Management of glioblastoma multiforme in pregnancy

A review

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Glioblastoma multiforme presenting during pregnancy presents unique challenges to the clinician. In planning treatment, potential benefits to the mother must be balanced against the risks to the fetus. In addition, evidence relating to timing of surgery and the use of radiotherapy and chemotherapy in pregnancy is limited. Management of peritumoral edema and seizures in pregnancy is also complicated by the potential for drug-related teratogenic effects and adverse neonatal outcomes on the fetus. The general anesthetic used for surgery must factor obstetric and neurosurgical considerations.

In this review article, the authors seek to examine the role, safety, and timing of therapies for glioblastoma in the context of pregnancy. This covers the use of radiotherapy and chemotherapy, timing of surgery, postoperative care, anesthetic considerations, and use of anticonvulsant medications and steroids. The authors hope that this will provide a framework for clinicians treating pregnant patients with glioblastomas.

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Key Words • pregnancy • glioblastoma • surgery • radiotherapy • chemotherapy • anesthesia • oncology

The annual global incidence of primary malignant brain tumors in women is 2.6/100,000.2 The incidence has been reported to be slightly lower in pregnant women, but the relative frequencies of each brain tumor type appear similar.35 In both groups, gliomas feature as the most prevalent histological type. Regardless, management of pregnant patients with gliomas presents unique challenges, with potential ramifications of treatment on outcome for the mother and her offspring. Ethical, philosophical, and religious persuasions of patients factor heavily in the decision-making process. There is little guidance or suggestion in the literature of how to manage such patients and of the peculiar considerations.

This review article seeks to examine the role, safety, and timing of treatment modalities for glioblastoma in the context of pregnancy. These include neurosurgery, radiotherapy, chemotherapy, postoperative care, neuroanesthesia, and use of anticonvulsant medications and steroids. We hope that this will provide a framework in planning treatment and a stimulus for further work.

Abbreviations used in this paper: AED = antiepileptic drug; ICP = intracranial pressure; NOAEL = no observable adverse effect level.

Radiation Exposure in Pregnancy: Radiotherapy and CT Scanning

Investigation and management of suspected and confirmed intracranial malignancies are heavily dependent on imaging modalities, such as CT scanning and MRI. Treatment of cancerous tumors often entails deliberate exposure to ionizing radiation. In the context of pregnancy, fetal exposure to ionizing radiation needs to be considered.

Deleterious effects of ionizing radiation on the conceptus relate to the fetal-absorbed dose and gestational age.3 The dose absorbed by the fetus depends on the maternal site irradiated. For instance, CT scans of the abdomen and pelvis involve direct irradiation of the fetus. More remote imaging, such as of the head, entails negligible direct irradiation and is related to internal scatter. Therefore, the site irradiated, imaging modality, dose, and maternal factors such as weight determine the fetal-absorbed dose.

Risks to the fetus include in utero death, malformations, retardation of growth and cognition, and oncogenesis.3 Carcinogenesis is the only stochastic phenomenon; the remaining are threshold, that is, the effect is only seen...
above a threshold dose. Evaluations of fetal toxicity on exposure to ionizing radiation have drawn on data from epidemiological and animal studies. Developing embryos pass through the following 3 stages: preimplantation, organogenesis, and fetal growth (fetogenesis), with specific sensitivities to the effects of radiation.

Preimplantation exposure data are based on animal studies, as the human preimplantation embryo cannot be detected by current assays. Overexposure is lethal, and embryos that survive are generally free from any abnormalities. This reflects the fatal consequences of genetic change at this stage and the omnipotent capacity of remaining cells to repopulate all damaged tissue. The only exception in the literature seems related to radiation-induced genome instability in genetically susceptible rats. Similarities in dose-response relationships for lethality and chromosomal damage suggest radiation-induced cytogenetic damage as the cause of death. The NOAEL in rats is roughly 0.15–0.2 Gy during preimplantation and increases throughout gestation.

Epidemiological studies of diagnostic exposure to irradiation failed to disclose a risk of congenital malformations. However, there are historical cases of malformation induction after gynecological radiotherapy. Current understanding and dose thresholds have been extrapolated from rodent experiments. Exposure during critical periods of organogenesis produces congenital anomalies in rodents, corresponding to the developmental phase of the organ or tissue involved. The NOAEL is 0.2 Gy in the rat during its most vulnerable stage (9 days postconception) and increases throughout gestation. Growth retardation, defined as a decrease in weight for gestational age, is observed in rodents with a threshold of 0.25 Gy during early organogenesis, and again increases with age postconception.

Neurological and cognitive outcome of in utero irradiation has been addressed by many studies examining the cohort of patients exposed to the atomic bombings at Hiroshima and Nagasaki. Borne out of these studies was an observed increase in frequency of mental retardation and decreased school performance and IQ scores. A weaker association with seizure disorders has been reported. These outcomes are limited to exposure during 8–25 weeks postconception, with particular sensitivity from 8 to 15 weeks. The regenerative capacity of remaining neurons and exclusion by embryonic death during Weeks 0–7, and radiodestruction from Weeks 26 to 40, is thought to account for the observed lack of effect during these periods. Limitations of the studies include crude outcomes measures such as a clinically defined mental retardation, the limited number of individuals exposed to high doses of irradiation, and reliance on a single study, the Japanese atomic bomb study. Factors such as maternal illness due to radiation exposure and higher rates of consanguinity and changes in physical environment closer to the epicenter have the potential to confound or bias the results, respectively. However, the observed severity and association with critical periods of susceptibility suggest a genuine effect. Contention surrounds the nature and dose relationship of neurobehavioral response to ionizing radiation. In Wistar rats, exposure to 0.2 Gy midgestation does not lead to behavioral differences compared with controls. However, a delay in acquisition of 1 reflex at 0.2 Gy has been noted. While many authors argue that it is not possible to determine if the effects of radiation on neurological/behavior outcome are stochastic or deterministic, based on epidemiological studies, Brent argued that a stochastic phenomenon is biologically implausible, given the lack of histological changes compared with brains in control animals with low-level exposure and the lack of any neurological/behavioral sequelae in animal exposure in utero midgestation below 0.2 Gy.

Contention surrounds the issue of increased postnatal incidence of malignancy after in utero radiation exposure. An increase in death due to childhood leukemia prompted a nationwide case-control study of deaths due to leukemia and other cancers in childhood. The authors reported 2-fold greater rates of abdominal x-ray exposure in mothers of children with leukemia and solid cancer compared with controls. Further case-control studies have reported similar associations with in utero exposure to diagnostic radiation and risk of leukemia and solid cancer.

Whether such an association of low-level intrauterine radiation exposure and childhood cancer reflects a causal relationship is still contested. Arguments in favor of low-level intrauterine radiation-induced oncogenesis include the following: consistency of the association of low-level in utero radiation exposure and childhood solid malignancy and leukemia across many case-control studies, a dose-response relationship with higher relative risks associated with increasing number of x-ray examinations, and a dose-response relationship with a reduction in risk noted for cohorts experiencing reduced fetal doses of irradiation per x-ray examination. Furthermore, lack of identification of potential confounding factors, exclusion of recall bias by studies examining medical case records, and similar findings in studies of twins, suggesting selection bias does not contribute to the findings (as twin pregnancies in these studies presumably underwent x-ray imaging to determine fetal position, rather than because of maternal illness that might predispose the child to malignancy), lend credence to this contention. Grounds for uncertainty in a causal relationship are raised by the following points: larger cohort studies not demonstrating an elevated risk with low-level intrauterine radiation exposure; poor corroboration from animal studies; lack of excess cases of cancer deaths in in utero–exposed atomic bomb survivors; lower risk of cancer in twin pregnancies with more frequent x-ray imaging; and suspicious elevation in risk of solid cancers in utero compared with postnatal exposure and perplexing similarity in risk of solid cancers and leukemia given the known difference in radiosensitivity of tissues.

Whatever the uncertainty regarding oncogenic risk of low-level irradiation on the fetus, the predicted increase in risk is small in comparison with other risk factors, for example, being the sibling of a child with leukemia. As Brent highlighted, the increased leukemia risk associated with 0.02-Gy fetal exposure would be 1 in 2000 compared with 1 in 3000 for unexposed controls. Exposure after 3–4 weeks of gestation is associated with a doubling of childhood cancer risk with 25 mGy, which equates to
an excess absolute childhood cancer risk coefficient of 1
in 13,000 per milli-Gray of exposure.49

The typical fetal dose from a head CT scan is 0.001–
0.01 Gy.49 Mazonakis et al.26 estimated fetal doses follow-
ing irradiation of a “brain tumor” in a phantom preg-
nancy model with a linear accelerator (Philips SL 75/5).
For a cumulative isocenter dose of 65 Gy, the maximum
fetal absorbed dose was 80.9 mGy (0.089 Gy) in a 24-
week gestation unshielded phantom. Haba et al.16 es-
timated fetal dose after tumor exposure of 54 Gy with
Varian and Asea Brown Boveri linear accelerators. The
fetal absorbed dose without abdominal shielding was 22
mGy (0.022 Gy) for the Varian unit and 490–590 mGy
(0.49–0.59 Gy) for the Asea Brown Boveri unit.

In summary, doubt regarding safe threshold doses for
deleterious effects is reflected by the reluctance to pub-
lish explicitly safe doses and conflicting quoted dosages.
Brent3 quoted 0.2 Gy as the threshold for deterministic
effects such as congenital malformations, pregnancy loss,
and retardation of growth and cognition. The internation-
al commission for radiation protection concluded that no
deterministic effect of practical significance would occur
below 0.1 Gy.2 Given the fetal doses quoted in the afore-
mentioned studies, it is likely, with an appropriate linear
accelerator and use of precautionary measures such as
abdominal shielding, that radiotherapy could be admin-
istered without an elevation in risk of deterministic ef-
facts. At present, it is not possible to exclude an increase
in the risk of childhood cancer. Assuming this is the case,
the risk associated with some linear accelerators maybe
double that background risk.

Misperception of the risks of fetal ionizing radiation
exposure could alter the management of pregnant patients
with malignant gliomas. Typical fetal doses from CT head
scans are below the NOAEL; however, MRI as a safer al-
ternative renders this modality redundant in an elective
setting. This should not discourage use in the context of
an emergency. Radiotherapy should be considered after
formal estimation of fetal absorbed dose and discussion
with the family. Conveying uncertainty in current under-
standing of radiation-induced fetal toxicity is a challeng-
ing but critical facet in counseling patients.

Chemotherapy for Brain Tumors

Evidence on use of chemotherapy in pregnancy is
limited, particularly with regard to primary brain neo-
plasms, and is based in large part on animal data. Most
chemotherapeutic agents are generally smaller than 600
kD and can easily cross the placenta.33 Physiological
changes including increased hepatic oxidation and renal
clearance, as well as decreased serum levels of drug bind-
ing to albumin, complicate pharmacokinetic and phar-
macodynamic relationships in pregnancy. This makes
predictions of toxicity and efficacy difficult. In general,
exposure during organogenesis can precipitate major
malformations, spontaneous abortion, and intrauterine
fetal death.4

Use of chemotherapy during the second and third tri-
imesters can result in intrauterine growth retardation, low
birth weight, premature delivery, and stillbirth. The CNS,
hematological system, genitalia, and eyes remain suscep-
tible to the effects of chemotherapy, with consequential
neonatal myelosuppression, sterility, and neurobehavioral
disorders.4

The pivotal trial by the European Organization for
Research and Treatment of Cancer (EORTC) and the Na-
tional Cancer Institute of Canada (NCIC) demonstrated
substantial survival benefits in patients treated with ra-
diotherapy and concomitant and adjuvant temozolomide,
compared with radiotherapy alone.41

No articles relating to use of temozolomide in preg-
nancy were found in a PubMed search. The use of car-
mustine (BiCNU)—containing Gliadel wafers in preg-
nancy has not been reported. However, given that studies sug-
gest practically undetectable levels in the circulation, this
would presumably have little effect on the conceptus.33

Given the lack of data, recommendations on the use
of chemotherapy during pregnancy are difficult. Frank
discussion regarding potential adverse outcome and un-
certainty should take place with the patient in conjunction
with an oncologist.

Timing of Surgery and Delivery in Pregnancy

No clear evidence exists on the exact timing of neu-
rosurgical intervention in pregnant patients. Authors of
case series have considered surgery and delivery in rela-
tion to severity of neurological symptoms and gestation.
After reviewing the literature, Tewari et al.43 made the
following recommendations. In stable patients present-
ing in the first or early second trimester, with no evidence
of neurological deterioration, gestational advancement
should be permitted to the early second trimester before
neurosurgery and radiotherapy. Unstable patients with
impending brain herniation require neurosurgery and
should be forewarned of the risk of fetal loss.

In patients in their late second trimester and third
trimester, Tewari et al. recommend that surgery should
be avoided because of the high risk of intracranial hem-
orrhage associated with increased maternal intravascular
volume. Stable patients should be observed closely with
gestational advancement to fetal maturity. In patients
with progressive neurological deficit, radiotherapy may
be considered. For patients who are clinically unstable
with a risk of brain herniation, delivery of the child by
cesarean section under general anesthesia with subse-
quent neurosurgical decompression during the same an-
esthetic was recommended. A vaginal delivery is possible
but should be reserved for those patients who are stable.
A short second stage of labor is important, given the in-
crease in ICP with bearing down efforts.43

Lynch et al.24 advised operative intervention for all
cases of malignant glioma regardless of gestation period
to maximize tumor resection at presentation.

Given the increased risk of miscarriage associated
with surgery in the first trimester and the suggestion in
the literature of an increase in risk of birth defects (al-
though not significant), we suggest that surgery should be
delayed when possible until the early second trimester.5
Most obstetricians and neonatologists would defer deliv-
er when possible to 32 weeks of gestation to ensure fetal
maturity and survival.
Postoperative Management of Pregnant Neurosurgical Patients

After craniotomy, attention should be paid to adequate analgesia, antiemesis, and thromboprophylaxis. Pain control is achieved through a combination of scalp infiltration with local anesthesia, opioids, and paracetamol. Given tramadol’s propensity to lower the seizure threshold, it should be used cautiously in neurosurgical patients. Sudheer et al. demonstrated better analgesia with use of a morphine patient-controlled analgesia pump compared with codeine or a tramadol patient-controlled analgesia pump, without adverse respiratory effects, excessive sedation, or vomiting. Promethazine is the most studied antemiotic in pregnancy and is safe. Metoclopramide and antihistamines such as cyclazine are also safe in pregnancy as antiemetics. In younger women, however, there is a risk of extrapyramidal side effects and oculogyric crises. Ondansetron also appears to be effective, and there have been no reports of teratogenicity.

Pregnant patients are hypercoagulable, especially following an operation. Venous thromboembolism is the most frequent cause of direct maternal death. Nonpharmacological thromboprophylactic measure should always be instituted. Timing of pharmacological thromboprophylaxis should be discussed with the neurosurgical team, given the attendant risks of intracranial hemorrhage.

Specific Anesthetic Considerations in Pregnant Patients Undergoing Neurosurgery

Anesthesiology in pregnancy must take into account that any change in maternal physiology will have an impact on uteroplacental perfusion and fetal gas exchange. In addition, the anesthetist must be cognizant of the myriad of physiological changes in pregnancy. Close liaison between the obstetrician and neuroanesthetist is required. Most agents used for induction and maintenance of general anesthesia are not known to be teratogenic. General considerations for anesthesia in pregnant patients undergoing nonobstetric operations have already been covered in several review articles.

During labor, blood pressure and ICP may increase during contractions. First-stage contractions can increase ICP by 31 cm H2O, and second-stage contractions can increase ICP by 71 cm H2O in patients with no intracranial masses. Pregnant patients with intracranial neoplasms may experience greater increases in ICP. Sudheer et al. demonstrated better analgesia with use of a morphine patient-controlled analgesia pump compared with codeine or a tramadol patient-controlled analgesia pump, without adverse respiratory effects, excessive sedation, or vomiting. Promethazine is the most studied antemiotic in pregnancy and is safe. Metoclopramide and antihistamines such as cyclazine are also safe in pregnancy as antiemetics. In younger women, however, there is a risk of extrapyramidal side effects and oculogyric crises. Ondansetron also appears to be effective, and there have been no reports of teratogenicity.

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Use of Anticonvulsants

Epilepsy is a common feature of patients with brain tumors. First presentation with seizures is seen in 30%–50% of patients. Electrical quiescence of the primary lesion suggests epileptogenesis in the adjacent cortex. Seizure incidence relates to tumor type and location. Primary brain tumors manifest with seizures more fre-
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...quent than metastases. Cortical location is predictive of epilepsy, and frontal and temporal lobe tumors have the highest risk of epilepsy. Van Breemen et al. highlighted the difficulties in managing epilepsy in the context of brain tumors. These include the refractory nature of the seizures, adverse cognitive outcomes to the patient, and interactions between AEDs, chemotherapeutic agents, and corticosteroids.

The choice of anticonvulsant in the context of brain tumors during pregnancy is difficult. Few studies have compared AED efficacy in patients with brain tumors, let alone in the context of pregnancy. Wick et al. examined seizure recurrence in 104 patients with low- and high-grade gliomas. Seizures recurred less frequently with valproate (44%) than lamotrigine (51%) or carbamazepine (70%). Optimal treatment may not differ from other causes of simple or complex partial seizures. However, drug interactions with chemotherapeutic agents and fetal toxicity need to be considered. Carbamazepine and valproate have a higher propensity to interact with chemotherapeutic agents and corticosteroids than lamotrigine. Villanueva et al. recommend the use of newer AEDs such as levetiracetam, gabapentin, and pregabalin as first-line agents, given their favorable pharmacokinetic characteristics, that is, they are not enzyme inducers or inhibitors. However, evidence on use in pregnancy is less extensive for these agents. Lamotrigine, oxcarbazepine, topiramate, and zonisamide do not influence, but are influenced by, chemotherapeutic agents. Altered metabolism during pregnancy should also be kept in mind with close monitoring of therapeutic levels of anticonvulsants.

The choice of AED in women of childbearing age is very important. Delterious effects to offspring, in the form of teratogenesis and poor perinatal and long-term cognitive outcomes, warrant consideration in pregnant patients with brain tumors.

It is now well established that there is an increased risk of major congenital malformations in the babies of women with epilepsy who take AEDs. Polytherapy confers a greater risk than monotherapy. Sodium valproate confers the greatest risk and in particular increases the risk of neural tube defects. Carbamazepine, lamotrigine, and levetiracetam are associated with the lowest risk. Phenytoin, phenobarbitone, and topiramate also influence the risk. The risk of major congenital malformations is influenced not only by the type of AED but also by dose, which should be taken into account in the management of epilepsy in women of childbearing potential, and, therefore, limiting the dose of AEDs, if possible, is advised.

There is now also evidence that AED use during pregnancy may increase the risk of cognitive impairment in the baby. Valproate exposure increases the risk of poor cognitive outcome, while phenytoin and phenobarbital likely also increase the risk. Carbamazepine is probably not associated with increased risk. Levetiracetam and lamotrigine have not been found to be associated with an increased risk of poor cognitive outcome. Again, polytherapy likely increases the risk compared with mono-therapy.

In their special report, Harden et al. reported a probable increase in the risk of being small for gestational age in women taking AEDs and a possible risk of a 1-minute Apgar score of less than 7. They concluded that perinatal death was not likely increased with AEDs.

Decisions regarding AEDs in pregnant patients with brain tumors should be multidisciplinary, involving oncologists and neurologists with an interest in epilepsy, and should factor in the use of chemotherapy and other medications. Lamotrigine, levetiracetam, and carbamazepine are the safest agents for the developing baby and should be used as first-line therapy, if possible. Moreover, polytherapy should be avoided if possible.

Prophylaxis with anticonvulsants in patients with brain tumors has been suggested, given the high incidence of seizures. The Quality Standards Subcommittee of the American Academy of Neurology made the following point: the incidence and severity of anticonvulsant side effects are greater in the population of patients with brain tumors. Antiepileptic drugs can interact with corticosteroids and chemotherapeutic agents, reducing their efficacy. Conversely, corticosteroids and chemotherapeutic agents can alter the pharmacokinetics of AEDs, increasing the likelihood of over- and underdosing. Adverse effects are not offset by benefit in terms of seizure reduction. On this basis, the committee did not recommend routine use of anticonvulsant medication for prophylaxis in patients with brain tumors. In the context of pregnancy, one should also be cognizant of potential adverse fetal outcome. Evidence on the use of prophylactic AEDs in patients undergoing craniotomy is conflicting. In their meta-analyses, Sirven et al. found no benefit of AEDs in the 1st postoperative week with regard to seizure reduction. The aforementioned committee highlighted the lack of evidence in perioperative use of anticonvulsants. The quality of evidence available prompted the committee to limit its recommendation to the withdrawal of therapy after 1 week postprocedure.

However, once commenced for seizures, AEDs should be continued, depending on life expectancy, frequent recurrence despite medication, and inadequate evidence regarding withdrawal of anticonvulsants in brain tumor patients.

**Steroids in Pregnant Patients**

Steroids are commonly used in patients with gliomas to reduce peritumoral edema. They also permit expedited delivery in preterm pregnant patients by promoting fetal lung maturation, reducing the risk of intraventricular hemorrhage, and decreasing mortality in preterm infants. A Cochrane review reported that in women at risk for preterm birth treated with a single course of corticosteroids, there was a significant reduction in neonatal death, respiratory distress syndrome, and intraventricular hemorrhage. The Royal College of Obstetricians and Gynaecologists’ green top guideline number 7 suggests offering a single course of antenatal corticosteroids in women at risk for spontaneous or iatrogenic preterm birth between 24 weeks and 34 weeks and 6 days. The guideline also advises administering antenatal corticosteroids in an elective cesarean section prior to 38 weeks.
and 6 days. The corticosteroids of choice are 2 doses of betamethasone 12 mg intramuscularly or 4 doses of dexamethasone 6 mg intramuscularly. While dexamethasone is commonly used for neurosurgical patients, observational data suggest that betamethasone may be preferable in reducing neonatal mortality.23

Evidence on repeated antenatal steroid administration and outcome in pregnant glioma patients is lacking. However, repeated antenatal steroid administration in nonneurosurgical pregnant patients is discouraged based on a body of evidence of adverse short- and long-term outcomes to the child. Animal studies have suggested that steroids cause decreased birth weight, decreased brain weight and myelination, and hypothalampituitary adrenal axis suppression with repeated administration of antenatal corticosteroids.30 However, these findings have not been corroborated in human studies. There is evidence from randomized trials of reduced birth weight, length, and head circumference in infants delivered from mothers receiving multiple doses of antenatal corticosteroids compared with those receiving a single dose.29 These findings have not been consistently reproduced in other trials.23 However, Schatz et al.37 reported significantly higher frequencies of preterm birth and low birth weight in mothers treated with oral corticosteroids for asthma, even after adjusting for relevant covariables. In addition, long-term follow-up in one trial reported no difference in body size between repeated- and single-dose treatment arms.6 Studies on long-term neurodevelopmental outcome and possible hypothalampituitary axis suppression are conflicting and incomplete.23 The Royal College of Obstetricians and Gynaecologists advises against a repeat course of antenatal corticosteroids for obstetric indications, unless the first course was administered prior to 26 weeks of gestation, in which case senior advice should be sought.36

Outcomes with steroid use in early pregnancy or preconception are less clear. Other adverse effects of steroids, including myopathy, osteoporosis, peptic ulceration, weight gain, increased risk of thromboembolism, glaucoma, skin changes, immunosuppression and exogenous Cushing’s syndrome are well described and covered in other reviews.22,51 All patients should be covered with pharmacological gastric protection.

Clear communication of potential risks to mother and offspring, the uncertainty in current understanding, and poor outcome to mother and unborn child by avoidance of steroids should be made before commencing steroids for peritumoral edema. This should be done in conjunction with or following discussion with an obstetrician and neonatologist.

Conclusions

The literature on treatment of glioblastoma multiforme in pregnancy is limited to case reports and case series. Risks and benefits of treatment are largely extrapolated from animal studies, or epidemiological and observation studies of pregnant patients without glioblastoma multiforme. However, based on the discussion above, we make the following recommendations regarding the management of pregnant patients who present with a suspected glioblastoma. We emphasize that this advice represents Level 3 evidence, that is, expert opinion.

Initial investigation of the stable patient should entail an MRI scan when facilities permit. In unstable patients for whom MRI facilities are not easily accessible, a head CT scan would not place the fetus at increased risk of deterministic effects (for example, in utero death, malformations, and retardation of growth and cognition), although patients must be counseled on the potentially increased risk of childhood cancer.

In stable patients in their first trimester, delaying biopsy or debulking until the second trimester should be considered. For patients in their late second and third trimesters who are clinically stable, gestational advancement until fetal maturity should be considered when possible, with delivery prior to neurosurgical treatment. Stable patients who are at term can deliver prior to neurosurgery. Vaginal delivery with special attention to adequate pain relief and a shortened second stage can be attempted in selected cases.

Steroids can be used to control peritumoral edema; however, the future parents must be forewarned of the risks reported in some studies of low birth weight and body size, highlighting the uncertainty regarding this in the literature.

Anticonvulsants for seizure prophylaxis should not be routinely prescribed perioperatively. In patients who do suffer seizures, lamotrigine, levetiracetam, or carbamazepine would be appropriate first-line agents. The decision regarding the use of anticonvulsant medication should be made in conjunction with neurologists and oncologists, and factor in use of other potentially interactive medications and chemotherapeutic agents.

Future parents should be counseled on the benefits and risks of radiotherapy. In communicating risks, the lack of data in pregnant women with glioblastoma should be clarified, along with the fact that current recommendations are based on animal studies and epidemiological studies. However, current evidence and recommendations would suggest that with suitable equipment the fetal-absorbed dose may be kept below the NOAEL for deterministic effects. There is uncertainty in the risk of childhood cancer and leukemia; however, in comparison with other risk factors for childhood cancer and leukemia, this would seem small. Consideration should be given to attempting calculation of the potential fetal-absorbed dose for the patient. There is limited evidence to make recommendations on the use of chemotherapeutic agents such as temozolomide in pregnancy.

In patients with neurological deterioration, further radiological investigation should be considered, and the use of radiotherapy should be discussed, if necessary. At all gestational periods, unstable patients should undergo neurosurgery if clinically appropriate for the mother. In patients with a fetus at a viable age, a combined cesarean section followed by craniotomy should be considered.

Decisions regarding management of the pregnant patient with glioblastoma should involve neurosurgeons, neurologists, oncologists, obstetricians, and anesthetists with experience in obstetrics and neurosurgery. The ad-
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vice of pediatricians and neonatologists should also be sought when delivery is considered. Each case should be coordinated in a multidisciplinary fashion with a team-based approach. Early involvement of palliative care teams may be beneficial. Counseling patients and conveying risks of therapy with the inherent uncertainty in the literature are challenging but critical in permitting patients to make informed decisions regarding their treatment.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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