A Review of the Neurosurgical Management of Brain Metastases During Pregnancy

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Abstract: Objective: Patients with pregnancy-associated secondary brain tumors (PASBT) are challenging to manage. Because no guidelines for the management of such patients currently exist, we performed a systematic review of the literature using PRISMA guidelines with a discussion of management from a neurosurgeon’s perspective. Method: Systematic review of the literature using PRISMA guidelines from 1999 to 2018. Results: We identified 301 studies of which 16 publications (22 patients reporting 25 pregnancies, 20 deliveries, 5 early terminations) were suitable for final analysis. The most frequent primary cancers were breast (8/22, 36.36%), skin (6/22, 27.27%), and lung (5/22, 22.73%). Four patients (18.18%) had neurosurgical procedures during their pregnancies. Five patients (22.73%) received neurosurgical resection after their pregnancies. Nine patients (40.91%) received radiation therapy and seven patients (31.82%) received chemotherapy during pregnancy while seven patients (31.82%) received chemotherapy and radiation after pregnancy. Conclusion: Management of PASBT remains a challenging issue. Maternal and fetal risks associated with surgical resection and teratogenicity due to adjuvant therapy should be discussed in the context of a multidisciplinary team. Timing of surgery and the use of systemic chemoradiation depends on the gestational age (GA) of the fetus, extent, and control of the mother’s primary and metastatic disease. Guidelines need to be established to help neuro-oncology teams safely and effectively manage this group of patients.

RéSUMÉ : Étude de la prise en charge neurochirurgicale de métastases cérébrales détectées pendant la grossesse. Objectif : La prise en charge de patientes enceintes chez qui l’on a diagnostiqué des tumeurs cérébrales secondaires n’est pas chose facile. Sachant qu’il n’existe actuellement aucune ligne directrice en matière de prise en charge, nous avons réalisé une revue systématique de littérature au moyen des lignes directrices PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) tout en proposant une discussion sur le sujet d’un point de vue neurochirurgical. Méthode : Une revue systématique de littérature au moyen des lignes directrices PRISMA, et ce, de 1999 à 2018. Résultats : Au total, nous avons identifié 301 études. De ce nombre, 16 d’entre elles ont pu se prêter à une analyse finale. À noter que ces 16 études incluaient 22 patientes ayant rapporté 25 grossesses, 20 accouchements et 5 interruptions de grossesse prématurées. Les cancers primitifs les plus fréquents étaient ceux du sein (8/22, soit 36,36 %), de la peau (6/22, soit 27,27 %) et du poumon (5/22, soit 22,73 %). Soulignons que 4 patientes (18,18 %) ont subi des interventions neurochirurgicales en cours de grossesse tandis que 5 d’entre elles (22,73 %) ont bénéficié de résection neurochirurgicale après leur accouchement. De plus, 9 patientes (40,91 %) ont reçu des traitements de radiothérapie, 7 d’entre elles (31,82 %) ont reçu des traitements de chimiothérapie en cours de grossesse et 7 autres (31,82 %) ont reçu à la fois des traitements de radiothérapie et de chimiothérapie à la suite de leur accouchement. Sur 20 accouchements de fœtus jugés en bonne santé, on a constaté un décès (5 %). Enfin, 5 grossesses, soit 20 %, ont dû être interrompues lors du premier trimestre en raison d’une intervention neurochirurgicale urgente. Conclusion : La prise en charge de patientes enceintes chez qui l’on a diagnostiqué des tumeurs cérébrales secondaires demeure un enjeu compliqué à aborder. Les risques associés à la résection chirurgicale et à la tératogénicité de la chimiothérapie adjuvante auxquels font face mères et fœtus devraient être discutés dans le cadre d’une équipe multidisciplinaire. Le moment choisi pour une intervention chirurgicale et l’utilisation systématique de chimio-radiation dépendent entre autres de l’âge gestationnel du fœtus mais aussi de l’étendue et du contrôle de la maladie métastatique primitive de la mère. Chose certaine, des lignes directrices devraient être établies en vue d’aider les équipes de neuro-oncologie à prendre en charge ces patientes de manière sûre et efficace.

Keywords: Brain metastases, Pregnancy, Pregnancy-associated secondary tumors, Neurosurgery, Chemotherapy, Radiation therapy

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INTRODUCTION

There has been a trend toward delaying motherhood in developed countries, resulting in an average age of 26.3 years for mothers delivering their first-born child in the USA in 2014.\(^6\) Unfortunately, this delay in motherhood has led to an overlap with the period of increasing natural incidences of certain cancers. At present, the cumulative incidence of cancers in pregnant women has been estimated to be at around 1 in 1000–2000 pregnancies,\(^3\) further creating a unique and challenging clinical scenario of pregnancy-associated secondary brain tumors (PASBT). Among these, there has been an increased incidence of breast, melanoma, and lung cancer, all of which have propensities to metastasize to the brain.\(^3,5\)

There are obvious risks to the fetus when treating expectant mothers diagnosed with cancer using chemoradiation. Beyond that, there are elevated anesthesia risks and other comorbidities associated with many non-obstetrics-related surgical procedures when performed during pregnancy.\(^1,12,14,28\) It is noteworthy that there are currently no guidelines regarding the neurosurgical treatment of PASBT. To address this void, we performed a systematic review of the literature with a focus on PASBT to coalesce common and unique challenges in this setting and to discuss key aspects in managing these patients from a neurosurgeon’s perspective.

MATERIALS AND METHODS

Data Sources

A PRISMA-guided literature search in MEDLINE (PubMed) was conducted using the search phrases “brain”, “intracranial”, “intracerebral”, “cancer”, “metastasis”, “pregnancy”. An additional search was conducted using Google Scholar to avoid missing articles that may have lacked one or more of the above search terms.

Search Criteria

Studies had to meet the following criteria to be included in our analysis: (1) Published in the MRI era between January 1990 and August 2018; (2) English language; (3) Human subjects; and (4) Peer-reviewed publications. A PRISMA workflow diagram is provided in Figure 1.
Data Extraction

The following information had to be available in selected articles and was extracted from all suitable publications identified in our PubMed search: (a) Classification of primary malignancy; (b) Description of brain metastases; (c) Diagnostic method and criteria for detection of brain metastases; (d) Information regarding pregnancy status and management, including outcome; (e) Description of details regarding treatment of brain metastases during pregnancy; (f) Age of the mother; (g) Gestational age (GA) of the fetus at diagnosis and delivery; (h) Method of delivery.

RESULTS

A total of 301 studies were retrieved after the application of our PRISMA algorithm (Figure 1). Of these, 16 fulfilled all inclusion criteria, and 2 studies presented more than 1 case. This resulted in a pooled cohort of 22 cases of PASBT, which we included in our final analysis. Individual cases and reports are summarized in detail in Table 1.

Tumor Diagnoses

Eight of the 22 patients (36.36%) had breast cancer: Six with intraductal/infiltrative breast cancer and two with triple-negative breast cancer. Six patients (27.27%) presented with a primary skin tumor: three of those were classified as superficial spreading melanoma, and three as malignant melanomas. Five patients (22.73%) had lung cancer and the remaining three patients (13.64%) had various pathologies, including one Wilms’ tumor; one follicular thyroid carcinoma; and one primary mediastinal large B-cell non-Hodgkin’s lymphoma.

Chemotherapy Only

One patient presenting with spine and brain metastases due to large B-cell non-Hodgkin’s lymphoma at 18 weeks GA was treated with chemotherapy alone during the pregnancy.

Radiation Therapy Only

Four patients (18.18%) received single modality radiotherapy for the treatment of their brain metastases: three patients received stereotactic radiosurgery (SRS) during their pregnancy at 24 weeks GA, 25 weeks GA, and 26 weeks GA. One patient received whole-brain radiotherapy (WBRT) after her elective C-section at 30 weeks GA.

Neurosurgical Procedure Only

Three patients (13.64%) had neurosurgical interventions after their pregnancies: One patient had an insertion of a ventriculoperitoneal (VP) shunt after early termination of her pregnancy at 9 weeks GA; Two patients had surgical resection of their tumors after successful term deliveries.

Chemoradiation Only

Seven patients (31.82%) received combination chemotherapy and radiation. Five patients received chemotherapy and radiation both during and after their pregnancies, while two patients received treatments after their pregnancies.

Combined Neurosurgical Intervention and Chemoradiation Therapy

Four patients had combined interventions: One patient had chemotherapy during her pregnancy followed by neurosurgical resection and chemoradiation after successful delivery of her child; the second patient received surgical resection of her metastasis during pregnancy followed by WBRT and chemotherapy after successful delivery of her child; the third patient received chemoradiation prior to neurosurgical resection followed by further resection at the time of recurrence and WBRT during her pregnancy with the successful delivery of a healthy fetus. Timing of the above interventions with maternal/fetal outcomes is summarized in Table 1.

DISCUSSION

The detection of brain metastasis during pregnancy is a rare occurrence. However, the risks surrounding the treatment of the mother’s primary tumor and metastatic disease have to be balanced against maintaining the health and viability of the fetus and those competing treatment goals pose significant challenges to the neurosurgeon.

It is estimated that 20% of cancer patients will develop brain metastases. Of these, lung (20–56%), breast (5–20%), and melanoma (7–16%) most commonly metastasize to the brain with the prevalence of renal cell carcinoma and colorectal cancer on the rise. Lung cancer is the most frequent to metastasize to the brain irrespective of gender, but breast cancer metastases are the most common occurrence in women. Risk of brain metastases also varies with age and the type of primary, with breast cancer brain metastases being reported as highest in younger patients (20–39 years of age), lung cancer brain metastases the highest in middle-aged patients (40–49 years of age), and melanoma, renal cell carcinoma, and colorectal cancer brain metastases highest in older patients (50–59 years of age). Interestingly, the increased risk of brain metastases in patients younger than 35 years of age was independent of cancer subtype, however, triple-negative or HER2-positive breast cancer subtypes were associated with a higher risk of brain metastases in patients older than 35 years of age. These epidemiologic findings highlight the need for neurosurgical guidelines for the management of patients with PASBT, as the neurological disease causes up to 25% mortality in patients with brain metastases.

Guiding Algorithms

Safe Dosing of Radiation Therapy for Brain Metastases During Pregnancy

In a general cancer patient population of male and female nonpregnant individuals, there is Level 1 evidence that surgery followed by WBRT is recommended as first-line treatment in all patients with single brain metastases with a favorable performance status and limited extracranial disease, as outlined in the 2019 guidelines put out by the Congress of Neurological Surgeons. However, SRS to the tumor bed has recently been shown to have equivalent survival outcomes and just slightly inferior local control rates, and can thus be used as an effective alternative to WBRT (median survival of SRS = 12.2 months vs. WBRT = 11.6
Table 1: Summary table of relevant cases of PASBT identified through our PRISMA search

| Study                  | Patient age, GA at diagnosis | Primary cancer diagnosis | Location of brain metastasis | Timing and treatment for brain metastases | Pregnancy outcome | Maternal–fetal outcome |
|------------------------|------------------------------|--------------------------|------------------------------|------------------------------------------|-------------------|------------------------|
| Magne et al. 2001<sup>23</sup> | 38 years                    | Lung Cancer              | Right occipital lobe         | Gross total resection during second pregnancy at 24 weeks GA with five sessions of post-op WBRT and maternal–fetal lead body shielding with thermoluminescent dosimeters. | First pregnancy: termination of pregnancy at 18 weeks GA. | Mother and infant are alive at end of the study. |
| First pregnancy, 18 weeks GA |                             |                          |                              |                                          |                   |                        |
| Second pregnancy, 24 weeks GA |                             |                          |                              |                                          |                   |                        |
| Yu et al. 2003<sup>26</sup>   | 40 years, 24 weeks GA       | Malignant melanoma       | Right occipital lobe         | Single-dose GKRS during pregnancy at 25 weeks GA. Fetal radiation doses were assessed with phantom measurements before GKRS and using thermoluminescent dosimeters during GKRS. | C-section at 34 weeks GA following GKRS. | Both mother and infant did well and experienced no complications. Child development is considered normal at 14 months follow-up. |
| Pages et al. 2010<sup>16</sup> | 28 years, 17 weeks GA       | Superficial spreading melanoma | Unknown                      | Fotenmustine during pregnancy at 17, 18, 19, 24, and 28 weeks GA; WBRT during pregnancy at 23 weeks GA. | Emergency C-section at 30 weeks GA. | Mother died 8 days after delivery. Infant is alive at 23-months follow-up. |
| 36 years, 24 weeks GA       | Superficial spreading melanoma | Unknown                      |                              | Emergency C-section at 32 weeks GA. | Mother died 2 months after delivery. Infant is alive at 2 months. |
| 34 years, 30 weeks GA       | Superficial spreading melanoma | Unknown                      |                              | Emergency C-section at 31 weeks GA. | Mother died 3.5 months after treatment. Infant is alive at 60-months follow-up. |
| Goutham et al. 2011<sup>13</sup> | 27 years, 9 weeks GA       | Malignant melanoma        | Tumor emboli to right and left temporal lobes causing malignant cerebral edema, hydrocephalus | Venticuloperitoneal shunt for hydrocephalus after termination of pregnancy. | Termination of pregnancy at 9 weeks GA. | Mother succumbed to malignant cerebral edema. |
| Spine mets at T3–T4, T8, and T10–T11 |                             |                          |                              | T4–T8 laminectomy and decompression after the termination of pregnancy. |                   |                        |
| Mandrawa et al. 2011<sup>14</sup> | 25 years, 28 weeks GA       | Breast cancer             | Left frontal cortex, right frontoparietal cortex, posterior fossa | Trastuzumab during pregnancy. Posterior fossa decompression with WBRT and SRS boost to tumor resection followed by lapatinib and capecitabine after delivery. | Forceps delivery at 37 weeks GA. | Mother and child are alive at the time of study termination. |
| Study                  | Patient age, GA at diagnosis | Primary cancer diagnosis | Location of brain metastasis | Timing and treatment for brain metastases | Pregnancy outcome | Maternal–fetal outcome |
|-----------------------|------------------------------|--------------------------|-----------------------------|------------------------------------------|------------------|------------------------|
| Gupta et al. 201415   | 24 years, 22 weeks GA       | Breast cancer            | Left thalamus and parietal cortex | Trastuzumab was held at the beginning of pregnancy. WBRT was administered during pregnancy at 22 weeks GA with external shielding followed by trastuzumab. Switched to capecitabine and lapatinib after pregnancy. | C-section at 38 weeks GA. | Infant is delivered with normal Apgar scores. Mother died from metastases 6 months postpartum. Infant is healthy at the last follow-up of 6 months. |
| Verheecke et al. 201416 | 26 years, 17 weeks GA     | Lung cancer              | Two metastases, location unspecified | Radiotherapy with vinorelbine and cisplatin during pregnancy. Cisplatin and pemetrexed after pregnancy. | Termination of pregnancy of twins at 23 weeks GA due to oligohydramnios. | Mother died 12 months after primary diagnosis. |
|                       | 25 years, 17 weeks GA      | Wilms’ tumor             | Unspecified                  | WBRT after pregnancy.                  | C-section at 30 weeks GA. | Mother and child are alive and is stable at 4 years of age. |
|                       | 34 years, 28 weeks GA      | Lung cancer              | Unspecified                  | Radiotherapy, cisplatin, and teniposide after pregnancy. | C-section at 30 weeks GA. | Mother died 10 months after primary diagnosis. Child is alive and well at the age of 14 years. |
|                       | 30 years, 26 weeks GA      | Breast cancer            | Unspecified                  | Radiotherapy during pregnancy.         | C-section at 36 weeks GA. | Local relapse 1 month after delivery, stable disease at 2 years after diagnosis. Child is alive and well. |
|                       | 41 years, 33 weeks GA      | Melanoma                 | Unspecified                  | Cisplatin, decarbazine, and vinblastine after pregnancy. Radiotherapy after pregnancy. | C-section at 33 weeks GA. | Mother died 9 years and 9 months after primary diagnosis. Child is alive and well. |
| Vetter et al. 201416  | 29 years, 25 weeks GA      | Breast cancer            | Multiple, largest 3.5 cm. cerebellar lesions with brainstem compression | Resection of cerebellar mass during pregnancy. Palliative WBRT with docetaxel, trastuzumab, and pertuzumab after pregnancy. | C-section at 30 weeks GA. | Mother and child are alive at the time of study termination. |
| Holzmann et al. 201517 | 29 years, 26 weeks GA     | Lung cancer              | Multiple supratentorial and thoracic levels 2 and 3 spinal metastases | One cycle of docetaxel and carboplatin and radiotherapy to thoracic spine during pregnancy at 27 weeks GA. Geftinib started 2 days after C-section. | C-section at 30 weeks GA. | Mother died at 17 months after primary diagnosis. Child is alive and well. |
| Okuda et al. 201618   | 35 yo, 18 weeks GA         | Recurrent breast cancer  | Initial diagnosis: left temporal lobe | Surgical resection of temporal lobe metastasis after the delivery of her first pregnancy. | C-section of first pregnancy at 36 weeks GA. | The first child is alive and well at 5 years of age. |

**Note:**
- GA: Gestational Age
- WBRT: Whole Brain Radiation Therapy
- C-section: Cesarean Section
- Apgar: Neonatal Assessment Score
| Authors         | Age    | GA      | Diagnosis               | Lesions                                    | Treatment During Pregnancy                      | Delivery Mode          | Outcome                                                                 |
|-----------------|--------|---------|-------------------------|--------------------------------------------|------------------------------------------------|------------------------|-------------------------------------------------------------------------|
| Sharma et al. 2016 | 35 years, 9 weeks GA | Breast cancer | Right frontal lobe | Capecitabine, lapatinib, temozolomide, and CKRS during pregnancy at 9 weeks GA. Cranioectomy for recurrent disease during pregnancy at 16 weeks GA. 5-FU, adriamycin, and cyclophosphamide for disease recurrence during pregnancy at 22 weeks GA. Repeat craniotomy during pregnancy at 27 weeks GA. | C-section at 32 weeks GA. | Mother and child are alive and healthy at 6 weeks follow-up. |
| Huang et al. 2017 | 37 years, 21 weeks GA | Thyroid cancer | Large scalp lesion with bony invasion | Surgical resection of scalp and skull lesion after pregnancy. | Delivered at term gestation. | Mother and child are alive and healthy at 5 months follow-up. |
| Kumagai et al. 2017 | 37 years, 18 weeks GA | Large B-cell non-Hodgkin’s lymphoma | Multiple brain and spine lesions | Chemotherapy started during pregnancy at 18 weeks GA. | C-section at 33 weeks GA. | Mother died 23 days after C-section. Infant died at 18 days postpartum. |
| Paulsson et al. 2017 | 42 years, 29 weeks GA | Breast cancer | Multiple lesions in frontal and temporal lobes and cerebellum | Craniotomy and gross total resection of frontal metastasis during pregnancy at 24 weeks GA. Post-op GKRS at 25 weeks GA with fetal dose estimation and risk assessments. | C-section at 36 weeks GA. | Mother and child are alive and well at 3.5 years follow-up. |
| Trinca et al. 2017 | 35 years, 9 weeks GA | Breast cancer | Unspecific | WBRT, SRS, Temozolomide after early termination of pregnancy. | Early termination of first pregnancy. Second child was born 2 years after primary diagnosis. | Mother and child are alive and well at 4 years follow-up. |
| Wang et al. 2017 | 19 years, 38 weeks GA | Alveolar soft tissue sarcoma | Left occipital and left cerebellar lesions | Emergency craniotomy for raised ICP and resection of cerebellar lesion after delivery. | C-section at 38 weeks GA. | Mother and child are alive and well at 10 months follow-up. |

C-section = cesarean section; CKRS = CyberKnife Radiosurgery; GA = gestational age; GKRS = Gamma Knife Radiosurgery; ICP = intracranial pressure; SRS = stereotactic radiosurgery; WBRT = whole-brain radiotherapy; 5-FU = 5-Fluorouracil.
Timing of Neurosurgical Intervention During Pregnancy

Of the 11 cases requiring neurosurgical intervention, only 1 case required emergent craniotomy to alleviate increased intracranial pressure due to tumor mass effect. Both the mother and her fetus survived the surgery and the fetus was subsequently delivered via cesarean section at 38 weeks GA. Surgery should be delayed if possible until after the first trimester to minimize miscarriage risk, which can be as high as 10.5%. However, it is generally considered to be safe during the second and third trimesters with recommended dosimetry guidelines for safety.

To compare our study results to a larger patient population, we turned to a retrospective cohort study of pregnancy-related hospitalizations between 1998 and 2009 gathered from the Nationwide Inpatient Sample (NISQIP), a database of nonfederal US hospitalizations. Here, a recent study identified 19.75 million pregnancy-associated admissions, 397 associated with malignant US hospitalizations. Here, a recent study identified 19.75 million pregnancy-associated admissions, 397 associated with malignant brain tumors, including 165 associated deliveries (44%). Surgery should be delayed if possible until after the first trimester to minimize miscarriage risk, which can be as high as 10.5%. However, it is generally considered to be safe during the second and third trimesters with recommended dosimetry guidelines for safety.

Timing of Use of Antileptic Drugs During Pregnancy

Important to the neurosurgical management of patients with supratentorial tumors is the use of antiepileptic drugs (AEDs) to manage symptomatic lesions presenting with seizures. Older generation AEDs such as valproic acid and phenobarbital have been associated with increased rates of teratogenicity and congenital malformations (up to 9.3% and 5.5%, respectively) such as cardiac defects, cleft lip/palate, neural tube defects, and dysmorphic syndromes. However, newer agents such as lamotrigine and levetiracetam (currently, the most commonly used AED in neurosurgery) have improved safety profiles for use in pregnancy with much lower reported rates of congenital malformations between 0.7% and 2.4%. Doses of AEDs should be tapered to the minimally effective dose to achieve seizure control and used for the shortest period of time possible during pregnancy.

Surgical Considerations of the Pregnant Patient During Neurosurgical Procedures

Unique challenges exist during the positioning of the patient for non-obstetric surgeries during pregnancy. Prevention of positioning injuries to mother and fetus needs to be observed and the operating table should be centered and parallel to the longest wall in the room to minimize the need for relocation prior to the patient entering the operating room. When possible, the patient should be maintained in the left lateral recumbent position using a positioning wedge to avoid a flat supine position once transferred onto the operating table with attention to the application of non-constricting safety straps to not harm, yet prevent the patient from falling off the table. A uterine displacing wedge or chests rolls should be used to reduce pressure from the pregnant uterus on the vena cava and straps across the chest are discouraged to avoid restricting respiratory effectiveness. Pressure points on the mother’s body should be well padded to prevent ulcers and peripheral neuropathies during surgery. Hypothermia should be carefully avoided (e.g. with the use of a warming blanket). Intraoperative electronic fetal monitoring past 26 weeks GA may be applied if the fetus is viable, if the monitor does not physically interfere with the procedure, if an obstetrician is available with prior consent obtained to perform an emergency C-section for fetal distress, and if the type of surgery is safe for the interruption to perform an emergency delivery if warranted.

Anesthetic Considerations for the Pregnant Patient

Important to the neurosurgical management of patients with supratentorial tumors is the use of antiepileptic drugs (AEDs) to manage symptomatic lesions presenting with seizures. Older generation AEDs such as valproic acid and phenobarbital have been associated with increased rates of teratogenicity and congenital malformations (up to 9.3% and 5.5%, respectively) such as cardiac defects, cleft lip/palate, neural tube defects, and dysmorphic syndromes. However, newer agents such as lamotrigine and levetiracetam (currently, the most commonly used AED in neurosurgery) have improved safety profiles for use in pregnancy with much lower reported rates of congenital malformations between 0.7% and 2.4%. Doses of AEDs should be tapered to the minimally effective dose to achieve seizure control and used for the shortest period of time possible during pregnancy.
Suggested Algorithm for the Treatment of Brain Metastases in the Pregnant Patient

We recently published a case series reviewing the surgical management of 104 meningioma patients during pregnancy and proposed an algorithm dividing the date of diagnosis with GA of the fetus for the surgical management of these patients into two groups.22 Using a similar algorithm based on studies in our systematic review and current literature, we propose dividing patients with PASBT into three groups in order to guide the timing of neurosurgical interventions:

1) Group A – Patients at \( \leq 13 \) weeks GA

- Surgery and/or systemic chemotherapy or radiotherapy should be delayed past the first and second trimesters if possible to prevent teratogenic effects of anesthetic drugs, chemotherapy, and radiation, as well as premature labor caused by anesthesia-induced hypotension to the placenta and uterus.
- If patients require radiation therapy, SRS is preferred over WBRT to reduce long-term neurocognitive dysfunction to the mother and congenital malformations to the fetus. Body shielding should be used to minimize radiation exposure to the fetus.
- If surgery and/or chemoradiation cannot be avoided, then a frank discussion should be had with the patient explaining adverse effects to the fetus and options including early termination of pregnancy.
- Any practical aspects of survival intervention (positioning/pinning) are usually not compromised yet in this patient subgroup, as the pregnant uterus remains small and patients can even be positioned prone without significant concerns.

2) Group B – Patients between 13 and 26 weeks GA

- The same algorithm as in Group A can be applied to Group B patients but if the patient is diagnosed or becomes symptomatic at around 26 weeks GA, the option of C-section to deliver the fetus with support in a neonatal intensive care unit should be presented to the patient prior to treatment for her symptomatic brain metastases. Here, and only if circumstances allow, the goal for initial treatment would remain to bring the baby as close to 30 weeks of GA as possible, since the relative risk reduction of infant mortality per week is greatest before that date.43
- If surgical intervention is required, the left lateral decubitus or supine position is the preferred way to perform surgery at this stage.

3) Group C – Patients at \( \geq 26 \) weeks GA

- Symptomatic patients requiring surgery and/or chemoradiation should be presented with the delivery of their fetus via C-section or forceps-assisted delivery (to avoid raised intracranial pressures that may be associated with straining during labor) prior to their neurosurgical intervention.
- Late into the third trimester, the teratogenic effects of chemotherapy and radiation exposure are much lessened and may allow for treatment of the mother without needing to deliver the fetus but risks need to be discussed with the mother.
- As above, if surgical intervention is required, the left lateral decubitus or supine position is the preferred way to perform surgery at this stage.

Finally, current advances in targeted therapies for the treatment of breast, lung, and melanoma cancers may dramatically change the way we approach the treatment of PASBT in the future. While there remains a paucity of information regarding the long-term teratogenicity of targeted therapies, the HER2-neu receptor antagonist trastuzumab has been used for the treatment of breast cancer during pregnancy.24 The BRAF inhibitor dabrafenib is classified as a category D agent and therefore contraindicated for the treatment of metastatic melanoma during pregnancy.26 Similarly, there is a lack of data pertaining to fetal safety for the EGFR inhibitor erlotinib, currently, the standard of care treatment for EGFR-mutated lung cancer in the USA,20 hence conventional standard chemotherapy remains recommended in the treatment of pregnant patients with lung cancer. We eagerly await longitudinal data using immunotherapies and other novel modalities for the treatment of brain metastases, which may be added to increase the neurosurgeon’s armamentarium in managing PABST.1

CONCLUSION

In conclusion, neurosurgical management of PABST is a challenging problem and should involve a multidisciplinary team of neuro-oncologists, anesthesiologists, obstetricians, neonatologists, and ethicists in order to fully inform the mother of the risks to herself and her unborn fetus. The increasing ability of systemic targeted therapies to effectively control a patient’s primary disease combined with research into understanding the process of brain metastasis formation will hopefully lead to novel therapies, which are both effective and safe for the health and viability of the mother and fetus.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

P.J.P, F.C.L. designed, wrote, and analyzed the data. S.S., B.C.Y., and Y.L. edited the manuscript. E.M.K. supervised, designed, and edited the manuscript.

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