Pregnancy and glial brain tumors


Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas (S.Y.-K., J.F.d.G., M.D.A., C.A.C., M.R.G., T.S.A.); Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas (D.L., J.W., Y.Y.); Department of Gynecologic Oncology and Reproductive Medicine, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas (A.M.)

Corresponding Author: Shlomit Yust-Katz, MD, Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 431, Houston, Texas, 77030 (syust@mdanderson.org).

Background. Improvements in brain tumor treatments have led to an increase in the number of young women with brain tumors who are now considering pregnancy. The aim of this study is to evaluate the influence of pregnancy on brain tumor biology.

Methods. In this institutional review board-approved retrospective study, we searched the institution’s database for patients with glial brain tumors who were pregnant at the time of diagnosis or became pregnant during the course of their illness. We identified 34 such patients and reviewed their charts to determine each patient’s clinical course and pregnancy outcome.

Results. Fifteen patients were diagnosed with a primary brain tumor during pregnancy: 3 with glioblastomas, 6 with grade III gliomas, and 6 with grade II gliomas. Pregnancy was terminated in only 2 of these patients, and the remainder delivered healthy babies. Twenty-three patients became pregnant after diagnosis (4 patients were pregnant at diagnosis and again after diagnosis). Of the patients who became pregnant after diagnosis, the 5 with grade I tumors had stable disease during and after pregnancy. However, of the 18 patients with grade II or III gliomas, 8 (44%) had confirmed tumor progression during pregnancy or within 8 weeks of delivery.

Conclusions. In contrast to grade I gliomas, the tumor biology of grades II and III gliomas may be altered during pregnancy, leading to an increased risk of tumor progression. These findings support the need for increased tumor surveillance and patient counseling and for additional data collection to further refine these results.

Keywords: brain tumors, pregnancy.

The annual incidence of primary malignant brain tumors in women in the United States is 2.6 per 100,000; glioma is the most prevalent histological type. The reported incidence of primary brain tumors in pregnant women is slightly lower, but the relative frequencies of each brain tumor type appear to be similar for pregnant and nonpregnant women. Overall improvements in brain tumor treatments, particularly for the lower-grade gliomas, have resulted in overall better prognosis for patients with these tumors. As a result, a higher percentage of patients, particularly young adults, have sustained periods of disease control. This has led to an increase in the number of young women with brain tumors who are now considering pregnancy. Unfortunately, only small case series and a limited number of reports have addressed the impact of pregnancy on brain tumor growth.

In 2 retrospective case series of patients with grade II glioma, one study suggested that tumor growth accelerated during pregnancy. The increased growth rate was associated with a higher frequency of seizures. In the second case series, clinical worsening and increases in tumor growth and grade were seen in 6 of 8 pregnant patients. These small case series provided insight into the potential impact of pregnancy on glioma growth and transformation to higher-grade tumors. An additional retrospective study evaluated the outcomes of pregnancy in patients with brain tumors and concluded that the tumors adversely affected pregnancy outcomes; for example, the patients had a higher rate of cesarean delivery than expected. This study also included patients with meningiomas and pituitary tumors, potentially limiting the applicability of these conclusions to patients with...
malignant gliomas. In another study, pregnancy was shown to accelerate tumor growth in patients with meningiomas.10 The concern that pregnancy may affect tumor biology stems from the observation that multiple hormones and growth factors produced during pregnancy and fetal development also enhance tumor growth. For example, fetal development requires the production of angiogenic factors such as placental growth factor, a well-established angiogenic factor in gliomas.

The aim of this retrospective review was to provide additional information about the influence of pregnancy on outcomes in patients with primary brain tumors.

Materials and Methods

After securing institutional board review approval (protocol PA12-0992), we queried The University of Texas MD Anderson Cancer Center Department of Neuro-Oncology Longitudinal Patient Database for patients diagnosed with gliomas between 1995 and 2012 who were pregnant at some point during the course of their illness.

Data collected included demographic characteristics (date of birth, race, date of death, age), tumor characteristics (histologic type, WHO grade, location, results of imaging studies), cancer treatments (including extent of surgery, radiation, and chemotherapy administered), and clinical characteristics (comorbid conditions, concomitant medications, pregnancy date and outcome, clinical course during the pregnancy, and date of disease progression, death, or last follow-up).

Patients were classified into 2 groups: those who were pregnant at the time of the brain tumor diagnosis (ie, onset of presenting symptoms during pregnancy or within 2 weeks after delivery) and those who became pregnant after diagnosis.

Statistical Analysis

Data were summarized using standard descriptive statistics and frequency tabulation. The time-to-event endpoints, including overall survival, were estimated using the Kaplan–Meier method.11 All computations were carried out using SAS 9.2 (SAS Institute) and R 3.0.1 (http://www.r-project.org) software.

Results

We identified records for 34 women with glial brain tumors who were pregnant at some point during the course of their illness. An additional 2 patient records had incomplete data and were not included in the analysis. Six of the 34 patients were pregnant twice during the course of their illness (4 were pregnant at the time of their tumor diagnosis and afterwards). Therefore, a total of 40 pregnancies were evaluated.

Patients Pregnant at Time of Diagnosis

Fifteen patients presented with a brain tumor while they were pregnant or immediately afterward. Three of these tumors were diagnosed as glioblastoma multiforme (GBM), 6 as grade III glioma, and 6 as grade II glioma (Table 1 and Supplemental Table 1). The most common presenting symptom related to the tumor was seizures. The presenting symptom occurred at a median 13 weeks of pregnancy. The time at which the presenting symptom occurred ranged from 0 weeks of pregnancy to 4 weeks after delivery. (The lower range was 0 because one patient had a seizure before pregnancy; however, her symptoms progressed, and she was diagnosed while she was pregnant.) These patients underwent surgery and pathological diagnosis at a median 17 weeks of pregnancy; this time ranged from 4 weeks of pregnancy to a year after delivery.

Ten patients underwent surgery during pregnancy, and 3 of these patients underwent brain biopsy. One patient diagnosed with GBM had an urgent surgery. One patient with GBM received radiation therapy during pregnancy, and none were treated with chemotherapy.

Two patients (one with GBM and one with a grade III anaplastic astrocytoma) terminated their pregnancy; the rest delivered healthy babies. Of the 15 women diagnosed with brain tumors during pregnancy, 7 underwent cesarean sections, 3 had vaginal deliveries, and the method of delivery was unknown for 3. Of the 3 patients who underwent vaginal delivery, 2 underwent tumor resection before delivery, and the third was diagnosed only after delivery. Of the patients who underwent cesarean section, one patient with GBM underwent surgery and radiation therapy during pregnancy, 2 underwent biopsy, and 3 had no treatment during pregnancy. Six of the 7 cesarean sections were performed at term. One patient, who had GBM, underwent cesarean section at 32 weeks gestation because the fetus developed intrauterine growth retardation.

Four women had a second pregnancy during the course of their illness. The mean time between first and second pregnancies was 2.5 years (median, 1.25y). Three of these patients’

Table 1. Characteristics of patients who were pregnant at the time of brain tumor diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. patients (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>30 (24 – 38)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
</tr>
<tr>
<td>Treatment during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>10 (3 biopsies)</td>
</tr>
<tr>
<td>Biopsy only</td>
<td>3</td>
</tr>
<tr>
<td>Radiation</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>5</td>
</tr>
<tr>
<td>Delivery method</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>7</td>
</tr>
<tr>
<td>Vaginal</td>
<td>3</td>
</tr>
<tr>
<td>Abortion</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Outcome of pregnancy</td>
<td></td>
</tr>
<tr>
<td>Healthy infant</td>
<td>12</td>
</tr>
<tr>
<td>Malformations</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Patient’ vital status</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
</tr>
<tr>
<td>Alive</td>
<td>10</td>
</tr>
<tr>
<td>Median follow-up (range), y</td>
<td>4.7 (0.2 – 8.1)</td>
</tr>
</tbody>
</table>
disease progressed after the second pregnancy, and one patient whose disease progressed died. The fourth patient was alive with stable disease at the time of analysis.

At the time of this analysis, 5 patients had died, and 10 remained alive. The estimated median overall survival for patients who were diagnosed while pregnant varied by tumor grade. For patients with grade II tumors, the median overall survival could not be determined because 5 of the 6 patients were still alive (95% CI, 6.1y–not applicable [NA]; range, 1.8y–8.1y). The median overall survival durations were 4.7 years (95% CI, 1.9 y–NA; range, 0.2y–10.9y) for patients with grade III tumors and 4.6 years (95% CI, 2.0y–NA; range, 0.27y–9y) for patients with GBM.

**Patients Pregnant after Diagnosis**

There were 23 patients who became pregnant after their glioma diagnosis. The median time from tumor diagnosis to pregnancy was 12 months (range, 2mo–90mo). Two patients were pregnant twice after diagnosis. Five patients had grade I tumors, 9 had grade II tumors, and 9 had grade III tumors. We did not find patients with GBM who became pregnant after diagnosis.

In the patients who became pregnant after their glioma diagnosis, the grade I tumors were gangliogioma (n = 2), pilocytic astrocytoma (n = 2), and dysembryoplastic neuroepithelial tumor (n = 1). Complete resection of the tumor was achieved in 3 of these patients before pregnancy, and partial resection with nonenhancing residual disease was achieved before pregnancy in 2 (one with a dysembryoplastic neuroepithelial tumor and one with a pilocytic astrocytoma). All 5 women had stable disease when they became pregnant, and their disease remained stable during pregnancy. One of the patients with gangliogioma was pregnant twice after diagnosis. At the time of this analysis, all patients with grade I gliomas were alive and without tumor progression (median follow-up, 4y; range, 2.5y–7y). In this cohort, the mean time from tumor diagnosis to pregnancy was 1.4 years (median, 1y; range, 0.25y–2.5y).

There were 18 patients with grade II or III glioma who became pregnant after diagnosis (Table 2, Supplementary Table 2). Eight (44%) of these patients, 5 with grade II tumors and 3 with grade III tumors, were found to have tumor progression either during or immediately after pregnancy (up to 8 weeks after pregnancy). Importantly, 4 of these 8 patients underwent surgery during or immediately after pregnancy and were found to have a higher-grade tumor (Table 2). Only one patient, whose disease progressed during pregnancy, had tumor progression before pregnancy (3 years before pregnancy); the rest of these patients had stable disease before pregnancy occurred. Although there was no association between tumor grade and likelihood of recurrence, the extent of original tumor resection corresponded with recurrence risk. All the patients whose disease progressed during or immediately after pregnancy had only a biopsy or partial resection at diagnosis; whereas, among the patients without disease progression during or immediately after pregnancy, 5 had gross total resections and 4 had subtotal resections. All patients who underwent gross total resection remained stable during pregnancy. The extent of resection was unknown for one patient.

Six of the patients whose disease progressed during or immediately after pregnancy had significant tumor contrast enhancement on imaging after progression (3 of these had faint enhancement before progression).

There was no difference (P = .7901) in the median time from diagnosis to pregnancy between patients whose disease progressed during or immediately after pregnancy (median, 12mo; range, 2mo–90mo) and those whose disease remained stable (median, 18mo; range, 3mo–72mo).

Neurological symptoms indicated disease progression in 5 of the 8 patients with disease progression during or immediately after pregnancy. In the other 3 patients, disease progression was found on surveillance imaging. None of the patients with stable grade II or grade III tumors experienced any new neurological symptoms.

**Treatment During Pregnancy for Grades II–III Tumors and Pregnancy Outcomes**

Two patients whose disease progressed during or immediately after pregnancy underwent tumor resection, and another received temozolomide. The patient who received temozolomide terminated her pregnancy. Three of the patients whose disease remained stable during and immediately after pregnancy were undergoing treatment (chemoradiation in one, temozolomide in one, PCV [procarbazine, CCNU, vincristine] in one) when they were found to be pregnant. Once aware, 2 of those patients terminated their pregnancies. The third patient, who was receiving temozolomide and valproic acid, had these medications stopped and decided to continue with the pregnancy. Unfortunately, the child was born with a neural tube defect and cerebral palsy. The rest of the patients who had disease progression while pregnant were treated after delivery.
Of the 8 patients whose disease progressed during or immediately after pregnancy, one had a spontaneous abortion, and 3 terminated their pregnancies. The rest delivered healthy babies. Of the 10 patients with stable tumors, 2 terminated their pregnancies. The other 8 patients delivered healthy babies.

Survival Analysis

Four of the 8 patients with grade II or III tumors that progressed during or immediately after pregnancy died of their disease, with an average follow-up period of 4 years. These patients died within 2 years of delivery, and the fourth patient died 9 years after delivery.

The majority of patients (7 of 10) with grade II or III tumors who remained stable while they were pregnant continued to have stable disease during the follow-up period (median, 8.2 years; range, 2.6–19.4 years). The other 3 patients had disease progression and died 4, 10, and 14 years after delivery.

Among patients who became pregnant after their tumor diagnosis, the median overall survival from the time of tumor diagnosis was 19.4 years (95% CI, 4.97–NA; range, 1.8–19.9 years) for those with grade II tumors and 18.2 years (95% CI, 1.89–NA; range, 1.9–18.2 years) for those with grade III tumors. Overall survival from delivery was 14.7 years (95% CI, 1.0–NA; range, 1.4–14.7 years) for patients with grade II tumors and 13.8 years (95% CI, 0.33–NA; range, 0.8–13.8 years) for patients with grade III tumors. For the patients whose disease progressed during or immediately after pregnancy, the estimated overall survival from delivery was 2.7 years (95% CI, NA; range, 0.3–8.9 years). For those whose disease remained stable during or immediately after pregnancy, the estimated overall survival was 13.81 years (95% CI, 9.17–14.72 years). For women who were pregnant twice, survival from delivery was calculated from the first delivery.

Discussion

In this study, we present a case series of 34 women with glial tumors who were pregnant at some point during the course of their illness. These women had a total of 40 pregnancies. Nearly half the patients with grades II–III glial tumors who became pregnant after diagnosis experienced disease progression during or immediately after pregnancy.

This finding is in accordance with previous case series describing patients with grade II glial brain tumors. Together, these reports raise important concerns related to the potential negative impact of pregnancy on tumor progression and have important implications for the frequency of patient evaluations and counseling.

Several theories have been proposed to explain the progression of brain tumors during pregnancy. Reports suggest that hormonal changes and increases in the levels of growth factors and angiogenic factors during pregnancy influence the rate of growth of brain tumors. Increased levels of vascular endothelial growth factor (VEGF) and placental growth factor are well-established angiogenic factors in glioblastoma. Moreover, placental growth factor is considered one means of promoting angiogenesis when VEGF is inhibited by bevacizumab or other antiangiogenic agents, and the level of placental growth factor has been shown to increase in response to anti-VEGF treatment. Furthermore, the increase in maternal blood volume may lead to increased cerebral blood flow and might cause increased edema around the tumor. The increased edema can cause symptoms as well as changes in imaging studies.

Our study suggests that early tumor progression may occur without overt symptoms; therefore, radiographic evaluation during pregnancy should be continued. However, although most studies evaluating MRI safety during pregnancy show no ill effects, animal studies have shown intravenous gadolinium to be teratogenic at high and repeated doses. These teratogenic effects have not been observed in a small number of human studies in which gadolinium has been given in pregnancy. Therefore, in the absence of complete safety data, it is recommended that gadolinium not be administered during pregnancy unless there is an essential clinical indication. In our dataset, only 6 patients received gadolinium during pregnancy (5 of them had newly diagnosed tumors); 2 of these patients subsequently terminated their pregnancies. The rest delivered healthy babies.

Our patient series showed a correlation between the extent of tumor resection and the likelihood of tumor progression during pregnancy. All patients who had an initial gross total resection had disease that remained stable, whereas 62% of patients who had a subtotal resection or underwent biopsy without tumor resection had tumor progression. In agreement with prior studies, this finding emphasizes the effect of tumor resection on relapse risk. This phenomenon may be either a consequence of hormonal effects on the larger tumor burden in patients without gross total resection or, alternatively, a reflection of a more aggressive tumor biology that precluded extensive primary resection. Not surprisingly, the survival durations and pregnancy outcomes for patients in our study whose disease progressed during or immediately after pregnancy were worse compared with those whose disease remained stable.

In contrast to our observation of a high rate of disease progression during pregnancy in patients with grades II and III tumors, grade I tumors remained stable during and after pregnancy in the cases we studied. The different tumor biology, characterized by minimal tumor infiltration and risk of malignant transformation resulting in the possibility of cure with surgery, is a likely explanation for the absence of tumor progression during pregnancy. Another explanation for the stability of those tumors is that their progression might not be angiogenesis dependent. For example, pilocytic astrocytoma progression is not dependent on angiogenesis, and in fact nonrecurrent tumors may display a greater degree of VEGF expression. In contrast, in hemangioblastoma, which is a highly vascular tumor with high levels of VEGF, progression related to pregnancy has been described.

In meningioma, the VEGF level is related to peritumoral edema and invasiveness; accordingly, tumor progression during pregnancy has accordingly been described in meningioma patients. However, meningioma progression during pregnancy might be related to hormonal changes, as up to 80% of benign meningiomas express progestosterone receptor.

Our series included 15 patients who presented with brain tumors while they were pregnant. The rate of cesarean sections in those patients was high, which is in accordance with a previous study of the outcomes of hospitalization in pregnant women with central nervous system neoplasms. We believe that the decision whether to proceed with vaginal delivery or cesarean section was influenced by the tumor burden. Two of the 3 patients who underwent vaginal delivery had a
tumor resection during pregnancy (the third patient was diagnosed after delivery). Of the 7 patients who underwent cesarean section, 3 had no surgery before delivery, and 2 underwent biopsy without surgery. Despite the concurrent brain tumor diagnosis, all but one of the cesarean sections in these patients were performed at term.

Comparison of the overall survival of the patients in this report with tumor registry data is difficult owing to the spectrum of disease grade and the relatively young age of our patients compared with the registry data. A case-control comparison could be considered, but the relatively small numbers of patients with each tumor grade in our series and the inherent selection bias would limit the utility of survival comparisons. The prolonged survival of the patients with GBM who were pregnant at diagnosis might be related to their young age and high functional status.

Although this report represents one of the largest series evaluating the effect of pregnancy on outcomes in women with grades II–IV gliomas, several limitations of this report warrant consideration when interpreting the results. This was a retrospective study over a prolonged period during which treatments changed and additional diagnostic markers, such as allelic loss of chromosome 1p and 19q, were added to disease classifications. These changes had an effect on treatment decisions.

We cannot assume that the growth rate is accelerated, but the high rate of tumor progression and malignant transformation during pregnancy does support prior observations and raises concerns for women with gliomas considering childbearing. Further multi-institutional evaluation is required.

**Supplementary Material**

Supplementary material is available online at Neuro-Oncology (http://neuro-oncology.oxfordjournals.org/).

**Funding**

None declared.

Conflict of interest statement: Shlomit Yust-Katz, Diane Liu, Jimin Wu, Ying Yuan, and Mark D. Anderson have no disclosures; Terri S. Armstrong has received research support from Merck and Genentech; Mark R. Gilbert has received honoraria from and is on the advisory board of Merck, Genentech, and Abbott; John F. de Groot has an advisory relationship with Genentech, VBL Therapeutics, Novartis, and Deciphera Therapeutics and has received an honorarium from Merck and research funding from Sanofi-Aventis, AstraZeneca, and EMD-Serono.

**References**


