

Pregnancy and neonatal outcomes in patients treated for glioma before or during pregnancy: a single-institution series

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Abstract

Background: Glioma diagnosed during pregnancy and pregnancy following glioma treatment present complex management challenges. The safety of glioma treatment during pregnancy is not well established. The ability to counsel patients on timing of conception after treatment remains limited. The aim of this study was to review our institution's experience with glioma during and before pregnancy.

Methods: In this single-institution study, we retrospectively identified patients diagnosed with glioma during or prior to pregnancy and reviewed treatment course and maternal and neonatal outcomes.

Results: Twenty-one female patients were included in our study. Glioma diagnoses included 12 high-grade tumors and 9 low-grade tumors. Cohort A consisted of 8 patients who presented with glioma during pregnancy, of which, 7 underwent glioma treatment during pregnancy. All pregnancies in cohort A were without significant maternal complications and resulted in delivery of a healthy neonate. Cohort B consisted of 13 patients who experienced pregnancy after a prior diagnosis of glioma, totaling 23 pregnancies. Antepartum course was complicated by seizure in three pregnancies. Functionally inconsequential anatomic abnormalities in childhood offspring of cohort B occurred in 5 (27.8%) of the pregnancies. Four of the offspring with anatomic abnormalities had exposure to TMZ prior to conception.

Conclusions: In this retrospective series, diagnosis of glioma before or during pregnancy was associated with generally favorable maternal, fetal and childhood outcomes. We observed a higher-than-expected rate of anatomic abnormalities in the post-diagnosis cohort, though none carried meaningful functional consequences. These findings add to the limited literature exploring maternal and fetal outcomes in patients with glioma.

Key points

- Treatment of glioma during pregnancy was associated with generally favorable fetal and maternal outcomes
- Pregnancy complications after prior glioma treatment were limited
- Risk of birth rate defect after prior treatment of glioma may be increased

Importance of the study

This study adds to the very limited literature exploring maternal and fetal outcomes in patients who are treated for glioma during pregnancy or patients who experience a pregnancy after a history of glioma treatment. This is the first case series to document time between last temozolomide exposure and conception as well as longitudinal childhood outcomes.

Introduction

Gliomas represent a heterogeneous group of central nervous system (CNS) tumors with variable presentation and prognosis based on their specific diagnostic World Health Organization (WHO) Classification and anatomic location¹. High-grade gliomas, such as glioblastoma and H3K27-altered diffuse midline glioma, are life-limiting malignancies that can progress rapidly and require rapid initiation of treatment². Although low-grade gliomas demonstrate superior prognosis compared to high-grade gliomas, these tumors still represent life-limiting disease despite initial favorable responses to therapy as recurrence is common³. Treatment of both high-grade and low-grade gliomas require a multimodality approach with surgical resection, radiation therapy (RT), and chemotherapy pending the specific entity^{2,3}. Diagnosis of glioma before or during pregnancy is a rare and challenging clinical situation. Maternal-fetal safety and the long-term sequelae of anticancer treatments on pregnancy outcomes are often detrimental or uncertain⁴. In this single institution retrospective study, we identified patients who were diagnosed with glioma either during or prior to pregnancy and reviewed their oncologic clinical courses, obstetric outcomes and fetal outcomes to describe our institution's experience in such cases.

Methods

After obtaining IRB approval, we identified all patients from our institution's electronic medical record (EMR) with diagnostic codes of glioma and pregnancy between the years of 1990–2026 were identified. All cases were retrospectively reviewed by the authors and those with a pathologically proven diagnosis of glioma who presented during pregnancy or those who became pregnant after a prior pathologically proven diagnosis of glioma were included in the study if clinical records were available. Clinical information was obtained through documentation review of the EMR. Data regarding oncologic treatments, as well as fetal and maternal antepartum, peripartum and post-partum complications, neonatal outcomes, and childhood outcomes were collected. We identified the pregnancy(ies) of interest as the pregnancy(ies) that occurred during or after glioma diagnosis. When the offspring of the pregnancy(ies) of interest had a clinical record available within our institution's EMR, their medical record was also retrospectively reviewed to gather childhood medical history. All data was de-identified for patient privacy and collected in a system secured spreadsheet. Pertinent descriptive statistics were calculated and reported under the results section. Time from chemotherapy to conception was calculated by measuring the difference between the estimated date of conception and the last day of chemotherapy administration, rounded to the nearest whole month. Estimated date of conception was calculated assuming a 28-day cycle from the documented estimated date of delivery from either last menstrual period (LMP) or early ultrasound if LMP was unknown or irregular.

Results

Patient demographics, initial oncologic course, and tumor targeting treatments received during pregnancy:

Twenty-one patients met the study's inclusion criteria. All patients were female with a median age of 29 years (range 24–40) at the time of glioma diagnosis. Although some diagnoses occurred prior to initiation of the 2021 WHO CNS tumor criteria, we have adjusted the initial diagnosis per the 2021 criteria as able based on available tumor genetics. Glioma diagnoses included 12 high-grade tumors (glioblastoma: n = 3, IDH-mutant astrocytoma WHO grade 3: n = 5, IDH-mutant astrocytoma WHO grade 4 n:2, H3 K27M mutant midline glioma: n = 1, and oligoastrocytoma: n = 1), and 9 low-grade tumors (oligodendroglioma: n = 3, IDH-mutant astrocytoma WHO grade 2: n = 4, pediatric diffuse low grade glioma MAPK pathway altered: n = 1, and oligoastrocytoma: n = 1).

Patients were split into two cohorts. Cohort A consisted of patients diagnosed with glioma during pregnancy (n = 8). Baseline patient demographics, specific glioma diagnosis, and initial tumor treatment therapies for patients in cohort A are summarized in Table 1. Of the 8 patients in cohort A, 7 (87.5%) chose to undergo further diagnostic evaluation and tumor targeting treatment during pregnancy, while one patient with radiographic features suggestive of low-grade glioma deferred further medical interventions including diagnosis until after their pregnancy delivery at 40 weeks gestation. The median weeks gestation for patients presenting with glioma during pregnancy was 18.6 (range 6–29 weeks).

Table 1
Cohort A patient demographics, tumor diagnosis, and initial tumor targeting therapies

Pt	Age at glioma diagnosis (y)	Pathologic diagnosis and tumor genetics	Surgery	Radiotherapy	Chemotherapy	Initial therapies that occurred during pregnancy
1	25	Glioblastoma	GTR	Photon 60 Gy in 30 fractions	Concurrent & adjuvant TMZ (2 cycles)	Surgery (23 weeks gestation), RT, concurrent TMZ (initiated 26 weeks gestation)
2	30	Glioblastoma with primitive neuronal component	GTR	Photon 60 Gy in 32 fractions	Concurrent TMZ	Surgery (23 weeks), RT, concurrent TMZ (initiated at 24 weeks gestation)
3	40	Glioblastoma, MGMT methylated	STR	Photon 60 Gy in 30 fractions	Adjuvant TMZ (8 cycles)	Surgery (18 weeks), RT
4	28	Midline glioma, H3 K27M mutant, MGMT unmethylated	3rd ventriculostomy, biopsy	Photon 59.4 Gy in 33 fractions	Adjuvant TMZ (6 cycles)	Surgery (26 weeks), RT
5	27	IDH-mutant astrocytoma, WHO III	GTR	Photon 54 Gy in 30 fractions	--	Surgery (20 weeks), RT
6	24	IDH-mutant astrocytoma, WHO II	GTR	Photon 54 Gy in 30 fractions	--	--
7	36	IDH-mutant astrocytoma, WHO IV, MGMT methylated	STR	Photon 60 Gy in 30 fractions	Concurrent and adjuvant TMZ (6 cycles)	Surgery (27 weeks), RT, TMZ (initiated 31 weeks gestation)
8	31	IDH mutant astrocytoma, WHO III	STR	Photon 57 Gy in 30 fractions	Adjuvant TMZ (6 cycles)	Surgery (20 weeks), RT
Pt: patient, GTR: gross total resection, STR: subtotal resection, TMZ: temozolomide, WHO: World Health Organization, MGMT: O-6-methylguanine-DNA methyltransferase, IDH: isocitrate dehydrogenase, RT: radiation therapy, Gy: Gray						

Cohort B consisted of patients who had a prior established diagnosis of glioma and became pregnant after their diagnosis (n = 13). Baseline patient demographics, specific glioma diagnosis, and initial tumor treatment therapies for patients in cohort B are summarized in Table 2. Of the 13 patients with glioma diagnosis prior to pregnancy, 2 patients received while receiving anti-cancer therapies due to tumor recurrence prior to conception in both patients.

Table 2
Cohort B patient demographics, tumor diagnosis, and initial tumor targeting therapies

Pt	Age at glioma diagnosis (y)	Pathologic diagnosis and tumor genetics	Surgery	Radiotherapy	Chemotherapy	Initial therapies that occurred during pregnancy
9	23	Oligodendroglioma, WHO II	Biopsy	--	TMZ (12 cycles)	--
10	24	Oligodendroglioma, WHO II	STR	--	TMZ (12 cycles)	--
11	34	IDH-mutant astrocytoma, WHO III, MGMT unmethylated	STR	Proton 57 Gy in 30 fractions	Adjuvant TMZ (6 cycles), no concurrent TMZ due to egg harvesting	--
12	29	IDH-mutant astrocytoma, WHO II	STR	Proton 50 Gy in 28 fractions	--	--
13	36	Oligodendroglioma, WHO II	GTR	--	----	--
14	27	Pediatric diffuse glioma, MAPK pathway altered, WHO II	GTR	--	--	--
15	24	Oligoastrocytoma, WHO II	GTR	--	--	--
16	26	IDH-mutant astrocytoma, WHO III	STR	F-DOPA guided 76 Gy in 30 fractions	Concurrent and adjuvant TMZ (5 cycles, discontinued due to toxicity)	--
17	38	IDH-mutant, astrocytoma, WHO III	GTR	IMRT 50 Gy in 30 fractions	Concurrent and adjuvant TMZ (6 cycles)	--
18	29	IDH-mutant astrocytoma, WHO II, MYCN amplification	STR	Proton 54 Gy in 30 fractions	Adjuvant TMZ (6 cycles), no concurrent due to wound infection	--
19	30	IDH-mutant astrocytoma, WHO II	GTR	--	--	--
20	33	IDH-mutant astrocytoma, WHO IV, MGMT methylated	STR	Proton 60 Gy in 30 fractions	Concurrent and adjuvant TMZ (6 cycles)	--
21	22	Oligoastrocytoma, WHO III	GTR	Photon, dose unknown	Procarbazine hydrochloride, lomustine, vincristine sulfate (6 cycles)	--
Pt: patient, GTR: gross total resection, STR: subtotal resection, TMZ: temozolomide, WHO: World Health Organization, MGMT: O-6-methylguanine-DNA methyltransferase, IDH: isocitrate dehydrogenase, RT: radiation therapy, Gy: Gray, IMRT: Intensity-modulated radiation therapy, F-DOPA: Fluorodopa						

Treatments received during pregnancy for patients in both cohort A and B are summarized in Table 3. Eight patients had surgical intervention during pregnancy, with median weeks gestation at the time of surgery of 21.5 (range 12–30 weeks). One patient at 26 weeks gestation experienced a deep venous sinus thrombosis following surgery, otherwise, surgical interventions during pregnancy were uncomplicated for the patient or fetus. Eight patients had RT during pregnancy with a median of 27 weeks gestation (range 20–31) at RT initiation. There were no reported adverse events outside of common and mild RT side effects (e.g. alopecia, fatigue). Four patients received chemotherapy (temozolomide) while pregnant. One patient unknowingly conceived their pregnancy while on temozolomide (TMZ). TMZ was discontinued upon discovery of pregnancy but ultimately restarted at low (50 mg/m²) daily dosing at 31 weeks gestation due to symptomatic tumor progression. Three patients newly diagnosed with glioma during pregnancy were initiated on adjuvant TMZ at 21, 24 and 26 weeks gestation.

Table 3
Summary of targeted cancer therapies delivered during pregnancy

Pt	Patient Cohort	Surgery	Weeks gestation at time of surgery	Post-surgical complications	Radiation therapy	RT adverse events	Weeks gestation at RT initiation	Chemo	Chemo adverse events	Weeks gestation of chemo initiation
1	A	GTR	23	DVT	EBRT 60 Gy in 30 frax	Alopecia	27w	Concurrent TMZ	Constipation	26
2	A	GTR	23	None	EBRT 60 Gy in 32 frax	Alopecia	27w	Concurrent TMZ	Rash	24
3	A	GTR	18	None	Photon 60 Gy in 30 frax	Fatigue	20w	None	--	--
4	A	--	--	--	Photon 50.4 Gy in 30 frax	Fatigue	28w	None	--	--
5	A	GTR	20	None	Photon 59.4 Gy in 33 frax	Alopecia	24w	None	--	--
7	A	STR	27	None	IMRT 60 Gy in 30 frax	None	31w	Concurrent TMZ	Nausea, fatigue	21
8	A	STR	28	None	Proton 57 Gy in 30 frax	None	31w	None	--	--
11	B	STR	20	None	Proton 35 Gy 10 frax	None	23w	TMZ	Nausea	Conception & resumed at 30w with low daily dosing
16	B	STR	12	None	None	--	--	None	--	--
Pt: patient, GTR: gross total resection, STR: subtotal resection, DVT: deep venous thrombosis, EBRT: external beam radiation therapy, Gy: Gray, Frax: fractions, TMZ: temozolomide, IMRT: Intensity-modulated radiation therapy										

Patient obstetric history and pregnancy outcomes:

Obstetric history both before and after diagnosis of glioma are outlined in Table 4 for patients in cohort A and Table 5 for patients in cohort B. Pregnancy outcomes, including offspring health history and/or anatomic deformities are also outlined in Table 4 and Table 5.

Table 4
Cohort A obstetric history prior to glioma diagnosis and pregnancy outcomes for pregnancies during glioma diagnosis

Pt	Gravity and parity before glioma diagnosis	Maternal or fetal complications in pregnancies prior to glioma diagnosis	Number of pregnancies during/after glioma diagnosis	Duration between chemo and conception	Maternal or fetal antepartum complications	Maternal postpartum complications	Fetal postpartum complications	Gestation at delivery	Apgar score	NICU stay	Child adv out
1	G1P1001	None	1	TMZ during pregnancy (initiated 26w gestation)	GBS positive	Seizure	Transient tachypnea of newborn	37w	8,9	Yes	EMI ava
2	G2P1011	None	1	TMZ during Pregnancy (initiated 24w gestation)	None	Uterine infection	Support for prematurity	34w4d	8,9	Yes	Nor
3	G3P1021	None	1	None	None	None	Support for prematurity	34w	8,9	Yes	EMI ava
4	G0P0000	--	1	None	Gestational hypertension	None	Hyperbili-rubinemia	38w2d	8,9	No	EMI ava
5	G1P1001	None	1	None	None	None	None	40w	N/A	N/A	EMI ava
6	G3P3003	None	1	None	None	None	None	40w	9,9	No	Nor
7	G1P1	C-Section	1	TMZ during pregnancy (initiated 31w gestation)	AMA, low lying placenta, intrauterine fetal growth restriction (33 weeks)	PPH	Hyperbili-rubinemia, poor weight gain	37w	8,8	Yes	Nor
8	G5P0032	History of recurrent miscarriage	1	None	None	None	Neonatal hypo-glycemia, macrosomia	39w1d	9,9	No	Nor
Pt: patient, TMZ: temozolomide, GBS: group B strep, EMR: electronic medical record, AMA: advanced maternal age, PPH: post-partum hemorrhage											

Table 5
Cohort B obstetric history prior to glioma diagnosis and pregnancy outcomes for pregnancies after glioma diagnosis

Pt	Gravity and parity before glioma diagnosis	Maternal or fetal complications with prior pregnancies	Number of pregnancies during or after glioma diagnosis	Duration between chemotherapy and conception	Antepartum complications	Maternal postpartum complications	Fetal postpartum complications	Gestation at delivery	Apgar score	NICU stay
9	G0P0000	--	2	84m (TMZ) 11m (CCNU)	Shingles	None	None	40w	8,9	No
			Pregnancy 1	94m (TMZ)	PPROM	None	Hypoglycemia	36w	8,9	No
			Pregnancy 2	24m (CCNU)						
10	G0P0000	--	2	2m (TMZ)	None	None	None	39w	8,9	No
			Pregnancy 1	48m (TMZ)	None	None	None	39w	7,8	No
			Pregnancy 2							
11	G0P0000	--	2	12m (TMZ)	AMA, Pre-eclampsia	Hypertensive urgency	Fetal bradycardia	36w4d	6,7	Yes
			Pregnancy 1	Conceived while on TMZ, Proton RT during pregnancy	AMA, Pre-eclampsia, maternal seizure, intrauterine growth restriction	None	Respiratory support	32w	1,5	Yes
			Pregnancy 2							
12	G1 P1001	None	2	10 m	Miscarriage	--	--	--	--	--
			Pregnancy 1	14 m	Maternal hemolytic anemia requiring transfusions	None	None	39w4d	9,9	No
			Pregnancy 2							
13	G1P1001	Gestational hpn, shoulder dystocia c/b clavicle fracture	1	None	Gestational hpn, marginal cord insertion	None	None	38w5d	8,9	No
14	G0P0000	--	2	None	None	None	None	37w	8,9	No
			Pregnancy 1	None	None	None	None	39w	9,10	No
			Pregnancy 2							
15	G1P1001	None	1	None	Maternal seizure during pregnancy	None	Nuchal cord	39w	7,8	No
16	G0P0000	--	1	8 m (TMZ)	Pre-eclampsia, maternal seizures	None	Runs of SVT	29w6d	7,8	Yes
17	G1P1001	PPROM	1	11 m (TMZ)	None	None	None	37w	9,9	No
18	G2P2002	None	1	4 m (TMZ)	Obesity	None	None	39w	8,9	No
19	G0P0000	--	1	None	None	None	None	37w6d	9,9	No
20	G4P4004	C-Section	1	6 m (TMZ)	Severe anxiety	None	None	37w		No
21	G0P0000	--	6	9 y (PCV)	Diminished ovarian reserve, AMA	--	--	--	--	--
			Pregnancy 1	10y (PCV)		--	--	--	--	--

ASD: atrial septal defect, CCNU: lomustine, PCV: procarbazine hydrochloride, lomustine, vincristine sulfate, PPRM: preterm premature rupture of membranes

Pt	Gravity and parity before glioma diagnosis	Maternal or fetal complications with prior pregnancies	Number of pregnancies during or after glioma diagnosis	Duration between chemotherapy and conception	Antepartum complications	Maternal postpartum complications	Fetal postpartum complications	Gestation at delivery	Apgar score	NICU stay
			Pregnancy 2	11y (PCV)	Spontaneous miscarriage, aneuploidy	--	--	--	--	--
			Pregnancy 3	16y (PCV)	Incision cellulitis and hematoma	Feeding support	35w6d	6,9	Yes	
			Pregnancy 4	12y (PCV)	Spontaneous miscarriage	None	Passing of neonates	20w	--	--
			Pregnancy 5	17y (PCV)	Spontaneous miscarriage	None	Hypotension requiring dobutamine, feeding support, hyperbilirubinemia, multifocal cutaneous infantile hemangiomatosis	26w	2,6	Yes
			Pregnancy 6		Egg donor, AMA, pre-eclampsia					
					IVF with donor egg, twin pregnancy, PPRM					
					PPROM					
	ASD: atrial septal defect, CCNU: lomustine, PCV: procarbazine hydrochloride, lomustine, vincristine sulfate, PPRM: preterm premature rupture of membran									

Among the patients in cohort A, there were a total of 8 pregnancies of interest (Table 4). No pregnancies resulted in loss. Maternal complications during pregnancy included gestational hypertension (n = 1) and low-lying placenta (n = 1). Maternal post-partum complications occurred in 3 (37.5%) pregnancies and included seizure (n = 1), puerperal uterine infection (n = 1), and post-partum hemorrhage (n = 1). Fetal complications during pregnancy included intrauterine growth restriction, occurring in 1 of the 8 pregnancies. There were no other notable antepartum fetal complications. Median weeks gestation for delivery of pregnancies in cohort A was 37.5 (range 34–30 weeks). Four (50%) of the eight pregnancies required a NICU stay for the neonate. Six (75%) of the neonates had a documented fetal postpartum complication, including hyperbilirubinemia (n = 2), respiratory and feeding support for prematurity (n = 2), transient tachypnea of newborn (n = 1), and hypoglycemia (n = 1). Of the pregnancies in cohort A that had childhood follow up available, there were no documented adverse childhood outcomes.

Among the 13 patients in cohort B, there were a total of 23 pregnancies occurring after prior established diagnosis of glioma. Five (21.7%) of the 23 pregnancies resulted in early or late pregnancy loss. Conception of one pregnancy resulting in early miscarriage occurred approximately 10 months after discontinuation of TMZ. The remaining four early or late term pregnancy losses occurred within a single patient, who had exposure to 6 cycles of procarbazine, lomustine and vincristine (PCV) approximately 9 years prior to the first pregnancy loss. Eighteen of the 23 pregnancies resulted in delivery of a living neonate.

Of the 18 pregnancies carried to live birth in Cohort B, four (22.2%) were complicated by pre-eclampsia. Three (16.6%) of the pregnancies were complicated by seizure during the antepartum period. Maternal post-partum complications occurred in 2 pregnancies, consisting of hypertensive urgency (n = 1) and wound infection (n = 1). Five (27.8%) of the 18 deliveries required a NICU stay for the neonate. Five (27.8%) of the 18 deliveries in cohort B resulted in an anatomic abnormality, all without significant functional consequences. Anatomic abnormalities included spina bifida occulta (n = 1), right sided aortic arch (n = 1), pulmonic valve stenosis with atrial septal defect (n = 1), bilateral pes planovagus (n = 1), and abnormal unilateral ear cartilage (n = 1). All but one of the pregnancy outcomes with anatomic abnormalities had exposure to TMZ prior to or at the time of conception, as outlined in Table 5.

Discussion

Diagnosis of glioma before or during pregnancy is a rare and challenging clinical situation. Due to the rarity of the dual diagnosis of glioma and pregnancy, there are no standard management recommendations for pregnant patients with glioma and current evidence on pregnancy outcomes and management is limited to small case series and expert opinions^{4,5}. Little information is known regarding the risk of antepartum, peripartum or postpartum complications in the setting of glioma diagnosis or on the fetal and childhood adverse effects of tumor targeting therapies delivered before or during pregnancy. We aimed to describe our institution's experience regarding dual occurrence of glioma and pregnancy to add to the limited data available for review.

In our first patient cohort (cohort A), we identified 8 patients who presented with a new diagnosis of glioma during pregnancy. Consistent with prior retrospective studies, most patients presented in the second trimester^{6,7}. Common maternal antepartum complications (e.g. low-lying placenta, gestational hypertension) and post-partum complications (e.g. postpartum hemorrhage, uterine infection) were reported, but no significant events resulting in maternal or fetal morbidity or mortality were reported, suggesting obstetric risk may not be significantly complicated by glioma. However, one patient experienced a first time focal to generalized seizure post-partum. Of the 8 deliveries for the patients who presented with glioma during pregnancy, 50% resulted in a NICU stay for the newborn, notably higher than the documented 9–10% NICU admission rate for pregnancies not complicated by diagnosis of glioma. Statistical significance regarding this finding cannot be assessed due to our low number of cases⁸. Of our patients who presented with glioma during pregnancy, all went on to deliver healthy babies with no significant infant or childhood adverse outcomes.

Our second patient cohort (cohort B) consisted of patients who became pregnant after a prior diagnosis of glioma, which consisted of a total of 23 pregnancies among 13 patients. The rate of early or late term pregnancy loss in this cohort was 21.7%, similar to the national pregnancy loss rate of 21.6% in pregnant patients without history of glioma⁹. There was an increased rate of pre-eclampsia diagnoses, 22.2% in our cohort, compared to the national average of 4%, raising question as to whether there may be an association between these two co-morbidities, but this finding is limited to our small sample size. The antepartum period was also complicated by seizure in 16.6% of our pregnancies. Outside of these trends, pregnancy after prior diagnosis of glioma was relatively uncomplicated in this cohort, consistent with prior case series⁷.

Between our two cohorts, there were a total of nine patients who underwent active tumor targeting therapy while pregnant due to new diagnosis of glioma or recurrence of prior diagnosis. Of our eight patients who underwent surgery while pregnant, one surgical intervention was complicated by post-operative DVT, but surgical interventions were otherwise uncomplicated. This is consistent with prior case series supporting the safety of surgical intervention for patients pregnant with glioma, especially after the first trimester¹⁰⁻¹⁵. Larger case series evaluating neurosurgical intervention during pregnancy not specific to glioma also supports the safety of neurosurgical intervention to both mother and fetus.¹⁶ Data regarding RT safety during pregnancy with glioma diagnosis is also limited to case studies and series^{10,15,17}. Reassuringly, two case reports have demonstrated very low radiation exposure to the fetus using modern techniques^{17,18}. Eight of our patients received RT while pregnant, two of which received proton beam irradiation. All were without significant maternal complications during RT. Documented safety and/or adverse effects of TMZ during pregnancy are especially limited¹⁹. The Federal Drug Administration label for TMZ carries a boxed-level embryo-fetal toxicity warning based on animal data and postmarketing human reports of polymalformations involving the CNS, face, heart, skeleton, and genitourinary system. A prior cohort study of glioma patients who received chemotherapy and/or RT during pregnancy had increased risk of birth defects or birth complications compared to fetuses not exposed to chemotherapy and/or RT⁷. One case series of 6 patients with unplanned pregnancies while receiving active PCV or TMZ resulted in deliveries of healthy newborns without congenital malformations²⁰. Therefore, data regarding safety or adverse effects of chemotherapy administration during pregnancy is not only limited, but also somewhat conflicting. There is no clear data regarding TMZ safety in the second or third trimester of pregnancy after critical neonatal organogenesis has occurred. In our study, four patients received TMZ while pregnant, initiated at 21, 24, 26 and 30 weeks gestation. One of these pregnancies was complicated by intrauterine growth restriction after starting TMZ and one child with TMZ exposure at conception and again at 30 weeks gestation was born with a right-sided aortic arch. TMZ received during pregnancy was otherwise uncomplicated on the mother or fetus. These observations may suggest administration of TMZ may be relatively safe during the second and third trimesters of pregnancy and may not confer an increased risk of pregnancy complications or adversely impact child development and delaying surgery or the initiation of RT or chemotherapy until completion of pregnancy may not be needed when clinically indicated.

For patients considering a pregnancy after a new or known diagnosis of glioma, likely their greatest concern is whether tumor targeting therapies will have any adverse effect on their offspring even when the patient is no longer on active treatment. Physiologically, the most relevant issue is prior chemotherapy exposure and its impact on oocyte reserve. The FDA drug label for TMZ recommends effective contraception for 6 months during treatment with TMZ and 6 months after discontinuation of treatment. There is limited data specifically evaluating pregnancy outcomes after prior exposure to TMZ. One case reported a healthy pregnancy with conception occurring less than 3 weeks after last TMZ exposure²¹. To add to this limited literature, we calculated the time between last chemotherapy exposure and estimated date of conception in cohort B to summarize our institution's experience with pregnancy outcomes after TMZ exposure. Although significant statistical conclusions cannot be drawn due to our small sample size, it likely is of clinical significance to note that the rate of anatomic abnormalities in our cohort was 27.8%, which is significantly higher than the national average of 3%²². However, none of the reported anatomic abnormalities in our patients' offspring had significant implications on the child's overall health and/or function. These findings support that patients should continue to discuss fertility wishes with their neuro-oncologist and consider referral to reproductive medicine specialists prior to initiation of chemotherapy for treatment of glioma, though the timeliness of treatment of the glioma often precedes consultation and involvement with reproductive medicine. A prior survey study found that only 30% of glioma patients receiving chemotherapy reported having a discussion regarding fertility preservation prior to beginning treatment²³.

We recognize the most significant limitation of our case series is the small number of patients. Broad conclusions regarding administration of RT or chemotherapy on maternal and fetal health during pregnancy should not be drawn based on this limited case series. The heterogeneity of the tumors included in the series and incomplete tumor molecular data limits interpretation of treatment response and value of initiating therapy during pregnancy compared to waiting until the postpartum period. We also recognize the limitations on broad conclusions regarding pregnancy outcomes in history of prior glioma treatment exposure as we are unable to account for other confounding risk factors for birth defect development or statistically evaluate the effect of conception timing and last chemotherapy exposure due to our small sample size.

Conclusions

In this retrospective series, diagnosis of glioma before or during pregnancy was associated with generally favorable maternal, fetal and childhood outcomes. Tumor-targeting therapy during pregnancy – including surgery, radiation, and temozolomide in the second and third trimesters – was undertaken without major maternal or fetal morbidity, and pregnancy after a prior glioma diagnosis was largely uncomplicated. However, we did observe a higher-than-expected rate of anatomic abnormalities in offspring in the post-diagnosis cohort, though none carried meaningful functional consequences. These findings are limited by small sample size and cannot support broad management conclusions, but they add to the literature suggesting that necessary anticancer treatment for glioma need not always be deferred for pregnancy. Providers should continue to report cases of pregnancy during or after diagnosis of glioma as ongoing data is necessary to expand the risk-benefit ratio discussion when considering tumor treatment during pregnancy or conception of pregnancy after history of prior tumor treatment. Neuro-oncologists should continue discussing fertility plans and consider referral to reproductive medicine in all female patients of childbearing age who are diagnosed with glioma.

Declarations

Ethics. An appropriate institutional review board approved this project.

Funding. There was no dedicated funding for this project.

Conflict of Interest. All authors deny any conflicts of interest related to this project.

Authorship. AV, AR, and MR designed the research. PD gathered the patients of interest. AV, AR and AS performed data collection. AV and MF analyzed the data. AV prepared the tables. AV and MR wrote the initial manuscript. AV, AS, AR, US, JU, DL, BN, JC, TB, IP, FM, NL, and MR interpreted data and extensively reviewed, edited and approved of the manuscript.

Data Availability. Data will be made available upon request.

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