with pregnancy to be 0.38<sup>3</sup>.

In 1988, Simon<sup>4</sup> postulated a theory to predict the prevalence of brain tumours in pregnant patients by using the intersection of the probability of being pregnant at any given time with the probability of having a brain tumour at a specific age and sex. Based on this theory the author calculated that in the USA there are about 89 pregnant women per year that also have brain tumours.

Brain tumours in pregnant patients impose a unique risk to both the foetus and mother. There are no previous studies that proposed

any guidelines for the anaesthetic management of pregnant patients with brain tumours.

The aim of this case series is to characterize the current perioperative management of pregnant patients with brain tumours and to suggest guidelines for the proper anaesthetic management.

**Methods**

Information on pregnant patients diagnosed with brain tumours that underwent CS and/or brain tumour resection from May 2003 to June 2008 was obtained from the Department of General Anaesthesia and the Rose Ella Burkhardt Brain Tumour & Neuro-Oncology Centre (BBTC) IRB-approved databases at the Cleveland Clinic in OH, USA. Patients were managed by the Departments of Neurosurgery, Obstetrics and Gynaecology, Anaesthesiology and BBTC. We used the Anaesthesia Record Keeping System (ARKS) to obtain the electronic record of the anaesthetic management. Additional data from the patients' electronic and paper charts were used to complete the pre- and post-operative patient information.

**Results**

Five pregnant patients presented with brain tumours during their pregnancy. An additional two patients had their diagnosis of brain tumours made in the immediate postpartum period. Diagnoses (Table 1) included meningioma (1 patient) and glioma (6 patients). The mean age was 34.5 years (range 29–40 years) and parity was 0 (2 patients), 1 (1 patient), and >2 (4 patients). More than half of the patients (57%) underwent CS with craniotomy performed, on average, 45 days after the CS (range: 2–90 days). Two patients were diagnosed with a brain tumour during pregnancy and had a craniotomy (Table 2). All our patients were managed by general anaesthesia or monitored anaesthesia care (MAC). Inhalational anaesthetic agents (isoflurane and desflurane) were used under 1-minimal alveolar concentration for the maintenance of anaesthesia. Four drugs were used in our patients for both induction and maintenance

**Table 1. Anaesthetic techniques used for brain tumour resection at the Cleveland Clinic, Ohio (2003–2008).**

Case	Anaesthesia technique	Anaesthesia induction	Anaesthesia maintenance	Postoperative events	Pathology
1	General	Propofol/fentanyl succinylcholine	Isoflurane	Pulmonary Embolism	Tentorial meningioma
2	General	Propofol/fentanyl Rocuronium	Desflurane-remifentanyl	Seizures	Recurrent anaplastic glioma
3	General	Thiopental/fentanyl Rocuronium	Isoflurane-remifentanyl	Medical termination of pregnancy	Anaplastic glioma
4	Awake craniotomy	Propofol/alfentanyl	Propofol/alfentanyl	Deceased 16 months after craniotomy	Glioma
5	Awake craniotomy	Propofol/dexmedetomidine	Propofol/dexmedetomidine	Expressive aphasia	Low grade glioma
6	Awake craniotomy	Propofol/dexmedetomidine	Propofol/dexmedetomidine	Mild aphasia	Low grade glioma
7	General	Propofol/fentanyl succinylcholine	Isoflurane-remifentanyl	Deceased 36 months after craniotomy	Glioblastoma multiforme

\*FHR: Foetal Heart Rate

**Table 2. Preoperative information of pregnant patients with brain tumours at the Cleveland Clinic, Ohio (2003–2008).**

Case	Age	Gestational age at the time of diagnosis (weeks)	Preoperative anticonvulsant medications	CS followed by tumour excision	Time after delivery for craniotomy (days)	Gestational age at craniotomy (weeks)	Presentation	Size and tumour localization	Newborn condition
1	37	33	Lorazepam	Yes	2	33	Increased ICP*, headache	Right Temporal 6 × 4.5 cm	Normal Apgar scores
2	36	36	Lorazepam	No	Concomitant craniotomy and C-section	N/A	Increased ICP, headache	Left Frontal 5 × 4 cm	Normal Apgar scores
3	29	6	Phenytoin	No	Craniotomy during pregnancy	12	Seizures	Left Frontal 5.9 × 3.3 cm	-
4	40	18	-	No	Craniotomy during pregnancy	22	Seizures	Left Frontal 2.4 × 2.2 cm	Normal Apgar scores, Perioperative FHR* monitoring
5	30	18	-	Yes	30	N/A	Seizures	Left Frontal 7.5 × 4.5 cm	Normal Apgar scores
6	34	Postpartum- 1 week	-	Yes	60	N/A	Seizures	Right frontal 6.1 × 4.7 cm	Normal Apgar scores
7	36	Post-partum – 3 weeks	Phenytoin	Yes	90 (pregnancy was terminated)	N/A	Seizures and focal signs	Right frontal 2.8 × 2.3 cm	Normal Apgar scores

\*ICP: Intra-Cranial Pressure

**Table 3. Intraoperative management for brain tumour resection at the Cleveland Clinic, Ohio (2003–2008).**

Case	Intraoperative hypotension	*EBL (ml)	Use of colloids (ml)	Total intravenous fluids (ml)	Use of furosemide	Urine output (ml)	Highest BP (mmHg)	**ETCO <sub>2</sub> range (mmHg)
1	Yes	2200	1000	7500	Yes	2760	150/100	25–40
2	Yes	100	0	1800	No	790	140/80	22–43
3	Yes	1000	1000	4700	Yes	1700	150/80	26–38
4	Yes	500	0	5600	No	3700	120/70	26–34
5	No	100	0	4500	No	4400	170/90	N/A
6	No	400	0	4000	No	1045	160/100	20–30
7	No	100	0	3400	No	1800	140/60	22–36

\*EBL: Estimated Blood Loss

\*\* ETCO<sub>2</sub>: End Tidal CO<sub>2</sub>

of anaesthesia; propofol in 2 pregnant patients, remifentanyl in 2 pregnant patients and alfentanil in one patient. Foetal heart rate monitoring was applied in one patient receiving MAC for an “awake” craniotomy. Rapid sequence induction was not universally applied. Four cases had general anaesthesia and used rocuronium as a muscle relaxant to facilitate endotracheal intubation. There were no major intraoperative events (Table 1 and Table 3). The neonatal outcomes of the six patients with elective or emergent delivery were six viable infants with normal Apgar scores. Pregnancy was terminated in the 7<sup>th</sup> patient. There was neither operative mortality nor significant sustained morbidity in this series. One patient suffered a pulmonary embolus in the postoperative period.

## Discussion

Brain tumours tend to increase in size during pregnancy due to several factors such as fluid retention, increased blood volume and

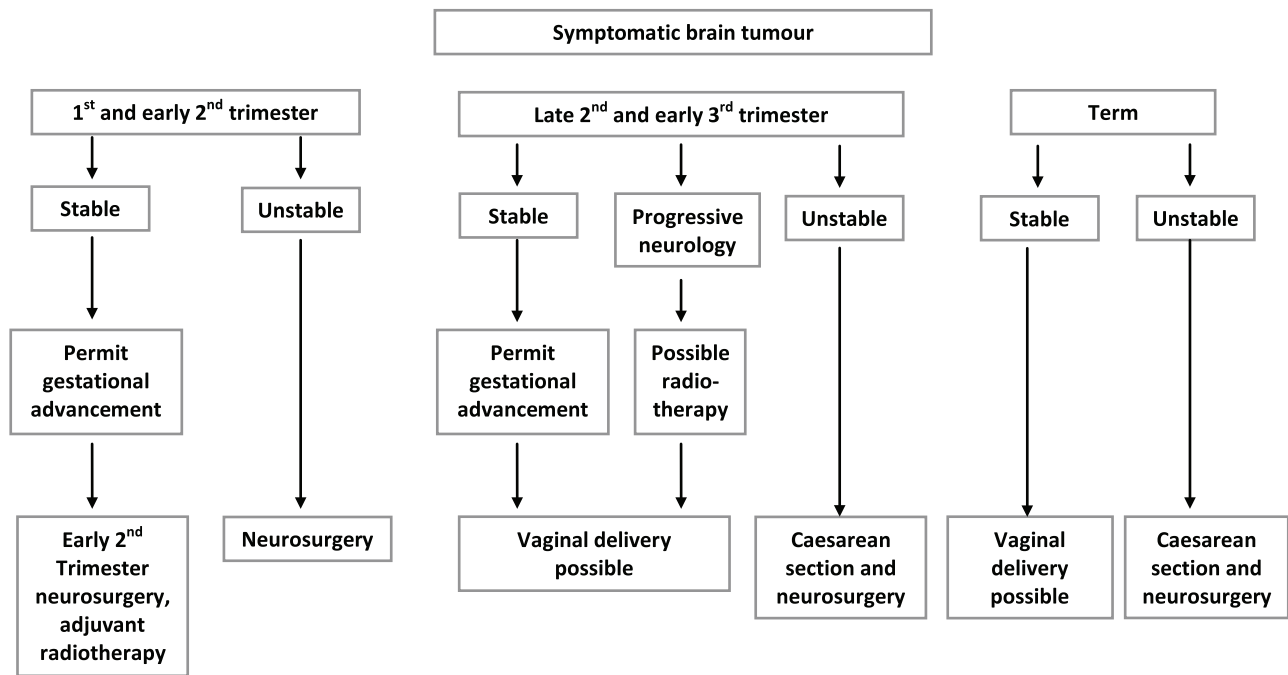
hormonal changes and therefore may be diagnosed earlier<sup>5</sup>. The decision to proceed with neurosurgery during pregnancy depends on the site, size, type of tumour, neurological signs and symptoms, age of the foetus, and the patient’s wishes<sup>6,7</sup>.

There are no guidelines for the management of intracranial tumours in pregnant women. A possible algorithm to follow is shown in Figure 1 (modified from Tewari *et al.*<sup>1</sup>).

## Management issues

Corticosteroids have been recommended as they are safe in pregnancy, promote foetal lung maturity and reduce cerebral oedemas<sup>1</sup>.

During the first and early second trimesters, if the patient is stable, it is acceptable to permit pregnancy to proceed into the early second trimester and surgery can then be performed at this time. It is also



**Figure 1.** Algorithm for management of brain tumours in pregnant women.

possible to administer radiotherapy, radio-surgery and image guided surgery beyond the first trimester. If the patient is unstable, undergoing an urgent neurosurgery is recommended<sup>1</sup>.

At the end of the second trimester; in stable patients, proceed with pregnancy with close observation. But if the patient has a worsening neurological status; radiotherapy can be used to delay surgery. If the patient is unstable and shows symptoms of impending herniation, it is recommended to use general anaesthesia to deliver the baby by CS which is followed by surgical decompression<sup>1</sup>.

At term; in a stable patient, induction of vaginal delivery is permitted<sup>8</sup>. A shortened second stage can be achieved with epidural anaesthesia<sup>9</sup>. CS should only be performed for accepted indications as it has been shown that CS does not seem to provide any advantage over vaginal delivery in protecting against increased intracranial pressure. In unstable patients, perform, as above, CS under general anaesthesia, followed by surgical decompression<sup>1</sup>.

Mannitol and hypocapnia were avoided in our patients to prevent foetal dehydration and cerebral ischemia/hypoxia, respectively.

General anaesthesia can be safe in pregnant patients with intracranial tumours. Tracheal intubation is very important as it allows maternal hyperventilation thereby controlling raised intracranial pressure<sup>10</sup>. Patients should be pre-medicated with ranitidine 50 mg I.V. to protect the patient against possible vomiting and aspiration.

Propofol was used in 2 pregnant patients without producing any side effects. The main side effect is that it has a relaxing effect on the gravid uterus<sup>11</sup>. It is still controversial whether its use is safe with

newborns. Bacon *et al.* did not report any adverse effects of propofol in newborns after emergency CS<sup>12</sup> while another study reported seizure, ataxia, and hallucinations after prolonged propofol anaesthesia for more than 6 hours<sup>13</sup>.

Meanwhile, isoflurane is known to produce many adverse effects on the foetus<sup>4,5</sup>. It was used in one of our pregnant patients but our records did not show any adverse effects. Desflurane was used in one of our patients with no complications. But the neurotoxicity of desflurane and sevoflurane is still a controversial issue<sup>16</sup>.

Remifentanyl was used in 2 pregnant patients without producing any adverse effects; this may be explained by the fact that it has a unique metabolism by plasma and tissue esterases and a context-sensitive half-life of 3 to 4 min, independent of the duration of infusion<sup>17</sup>. One concern is that the transfer of opioids, such as remifentanyl, across the placenta may lead to neonatal depression. However, remifentanyl can be metabolized and redistributed to both the mother and the foetus rapidly<sup>18</sup>. Remifentanyl has opioid properties that allow both control of the intraoperative stress response and a more rapid recovery compared to other opioids. Because of its metabolism and short duration of action, remifentanyl is therefore considered to be safe and effective for general anaesthesia for emergency CS in patients with neurological risk factors<sup>19</sup>.

Clinically relevant concentrations of remifentanyl induce rapid, persistent increases in NMDA-induced ion currents. Since NMDA-receptor blockade during a critical stage in brain development leads to depression of neuronal activity and as such is known to initiate the apoptotic cell death cascade in immature neurons, we suggest that remifentanyl may be safe for the developing brain. In addition,

remifentanyl is known to offer a neuron-protective effect in cases of opioid induced hyperalgesia or tolerance<sup>20</sup>. Dexmedetomidine use is recommended in pregnant patients<sup>21</sup>.

### Possible medications for cases of brain tumours during pregnancy not used in this case series

In the following paragraphs we will discuss drugs that were not used in our study but have been investigated before.

There are no human trials examining the effects of nitrous oxide on neuronal structure and neurocognitive performance in young children. Some case studies showed that the exposure of neonates to nitrous oxide *in utero* during the third trimester or during CS can result in transient neurological sequelae<sup>22</sup>.

Although sevoflurane is one of the most prevalent volatile anaesthetics, a recent study has suggested that it can cause epileptic seizure activity, neurotoxicity, and both acute and chronic impairment in synaptic plasticity in neonatal rats<sup>16</sup>.

Oxytocin has been used in patients with intracranial tumours without any adverse effects. Ergotamine can cause hypertensive responses, which may increase the intracranial cranial pressure and can lead to haemorrhage. It should be avoided in pregnant women with brain tumours<sup>7</sup>.

Dexamethasone has been traditionally used to reduce brain oedema. It may be safe to use it in an acute setting but its chronic use may be harmful to the foetus as it may cause hypoadrenalism. Weighting the risks and benefits for treating seizures with anticonvulsants; it is recommended to use them in this setting to avoid seizures that may lead to maternal and foetal hypoxia and acidosis<sup>23</sup>.

Several studies investigated the mechanism of anaesthesia-induced neurotoxicity. Previous reports suggested depression of neuronal activity due to anaesthesia induced GABA A receptor activation and NMDA receptor blockade during a critical stage in brain development<sup>20</sup>. Several adjuvants, such as estradiol, pilocarpine, melatonin and dexmedetomidine, have been identified in animal studies

to ameliorate anaesthesia induced neurodegeneration<sup>24–26</sup>. It is still controversial whether etomidate is neurotoxic or not. There is evidence that the rarely used anaesthetic, xenon, in clinical doses does not have neurodegenerative effects and may be neuroprotective<sup>27</sup>.

A recent study showed that the administration of lithium significantly increased the activation of a neuroprotective pathway in the hippocampus. Further studies and human trials are necessary to fully investigate the beneficial effects of lithium in the anaesthetic management of pregnant patients with brain tumours<sup>28</sup>.

### Conclusion

Management of brain tumours in pregnant women is mainly reliant on case reports and the doctor's personal experience. Therefore, close communication between the neurosurgeon, neuroanaesthetist, obstetrician and the patient is crucial. Good knowledge of the variable anesthetic agents and their effects on the fetus is very important in managing those patients.

### Author contributions

Alaa A Abd-Elseyed: designed, analyzed, interpreted data and wrote the manuscript. Jose Diaz Gomez: designed, analyzed and interpreted data. Gene H Barnett: designed the study and drafted the article. Andrea Kurz: interpreted data and drafted the article. Maria Inton-Santos: interpreted data and drafted the article. Sabri Barsoum: designed the study and drafted the article. Rafi Avistian: interpreted data and drafted the article. Zeyd Ebrahim: designed the study and drafted the article. Vesna J Todorovic: designed the study and drafted the article. Ehab Farag: substantial contribution to conception and design, acquisition, analysis and interpretation of data. All authors approved the final manuscript for publication.

### Competing interests

All authors declare that there are no competing interests.

### Grant information

The author(s) declared that no grants were involved in supporting this work.

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[PubMed Abstract](#) | [Publisher Full Text](#)



## Current Referee Status:

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### Referee Responses for Version 2



**Carolyn Weiniger**

Anesthesiology and Critical Care, Hadassah-University Medical Center, Jerusalem, Israel

**Approved: 08 January 2014**

**Referee Report:** 08 January 2014

This paper presents a small case series of pregnant women undergoing intracranial surgery, in addition to two postpartum neurosurgical patients. The paper is now much improved for clarity regarding patients who were actually pregnant during the surgery, and provides a short review of possible anesthetic management strategies for these patients.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.



**Michael James Paech**

School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

**Approved: 18 December 2013**

**Referee Report:** 18 December 2013

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

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### Referee Responses for Version 1



**Carolyn Weiniger**

Anesthesiology and Critical Care, Hadassah-University Medical Center, Jerusalem, Israel

**Approved with reservations: 24 October 2013**

**Referee Report:** 24 October 2013

The case series reports brain tumors and cesarean delivery (CD) over a five year period in Cleveland Clinics, Ohio. The stated aim was to elucidate management suggestions from previously performed cases



in their institution.

The case series includes seven patients; 5 with preCD and 2 with postCD diagnosis. The results state that "over half patients underwent CD with craniotomy up to 45 days post CD". Only one woman had craniotomy during pregnancy. Tables 1 and 2 somewhat clarify this confusing information. The authors report in the results that one patient had tumor diagnosed during pregnancy and had peripartum craniotomy, yet table 2 reports three such cases.

Table 1 reports the anesthesia drugs used for craniotomy surgery in the seven patients. Since only 3 patients had craniotomy with CD, it is not clear why Apgar scores are reported here for the patients who had post CD craniotomy.

Three patients, including one at 22 weeks gestation and two postCD had awake craniotomys. The authors report that fetal monitoring was used in only one of the awake craniotomy patients. It is my understanding that the other two had already delivered at time of craniotomy. The stated study aim was to provide management suggestions for anesthetic management of pregnant patients with brain tumors. I assumed this meant management for the CD. There are few details regarding the CD surgery, and four patients undergoing craniotomy were no longer pregnant at time of the craniotomy. Therefore table 3 also doesn't make sense- it is titled "management of pregnant patients for brain tumor resection" - again, four patients are no longer pregnant.

The authors present an algorithm for delivery of women with brain tumors. I could not find in their results any case of VD, all seemed to have CD. I wonder why the two postpartum diagnosed patients had CD? Their tumor was discovered 1 and 3 weeks postpartum.

The authors mention that VD is a delivery option, but their study does not bring new evidence for this. The algorithm combines information from other studies and is quite clear, but I wonder if their series adds to our knowledge. For example, stating that propofol was used in six patients and is controversial with newborns is not relevant for the four women who had craniotomy postpartum. Same goes for isoflurane and later - dexmetomidine. The literature review of pharmacological agents is nicely presented. However again the conclusion reporting safety of des/iso is not particularly relevant, as some women were not pregnant when the drugs were given.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

## 1 Comment

### Author Response

**Alaa Abd-Elsayed**, Community Medicine, Faculty of Medicine, Assiut University, Egypt

Posted: 11 Dec 2013

We would like to thank the reviewer for her valid points.

- *"The authors report in the results that one patient had tumor diagnosed during pregnancy and had peripartum craniotomy, yet table 2 reports three such cases"*  
We have changed this to two patients, as the third case had both managed together.
- *"Table 1 reports the anesthesia drugs used for craniotomy surgery in the seven patients. Since only 3 patients had craniotomy with CD, it is not clear why Apgar scores are reported here for the patients who had post CD craniotomy."*  
We wanted to show the outcomes of all pregnancies regardless of the final management, and we think it is important to mention the fetal outcome.
- *"There are few details regarding the CD surgery, and four patients undergoing craniotomy were no longer pregnant at time of the craniotomy. Therefore table 3 also doesn't make sense- it is titled "management of pregnant patients for brain tumor resection" - again, four patients are no longer pregnant"*  
We agree with the reviewer - we still think it is important to have this table, but maybe we can change the title to "Intraoperative management".
- *"The authors present an algorithm for delivery of women with brain tumors. I could not find in their results any case of VD, all seemed to have CD. I wonder why the two postpartum diagnosed patients had CD?"*  
That is a very good point. We wanted to include the algorithm as part of our discussion, as it serves very well to help people managing their cases with the same disease. Our article mainly carries the message of what we did and what can be done better.
- *"The authors mention that VD is a delivery option, but their study does not bring new evidence for this. The algorithm combines information from other studies and is quite clear, but I wonder if their series adds to our knowledge. For example, stating that propofol was used in six patients and is controversial with newborns is not relevant for the four women who had craniotomy postpartum. Same goes for isoflurane and later - dexmetomidine. The literature review of pharmacological agents is nicely presented. However again the conclusion reporting safety of des/iso is not particularly relevant, as some women were not pregnant when the drugs were given."*  
We agree with the reviewer, and have changed this in the manuscript.

**Competing Interests:** No competing interests were disclosed.



**Hiroyuki Sumikura**

Department of Obstetric Anesthesia, National Center for Child Health and Development, Tokyo, Japan

**Approved: 07 October 2013**

**Referee Report: 07 October 2013**

I read this report with interest, as I have just experienced a case of cesarean section with a brain tumor. I wondered if spinal anesthesia was contraindicated for these patients, hence, if the author could add some discussion about this topic it would be greatly appreciated.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Competing Interests:** No competing interests were disclosed.

## 1 Comment

### Author Response

**Alaa Abd-Elseyed**, Community Medicine, Faculty of Medicine, Assiut University, Egypt

Posted: 11 Dec 2013

This is a very good point mentioned by the reviewer, we just think it is out of the scope of this article, and is a topic with a lot of controversy that really needs a full another manuscript to discuss. We focused on the good drugs and agents to use and not the technique of management.

**Competing Interests:** No competing interests were disclosed.



**Michael James Paech**

School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

**Approved with reservations: 27 August 2013**

**Referee Report:** 27 August 2013

There is not much information about modern management of cerebral tumours during pregnancy, so this paper is of some interest despite the small number of cases.

### Abstract

This draws a conclusion and makes general recommendations– yet there was no related discussion within the Discussion section of the body of the paper. It is inappropriate anyway to draw conclusions based on a small retrospective case series, so this needs revision. After describing the cases and the drugs used, I suggest the author indicates what follows next in the paper ie. a more detailed description of cases and discussion of the drugs used for general anaesthesia.

### Introduction

This reads well and is informative. I prefer the use of “fetus” and there is a good linguistic argument to be made for this spelling.

Guidelines should be evidence-based, or in the absence of reasonable evidence at least consensus based, from a group of experts. I don't think it is reasonable to suggest guidelines should come from ‘studies’ or be based on single institution experience with 7 cases – perhaps the authors should suggest a plan of obstetric and neurosurgical management.

### Results

- “Four patients (57%) underwent ...” Please replace “case” with “patient”.
- Remifentanil and alfentanil are misspelt in several places.
- Table 2 legend - change to “Intracranial pressure”. Correct Table 1 heading to “Postoperative events”.
- Delete “Only” from the last sentence.
- Neonatal condition would be better placed in Table 2, because Table 1 describes several patients in whom tumour resection was much later than delivery, and Table 2 has the obstetric data.
- The GA technique for tumour resection is mentioned but not the GA technique for CS, which becomes a source of confusion when you later discuss drugs and their effects on the developing brain etc. Can this be added?

## Discussion

- A comment should be made about the exclusive use of GA. Regional block may be appropriate (and preferred by the patient) for CS if there is no evidence of raised intracranial pressure or recent seizures – in this series all patients had increased ICP or seizures.
- A comment about the location of fetal monitoring might also be useful.
- Correct to “cerebral oedema” and “epidural analgesia” in Management Issues.
- Preoperative seizure control and the implications of anticonvulsant therapy warrant a mention.
- ‘Motherhood’ statements such as “general anaesthesia is safe to be used with intracranial tumours” should be removed.

The discussion of propofol should be re-focused and expanded a little – this is now widely considered suitable for induction in pregnancy, and the main issues are the dose-response curve compared with thiopentone and the neonatal outcome, rather than uterine relaxation. The potential neurotoxicity is not mentioned, yet later the volatiles are implicated and other drugs considered. This area of science is very interesting but no clinical conclusions have been drawn as yet, and I think it has been over-emphasised throughout the author's Discussion, to the detriment of clinical studies and information about the implications of drugs during neurosurgery.

In relation to animal neurotoxicity studies, I suggest only drawing comparisons between various drugs and balance these with clinical information. The evidence condemning isoflurane is not supported by the references, which are paediatric case reports rather than fetal exposure. Few would consider isoflurane unacceptable, despite not being ideal; nor would desflurane or sevoflurane be avoided.

References after 17 are muddled and do not apply to the text. This needs full review. In addition there are some odd choices of reference – e.g. the case report by McCarroll on remifentanil and peripartum cardiomyopathy is used to justify a comment about anticonvulsants, and ergometrine is discussed using a reference about craniotomy (or – all perhaps the McCarroll case? – but this would still be inappropriate).

Again, suggesting that remifentanil is safe for the developing brain is premature if based only on mechanistic action considerations. Likewise use of dexmedetomidine, quoting a single case report! Please discuss mechanisms but don't generalise. It would make more sense to discuss other drugs, some of which were surely used in the patients, in a more logical sequence (no information provided about GA technique for CS, but presumably oxytocin must have been used, possibly also nitrous oxide?). A restructure of the Discussion section with different headings should be considered.

Please do not draw conclusions about safety based on a 7 patient case series.

**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

**Competing Interests:** No competing interests were disclosed.

## 1 Comment

### Author Response

**Alaa Abd-Elseyed**, Community Medicine, Faculty of Medicine, Assiut University, Egypt

Posted: 11 Dec 2013

- *"After describing the cases and the drugs used, I suggest the author indicates what follows next in the paper"*  
We have changed the conclusion as advised by the referee.
- *"I prefer the use of "fetus" and there is a good linguistic argument to be made for this spelling"*  
The spelling of "fetus" was suggested by the journal.
- *"I don't think it is reasonable to suggest guidelines should come from 'studies' or be based on single institution experience with 7 cases"*  
We have discussed the evidence from the literature. Having 7 cases from one institute with pregnant patients with brain tumors is a reasonable number, and we are not aware of any other institutions who have published in this topic. It is a rare condition and not that common.
- *"Neonatal condition would be better placed in Table 2"*  
Table 2 is already busy, but we will be happy to do this if okay with the journal format.
- *"The GA technique for tumour resection is mentioned but not the GA technique for CS"*  
We think this is not relevant to the topic we wanted to discuss. We have corrected the manuscript by changing the number of patients to the pregnant patients who had the tumor resection during pregnancy, to make sure it is relevant to the discussion of the effects of variable anesthetics on the developing fetus.
- *"A comment should be made about the exclusive use of GA"*  
We just described what was done, multiple anesthesiologists managed our patients and each did it according to his beliefs and practice. We did not state we did the best management, as there are not clear guidelines for the management. And this is the message - we need to have some guidelines for managing these patients.
- *"A comment about the location of fetal monitoring might also be useful"*  
It is always done using external monitoring.

- *"Correct to "cerebral oedema" and "epidural analgesia" in Management Issues"*  
We are not sure to what correction the referee refers.
- *"Preoperative seizure control and the implications of anticonvulsant therapy warrant a mention"*  
These are already mentioned in the discussion section.
- *"The discussion of propofol should be re-focused and expanded a little – this is now widely considered suitable for induction in pregnancy, and the main issues are the dose-response curve compared with thiopentone and the neonatal outcome, rather than uterine relaxation"*  
We have modified the conclusion. Thiopentone is not widely used in our insitute.
- *"In relation to animal neurotoxicity studies, I suggest only drawing comparisons between various drugs and balance these with clinical information"*  
This has been mentioned in our discussion.
- *"...suggesting that remifentanil is safe for the developing brain is premature if based only on mechanistic action considerations. Likewise use of dexmedetomidine, quoting a single case report! Please discuss mechanisms but don't generalise."*  
There has not been much published on these topics, and we quoted the case reports as this is what has been published.
- *"Please do not draw conclusions about safety based on a 7 patient case series"*  
We have changed the conclusion.
- We have addressed and corrected the wordings advised by the referee. The issue with the references has also been checked.

**Competing Interests:** No competing interests were disclosed.

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