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ORIGINAL ARTICLE - BRAIN TUMORS

Influence of pregnancy on glioma patients

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Abstract

Background Data about the influence of pregnancy on progression-free survival and overall survival of glioma patients are sparse and controversial. We aimed at providing further evidence on this relation.

Methods The course of 18 glioma patients giving birth to 23 children after tumor surgery was reviewed and compared to the course of 18 nulliparous female patients matched for tumor diagnosis including molecular markers, extent of resection, and tumor location.

Results Tumor pathology was astrocytoma, oligodendroglioma, and ependymoma in 9, 6, and 3 patients, respectively. Time interval between tumor resection and delivery was 5.3 ± 4.4 years. All newborns were healthy after uneventful deliveries. Tumor progression was diagnosed before pregnancy in 4 patients and during pregnancy in 1 patient, and 4 patients displayed progressive disease 31.0 ± 11 months after delivery. Three of these latter patients underwent second surgery, whereas resection of recurrent tumor had been performed in 2 women before pregnancy. Among nulliparous patients, 9 women suffered from tumor progression, resulting in re-operation in 7 patients and/or further adjuvant treatment in 6 cases. Progression-free survival did not differ between patients with and patients without children ($p = 0.4$). Moreover, in both groups, median overall survival was not reached after a mean follow-up period of 9.7 ± 5.7 years in glioma patients who gave birth to a child and 8.9 ± 4.2 years in nulliparous glioma patients.

Conclusion Pregnancy does not seem to influence the clinical course of glioma patients. Likewise, glioma seems not to have an impact on delivered children's health.

Keywords Brain tumor · Glioma · Matched-pairs analysis · Pregnancy

Introduction

In the clinical routine, physicians are often confronted with young female brain tumor patients considering childbearing. These patients need to be counseled on the interaction of their disease and pregnancy, and, once being pregnant, whether to continue pregnancy or not. Literature and thus, robust data addressing these questions are sparse.

While several studies demonstrated neurological deterioration, an acceleration of tumor growth and/or tumor

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progression in women with a known low-grade glioma during pregnancy [21, 22, 31, 32], data from the Cancer Registry of Norway, did not display a difference in overall survival of female low-grade glioma patients when dichotomized into childbearing after diagnosis and nulliparous patients [25]. In this well-defined cohort study, 65 patients giving birth after low-grade glioma diagnosis were investigated. Nevertheless, an according case-control comparison still is lacking.

Therefore, the goal of the present study was to investigate the clinical course of glioma patients whose tumors were diagnosed prior to pregnancy in comparison to patients suffering from tumors of similar histology and being followed-up over a similar period of time, aiming at better counseling glioma patients wishing to give birth to a child.

Materials and methods

Data source and collection

Data of patients diagnosed with glioma WHO grade II or III or with intracranial ependymoma prior to pregnancy were prospectively collected since 2002. For two patients who had undergone surgery before 2002, their data were added in retrospect at the moment of their routine oncological follow-up, followed by the prospective collection of data on their further clinical course. Data included patients' clinical characteristics (symptoms before and after tumor resection, during pregnancy and the follow-up, delivery and child outcome, tumor progression, death), tumor characteristics (histological morphology and molecular features, tumor location, imaging data), and oncological treatment (extent of tumor resection (EoR), radio- and chemotherapy). If not available at the time of tumor diagnosis, and in case of available tissue, the isocitrate dehydrogenase (IDH) 1-R132H mutational status, ATRX loss, and 1p19q-co-deletion were retrospectively evaluated by immunohistochemistry (Table 1).

In order to evaluate the possible influence of pregnancy on the course of disease of brain tumor patients, a comparable cohort of nulliparous female patients was identified within our institutional database for patients with brain tumors who underwent surgery between 2000 and 2016. Patients within this cohort were first matched for histology including molecular markers, if available, second, for EoR (i.e., gross total, subtotal, and partial resection), and third for tumor location. Finally, the year of tumor surgery, acknowledging the prevailing adjuvant treatment, was best possible taken into consideration. Of note, due to the relatively low incidence of glioma WHO grade II and III and of ependymoma, patients could not always be matched for age. However, all patients were below 50 years of age; a cutoff having been shown to influence overall survival [7, 10].

All patients underwent regular MRI scans, and response to tumor treatment was defined according to RANO criteria [13, 27].

Ethical approval

The local ethics committee (ethics committee of the University Hospital Frankfurt) approved the protocol and conduction of this study (SNO/ 01/-2018), and all procedures were in accordance with the 1964 Helsinki Declaration. All patients gave their written informed consent for scientific work with their clinical and medical imaging data.

Statistics

For continuous variables, results were expressed as the mean ± standard deviation. Comparison of matched patients was performed using the chi-square test and the Mann-Whitney U test. P values ≤ 0.05 were considered statistically significant. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier estimates. All statistical analyses were computed with SPSS version 22 (IBM, Armonk, New York, USA).

Results

Pregnant glioma patients

Eighteen patients, who became pregnant after resection of astrocytoma, oligodendroglioma, or cerebral ependymoma WHO grade II and III, were identified (Table 1). They gave birth to 29 children. Twenty-three of those children were conceived after tumor treatment. Time from tumor resection to onset of pregnancy was 4.8 ± 4.4 years (range 0.3–13.4 years).

Histopathological assessment of initially resected tumor revealed astrocytoma WHO grade II in 9 patients, oligodendroglioma WHO grade II and WHO grade III in 4 and 2 patients, respectively, ependymoma WHO grade II in 2 patients, and ependymoma WHO grade III in 1 patient. Resection of recurrent tumor prior to pregnancy was necessary in 2 patients, of whom 1 patient was operated 8.5 years after gross total resection of astrocytoma with IDH1-R132H mutation and ATRX loss, WHO grade II, and 1.8 years before pregnancy. The other patient experienced first tumor recurrence 5.8 years after complete resection of diffuse IDH1-R132H negative, ATRX lost glioma, and WHO grade II. At this time-point, as well as 3 and 5 years later, resection of recurrent tumor was performed. Tumor progression made third re-resection necessary after further 2 years, which was during the first month of unknown pregnancy, and the patient died because of ongoing disease progression 1 month after delivery of a healthy son despite radio-chemotherapy after delivery. Two more patients were diagnosed with recurrent

Table 1 Baseline characteristics of pairs of patients, matched for histopathological diagnosis and extent of tumor resection

Pair of patients	Type of glioma morphology	WHO grade	Pregnant patients				Nulliparous patients				EOR
			IDH1-R132H	ATRX	1p19q-codel	Year of surgery	IDH1-R132H	ATRX	1p19q-codel	Year of surgery	
1	astro	II	+	–	n.a.	2007	+	+	n.a.	2007	GTR
2	astro	II	–	+	n.a.	2004	–	n.a.	n.a.	2001	GTR
3	astro	II	–	–	n.a.	2010	+	–	–	2013	STR
4	astro	II	+	+	n.a.	2003	n.a.	n.a.	n.a.	2008	PR
5	astro	II	–	–	n.a.	1992	+	–	n.a.	2005	GTR
6	astro	II	+	inc.	–	2015	+	+	–	2014	GTR
7	astro	II	+	n.a.	n.a.	2012	+	–	–	2013	GTR
8	astro	II	+	n.a.	–	2013	+	–	–	2006	GTR
9	astro	II	+	inc.	n.a.	2004	+	n.a.	n.a.	2000	GTR
10	oligo	II	+	n.a.	+	2006	+	+	+	2009	GTR
11	oligo	II	+	n.a.	+	2003	n.a.	n.a.	n.a.	2006	STR
12	oligo	II	n.a.	n.a.	n.a.	2006	inc.	+	n.a.	2007	GTR
13	oligo	II	+	n.a.	+	2009	+	n.a.	+	2006	PR
14	oligo	III	–	n.a.	n.a.	2005	+	n.a.	+	2007	GTR
15	oligo	III	+	+	+	2015	+	n.a.	+	2010	STR
16	ependy	II				2003				2013	GTR
17	ependy	II				1991				2008	PR
18	ependy	III				2007				2006	GTR

astro, astrocytoma; *ependy*, ependymoma; *EOR*, extent of resection; *inc.*, inconclusive; *GTR*, gross total resection; *n.a.*, not available; −, negative; *oligo*, oligodendroglioma; +, positive; *PR*, partial resection; *STR*, subtotal resection

diffuse WHO grade II glioma 2 and 5 months prior to pregnancy, respectively. While tumor resection was performed 3 months after birth in the first patient, the other patient has renounced to surgical and adjuvant treatment so far, resulting in slow progression of low-grade glioma during 2.5 years since diagnosis of progressive disease.

Disease progression prior to or during pregnancy did not correspond to extent of initial tumor resection, but initial diagnosis was WHO grade II glioma in all cases. Time from diagnosis to pregnancy did not differ between patients whose tumors progressed before or during pregnancy and patients without disease progression until childbearing ($p = 0.72$; 6.1 ± 4.9 vs. 5.6 ± 4.3 years).

Progressive disease after pregnancy was diagnosed in further 4 patients 2.2 ± 1.5 years after birth. In contrast, 9 patients showed stable disease over their follow-up period of 8.4 ± 4.5 years. The overall follow-up period of all pregnant glioma patients was 9.7 ± 5.7 years.

Detailed information on patients' characteristics is provided in Table 2.

Nulliparous glioma patients

For the matched-pair control group, 18 women without any history of pregnancy were identified and were matched for type of glioma, tumor location, EoR, and best possible for the year of tumor surgery. Characteristics of nulliparous glioma patients are equally listed in Table 2.

Comparison of pregnant patients and nulliparous patients with regard on disease progression and overall survival

Among glioma patients giving birth to a child, tumor progression was diagnosed before and during pregnancy in 4 and 1 patients, respectively, as described above. Further, 4 patients experienced disease progression 2.2 ± 1.5 years after birth. In contrast, half of the 18 patients who became pregnant after tumor diagnosis showed stable disease over their follow-up period of 8.4 ± 4.5 years and 3.5 ± 3.1 years after pregnancy.

Among the control group of nulliparous glioma patients, 11 women experienced tumor progression after 6.3 ± 2.7 years, whereas the other 7 patients had stable disease over 8.3 ± 4.6 years. Thus, no difference was found in PFS between glioma patients giving birth to a child and nulliparous glioma patients in the univariate analysis ($p = 0.93$), as depicted in Fig. 1.

Median OS was not reached for glioma patients with children at a mean follow-up of 9.7 ± 5.7 years. Three of these 18 patients died of their disease 4.2 ± 3.7 years after initial tumor surgery and 3.7 ± 2.6 years after first delivery, respectively. In

Table 2 Comparison of patients' clinical course and outcome

	Pregnant patients ($n = 18$)	Nulliparous patients ($n = 18$)	p value
Age at diagnosis (year)	25.4 ± 5.9	32.7 ± 8.0	0.004‡
Follow-up after surgery (year)	9.7 ± 5.7	8.9 ± 4.2	0.562‡
Tumor progression, n (%)	9 (50)	11 (61)	0.502*
Treatment of progressive disease			
Re-resection, n (%)	5 (28)	7 (39)	0.480*
Oncological treatment, n (%)			
Chemotherapy	7 (39)	10 (56)	0.317*
Radiotherapy	7 (39)	10 (56)	0.317*
Combined therapy	7 (39)	8 (44)	0.735*
Death during follow-up, n (%)	3 (17)	0	0.070*
Median KPS at follow-up, without deaths (range)	90 (90–100)	90 (80–100)	0.098*

*Chi-squared test; ‡ Mann-Whitney U test

these 3 patients, tumor progression was diagnosed prior to conception, during pregnancy, and after delivery, each in 1 patient.

Nulliparous patients all were alive at a mean follow-up of 9.7 ± 4.4 years. Nevertheless, OS did not differ significantly between glioma patients giving birth to a child and nulliparous patients ($p = 0.79$), as shown in Fig. 2.

Investigating the influence of baseline characteristics on PFS and OS, the univariate analysis revealed chemotherapy ($p = 0.03$) and combined radio-chemotherapy ($p = 0.03$) to be associated with increased PFS, whereas OS was only positively influenced by re-resection ($p = 0.04$). However, in the multivariate analysis, no independent parameter could be identified to be positively associated with PFS or OS (Table 3). Thus, age and EoR had no influence on both, patients' PFS and OS.

Gestational outcomes

While none of the pregnancies had to be interrupted, 1 patient experienced spontaneous abortion 2 years after initial subtotal tumor resection and 1 month before diagnosis of tumor progression. Twelve babies were born by caesarian section, either because of the patient's wish or due to the obstetrician's recommendation, and 5 deliveries were spontaneous births. In 6 cases, the mode of delivery is unknown. All babies were in good health and without any fetal abnormalities.

Discussion

The comparison of glioma patients who gave birth to a child and glioma patients who were similar in tumor histology, EoR, and tumor location, but nulliparous, provides evidence that pregnancy and child delivery seem not to have an impact on disease progression and on OS of glioma patients. Furthermore, in the present study, gliomas neither had an impact on delivery nor on the children's development.

Recently, similar results were observed by a Norwegian study examining the data of the Medical Birth Registry of Norway and the Cancer Registry of Norway [25]. They identified 65 patients giving birth to 95 children after low-grade glioma diagnosis as well as 281 female low-grade glioma patients without history of gravidity. Interestingly, increasing parity was associated with longer survival in the univariate

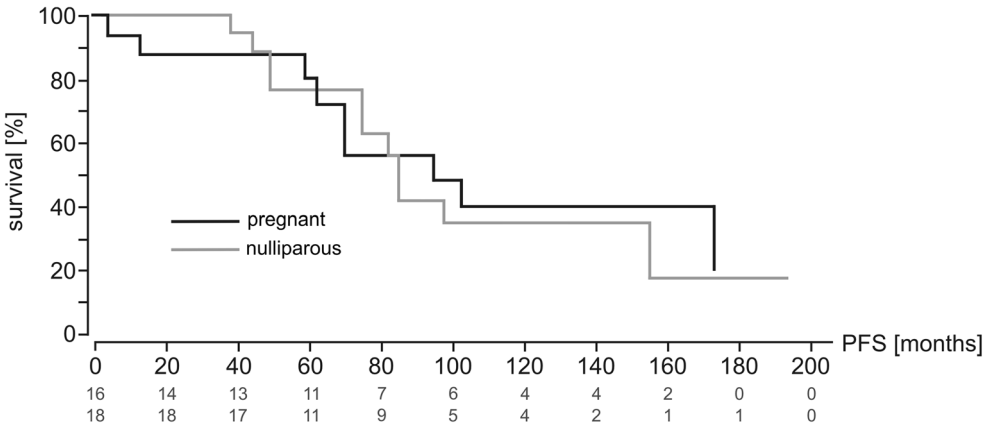

Fig. 1 Kaplan-Meier survival estimates of PFS in glioma patients who became pregnant and in nulliparous glioma patients

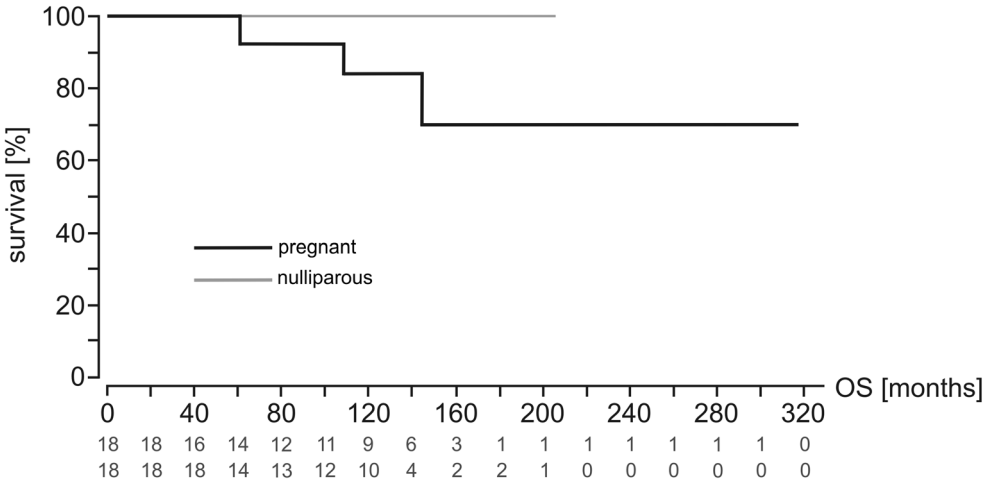

Fig. 2 Kaplan-Meier survival estimates of OS in glioma patients who became pregnant and in nulliparous glioma patients

model, but failed to be of significance in the adjusted Cox analysis. However, in contrast to our present work, and although this analysis only comprised patients with low-grade gliomas, molecular markers were not taken into consideration, neither were tumor location EoR.

To our knowledge, no other study compared the clinical course of pregnant and nulliparous glioma patients in a matched-pair analysis.

Evolution of glioma during pregnancy

Only recently, a systematic review on pregnancy in glioma patients has been performed by van Westrhenen et al., considering not only neuro-oncological, but also medical and obstetrical treatment of pregnant glioma patients [28]. According to our literature review, data of 136 patients with a known WHO grade II or WHO grade III glioma prior to pregnancy have been reported on so far [4, 12, 14, 20–22, 25, 28, 31, 32]. Three of these publications originated from the same French study group and investigated tumor growth rates during altogether 41 pregnancies in 38 patients [20–22]. In all but 4 cases of available MRIs during pregnancy (27/31), an increase in the velocity of diametric expansion (VDE) of the tumor was diagnosed. Despite the observation of clinical deterioration driven by tumor-related symptoms in 41.5% (17/41) of pregnancies, Peeters et al. did not find a correlation of tumor growth with clinical symptoms [22]. However, they identified the need of oncological treatment after birth to be

Table 3 Univariate and multivariate analysis of parameters associated with progression-free and overall survival

		Progression-free survival (months)			Overall survival (months)		
		Univariate analysis		Multivariate analysis	Univariate analysis		Multivariate analysis
		Median (95% CI)	*p* value	*p* value	Median (95% CI)	*p* value	*p* value
Pregnancy	Yes	86.4 (60.2–112.6)	0.93	0.69	116.8 (82.7–150.9)	0.79	0.99
	No	85.0 (63.7–106.3)			111.5 (88.0–135.0)		
Age	< 27.3	97.7 (69.7–125.6)	0.15	0.16	129.8 (95.3–164.3)	0.13	0.91
	> 27.3	75.0 (56.6–93.4)			100.1 (77.8–122.3)		
Resection	GTR	88.3 (69.3–107.2)	0.65	0.84	109.0 (88.7–129.4)	0.47	0.85
	STR/PR	80.6 (46.6–114.7)			124.3 (76.2–172.4)		
Re-resection	Yes	88.0 (62.5–113.5)	0.84	0.95	141.5 (97.1–185.8)	0.04	0.50
	No	84.6 (62.9–106.2)			100.5 (80.5–120.4)		
Chemotherapy	Yes	67.4 (48.5–86.2)	0.03	0.06	115.6 (81.4–149.9)	0.89	0.96
	No	102.1 (77.8–126.5)			112.8 (88.1–137.5)		
Radiotherapy	Yes	71.9 (51.2–92.7)	0.10	0.91	113.1 (79.1–147.1)	0.92	0.97
	No	98.0 (73.7–122.4)			115.0 (90.1–140.0)		
Radio- and Chemotherapy	Yes	65.9 (44.4–87.4)	0.03	0.92	112.5 (73.4–151.6)	0.89	0.99
	No	99.9 (77.8–121.9)			115.3 (92.9–137.7)		

significantly associated with increased tumor growth during pregnancy, with a median interval between oncological treatment and delivery coming up to 2 months.

Concerning tumor progression during or after pregnancy, Yust-Katz et al. made a similar observation [31]. In their study, 8 of 18 patients with WHO grade II or WHO grade III were diagnosed with progressive disease during pregnancy or immediately after delivery. Nonetheless, since all these patients only had undergone biopsy or partial resection before, the direct correlation of tumor progression and pregnancy had to remain unclear.

In the present study, MRI was avoided in all but one patient during pregnancy, according to the Guidelines for Diagnostic Imaging During Pregnancy and Lactation [9]. Therefore, the VDE of tumors could not be determined during this period. However, we did not observe an association of tumor progression with pregnancy, carrying out MRI controls 4.3 ± 3.6 months after birth. In total, disease progression was diagnosed during the first trimester and after pregnancy in one and four patients, respectively, resulting in death in one patient only a few weeks after delivery, as described in the "Results" section. In 3 patients, tumor progression resulted in oncological treatment at a median of 47.6 months after birth; the remaining patient wished to undergo further controls before oncological treatment. Interestingly, in our group, there was no difference in PFS ($p = 0.93$ and $p = 0.69$) comparing child-bearing and nulliparous patients in matched-pair analyses. Despite the cohort's inhomogeneity—due to the inclusion of patients with WHO grade II and WHO grade III gliomas of different molecular markers, their difference in EoR, and in adjuvant treatment—the observed median time to progression of 5.8 years and 6.2 years in glioma patients with and without a history of gravidity is in line with previously reported periods to progression of low-grade gliomas and even slightly longer [6, 16, 26].

Influence of pregnancy on OS in glioma patients

In both groups of glioma patients, OS after tumor diagnosis was similar to higher compared to data reported in the literature [6, 8, 15, 26, 29]. The prolonged OS may be attributed to the cohort's young age and female sex, both known to be independent prognostic factors [5, 8]. Equally, this prolonged OS might have been influenced by the high amount of gross total or subtotal tumor resection, the latter being defined as EoR > 90%, although EoR could not be identified as a prognostic factor for OS in the uni- and multivariate analysis. Thus, 5-year overall survival after first surgery was 100% for all patients, with exception of 3 patients in each group who were followed-up less than 5 years since tumor diagnosis. All but 3 patients who gave birth to a child were alive at a mean follow-up of 9.7 ± 5.7 years, whereas all nulliparous patients were still alive after a mean follow-up of 8.9 ± 4.2 years. Neither the univariate nor the multivariate analysis revealed a difference in OS between patients with and patients without a history of gravidity. Interestingly, Roenning et al. found radiotherapy to be associated with reduced survival in 346 young female low-grade glioma patients at a median follow-up over 15.2 years, whereas chemotherapy had no influence on patients' survival [25]. While Smith et al. observed comparable results when evaluating the outcome of 216 patients suffering from low-grade glioma [26], the EORTC 22033-26033 trial including 477 patients with low-grade glioma did not find a difference in outcome at a median of 4 years after randomization to temozolomide chemotherapy or radiotherapy alone [3]. Median OS was not reached in the EORTC 22033-26033 trial, and patients with mutations of IDH 1 or 2 genes and no co-deletion of chromosomal arms 1p/19q did not display a prolonged PFS with radiotherapy compared with temozolomide chemotherapy. Of note, none of these studies included EoR in their analyses. Only recently, new evidence has been provided that not only extent of low-grade glioma resection but mainly postoperative tumor volume significantly influences PFS and OS [24, 26, 30]. As shown by Wijnenga et al., even very small tumor remnants may negatively affect OS, particularly in IDH mutated glioma patients, whereas irradiation and chemotherapy after tumor resection had no impact on OS [30]. Interestingly, in the present study, EoR had no impact on PFS and OS. It is very probable that the overall small number of patients, the small number of patients who underwent only partial resection ($n = 3$), and our definition of subtotal resection being determined as EoR > 90% may all have contributed to this finding.

Although whether irradiation nor chemotherapy affected OS in both, glioma patients who gave birth to a child and nulliparous glioma patients, PFS was significantly increased in patients having been treated by chemotherapy after surgery. By contrast, prolonged OS was exclusively associated with re-resection of recurrent tumor, but only in the univariate analysis, whereas none of the parameters investigated showed to be of significant influence for OS in the multivariate analysis.

Effect of hormones on glioma

The influence of endogenous and exogenous hormones on glioma risk has been addressed by several studies during the last years [1, 2, 11, 17, 19, 23]. Thus, both hormone-replacement therapy and oral contraception have been shown to lower the cumulative risk for glioma in case-control and cohort studies [17]. Evidence for the protective nature of childbearing on glioma risk has been provided by a meta-analysis including 6 studies that analyzed the influence of pregnancy on the development of glioma [23]. The calculated pooled relative risk for parous versus nulliparous women was 0.837 (95% CI: 0.674–1.040). All of these results indicate that hormones may have a protective effect on glioma pathogenesis.

Taking these findings into account, and regarding the results of our present study, we deduce that pregnancy has no

negative effect on already existing glioma. However, whether childbearing is perhaps even protective against tumor progression has to remain unclear, considering the small number of glioma patients becoming pregnant and the number of confounding variables.

Strengths and limitations

Despite the low level of evidence of the study design as a case-control study, and although only recently a cohort study on a higher number of patients has been published [25], to our knowledge, this is the first study taking molecular markers and EoR into account when comparing glioma patients with and without a history of gravidity. Furthermore, their long follow-up period of 9.7 ± 5.7 years and 8.9 ± 4.2 years, respectively, allowed for a valid evaluation of patients' clinical course and oncological results.

Nevertheless, a major limitation of this study is its small number of patients, thus not allowing a powerful analysis of data. In fact, the number of young female glioma patients is small and becomes even smaller for young female glioma patients becoming pregnant after tumor treatment. Furthermore, the inclusion of gliomas of different molecular subgroups and the different adjuvant chemotherapeutical strategies applied in these patients did not allow for a meaningful respective correction. Moreover, molecular markers of gliomas were not available in all patients—because tumor tissues were either no longer existing or of poor quality for immunohistochemistry—so that matching of patients was mainly driven by types of glioma. Gliomas being negative for IDH1-R132H and with loss of ATRX were highly suspicious of carrying IDH mutations other than IDH1-R132H. In one case of astrocytoma WHO grade II, the retrospective diagnosis of IDH1-R132H negative, ATRX positive glioma, being suspicious for high-grade glioma, was not respected because of the patient's progression-free survival for 12.3 years after solely tumor resection.

Obviously, inherent to the retrospective nature of the study, a selection bias cannot be excluded. However, we sought to increase the quality of the data by performing a matched-pair analysis. Control patients' selection was exclusively driven by the characteristics of glioma patients who became pregnant after tumor diagnosis.

In our opinion, a prospective multicenter registry is needed for further advancing our knowledge in this field.

Conclusion

Young glioma patients should always be counseled on eventual desired pregnancy. While obstetricians may inform patients on fertility-preservation such as cryo-conservation [18], oncologists should be aware of the interaction of glioma, adjuvant treatment, and pregnancy.

In our opinion and corresponding to the findings of our study, patients with stable low-grade glioma considering childbearing can be assisted in their pursuit of becoming pregnant. The comparison of glioma patients giving birth to a child and of nulliparous glioma patients did not reveal a difference in their course of disease, and all children born to glioma patients were in good health and without congenital malformations. Furthermore, according to our data, there is no need for abortion in pregnant glioma patients. Furthermore, according to our data, abortion seems not to be necessary in pregnant glioma patients with stable disease at the moment of conception. However, patients equally need to be conscientiously informed about their limited life expectation due to glioma, regardless of giving birth to a child.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (ethics committee of the University Hospital Frankfurt) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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