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Review

Status epilepticus in pregnancy – Can we frame a uniform treatment protocol?

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ABSTRACT

Background: There is lack of uniform treatment protocol for status epilepticus (SE) in pregnancy, with majority of data being limited to individual cases or case series. Devising a uniform treatment protocol will facilitate prompt control of SE in pregnancy and reduce adverse maternal and fetal outcomes.
Methods: Literature search was done in various databases including PubMed, CINAHL, EMBASE, TRIP, and the gray literature, including relevant organizational websites, for the topics "Status Epilepticus" and "Pregnancy". English language original research articles, case reports, and systematic reviews that were published in the last 18 years (2000–2018) and addressed SE in relation to pregnancy (i.e., antepartum, labor, or postpartum) were considered for inclusion.
Results: Over the past 15 years, a total of seven articles reporting 29 cases of SE related to pregnancy, satisfying the inclusion criteria were analyzed. The most common cause of SE was posterior reversible encephalopathy syndrome (PRES)/reversible cerebral vasoconstriction syndrome (RCVS) spectrum (n = 11, 38%), followed by cortical venous sinus thrombosis (CVT) and autoimmune encephalitis (n = 5, 17%). Twenty-three out of 29 cases (79%) had good maternal outcomes in terms of recovery to baseline. Seventeen fetuses (58%) were delivered at term and seven at preterm (2.4%). First-line agent used was lorazepam in 15 patients (52%) and midazolam in two patients (7%). The most common antiepileptic drug (AED) and anesthesia used for treatment of SE and refractory SE were phenytoin/fosphenytoin (n = 21, 72%) and midazolam (n = 12, 52%), respectively. In all cases due to eclampsia (n = 5), magnesium sulfate was the preferred first-line drug.
Conclusion: Management of SE in pregnancy is influenced by etiology of SE and duration of pregnancy. It carries a good prognosis if detected early and treated appropriately. Large-scale multicentric studies are warranted for formulating definite guidelines for management of SE in pregnancy.
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1. Introduction

Status epilepticus (SE) in pregnancy is rare and carries a significant risk to both mother and fetus. Based on available literature data, eclampsia is the most common etiology of SE, and various other diverse etiologies have also been implicated to be causing SE in pregnancy [1–8]. The challenge regarding management of SE in pregnancy lies in prompt control of SE, taking into consideration the safety and tolerability of antiepileptic drugs (AEDs) and anesthetic agents for control of SE.

There is lack of uniform treatment protocol for SE in pregnancy, with majority of data being limited to individual or case series reports. With majority of patients being from the developing countries where the patient is managed essentially by the obstetricians with lack of neurological expertise;, a uniform treatment protocol will facilitate prompt control of SE and reduce adverse maternal and fetal outcomes.

2. Methods

We searched various databases including PubMed, CINAHL, EMBASE, TRIP, and the gray literature, including relevant organizational websites, for the topics "Status Epilepticus" and "Pregnancy". English language original research articles, case reports, and systematic reviews that were published in the last 18 years (2000–2018) and addressed SE in relation to pregnancy (i.e., antepartum, labor, or postpartum) were considered for inclusion. Excluded were cases who had SE not related

Abbreviations: SE, Status epilepticus; AED, antiepileptic drug; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; CVT, cortical venous sinus thrombosis; SAH, subarachnoid hemorrhage; MgSO4, magnesium sulfate.

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to pregnancy or not satisfying the definition of SE (single epileptic seizure lasting more than 5 min or two or more seizures occurring within a 5-min period without the person returning to normal between them) [9].

3. Results

Over the past 15 years, a total of seven articles reporting 29 cases of SE related to pregnancy, satisfying the inclusion criteria were analyzed. The mean age of study population was 27.69 ± 3.53 years. Based on pregnancy duration, it was observed that there were four women in second trimester and five each in first and third trimesters. The remaining 15 women developed SE in the postpartum period. Data on etiology, time of presentation of SE in pregnancy, treatment, and pregnancy outcome are summarized in Table 1.

In our literature published on 17 women with pregnancy and SE which is the largest cohort described so far [1,2], all women who developed SE related to pregnancy (gestation, labor, or puerperium) between January 2000 and December 2016 were included in the study. Data were collected from our SE registry, maintained, and archived in the institute. During the study period, a total of 348 SE events were recorded in 294 patients. Among these, there were 138 women, of which 17 had SE related to pregnancy. Maternal outcomes were assessed using Functional independence measure (FIM) outcome score (Appendix A) and Modified Rankin Scale (mRS) (Appendix B). The severity of SE was assessed using Status Epilepticus Severity Score (STESS) (Appendix C).

Our patients were grouped based on the condition at the time of discharge into "good outcome" (FIM score: 4–7; mRS: 0–2) and "poor outcome" (FIM score: 1–3; mRS >3). The fetal outcome after delivery was divided into "healthy alive fetus without any complications" (Category 1) and "fetal death or perinatal complications needing admission to the neonatal intensive care unit" (Category 2).

The etiology of SE was remote symptomatic in two and acute symptomatic in 15 patients. The various causes detected after initial evaluation for acute symptomatic SE were eclampsia (n = 4), posterior reversible encephalopathy syndrome (PRES) due to various causes other than eclampsia (n = 6), cortical venous sinus thrombosis (n = 3), subarachnoid hemorrhage (SAH) (n= 1), and NMDA (Anti-N-methyl-d-aspartate receptor) encephalitis (n = 1). Thirteen of 17 women with SE (76%) had good outcome. Majority of the fetuses had good outcomes, i.e., Category 1 (n = 9, 57%). Duration of intensive care unit stay (p = 0.029) and STESS (p = 0.0324) at admission were found to be significantly associated with poor outcomes.

3.1. Etiology and outcome of refractory SE in pregnancy (pooled data)

The etiology of SE was acute symptomatic in 26 cases and remote symptomatic in three cases. The most common cause of SE was PRES/reversible cerebral vasoconstriction syndrome (RCVS) spectrum (n = 11, 38%). Among these, five patients had eclampsia (45%), and rest six had PRES because of diverse etiologies other than eclampsia (55%). The next most common causes were cortical venous sinus thrombosis (CVT) and autoimmune encephalitis (n = 5, 17%). The rest of cases were related to AED default (n = 3, 10%) and one case each (3%) due to herpes simplex encephalitis, SAH, cavernous angioma, porphyria, and pyridoxine deficiency.

Twenty-three out of 29 cases (79%) had good maternal outcomes in terms of recovery to baseline. The remaining six cases (21%) had poor outcomes, among which two cases died (mortality rate: 7%). Seventeen fetuses (58%) were delivered at term and seven at preterm (2.4%). Medical termination of pregnancy was performed in three cases, and there were one case each who went for spontaneous abortion and intrauterine fetal death.

3.2. Treatment of SE in pregnancy

From the available data, the first-line agent used for treatment of SE was lorazepam in 15 patients (52%) and midazolam in two patients

Table 1
Summary of literature on etiology, management, and outcomes of status epilepticus in pregnancy.

Sl no.	Authors	No. of cases with SE	Pregnancy status (trimester)	Etiology	AEDs tried	Anesthetic drugs tried	Outcomes maternal fetal	
1.	Rajiv et al. [1,2]	17	2nd (2) 3rd (2) PP (13)	AED default (2) AIE (1) CVT (3) Eclampsia (4) PRES syndrome (without eclampsia) (6) SAH (1)	FPHT (14) PB (9) LEV (4) MgSO4 (2) VPA (2)	MDZ (6) PPFL (3) THIO (1) PPF (1)	Cesarean section: 4 (24%) Recovery to baseline: 13 (76%) Deaths: nil	Preterm delivery: 6 (35%) Term delivery: 11 (65%)
2.	Lu et al. [3]	7	1st (3) 2nd (1) 3rd (1) PP (2)	AED default (1) AIE (4) CVT (2)	LEV (6) VPA (5) PB (4) PHT (3) TPM (3) CLZ (2) CLB (1) OXC (1)	MDZ (4) THIO (2) PPF (2)	Cesarean section: 2 (27%) Recovery to baseline: 5 (73%) Deaths: 2 (27%)	Abortions: 1 (14%) Preterm delivery: 1 (14%) Intrauterine death: 1 (14%) Term delivery: 4 (57%)
3.	Legriel et al. [4]	1	3rd (1)	RCVS (1)	MgSO4 (1)	MDZ (1)	Cesarean section (1) Recovery to baseline (1)	Term delivery (1)
4.	Aladdin et al. [5]	1	3rd (1)	Cavernous angioma (1)	PHT (1) CLB (1) CBZ (1)	PPFL (1)	Recovery to baseline (1)	MTP (1)
5.	Gunduz et al. [6]	1	2nd (1)	HSV encephalitis (1)	CBZ (1) PHT (1) DZP (1)	–	Recovery to baseline (1)	MTP (1)
6.	Engelhardt et al. [7]	1	1st (1)	Porphyria (1)	PHT (1) LEV (1)	THIO (1)	Recovery to baseline (1)	MTP (1)
7.	Schulze-Bonhage et al. [8]	1	1st (1)	Vitamin B6 deficiency (1)	PHT (1) PB (1)	MDZ (1)	Recovery to baseline (1)	Term delivery (1)

AED – antiepileptic drug, AIE – autoimmune encephalitis, CBZ – carbamazepine, CLB – clobazam, CLZ – clonazepam, CVT – cavernous sinus thrombosis, DZP – diazepam, FPHT – fosphenytoin, HSV – herpes simplex virus, LEV – levetiracetam, MgSO4 – magnesium sulfate, MDZ – midazolam, OXC – oxcarbazepine, MTP – medical termination of pregnancy, PHT – phenytoin, PB – phenobarbitone, PP – postpartum, PF – propofol, PRES – posterior reversible encephalopathy syndrome, RCVS – reversible cerebral vasoconstriction syndrome, RSE – refractory status epilepticus, SAH – subarachnoid hemorrhage, THIO – thiopentone sodium, VPA – valproate.

(7%). The most common AED used for treatment of SE was phenytoin/fosphenytoin (n = 21, 72%) followed by phenobarbitone (n = 14) and levetiracetam (n = 11). The choice of anesthetic agent for management of refractory status epilepticus (RSE) was midazolam (n = 12, 52%), followed by propofol (n = 7, 30%) and thiopentone (n = 4, 17%). In all cases due to eclampsia (n = 5), magnesium sulfate (MgSO4) was the preferred 1st-line drug, and in two patients who developed eclampsia-induced RSE which could not be controlled with MgSO4 administered as per Pritchard regimen [10], fosphenytoin followed by phenobarbitone and propofol was subsequently used for controlling SE.

In addition to use of antiepileptic medications and anesthetic drugs, the mainstay of treatment in cases of RSE comprised of appropriate etiological treatment;, such as intravenous steroids in cases of autoimmune encephalitis, anticoagulation in CVT, antiedema measures in SAH, and pyridoxine supplementation in the rare case of vitamin B6 deficiency.

4. Discussion

The scarcity of literature on SE in pregnancy is by virtue of majority of these cases being managed by the obstetrician and the neurologist being called into picture only in refractory cases. The formulation of uniform treatment protocol for such cases so far was largely hampered by lack of meta-analysis because of scarcity of available data. This pooled analysis provides valuable insights regarding the etiologies, treatment, and outcomes of SE related to pregnancy, and we could devise a pragmatic protocol for management of such cases (Fig. 1).

This analysis shows that the management of SE in pregnancy is largely influenced by two factors, i) etiology of SE and ii) duration of pregnancy. Eclampsia is widely presumed to be the most common cause, and these data show that the treating obstetrician and the referral neurologist need to be alerted about other causes such as noneclamptic PRES, autoimmune encephalitis, and CVT;, which if detected and treated promptly carry a good prognosis.

With regard to the etiology, various trials have shown that MgSO4 is the treatment of choice for eclampsia in pregnancy [11,12]. Other than in eclampsia, there are no established guidelines for management of pregnancy-related SE. The emergency management of SE in pregnancy in such cases should be carried on similar lines to treatment of SE in general. It involves initial stabilization of airway, breathing, and circulation. Benzodiazepines should be first-line agents used, and the choice that is as demonstrated by the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) trial [13]; can vary between IV lorazepam or IM/IV midazolam in cases without emergent intravenous access. In patients who continue having seizures despite this measure, our pooled data show that phenytoin and phenobarbitone are still most preferentially used;, largely due to their widespread availability and often

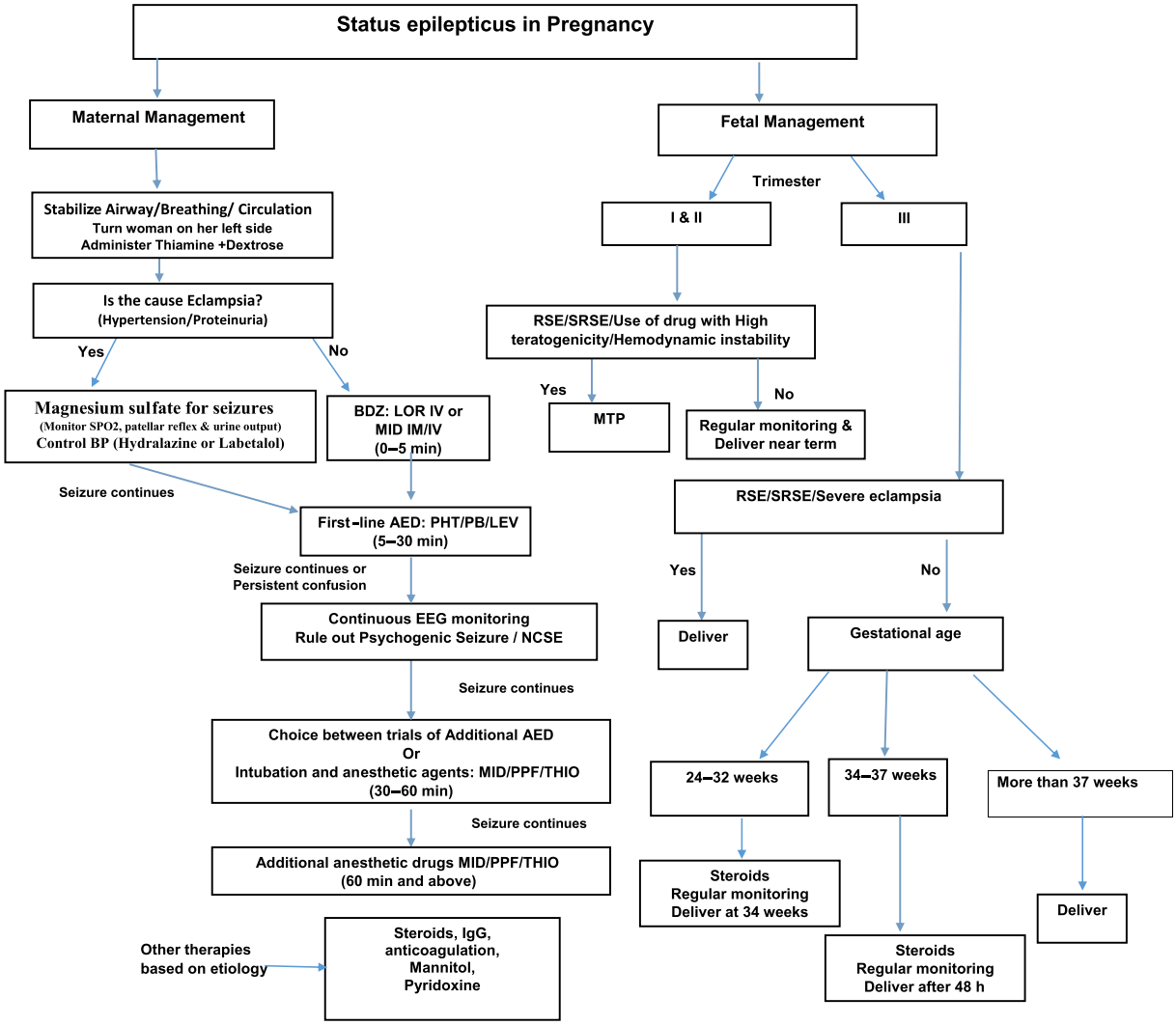

Fig. 1. Protocol for management of SE in pregnancy. AED – antiepileptic drug, BDZ – benzodiazepine, DZP – diazepam, IgG – immunoglobulin G, LEV – levetiracetam, LOR – lorazepam, MID – midazolam, MTP – medical termination of pregnancy, NCSE – nonconvulsive status epilepticus, PB – phenobarbitone, PHT – phenytoin, PPFL – propofol, RSE – refractory status epilepticus, SRSE – super refractory status epilepticus, SPO2 – oxygen saturation, THIO – thiopentone sodium.
Modified from Rajiv et al. Neurol India. 2018; 66:1629–1633 [2].

being available free of cost in the primary health centers in developing nations. Among newer AEDs, levetiracetam is a good option because of its reported efficacy in SE as demonstrated by provisional findings from Established Status Epilepticus Treatment Trial (ESETT) trial [14];, as well as relative safety and tolerability among various AEDs [15]. The use of valproate is restricted by high risk of teratogenicity [15,16]. In cases of RSE, use of anesthetic agents is warranted. The use of midazolam and propofol is largely influenced by their short half-life, cardiovascular stability, and lower risk of hepatotoxicity compared to thiopentone. Ketamine is another agent that can be safely used, but is not readily available, and its efficacy in pregnancy-related SE is not well established. In cases of super refractory SE, combination of two anesthetic drugs, with cycling every 24–48 h, is warranted [17].

The management of pregnancy depends upon the duration of pregnancy at the time of onset of SE. As noted in the current analysis, in case of RSE in first trimester, a medical termination of pregnancy may be suggested taking into consideration the teratogenicity of AEDs or anesthetic agents used and the of intrauterine hypoxia due to prolonged SE. In case of cases in second or third trimester of pregnancy, the management of pregnancy depends largely on the etiology;, i.e., in cases of eclampsia termination of pregnancy is warranted, and in other cases, stabilization followed by delivery near term is advocated to permit fetal maturity.

Our study on 17 women with SE and pregnancy was restricted by its retrospective nature and small sample size. Large-scale multicentric prospective studies are warranted to generate sufficient data to formulate guidelines for management of SE in pregnancy.

5. Conclusion

Management of SE in pregnancy is influenced by etiology of SE and duration of pregnancy. It carries a good prognosis if detected early and treated appropriately. Large-scale multicentric studies are warranted for formulating guidelines for management of SE.

Appendix A. Functional independence measure (FIM) outcome score

Score description
No helper required
7- Complete independence
6- Modified independence (patient requires use of a device, but no physical assistance)
Helper required (modified dependence)
5- Supervision or setup
4- Minimal contact assistance (patient can perform 75% or more of task)
3- Moderate assistance (patient can perform 50% to 74% of task)
Helper required (complete dependence)
2- Maximal assistance (patient can perform 25–49% of tasks)
1- Total assistance (patient can perform less than 25% of the task or requires more than one person to assist)

[Ref.] Keith RA, Granger CV, Hamilton BB, Sherwin FS. The functional independence measure: a new tool for rehabilitation. Adv Clin Rehabil 1987;1:6–18.

Appendix B. Modified Rankin Scale (mRS)

0- No symptoms.
1- No significant disability. Able to carry out all usual activities, despite some symptoms.
2- Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3- Moderate disability. Requires some help, but able to walk unassisted.
4- Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5- Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6- Dead.

[Ref.] Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry 1991;54:1044–54.

Appendix C. Status Epilepticus Severity Score (STESS)

Variable	Feature	Score
Level of consciousness	Alert or somnolent or confused	0
	Stuporous or comatosed	1
Type of SE	Simple partial, complex partial Myoclonic, absence	0
	Generalized convulsive	1
	Nonconvulsive SE in coma	2
Age in years	<65 years	0
	≥65 years	2
Past history of seizures	Yes	0
	No	1
Total score 0–6		

[Ref.] Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (STESS): a tool to orient early treatment strategy. J Neurol 2008;255:1561–6.

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