Pregnancies after Childhood Craniopharyngioma: Results of KRANIOPHARYNGEOM 2000/2007 and Review of the Literature

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Keywords

Craniopharyngioma · Hypopituitarism · Imaging · Pituitary tumors · Pregnancy · Reproduction

Abstract

Background: Data on female fertility, pregnancy, and outcome of offspring after childhood-onset craniopharyngioma (CP) are rare. **Study Design:** Observational study on pregnancy rate and offspring outcome in female CP patients recruited in KRANIOPHARYNGEOM 2000/2007 since 2000. **Results:** A total of 451 CP patients (223 female) have been recruited, and 269 (133 female) were postpubertal at study. Six of 133 female CP patients (4.5%) with a median age of 14.9 years at CP diagnosis had 9 pregnancies, giving birth to 10 newborns. Three patients achieved complete surgical resections. No patient underwent postoperative irradiation. Five natural pregnancies occurred in 3 CP patients without pituitary deficiencies. Four pregnancies in 3 CP patients with hypopituitarism were achieved under assisted reproductive techniques (ART) (median 4.5 cycles, range: 3–6 cycles). Median maternal age at pregnancy was 30 years (range: 22–41 years). Six babies (60%) were delivered by caesarean section. Median gestational age at delivery was 38 weeks (range: 34–43 weeks); median birth weight was 2,920 g (range: 2,270–

3,520 g), the rate of preterm delivery was 33%. Enlargements of CP cysts occurred in 2 women during pregnancy. Other complications during pregnancy, delivery, and postnatal period were not observed. **Conclusions:** Pregnancies after CP are rare and were only achieved after ART in patients with hypopituitarism. Close monitoring by an experienced reproductive physician is necessary. Due to a potentially increased risk for cystic enlargement, clinical, ophthalmological, and MRI monitoring are recommended in patients at risk. Severe perinatal complications, birth defects, and postnatal morbidity of mothers and offspring were not observed.

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Introduction

Craniopharyngioma (CP) is a rare benign embryonal malformation derived from ectoblastic remnants of Rathke's pouch [1–4]. Treatment options for CP include surgical resection with or without consecutive radiation therapy. Surgical interventions should be performed with the goal of preserving the function of vital neurovascular, optic, and hypothalamic structures [5]. Long-term morbidity of CP patients is caused by visual, neuroendocrine, and neurobehavioral sequelae. Social relations and part-

nerships are frequently impaired by neurobehavioral disturbances due to hypothalamic dysregulation [6–8]. Female CP patients with hypopituitarism frequently suffer from amenorrhea and infertility. Hypopituitarism is associated with pregnancy complications, such as abortion, anemia, pregnancy-induced hypertension, placental abruption, premature birth, postpartum hemorrhage [9], transverse line, and small-for-gestational-age (SGA) newborns [10]. Pregnancies in childhood-onset CP patients are uncommon and rarely reported in the literature.

Patients and Methods

This observational study included 223 female patients diagnosed with childhood-onset, adamantinomatous CP (aCP) who have been recruited in the multinational trials KRANIOPHARYNGEOM 2000/2007 since the year 2000. One hundred and thirty-three of 223 female CP patients were postpubertal at the time of study. We contacted all 133 female postpubertal patients recruited in KRANIOPHARYNGEOM 2000/2007 and asked by questionnaire and/or telephone interview about previous pregnancies including abortions. The pregnancy rate, ovulation induction, and obstetric and neonatal outcomes were investigated in this study.

The histological diagnosis of aCP was confirmed by a neuropathological reference panel in all cases. Pre- and postoperative imaging as well as follow-up imaging were reference-assessed by a neuroradiologist, blinded to clinical data. Neuroradiological assessment of CP location, degree of surgical resection, preoperative hypothalamic involvement (HI), and surgical hypothalamic lesions (HL) was performed on pre- and postoperative axial, coronal, and sagittal magnetic resonance imaging (MRI) as previously described [11, 12].

Statistical Methods

Descriptive data are provided. Patients' data are displayed as median (range) or frequency (percent).

Results

From the year 2000 onward, 451 patients (223 female/228 male) with childhood-onset aCP were recruited in the German trials KRANIOPHARYNGEOM 2000/2007 with a high grade of recruiting completeness. A total of 269 of these CP patients (133 female/136 male) were postpubertal at the time of study. The median age of 133 postpubertal females with aCP at the time of study was 24 years, ranging from 18 to 38 years (1st quartile: 21 years; 3rd quartile: 27 years). Six out of these 133 adult female CP patients (4.5%) reported 9 pregnancies resulting in the birth of 10 healthy newborns.

Pregnancy Cases

Case 1

An 8-year-old girl presented with precocious puberty leading to the diagnosis of aCP (tumor size: 2.04 cm²; solid tumor without cystic compartments), which extended to the suprasellar region with HI (grade 1). She underwent subtotal CP resection without postoperative irradiation. Subsequently, she developed isolated central diabetes insipidus (DI). As a result, she was treated with desmopressin as a treatment for central DI and a gonadotrophin-releasing hormone (GnRH) agonist for the treatment of precocious puberty. The desmopressin and GnRH agonist medication were finished at the age of 15 years without the necessity of hormonal substitution therapy later on. At the age of 22 years, she became naturally pregnant. A healthy 38-week male newborn was delivered by normal delivery weighing 2,880 g (25th centile [13, 14]). The mother breastfed her baby for 9 months.

Case 2

A 15-year-old girl presented with a reduced growth rate leading to the diagnosis of aCP (tumor size: 7.2 cm²), which could be completely resected. After surgery, she developed central hypothyroidism, adrenal insufficiency, and central DI. She received replacement therapy with L-thyroxine, hydrocortisone, and desmopressin. As she had the desire to have a child, she underwent six and three cycles of ovulation induction with human chorionic gonadotrophin (HCG) for her first and second pregnancy, consecutively. She conceived through the ovulation induction, and 2 healthy offspring were delivered by normal delivery at the gestational age of 38 and 38⁺⁶ weeks, respectively, weighing 2,660 g (15th centile [14]) and 2,960 g (25th centile [14]), respectively. The mother successfully breastfed both babies.

Case 3

A 21-year-old female presented with headaches. Subsequently, she was diagnosed with aCP, and her tumor was completely resected. She developed central DI, central hypothyroidism, central adrenal insufficiency, and gonadotrophin deficiency. Consequently, she required desmopressin, L-thyroxine, and hydrocortisone for hormonal substitution. She was diagnosed with type 2 diabetes mellitus when she was 24 years old. At the age of 37 years, she underwent fertility treatment and conceived after four cycles of ovulation induction with human menopausal gonadotrophin (HMG). Her body mass index at pregnancy was 41.4 kg/m². Following a cesarean section,

Fig. 1. Magnetic resonance imaging (T2 axial MRI) of the cystic craniopharyngioma progression (arrow) occurring during pregnancy in case 4 (a) and T2 axial MRI after resection of cystic CP during pregnancy in case 4 (b).

she delivered a female newborn weighing 3,520 g (91st centile [14]) at the gestational age of 37⁺² weeks. The mother was unable to breastfeed.

Case 4

A 15-year-old female was diagnosed with aCP due to a history of headaches. MRI of the brain revealed a cystic lesion at diagnosis. Her pituitary function was preserved after subtotal tumor resection without postoperative irradiation. Therefore, she did not require hormonal replacement. She became pregnant naturally two times, when she was 30 and 36 years old, respectively. Her pregnancies were otherwise uncomplicated apart from a significant enlargement of a pituitary cystic lesion during her first pregnancy (Fig. 1a). The cystic CP was completely resected during the first pregnancy (Fig. 1b). After complete resection, no cystic enlargement/relapse occurred during the second pregnancy. The patient underwent delivery by means of cesarean section for both pregnancies at the gestational ages of 40 and 41 weeks, respectively. The birth weight of the newborns was 2,270 g (50th centile [14]) and 2,350 g (50th centile [14]), consecutively. Both infants were bottle fed.

Case 5

A 10-year-old female presented with headaches. MRI revealed a solid CP without cystic compartments. An incomplete tumor resection was achieved without postoperative irradiation. Thereafter, she developed central adrenal insufficiency, central hypothyroidism, central DI, prolactin deficiency, and hypogonadotrophic hypogonadism. She was

on replacement therapy with hydrocortisone, L-thyroxine, desmopressin, and sex steroids. At the age of 34 years, she conceived dizygotic twins after five courses of HCG therapy. At 34 weeks of gestation, she developed preterm labor. Following a cesarean section, she delivered twins, a female infant weighing 2,270 g (50th centile [14]) and male infant weighing 2,350 g (50th centile [14]). The female newborn was diagnosed with a choroid plexus cyst. Artificial milk feeding was required due to lactation failure.

Case 6

A 26-year-old female complained of headaches and fatigue for 1 year. She had a normal past medical history and denied having any symptoms of endocrinopathy. The first MRI of the brain was conducted during her first pregnancy and demonstrated a partly cystic, sellar mass with typical imaging characteristics of CP. Her endocrine evaluation was normal. Thus, she did not receive any hormonal replacement therapy. No surgical intervention was performed. Apart from bleeding during early pregnancy, her first pregnancy was uneventful. At 43 weeks of gestation, a healthy male newborn was born with a birth weight of 3,800 g (25–50th centile [14]). Two years later, during her second natural pregnancy, it was discovered that her cystic lesion had significantly increased in size. Therefore, she underwent total tumor removal during pregnancy. The histopathological analysis showed the tumor to be aCP. She subsequently developed panhypopituitarism and required hormonal supplementation. She gave birth to a healthy late preterm baby weighing 2,800 g (50–75th centile [14]) by cesarean section.

Table 1. Characteristics of female patients recruited with childhood-onset adamantinomatous craniopharyngioma in KRANIOPHARYNGEOM 2000/2007 and postpubertal at the time of study

	Female CP patients without pregnancy	Female CP patients with pregnancy	Case					
			1	2	3	4	5	6
Patients, <i>n</i>	127	6	1	1	1	1	1	1
Age at CP diagnosis, years	12.0	14.9	7.8	14.8	20.5	15.1	10.1	29.0
BMI at CP diagnosis, SDS [49]	+0.66 (−3.23 to 10.02)	−0.10	+2.56	−0.10	−0.06	−0.50	−0.47	NA
Grade of preoperative HI [11], <i>n</i> (%)								
Grade 0	3 (2)	3 (50)		×		×	×	
Grade 1	18 (14)	1 (17)	×					
Grade 2	31 (24)	1 (17)			×			
NA	75 (59)	1 (17)						×
Presenting symptoms of CP at diagnosis, <i>n</i> (%)								
Headache	48 (38)	4 (67)			×	×	×	×
Reduced growth rate	18 (14)	1 (17)		×				
Precocious puberty	1 (1)	1 (17)	×					
Other	37 (29)	0						
NA	23 (18)	0						
Substituted hypothalamic-pituitary axes, <i>n</i> (%)								
No axes	3 (3)	2 (33)	×			×		
1 axis	3 (3)	1 (17)						×
2 axes	6 (7)	0						
3 axes	15 (17)	2 (33)		×	×			
4 axes	32 (36)	1 (17)					×	
5 axes	30 (34)	0						
Degree of resection at primary diagnosis, <i>n</i> (%)								
Complete resection	32 (25)	2 (33)		×	×			
Incomplete resection	83 (65)	3 (50)	×			×	×	
No surgery	3 (2)	1 (17)						×
NA	9 (7)	0						
Grade of surgical HL after initial surgery [11], <i>n</i> (%)								
Grade 0	13 (10)	3 (50)		×		×	×	
Grade 1	21 (16)	1 (17)	×					
Grade 2	21 (16)	1 (17)			×			
NA	72 (57)	1 (17)						×
Irradiation, <i>n</i> (%)	57 (45)	0 (0)						

Data are depicted for 127 patients without pregnancies and 6 patients giving birth to 10 newborns. Values for age and BMI at CP diagnosis are expressed as median (range). HI, hypothalamic involvement; HL, hypothalamic lesion; CP, childhood-onset craniopharyngioma; NA, not available.

The most common symptoms leading to CP diagnosis in these 6 patients were headaches, reduced growth rate, and precocious puberty. Median age at aCP diagnosis was 14.9 years, ranging from 7.8 to 29 years. Two of 6 patients presented with HI at initial CP diagnosis. Complete surgical resections could be achieved in 3 patients; one of them (case 3) presenting with presurgical HI. Surgical HL were observed in 2 patients (case 1: grade 1; case 3: grade 2) [11, 12].

Two of 6 patients presented with mainly cystic lesions at the time of CP diagnosis (cases 4 and 6). Pregnancies could be successfully achieved also in CP patients with initial presurgical HI and surgical HL (cases 1 and 3). No patient underwent irradiation. After surgery, 2 patients (cases 1 and 4) had normal pituitary function, while 4 others had multiple pituitary deficiencies requiring hormonal supplementation. Patient characteristics are shown in Table 1.

Table 2. Characteristics of female patients recruited with childhood-onset adamantinomatous craniopharyngioma in KRANIOPHARYNGEOM 2000/2007 and known pregnancies

Case	Age at pregnancy, years	Pregestational endocrine substitution	G/P/A	BMI at pregnancy, kg/m ²	Pregnancy type	Ovulation induction			Endocrine substitution during pregnancy	Pregnancy complications	MOD
						age at 1st attempt, years	induction regimen	cycles, n			
1	22	none	1/0/0	26.50	NP	none	none	none	none	none	ND
2	39	HC, L-T4, V	1/0/0	23.28	OI	38	HCG	6	HC, L-T4, V	none	ND
	41	HC, L-T4, V	2/1/0	23.31	OI		HCG	3	HC, L-T4, V	none	ND
3	38	insulin, HC L-T4, V	1/0/0	41.40	OI	37	HMG	4	insulin, HC L-T4, V	maternal hypoglycemia	CS
4	30	none	1/0/0	21.97	NP	none	none	none	none	cystic progression	CS
	36	none	2/1/0	25.31	NP	none	none	none	none	none	CS
5	28	HC, L-T4, V, sex steroids	1/0/0	32.80	OI	25	HCG	5	HC, L-T4, V	twin with preterm labor	CS
6	27	none	1/0/0	NA	NP	none	none	none	none	bleeding in early pregnancy	ND
	29	none	2/1/0	NA	NP	none	none	none	none	cystic progression	CS

Data are depicted for the course of pregnancy and the deliveries. A, abortus; BMI, body mass index; CS, caesarean section; G, gravida; HCG, human chorionic gonadotrophin; HMG, human menopausal gonadotrophin; HC, hydrocortisone; L-T4, L-thyroxine; MOD, mode of delivery; NP, natural pregnancy; ND, normal delivery; NA, not available; OI, ovulation induction; P, para; V, vasopressin.

Median age at pregnancy in 6 CP patients was 30 years, ranging from 22 to 41 years. Natural pregnancies occurred in 5 pregnancies of 3 CP patients with normal pituitary function. All patients with pituitary insufficiency required assisted reproductive techniques (ART) in order to conceive (after a median of 4.5 cycles of HCG or HMG, range: 3–6 cycles).

During two pregnancies after initial complete CP resection (cases 2 and 3), no relapses were observed. Furthermore, no progression of residual solid CP (without cystic compartments) occurred during pregnancy after initial incomplete CP resection (cases 1 and 5). In the 2 patients (cases 4 and 6) with cystic CP detectable on MRI who became pregnant, cystic enlargement was detectable during pregnancy. In case 4, cystic remnants of the CP after initial incomplete resection progressed. In case 6, a cystic CP was diagnosed by MRI during first pregnancy and progressed during second pregnancy leading to complete resection. Accordingly, progressions were detectable exclusively for cystic CP compartments during pregnancy. Other severe complications during pregnancy, delivery, and postnatal period such as abortion, pregnancy inducing hypertension, placental abruption, and postpartum hemorrhage were not observed.

There were 10 live births with no miscarriages or fetal deaths. Four babies, including one set of twins were born at gestational age less than 38 weeks. Median birth weight

was 2,920 g (on 25th centile [14]), ranging from 2,270 to 3,800 g. Only one baby was observed to be SGA with birth weight below the 10th centile [14] (case 4). Six of 10 babies were delivered by caesarean section. There were no reports of congenital abnormalities, although one baby was diagnosed with a choroid plexus cyst. Three patients were unable to breastfeed. Details of the 9 pregnancies, 8 singletons and one set of twins, are shown in Tables 2 and 3.

Discussion

There are two subtypes of CP: aCP and papillary CP (pCP) [15, 16]. The *BRAF V600E* mutation is characteristic of pCP, while most of aCP harbor a mutation of the β -catenin gene [15, 17]. ACP has a high incidence in children and adolescents [15]. Recurrence in aCP is associated with increased vascular endothelial growth factor (VEGF) and fibroblast growth factor expression [17]. The aim of CP treatment is to maximize disease control while minimizing patient morbidity [18]. Between 2001 and 2019, only 21% of CP patients recruited in KRANIOPHARYNGEOM 2000/2007 underwent gross total resection, while incomplete resection was achieved in 65% of CP patients, followed by irradiation in 40% of CP patients.

Table 3. Characteristics on pregnancy, delivery, and offspring of female patients recruited with childhood-onset adamantinomatous craniopharyngioma in KRANIOPHARYNGEOM 2000/2007

Case	GA, weeks	Gender	Apgar score	Birth weight, g (centile) [10]	Birth length, cm (centile) [10]	Fetal abnormality	Breastfeeding, months
1	38	M	10/10	2,880 (P25)	51 (P75)	none	9
2	38	F	10/10	2,660 (P9–25)	51 (P91)	none	12
	38 ⁺⁶	F	10/10	2,960 (P25)	51 (P75–91)	none	8
3	37 ⁺²	F	NA	3,520 (P91)	51 (P91)	none	none
4	40	M	9/10	~3,000 (P9–25)	~51 (P50)	none	12
	41	F	10/10	~3,000 (P9)	~51 (P50)	none	7
5	34	F	10/10	2,270 (P50)	44 (P50)	choroid plexus cyst	none
		M	10/10	2,350 (P50)	45 (P75)	none	none
6	43	M	10/10	3,800 (P25–50)	51 (P50)	none	none
	36	F	10/10	2,800 (P50–75)	48 (P75)	none	none

F, female; M, male; GA, gestational age; NA, not available; P, percentile.

Long-term outcome and quality of survival after CP are frequently impaired due to factors which also have direct implications for social and emotional behavior [6], partnership relations and bonding [19–22], and affectivity and neuropsychological balance. Sterkenburg et al. [20] reported on lower rates of partnership in CP with HI when compared to patients without HI and lower rates of partnerships and pregnancies in CP patients when compared with healthy siblings. This could explain the observed low pregnancy rate, as 38/32% of female CP patients included in our study presented with HI/damage, respectively. However, 2 patients (34%) with successful pregnancy were diagnosed with HI in our cohort (cases 1 and 3).

A recent study on changes of health-related quality of life during the first 3 years after surgery revealed that HI and surgical damage had a negative impact on social behavior towards friends whereas social behavior in the family was not influenced [22]. These observations might indicate that due to hypothalamic syndrome many CP patients stick to familial bonding, whereas social relations to friends and partnerships are less frequent and intense. Based on reported deficits in psychosocial abilities, neuropsychological sequelae and neuroendocrine secretion of oxytocin after childhood-onset CP [6–8], low pregnancy rates in these patients are likely to also reflect at least in part deficits in terms of social behavior.

In the literature, pregnancies in CP patients are rarely reported. Seven previous studies describing pregnancy outcomes in CP patients reported on 9 women with 16

pregnancies resulting in 12 live births, as shown in Table 4. Most of the patients (67%) underwent a caesarean delivery at a median gestational age of 38 weeks with no congenital abnormalities reported. Natural pregnancy was reported in 2 pregnancies of one CP patient with normal pituitary function [23]. Similar to the literature, we observed 5 naturally achieved pregnancies in 3 patients with a normal pituitary function. Accordingly, we conclude that treatment strategies preserving pituitary function are best for fertility after CP. However, pituitary integrity is rarely achieved in CP resection due to anatomical location of the tumor. All of the CP patients with hypopituitarism underwent ART in order to conceive. With regard to fetal growth, a higher rate of SGA (36%) was observed in the reviewed literature compared to our study (10%).

Pregnancy is associated with physiological pituitary enlargement reversible within 6 months postpartum [24]. Thus, sellar/parasellar masses such as CP should be monitored carefully during pregnancy [25]. We reviewed the literature concerning cases of CP diagnosed primarily during pregnancy. The first case was reported by Fischer in 1935 [26]. Previous case reports on primary diagnosis of CP and/or CP tumor progression during pregnancy are listed in Table 5. Nine women were diagnosed with primary CP during pregnancy [26–31]. Among these 9 women, there were 2 who presented with solid CP tumor progression during pregnancy [32, 33]. The CP tumor characteristics comprised 5 solid tumors, 2 cystic tumors, one mixed solid-cystic tumor, and one

Table 4. Published case reports on pregnancies and neonatal outcome in previously diagnosed CP patients

First author [Ref.], year	Case	Age at pregnancy, years	Pregnancy			endocrine substitution during pregnancy	complication	Neonatal outcome		
			gravida/ para/ abortion	type of pregnancy	ovulation induction age at 1st attempt, years			MOD	GA	birth weight (centile) [10] feeding
Overton [50], 2002	1	NA	1/0/0	OI	29	1	miscarriage at 10 weeks			
		NA	2/0/1	OI	1		miscarriage at 10 weeks			
		NA	3/0/2	OI	1		PROM at 34 weeks transverse lie and arm prolapse	CS	34	2,540 g (>50th)
		NA	4/1/2	OI	8		PROM at GA 35 weeks breach presentation	CS	35	2,650 g (50th)
		NA	1/0/0	OI	34	14	cortisone, L-thyroxine, desmopressin	CS	38	3,450 g (50th)
		NA	2/1/0	OI	4		none	CS	38	2,620 g (10th)
		NA	1/0/0	OI	33	3	HC, L-thyroxine, desmopressin	CS	39	2,580 g (<3rd)
Kübler [10], 2009	1	35	1/0/0	OI	30	3	HC, L-thyroxine, desmopressin	CS	38 ⁺⁶	2,950 g (25th)
Begon [51], 1993	1	NA	1/0/0	OI	28	NA	miscarriage at 7 weeks			
		NA	2/0/1	OI	NA	NA	miscarriage at 9 weeks			
		NA	3/0/2	OI	NA	NA	none	CS	term	NA
Corral [52], 1972	1	NA	1/0/0	OI	27	6	HC, L-thyroxine desoxycorticosterone, desmopressin	ND	term	2,500 g (<10th)
Hayashi [53], 2002	1	27	1/0/0	OI	NA	7	fetal distress	CS	40	2,764 g (<10th)
Volz [54], 2002	1	NA	1/0/0	OI	34	8	none	ND	37	3,450 g (90th)
Kodama [23], 1986	1	23	1/0/0	NP	none	none	none	ND	term	3,100 g (25–50th)
		28	2/1/0	NP	none	none	none	ND	term	2,340 g (<10th)

APH, antepartum hemorrhage; CS, caesarean section; GA, gestational age; HC, hydrocortisone; HT, hypertension; MOD, mode of delivery; NP, natural pregnancy; ND, normal delivery; NA, not available; OI, ovulation induction; OHSS, ovarian hyperstimulation syndrome; PROM, premature rupture of membranes.

Table 5. Published case reports on primary craniopharyngioma diagnosed during pregnancy, treatment, and neonatal outcome

First author [Ref.], year	Age at pregnancy, years	GA at CP diagnosis, weeks	Presenting symptoms	Disease status during pregnancy	Tumor characteristics	Treatment	Neonatal outcomes
Johnson [30], 1993	27	24	headache decreased VA	first diagnosis	mixed solid-cystic	complete resection	healthy, term newborn
Fischer [26], 1935	36 27	28 20	decreased VA decreased VA	first diagnosis first diagnosis	solid cystic	craniotomy craniotomy	preterm 34 weeks therapeutic abortion
Sachs [27], 1978	24	28	decreased VA	first diagnosis	cystic	total excision	healthy, term newborn
Van der Wildt [28], 1980	24	20	DI during pregnancy, decreased VA 5 months after delivery	first diagnosis	NA	NA	healthy, late preterm 36 weeks, BW 2,460 g (25–50th centile)
Hiett [29], 1990	22	27	decreased VA headache	first diagnosis	solid	total excision	healthy, preterm 34 weeks, BW 2,550 g
Maniker [32], 1996	35	8	headache, decreased VA	first diagnosis and disease progression	solid	total excision	healthy, preterm 33 weeks
Aydin [33], 1999	19	20	decreased VA	first diagnosis	solid	transsphenoidal resection	healthy, term newborn
	23	22	headache, decreased VA	disease progression	solid	total resection	healthy, term newborn
Zoia [31], 2014	32	30 ⁺¹	decreased VA	first diagnosis	hard-elastic mass	subtotal tumor removal	preterm 33 ⁺³ weeks

BW, birth weight; CP, craniopharyngioma; DI, diabetes insipidus; GA, gestational age; NA, not available; VA, visual acuity.

patient without available data. In these 10 pregnancies, MRI monitoring was performed during 3 pregnancies of 2 patients due to complaints about headaches and visual deterioration [32, 33]. The other 7 pregnancies had no MRI monitoring of CP during pregnancy. In the 3 pregnancies with MRI follow-ups, all MRIs of CP showed solid CP tumor enlargement exclusively, with no cystic progression observed. In our study, we observed 2 cystic CP tumor enlargements during 2 pregnancies. The only patient with solid residual CP after incomplete primary resection (case 5) experienced no solid tumor progression during pregnancy.

There are few molecular studies reporting on an increased expression of estrogen receptors mRNA in CP [34, 35]. Additionally, receptors for progesterone, leptin, insulin-like growth factor-1 (IGF-1), growth hormone (GH)-releasing hormone, and GH were detectable on CP surface [36]. The expression of estrogen and GH receptors positively correlated with tumor size and cell proliferation index [35]. A previous case report revealed an increase in CP size after receiving GH and estrogen substitution in one patient and estrogen substitution alone in 2 patients [37]. The *in vitro* study of Li et al. [38] indicated that GH and its endogenous mediator IGF-1 promote cell

growth, while tamoxifen inhibits CP growth. In clinical trials, GH substitution therapy was not associated with reduced 3-year event-free survival rates in childhood-onset CP patients [39]. Yu and Melmed [40] demonstrated that the overexpression of pituitary tumor transforming gene (PTTG) plays a major role in pituitary oncogenesis. PTTG mRNA expression is regulated by estrogen; a high level of estrogen leads to increased PTTG expression. Increased pituitary PTTG mRNA expression was reported to be associated with an approximately 3.4-fold increase in pituitary fibroblast growth factor and an approximately 2.2-fold increase in VEGF expression, which are linked to CP tumor progression [41]. VEGF, also known as the vascular permeability factor, is a key regulator of increased vascular permeability and neovascularization of a variety of tumors [42]. In an animal model, Senger et al. [43] could show that VEGF promotes the accumulation of ascites fluid. Stockhammer et al. [42] reported on an association between the elevation of VEGF and the progression of brain tumor cysts. Fourteen patients with primary cystic brain tumors of diverse histology, including 3 patients with CP were investigated for VEGF concentrations in cyst fluid. Aspirated fluids of all tumor cysts revealed high VEGF levels. Moreover, several studies ob-

served that cystic formation in cerebellar gliomas and hemangioblastomas was related to VEGF expression [44, 45], being associated with increased microvascular permeability and thus leading to extravasation of plasma proteins and fluid accumulation [46, 47]. We speculate that the physiological increase in VEGF levels during pregnancy could be a factor inducing cystic progression of CP during pregnancy. Due to estrogen normally being formed in the ovaries and also being produced by the placenta at elevated levels during pregnancy to help maintain a healthy pregnancy, we hypothesize that increased estrogen levels during pregnancy might play a role in the enlargement of cystic CP during pregnancy. However, further studies are required to confirm this estrogen effect in CP patients.

We analyzed the rate of pregnancies, gestational complications, and outcome of mothers and newborns in female patients after childhood-onset aCP. Due to the retrospective design and small cohort size, the results of our study are limited. Some observations and our discussion on pathophysiological mechanisms of cystic CP enlargement during pregnancy are speculative at this point. Pregnancies are rare events after CP, which on its own is a rare disease. However, due to the high degree of recruiting completeness in our Craniopharyngioma Registry, we conclude that the observed rate of pregnancies (4.5%) represents a valid and unique finding. However, several factors influencing pregnancy rates, such as male fertility factors and the patients' wish to become pregnant, were not analyzed in our study.

Our recommendation to monitor cystic CP during pregnancy for early detection of cystic enlargement is based on our observations in few cases and needs to be confirmed by studies on larger cohorts. Beneficial maternal and newborn outcome after CP is an important finding for patients and treating physicians but also needs further analysis in larger groups. The recommendation to resect CP while preserving pituitary gland and stalk integrity for best perspectives on fertility and natural conception is not realistic. Due to the anatomical location, pituitary gland and stalk frequently cannot be separated from the tumor and frequently need to be sacrificed during tumor resection of CP.

We conclude that pregnancies after CP are rare. ART have led to increased pregnancy rates in CP patients with pituitary insufficiency. With regard to the deficiencies of the hypothalamic-pituitary axes, close monitoring and care by an experienced reproductive physician is a vital factor in the achievement of successful pregnancy and neonatal outcomes. The most common pre-

sentations in patients who were diagnosed with CP during pregnancy were visual deterioration and headache. Accordingly, we recommend careful history and clinical examinations including ophthalmological assessment for pregnant CP patients. Especially for those CP patients with cystic compartments of their CP, we recommend an MRI without contrast and limited to sellar and parasellar slices [48] at the beginning of the second trimester for baseline assessment. MRI of CP should be performed in all CP patients who experience visual deterioration and headaches during pregnancy respecting the guidelines for MRI during pregnancy [48]. Severe complications during pregnancy, delivery, and the post-natal period as well as any birth defects were not observed.

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Statement of Ethics

All procedures performed in our study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The studies KRANIOPHARYNGEOM 2000 (Clinical trial registration number: NCT00258453) and KRANIOPHARYNGEOM 2007 (Clinical trial registration number: NCT01272622) were approved by the local standing committee on ethical practice of the Medizinische Fakultät, Julius-Maximilians-Universität Würzburg, Germany (140/99; 94/06, respectively), and written parental and/or patient consent was obtained in all cases.

Disclosure Statement

H.L.M. has received reimbursement of participation fees for scientific meetings and continuing medical education events from the following companies: Ferring, Lilly, Pfizer, Sandoz/Hexal, Novo Nordisk, Ipsen, and Merck Serono. He has received reimbursement of travel expenses from Ipsen and lecture honoraria from Pfizer. The other authors declare that they have no conflict of interest.

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Author Contributions

P.S. researched the data and wrote the manuscript. S.B. collected the data by questionnaire or telephone interview, contributed to the analytical plan and discussion and reviewed/edited the manuscript. B.B. did neuroradiological assessment of all imaging. B.B. is the neuroradiologist who performs reference as-

essment of imaging in all patients recruited in KRANIO-PHARYNGEOM 2000/2007. She prepared the imaging data and their presentation and reviewed/edited the manuscript. H.L.M. initiated and conducted the multicenter trials KRANIO-PHARYNGEOM 2000 and KRANIOPHARYNGEOM 2007, contributed to the analytical plan and discussion, and reviewed/edited the manuscript.

References

- Müller HL, Merchant TE, Puget S, Martinez-Barbera JP. New outlook on the diagnosis, treatment and follow-up of childhood-onset craniopharyngioma. *Nat Rev Endocrinol*. 2017 May;13(5):299–312.
- Bogusz A, Müller HL. Childhood-onset craniopharyngioma: latest insights into pathology, diagnostics, treatment, and follow-up. *Expert Rev Neurother*. 2018 Oct;18(10):793–806.
- Müller HL. MANAGEMENT OF ENDOCRINE DISEASE: Childhood-onset craniopharyngioma: state of the art of care in 2018. *Eur J Endocrinol*. 2019 Apr;180(4):R159–74.
- Müller HL, Merchant TE, Warmuth-Metz M, Martinez-Barbera JP, Puget S. Craniopharyngioma. *Nat Rev Dis Primers*. 2019 Nov;5(1):75.
- Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev*. 2006 Jun;27(4):371–97.
- Ozyurt J, Thiel CM, Lorenzen A, Gebhardt U, Calaminus G, Warmuth-Metz M, et al. Neuropsychological outcome in patients with childhood craniopharyngioma and hypothalamic involvement. *J Pediatr*. 2014 Apr;164(4):876–81 e4.
- Daubenbüchel AM, Hoffmann A, Eveslage M, Özyurt J, Lohle K, Reichel J, et al. Oxytocin in survivors of childhood-onset craniopharyngioma. *Endocrine*. 2016 Nov;54(2):524–31.
- Hoffmann A, Özyurt J, Lohle K, Reichel J, Thiel CM, Müller HL. First experiences with neuropsychological effects of oxytocin administration in childhood-onset craniopharyngioma. *Endocrine*. 2017 Apr;56(1):175–85.
- Du X, Yuan Q, Yao Y, Li Z, Zhang H. Hypopituitarism and successful pregnancy. *Int J Clin Exp Med*. 2014 Dec;7(12):4660–5.
- Kübler K, Klingmüller D, Gembruch U, Merz WM. High-risk pregnancy management in women with hypopituitarism. *J Perinatol*. 2009 Feb;29(2):89–95.
- Müller HL, Gebhardt U, Teske C, Faldum A, Zwiener I, Warmuth-Metz M, et al.; Study Committee of KRANIOPHARYNGEOM 2000. Post-operative hypothalamic lesions and obesity in childhood craniopharyngioma: results of the multinational prospective trial KRANIOPHARYNGEOM 2000 after 3-year follow-up. *Eur J Endocrinol*. 2011 Jul;165(1):17–24.
- Müller HL, Gebhardt U, Faldum A, Warmuth-Metz M, Pietsch T, Pohl F, et al.; Kraniopharyngioma 2000 Study Committee. Xanthogranuloma, Rathke's cyst, and childhood craniopharyngioma: results of prospective multinational studies of children and adolescents with rare sellar malformations. *J Clin Endocrinol Metab*. 2012 Nov;97(11):3935–43.
- Health RCoPaC. *UK-WHO charts-neonatal and infant close monitoring*. London: NICM; 2009.
- Wright CM, Williams AF, Elliman D, Bedford H, Birks E, Butler G, et al. Using the new UK-WHO growth charts. *BMJ*. 2010 Mar;340:c1140.
- Müller HL. Craniopharyngioma. *Endocr Rev*. 2014 Jun;35(3):513–43.
- Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol*. 2016 Jun;131(6):803–20.
- Gupta S, Bi WL, Giantini Larsen A, Al-Abdulmohsen S, Abedalthagafi M, Dunn IF. Craniopharyngioma: a roadmap for scientific translation. *Neurosurg Focus*. 2018 Jun;44(6):E12.
- Reddy GD, Hansen D, Patel A, Lin Y, Jea A, Lam S. Treatment options for pediatric craniopharyngioma. *Surg Neurol Int*. 2016 Mar;7(7 Suppl 6):S174–8.
- Müller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, et al. Obesity after childhood craniopharyngioma—german multicenter study on pre-operative risk factors and quality of life. *Klin Padiatr*. 2001 Jul-Aug;213(4):244–9.
- Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbüchel AM, Müller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro-oncol*. 2015 Jul;17(7):1029–38.
- Bogusz A, Boekhoff S, Warmuth-Metz M, Calaminus G, Eveslage M, Müller HL. Posterior hypothalamus-sparing surgery improves outcome after childhood craniopharyngioma. *Endocr Connect*. 2019 May;8(5):481–92.
- Eveslage M, Calaminus G, Warmuth-Metz M, Kortmann RD, Pohl F, Timmermann B, et al. The Postoperative Quality of Life in Children and Adolescents with Craniopharyngioma. *Dtsch Arztebl Int*. 2019 May;116(18):321–8.
- Kodama T, Matsukado Y, Miura M, Takada A. Natural pregnancy and normal delivery after intracapsular irradiation for symptomatic craniopharyngioma—case report. *Neurol Med Chir (Tokyo)*. 1986 Jan;26(1):40–3.
- Dinç H, Esen F, Demirci A, Sari A, Resit Gümele H. Pituitary dimensions and volume measurements in pregnancy and post partum. MR assessment. *Acta Radiol*. 1998 Jan;39(1):64–9.
- Karaca Z, Tanriverdi F, Unluhizarci K, Kelestimur F. Pregnancy and pituitary disorders. *Eur J Endocrinol*. 2010 Mar;162(3):453–75.
- Fischer F. Über die Ursachen bitemporaler Hemianopsie bei Schwangerschaft. *Ophthalmologica*. 1935;85(2-3):88–108.
- Sachs BP, Smith SK, Cassar J, Van Iddekinge B. Rapid enlargement of craniopharyngioma in pregnancy. *Br J Obstet Gynaecol*. 1978 Jul;85(7):577–8.
- van der Wildt B, Drayer BJ, Eskes TK. Diabetes insipidus in pregnancy as a first sign of a craniopharyngioma. *Eur J Obstet Gynecol Reprod Biol*. 1980 May;10(4):269–74.
- Hiett AK, Barton JR. Diabetes insipidus associated with craniopharyngioma in pregnancy. *Obstet Gynecol*. 1990 Nov;76(5 Pt 2):982–4.
- Johnson RJ Jr, Voorhies RM, Witkin M, Robichaux AG 3rd, Broussard WA Jr. Fertility following excision of a symptomatic craniopharyngioma during pregnancy: case report. *Surg Neurol*. 1993 Apr;39(4):257–62.
- Zoia C, Cattalani A, Turpini E, Custodi VM, Benazzo M, Pagella F, et al. Haemorrhagic presentation of a craniopharyngioma in a pregnant woman. *Case Rep Neurol Med*. 2014;2014:435208.
- Maniker AH, Krieger AJ. Rapid recurrence of craniopharyngioma during pregnancy with recovery of vision: a case report. *Surg Neurol*. 1996 Apr;45(4):324–7.
- Aydin Y, Can SM, Gülliklik A, Türkmenoglu O, Alatli C, Ziyal I. Rapid enlargement and recurrence of a preexisting intrasellar craniopharyngioma during the course of two pregnancies. Case report. *J Neurosurg*. 1999 Aug;91(2):322–4.
- Thapar K, Stefaneanu L, Kovacs K, Scheithauer BW, Lloyd RV, Muller PJ, et al. Estrogen receptor gene expression in craniopharyngiomas: an in situ hybridization study. *Neurosurgery*. 1994 Dec;35(6):1012–7.

- 35 Hofmann BM, Hoelsken A, Fahlbusch R, Blümcke I, Buslei R. Hormone receptor expression in craniopharyngiomas: a clinicopathological correlation. *Neurosurgery*. 2010 Sep;67(3):617–25.
- 36 Honegger J, Renner C, Fahlbusch R, Adams EF. Progesterone receptor gene expression in craniopharyngiomas and evidence for biological activity. *Neurosurgery*. 1997 Dec;41(6):1359–63.
- 37 Chentli F, Deghima S, Zellagui H, Azzoug S. Volume increase in craniopharyngiomas under growth hormone and/or sex hormones substitution: role of tumors receptors or mere coincidence? *J Pediatr Neurosci*. 2013 May; 8(2):113–6.
- 38 Li Q, You C, Liu L, Rao Z, Sima X, Zhou L, et al. Craniopharyngioma cell growth is promoted by growth hormone (GH) and is inhibited by tamoxifen: involvement of growth hormone receptor (GHR) and IGF-1 receptor (IGF-1R). *J Clin Neurosci*. 2013 Jan;20(1):153–7.
- 39 Müller HL, Gebhardt U, Schröder S, Pohl F, Kortmann RD, Faldum A, et al.; study committee of KRANIOPHARYNGEOM 2000/2007. Analyses of treatment variables for patients with childhood craniopharyngioma – results of the multicenter prospective trial KRANIOPHARYNGEOM 2000 after three years of follow-up. *Horm Res Paediatr*. 2010; 73(3):175–80.
- 40 Yu R, Melmed S. Oncogene activation in pituitary tumors. *Brain Pathol*. 2001 Jul;11(3):328–41.
- 41 Heaney AP, Fernando M, Melmed S. Functional role of estrogen in pituitary tumor pathogenesis. *J Clin Invest*. 2002 Jan;109(2):277–83.
- 42 Stockhammer G, Obwegeser A, Kostron H, Schumacher P, Muigg A, Felber S, et al. Vascular endothelial growth factor (VEGF) is elevated in brain tumor cysts and correlates with tumor progression. *Acta Neuropathol*. 2000 Jul;100(1):101–5.
- 43 Senger DR, Galli SJ, Dvorak AM, Perruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science*. 1983 Feb;219(4587):983–5.
- 44 Strugar JG, Criscuolo GR, Rothbart D, Harrington WN. Vascular endothelial growth/permeability factor expression in human glioma specimens: correlation with vasogenic brain edema and tumor-associated cysts. *J Neurosurg*. 1995 Oct;83(4):682–9.
- 45 Vaquero J, Zurita M, Oya S, Coca S, Salas C. Vascular permeability factor expression in cerebellar hemangioblastomas: correlation with tumor-associated cysts. *J Neurooncol*. 1999 Jan;41(1):3–7.
- 46 Takahashi H, Shibuya M. The vascular endothelial growth factor (VEGF)/VEGF receptor system and its role under physiological and pathological conditions. *Clin Sci (Lond)*. 2005 Sep;109(3):227–41.
- 47 Tammela T, Enhölm B, Alitalo K, Paavonen K. The biology of vascular endothelial growth factors. *Cardiovasc Res*. 2005 Feb;65(3):550–63.
- 48 Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association Between MRI Exposure During Pregnancy and Fetal and Childhood Outcomes. *JAMA*. 2016 Sep; 316(9):952–61.
- 49 Rolland-Cachera MF, Cole TJ, Sempé M, Tichet J, Rossignol C, Charraud A. Body Mass Index variations: centiles from birth to 87 years. *Eur J Clin Nutr*. 1991 Jan;45(1):13–21.
- 50 Overton CE, Davis CJ, West C, Davies MC, Conway GS. High risk pregnancies in hypopituitary women. *Hum Reprod*. 2002 Jun;17(6):1464–7.
- 51 Begon S, Leyendecker G, Fahlbusch R, Buchfelder M, Wildt L. Pulsatile administration of gonadotrophin releasing hormone as a diagnostic tool to distinguish hypothalamic from pituitary hypogonadism following neurosurgery. *Hum Reprod*. 1993 Nov;8 Suppl 2:200–3.
- 52 Corral J, Calderon J, Goldzieher JW. Induction of ovulation and term pregnancy in a hypophysectomized woman. A case report. *Obstet Gynecol*. 1972 Mar;39(3):397–400.
- 53 Hayashi M, Tomobe K, Hoshimoto K, Ohkura T. Successful pregnancy following gonadotropin therapy in a patient with hypogonadotropic hypogonadism resulting from craniopharyngioma. *Int J Clin Pract*. 2002 Mar; 56(2):149–51.
- 54 Volz J, Heinrich U, Volz-Köster S. Conception and spontaneous delivery after total hypophysectomy. *Fertil Steril*. 2002 Mar;77(3):624–5.