

Cerebral Cavernous Malformations (CCMs) Complicated Pregnancy; Clinical Case Outcome with a Systematic Review



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Introduction

Background: Cerebral cavernous malformations CCM are rare but considered among the important cerebral condition that associated with risk of intracranial hemorrhage, focal neurological deficits and seizure from CCM change in pregnant women. Yet there is a paucity of information in the medical literature relating to the perinatal outcomes, in particular conservative approach.

Objective: To evaluate the perinatal outcome of pregnant patients diagnosed with seizure-related to CCM managed conservatively. Also, to conduct a systematic review on the risk of intracranial hemorrhage ICH and focal neurological deficits FND from Cerebral Cavernous Malformations lesion during pregnancy and its implication on the timing and mode of delivery.

Methods: (1) Present a clinical case whose diagnosed with supratentorial lobar CCM and treated conservatively. (2) Conducted a systematic review for publications on cavernous malformation during pregnancy in PubMed database. The search term used were "cavernous malformation in pregnancy" and "epileptic seizure of cavernomas". A16 related articles and 32 case reports were found.

Result: The first case with CCM-related seizure was well-controlled on antiepileptic drugs AED while the other case of CCM was associated with no seizure symptomatology and managed conservatively without anticonvulsant treatment, both cases had good perinatal outcomes. Although, there is no available reports to support the approaches to not using antiepileptic drugs in pregnant patient with CCM? There is some studies that have reported that the initiations of conservative management (no surgical intervention) during antepartum or postpartum period may be used in the cases with asymptomatic or mildly symptomatic lesions but not in the cases with severe symptoms where neurosurgical intervention is warranted.

Conclusion: Pregnant patients with CCM who's unable to compliance on their antiepileptic medication and willing to carry the risk of cerebral bleeding; (1) they may eventually stop the antiepileptic medication prior to the conception and managed conservatively and (2) they may have favorable perinatal outcome (3) based on the available reports there is no increased risk for cerebral hemorrhage during pregnancy and Cesarean section is indicated for obstetrical condition rather than to be performed as preferred mode of delivery for CCM.

Keywords: Cerebral cavernous malformations; Anti-epileptic drugs (AED); Epileptic seizures; Maternal and fetal outcomes

Abbreviations: ICH: Intracranial Hemorrhage; FNDs: Focal Neurological Deficits; MRI: Magnetic Resonance Imaging; GA: gestational age; H: Hemorrhage; S: Seizures; D: Diplopia; FNS: Focal Neurological Deficit; HE: Hemiparesis; CS: Cesarean Section; VD: Vaginal Delivery; TOP: Termination of Pregnancy; CCMs: Cavernous Malformation; N/R: Not Reporting; Term: Term gestation more than 37 weeks

Abstract

Cerebral cavernous malformations CCM is characterized by vascular malformations in the brain and spinal cord comprising closely clustered, enlarged capillary channels (caverns) with a single layer of endothelium without mature vessel wall elements or normal intervening brain parenchyma [1]. These vessels account for 8% to 15% of all cerebrovascular malformations and exhibit distinct features of angioarchitecture and biological mechanisms of genesis and progression [1]. Though the CCM is a rare lesion with a prevalence of 0.4%-0.5% of the population, it considered among the important condition of cerebral haemorrhage in pregnant women as it may results in epileptic seizures, stroke, symptomatic intracranial haemorrhage ICH, new focal neurological deficit FND and carry more obstetrical problems during pregnancy [2]. Although seizure has been the most common neurological manifestation of symptomatic CCMs during pregnancy that can be managed by antiepileptic drug AED regimen, but this raises a concern on its safety and the adverse fetal risk that may associated with. In view of the limited data on the most appropriate obstetric management of cavernous malformations during pregnancy. Our aim was (1) to present our successful experience on managing the pregnant women with CCM conservatively, hoping to add useful, if possible, a reasonable practical point to our obstetrical management of pregnancy associated with CCM (2) to evaluate the impact of, based on the literature data, the management approaches for these lesions during pregnancy and delivery on the perinatal outcomes.

Introduction

These CCM lesions can occur throughout the central venous system with a prevalence of 0.4%-0.5% [2]. CCM have variable

presentations ranging from headache, Intracranial Hemorrhage (ICH) presenting with acute new Focal Neurological Deficits (FNDs) and epileptic seizures [3]. These lesions historically exhibited more benign features compared to their arteriovenous counterparts [4]. Because of the risk of morbidity and/or mortality due to severe hemorrhagic events and progressive neurological deterioration during pregnancy the consideration of the delivery time and mode is crucial [5]. The knowledge of these risks is useful for decision making regarding the treatment approaches in pregnant women. Neither of conservative management or neurosurgical excision options has been assessed in a randomized trial, and the use of neurosurgical excision remains controversial and challenging [6]. In view of the limited data on the most appropriate obstetric management of cavernous malformations during pregnancy. We sought to address these through

(1) presented our successful conservative management for discontinuing AEDs in pregnant women with CCM.

(2) conducting a systematic review to evaluate the available literature data on the implications of management approaches for these lesions during pregnancy and delivery on the perinatal outcomes.

Methods

1. Described perinatal outcomes for two cases of patients who have cerebral cavernous malformations and managed conservatively during the pregnancy.

a) **Case 1:** a healthy 28-year-old woman (gravida 2, abortion 1). The fetal anatomy scan at 20 weeks' gestation was normal. The woman's routine antenatal blood tests were all within normal. At 23 weeks' and 4 days gestation she presented with unwell symptoms like lethargy, fatigue and excessive daytime sleepiness. During the physical assessment the patient develops a generalized type of seizure for 2-3 minutes. The attack was accompanied by white-like foam spat from her mouth, but no eyeball turnover, no tongue bite or urinary incontinence was observed. The patient was suffering from dizziness and headache after the seizure ceased. After ten minutes, another attack of seizure occurred and lasted for 15 minutes with gradual regaining of consciousness. The diagnosis of status epilepticus was made. Management involves controlling the seizures by Diazepam. The patient was intubated and admitted to intensive care unit ICU. Laboratory test; revealed normal maternal glycaemia and complete blood count; no electrolyte disturbances. Serum calcium, magnesium levels and liver function tests were all within normal limits. Further investigations after stabilization; the fetal heart was normal. Cranial magnetic resonance imaging (MRI) scan performed and shows hypointense lesion (size: measuring

up to 7 mm) on T2 involving the medial aspect with central area of hyperintensity in the left frontal lobe. Fluid-attenuated inversion recovery FLAIR showed high signal intensity on T2, and diffusion-weighted imaging DWI showed isointensity on T1.

No obvious edema was found in adjacent brain parenchyma. The adjacent cortical sulci were not significantly widened. The patient was diagnosed with intracranial space-occupying lesion, likelihood cavernous hemangioma. Over the course of the admission there were no seizures episodes, the patient was stable, her consciousness and speech were normal. Considering the fetal age and the potential side effects of seizure on the perinatal outcome, whether neurosurgical procedures are needed and to decide on safety mode of the delivery on patient and fetus. The multidisciplinary team proposed that neurosurgical intervention was not necessary, and the patient managed conservatively. She was started on anti-epileptic drugs AED and her neurological symptoms remained stable during the period of pregnancy. During the 40th weeks of gestation, she delivered vaginally, and the outcome was a healthy baby girl with good Apgar score of 9, 10 at 1 and 5 min, weighing 3350g. The patient was maintained on AED treatment with no relapses of seizure and a repeated neuroimaging MRI showed no significant changes in the lesion size, signal and morphology of the left frontal lobe cavernous malformation.

b) **Case 2:** Five years later, the patient was planning to conceive and decided to discontinue her anticonvulsant medication. Therefore, based on her neurological status at that time; no seizures, no neurological dysfunction symptoms related to cerebral cavernous malformations and maintained stable left frontal lobe CCM features on MRI images, the decision was made to continue conservative management during pregnancy. Fetal scan at 20 weeks showed normal anatomy. Pregnancy has been uneventful thus far, there were no symptoms of neurological deficits FND. At completed 39 weeks' gestation, patient was delivered vaginally without major complications a baby girl with an Apgar score of 10, weighing 3601 g and discharged in satisfactory condition.

2) A systematic review was performed to identify all reports published in English till 2020 using search for "cavernous malformation during pregnancy or puerperium". Inclusion criteria were articles published in English with the primary topic being CCMs complicated with pregnancy and clear descriptions of the clinical presentation, management, and outcomes. Reference lists of the eligible articles were examined to identify other relevant articles. Articles that did not clearly describe the clinical presentation, management, and outcomes were excluded.

Results

a) CCM was diagnosed after the first new onset of seizure during pregnancy of patient first child at 23 weeks of gestation. This patient had undergone neurological management on AED. The second pregnancy was unremarkable. The patient was safely

discontinuing AED therapy prior to conception and managed conservatively with no seizure's attacks through the entire period of pregnancy. The mode of delivery was spontaneous vaginal delivery during term weeks of gestation.

b) Analyzing the published studies of cavernous malformation of central nervous system during pregnancy and/or puerperium revealed 60 related publications. 22 articles based on title/abstract assessment and 18 based on full-text assessment were found eligible. Of these articles, 18 were selected, resulting

in the inclusion of 16 articles and 32 single case reports published until 2020. Figure 1: Flowchart of the results of the search and the selection and inclusion of studies. Of the 16 articles, 14 included only one to three cases, one article included five cases, and another included six cases [7,8]. The clinical data on management of symptomatic CCM in pregnancy, gestational age at presentations and mode of delivery were listed in the (Table 1), which summarizes the obstetrical outcome of 16 published cases from the literature.

Table 1: Cases of cavernous malformations during pregnancy from the available in literature [6-21].

Authors	No. of patients	GA at presentation	Presenting symptoms					GA at delivery	Mode of delivery	Indication of C/Section	Neurosurgical intervention
			H	S	FND	D	HE				
Warner et al. [9]	1	4 months	x		x		x	Term	C/Section	N/R	No- vision recovered spontaneously
Pozzati et al. [10]	2	3 months	x					N/R	N/R		NO
		N/R		x				N/R	N/R		After delivery
Awada et al. [11]	2	Puerperium		x				N/R	N/R		NO
		4 months		x				N/R	N/R		NO
Hoeldtke et al. [12]	1	24 weeks		x				33 weeks	Vaginal for pre-eclampsia		NO
Flemming et al. [13]	1	27 weeks	x		x	x	x	36 weeks	C/S	CCMs	Yes at GA 27 weeks
Haque et al. [14]	1	20 weeks			x	x	x	N/R	N/R		No complete resolution 11 weeks post delivery
Aladdin et al. [15]	1	10 weeks		x				TOP for seizure refractory to AED			No immediate resolution of seizure
Ramírez-Zamora et al. [16]	1	N/R				x		N/R	vaginal		No symptoms resolved and managed conservatively
Cohen-Gadol et al. [17]	1	29 weeks	x		x	x		Term	C/S		Yes. At 29 weeks
Nossek et al. [18]	2	31 weeks				x		38 weeks	C/S		NO
		18 weeks		x				40 weeks	vaginal		NO
Burkhardt et al. [19]	3	11 weeks	x		x		x	40 weeks	Vaginal		Yes. Twice 1) during pregnancy at 12 weeks 2) 2 weeks post delivery
		6 weeks	x		x		x	N/R	N/R		Yes 1 week post delivery
		3rd trimester			x		x	N/R	N/R		Yes 3 months post delivery
Witiw et al. [20]	3	1st trimester	x					Term	vaginal		NO
		3rd trimester	x					Term	C/S	CCMs	NO
		3rd trimester	x					Term	C/S	CCMs	NO

Xu Y et al. [21]	1	36 weeks	x	x				36 weeks	C/S	Seizure/ CCMs	NO surgery was postponed as the patient had thyroid cancer
Safavi-Abbasi et al. [6]	1	3rdtrimester during, Peripartum	x		x		x	N/R	C/S	acute paraparesis	2 weeks after C/S
Kalani et al. [7]	4(total 5 pregnant)	N/R			X			N/R	vaginal		Yes After 10 years
		N/R		x				N/R	vaginal		NO
		N/R	x	x				N/R	vaginal		Yes 7 weeks post delivery
		N/R		x					vaginal		No
		N/R		x					C/S	CCMs	No
Simonazzi et al. [8]	6	30 weeks	x		x	x		30 w	C/S	CCMs	No
		20 weeks	x		x	x	x	TOP sever neurological symptoms			No
		33 weeks		x				37 w	C/S	CCMs	No
		Puerperium	x				x	37 w	C/S	Dystocia	No
		Puerperium			x	x		41 w	vaginal		No
		36 weeks	x		x	x	x	36 w	C/S	CCMs	Yes After 6 years

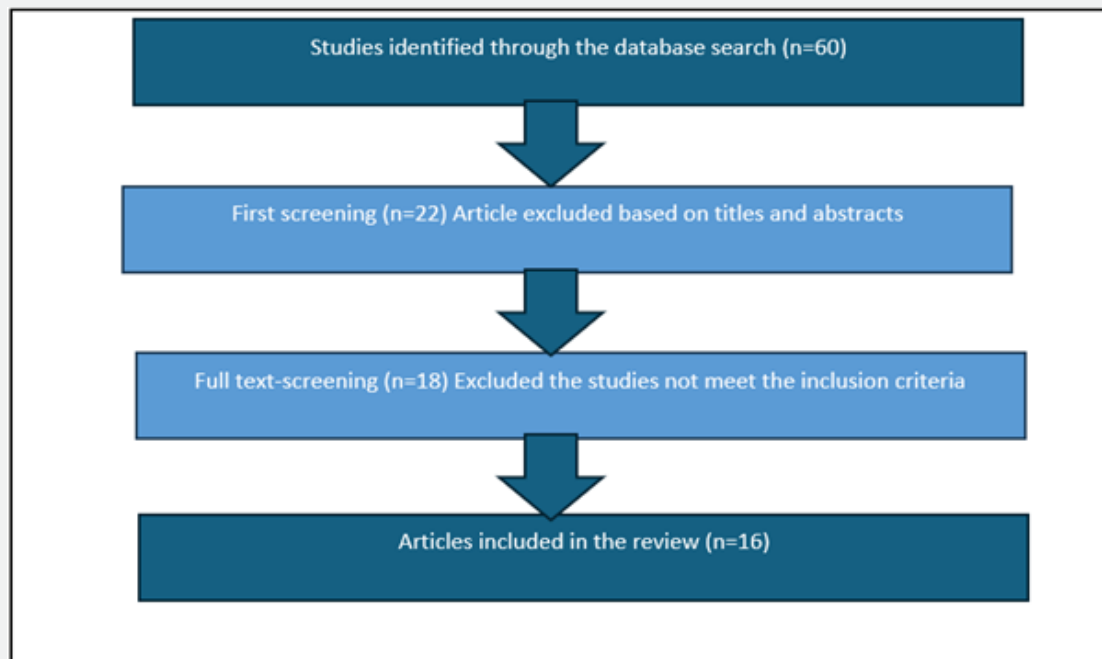


Figure 1: Flowchart of the results of the search and the selection and inclusion of studies.

Discussion

According to the literature majority of patients with symptomatic CCMs occurred during their course of pregnancy or period of (puerperium) 6-week postpartum. Out of the 32 patients reported in single case reports, the gestational age at the time of presentation of symptomatic CCMs has been documented for 22 (79%) patients. Of these 22 patients, 16 presented with symptomatic CCM antepartum (second or third trimesters). However, four patients (18%) showed early onset of CCM symptoms in the first trimester (6 weeks of gestation), and two showed delayed onset in the postpartum period. The 32 patients showed clinical presentations of symptomatic CCMs ranging from acute ICH and onset or worsening of neurological symptoms, including seizures, FNDs, diplopia, and hemiparesis. Notably, 19 of these 32 patients (59%) had ICH. New onset or exacerbation of seizures occurred in 10 patients (31%), and other 10 patients (31%) showed progressive symptoms of hemiparesis. Further, 13 of the 32 patients (40%) exhibited symptoms of FNDs, and other nine patients (28%) had a history of worsening symptomatic hemiparesis with diplopia. As regards the information on the obstetrical mode of delivery and gestational age at delivery was available only for 24 of the 32 patients (75%). Two of these 24 patients underwent abortion on each 20 weeks of gestation who showed worsening of neurological symptoms due to bulbar CCMs and required therapeutic termination, and the other at 10 weeks of pregnancy for obstetric indication due to severe preeclampsia. Of the 24 patients, nine pregnant women (31%) with symptomatic CCMs had uncomplicated vaginal delivery. The gestational age at the time of delivery was not reported for five of these nine patients, whereas three patients delivered successfully at term gestation and one patient required preterm delivery at 33 weeks because of severe preeclampsia symptoms. Of these nine patients, two underwent neurosurgical intervention after uncomplicated pregnancy and delivery; one at 7 weeks postpartum and another at 10 years after her last pregnancy [7]. The first patient had focal seizure episodes involving the right face and arm and underwent successful resection of left insular CCMs after pregnancy at 7 weeks. The second patient underwent surgery for CCMs in the cervical medullary junction because of progressive right-sided weakness 10 years after her last pregnancy [9,10].

Thirteen of the 24 patients (45%) underwent Cesarean delivery: six at term gestation, four at preterm gestation, and the gestational age at delivery was unreported for the remaining three cases. Of these 13 patients, eight underwent Cesarean delivery because of concerns over CCMs and to reduce the risks of bleeding, one underwent Cesarean delivery because of dystocia at 40 weeks, and the indication for Cesarean delivery was unreported in the remaining of three cases. Neurosurgical resection of CCMs was performed in 4 of the 13 patients who underwent Cesarean delivery. Two of these patients had symptomatic CCMs in the pons, one of whom underwent surgery at 27 weeks of gestation and another at 29 weeks of gestation [11-

22]. Burkhardt et al. [19] reported three patients who underwent neurosurgical intervention during and after pregnancy; One patient underwent Ponto-mesencephalic CCM resection during 12 weeks of gestation and 2 weeks after the uncomplicated delivery of her second child, this patient underwent complete resection of this lesion with favorable outcomes. The other two patients underwent CCM resection postpartum: one patient at 1week postpartum and the other at 3 months postpartum [19]. Although, a great knowledge has been gained in understanding of clinical presentation, imaging features of these complex lesions and their potential complications during pregnancy and puerperium, but their pathogenesis during pregnancy remain uncertain.

Gestational hormone attributed to symptomatic hemorrhage in CCM has received increasing attention in the last decades but the exact mechanism for bleeding from these lesions during pregnancy is not fully recognized. In this dissertation, there are some studies that have emphasized that the increased production of steroid hormones during pregnancy are associated with an increased risk of hemorrhage from CCMs. Other studies showed that pregnancy not only “estrogen and progesterone”, but also vascular growth factors including vascular endothelial growth factor VEGF were upregulating during pregnancy and has been proposed to be the main cause of increasing growth in the size and angiogenesis of CCM [7]. This has been compatible with Kaya et al. [23] observation which showed that there is a different pathway mediating the process of symptomatic hemorrhage during the pregnancy than flux of gestational hormone effects [23]. Our review revealed that only one patient who had severe symptomatic lesions underwent abortion because of the worsening of neurological symptoms at 20 weeks of gestation. However, the practice of choosing an elective Cesarean delivery, with the knowledge that vaginal delivery increases the risk of ICH, to reduce the risks of hemorrhage has been revised. With limited number of reported cases of CCMs in pregnancy, it appears that the risk of hemorrhage from CCMs remains similar antepartum and postpartum. In addition, no strong evidence is available showing that the mode of delivery influences the risk of hemorrhage from CCMs; hence, we believe that the decisions regarding the management of labor and mode of delivery should be based on obstetric indications. Witiw et al. [20] reported three cases of symptomatic hemorrhages that occurred during pregnancy. All three women delivered healthy newborns; one via vaginal delivery and the other two via Cesarean delivery because of neurological indication (hemifacial weakness, mild hemisensory symptoms, and diplopia).

Notably, all these patients recovered well from their hemorrhagic events. Seizures are the most frequent clinical manifestations of cerebral cavernous malformation, and it has been suggested to affect only a small group of pregnant women. This is compatible with our observation which showed CCM-related seizure was incidentally diagnosed after a first seizure in the first case and had associated with reduction risk of recurrence during the subsequent pregnancy [19]. According to the available

data, the lifetime risk for developing a new onset of epileptic seizures is higher in patient with CCM in cortical location, and the risk is approximately as high as 70% with supratentorial involvement [11]. Information on the obstetrical management of cases complicated with seizures were thought to be caused by CCM is very limited. According to the literature, a number of authors have been recommended that the conservative treatment with anti-epileptic drugs AED, regular neurological follow up, having clinical information about the auras symptoms that may represent seizure activity and re-evaluation post- delivery is an appropriate approach [11]. Regarding surgical intervention, there is no conclusive data for use this approach during pregnancy. However, treatment decisions must consider not only the epileptogenicity of a specific CCM lesion, but also must be weighed against maternal and fetal complications. There are some studies suggested that lesionectomy in cases of a life- threatening situation or rapidly progressive clinical symptoms must be performed right away, especially in the first week of gestation [19]. According to some other studies, postponed surgery after the delivery in patients have a minor symptoms or slowly progressive pattern within the second or third trimester may be a reasonable option [19]. Hence no available data or clinical experience to date on the potential risk of discontinuation of AED preconceptionally in stable patient with pre-existing CCM and whether discontinue AED would increase their seizure risk during the pregnancy? Therefore, in parallel with our understanding of the natural history of this lesion and using the common sense in this area along with regards to expert's viewpoint, we presented our management in patient with frontal lobe CCM who desire to conceive and stopped AED. Our decision to manage the patient conservatively was made based on

1) patient being preconceptionally asymptomatic without experiencing any neurological concerns (remaining seizure free) and the stability of lesion size with approximate size of 1.7 cm on MRI appearance [24]

2) respecting the patient's strong desire to stop the anti-epileptic medication along with understanding and willing to carry any adverse risk associated with discontinuing taking AEDs during pregnancy. To the best of our knowledge, this is the first case reported on perinatal outcome of patient with CCM who discontinue AED through pregnancy and had an uneventful vaginal delivery and experienced no pregnancy or delivery complications.

Conclusion

Cerebral cavernous malformations are more common than generally realized. Medical management must be tailored to everyone based on the specific circumstances. Pregnant patients harboring CCM lesion clinically asymptomatic and their neuroimaging study remains stable can be managed conservatively. Overall, pregnancy appears not has harmful effect on cavernomas course. We generally suggested, based on retrieved data and shared decision between the clinician and patient, that women with CCMs can be managed safely during trial of labor without a

significant risk of adverse perinatal outcomes, and consideration needs to be given to planned Cesarean section in patients with symptomatic CCMs or when prolonged labor anticipated.

Disclosure

Conflicts of interest: None

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