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Critical Care Neurology (H Hinson, Section Editor)

Neurocritical Care of the Pregnant Patient

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Abstract

Purpose of review To summarize recent changes in management and emerging therapies for pregnant neurocritical care patients.

Recent findings Diagnostic and treatment options for managing neurologic emergencies in pregnant patients have expanded with both greater understanding of the effects of imaging modalities and medications on pregnancy and application of standard treatments for non-pregnant patients to pregnant populations. Specifically, this includes cerebrovascular diseases (pregnancy-associated ischemic stroke, pregnancy-associated intracerebral hemorrhage, cerebral venous sinus thrombosis), post-maternal cardiac arrest care, seizures and status epilepticus, myasthenia gravis, and fetal somatic support in maternal death by neurologic criteria.

Summary With the exception of direct abdominal computed tomography (CT), most imaging studies are reasonably safe in pregnancy. When emergent imaging is needed to prevent maternal morbidity or mortality, any CT sequence with or without contrast is appropriate to pursue. Though new safety data on antiplatelets, antihypertensives, thrombolytics, and antiepileptic drugs have increased options for disease management

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in pregnancy, unfractionated and low-molecular weight heparin remain the safest options for anticoagulation. Early studies on hypothermia, ketamine, and immunomodulating therapies in pregnancy are promising. In myasthenia gravis, new data on adjunct devices may allow more patients to undergo safe vaginal delivery, avoiding cesarean section and the associated risk of crisis. When difficult decisions regarding preterm delivery arise, recent outcome studies can help inform discussion. Lastly, when the feared complication of maternal death by neurologic criteria occurs, fetal somatic support may help to save at least one life.

Introduction

The pregnant neurocritical care patient presents a unique challenge to neurointensive care, obstetric, neurosurgical, and neuroendovascular providers. None has the training to be experts in all aspects of their care. These patients are typically young, healthy, and otherwise at very low risk for critical illness or complications thereof. Furthermore, neurological complications during pregnancy are high-risk, low-occurrence events. If managed well, excellent outcomes for both mother and baby can be achieved, necessitating careful consideration of each treatment decision. Pregnancy is a state in which numerous physiological adaptations evolve to maintain the functions of both mother and fetus. Care of this population requires familiarity with key cardiopulmonary changes among these. During pregnancy, plasma volume expands by 20–100% (average 45%) above baseline which results from a 35–40% decrease in systemic vascular resistance (SVR) which starts as early as week 5 and nadirs in mid second trimester. These changes correspond to a decrease in mean arterial pressure (MAP) by 10–15 mmHg necessitating a reflex increase in heart rate by 10–20 beats per min (bpm) to sustain the increased cardiac output needed to support fetal circulation. Another cause for the increase in heart rate is physiological anemia of pregnancy. Hormones of pregnancy also play an important role in increasing sympathetic and renin-angiotensinogen tone causing a state of hypervolemic hyponatremia. From a pulmonary perspective, progesterone is responsible for inducing a considerable central hyperventilation lowering mean partial pressure of carbon dioxide ($PaCO_2$) down to 28 mmHg. The resulting dyspnea on exertion and peripheral edema compound with pregnancy-induced hypercoagulability to cause some of the most dreaded neurological complications of pregnancy [1, 2].

Neurological emergencies in pregnancy can be subcategorized into 3 main groups. Areas of particular focus with advancements in ICU management from January 2017 to August 2020 are italicized below:

I. Coincidental development of an acute primary neurological emergency

Cerebrovascular disease (CVD)
Pregnancy-associated acute ischemic stroke (PAS)
Ruptured vascular malformation
Aneurysmal subarachnoid hemorrhage (aSAH)
Cerebral venous sinus thrombosis (CVST)
Reversible vasoconstriction syndrome (RCVS)
Pregnancy-associated intracerebral hemorrhage (pICH)
Post-maternal cardiac arrest (CA) care
Somatic fetal support in mothers declared dead by neurologic criteria
Symptomatic status epilepticus
Traumatic brain injury

II. Exacerbation of pre-existing neurological disease

Multiple sclerosis
Myasthenia gravis
Epilepsy
Hormone sensitive intracranial neoplasms

III. Neurological complication of pregnancy

Sheehan's syndrome
Hypertensive disorders of pregnancy
Pre-eclampsia (PE)/eclampsia
Posterior reversible encephalopathy syndrome (PRES)
Hemolysis, elevated liver enzymes, low platelets (HELLP)

These complications are rare but significantly increase morbidity and mortality. A key tenet of management is to prioritize the outcome of the mother, while minimizing harm to the fetus when possible. Even therapies that carry considerable fetal harm, including fetal demise, may be necessary to satisfy this principle. Exclusion of pregnant women in clinical trials has led to a paucity of evidence to guide complex management decisions of neurological emergencies in pregnant women. Available evidence is mostly limited to small observational studies or recommendations based on expert opinion. Safety concerns, cost considerations, and potential fetal harm of the treatments discussed herein are summarized in Tables 1 and 2. While therapies have been presented along with the pathologies in which they were studied, the same data may inform the safety of broader application to other disease states. Unless specified for a particular medication, dosing is unchanged in pregnancy. In practice, the care of such patients demands close collaboration between experts in neurocritical care, epilepsy, endovascular neurology, obstetrics, neonatology, and neurosurgery in a specialized neuro ICU to optimize outcomes for mother and baby.

Diagnosis and treatment

Diagnostic evaluation

Imaging is essential for accurate diagnosis, stabilization, and definitive treatment of neurocritically ill patients. Additionally, these patients are susceptible to systemic complications that may necessitate non-neuroimaging. Roentgenogram (X-ray), computed tomography (CT), diagnostic digital subtraction angiography (DSA), nuclear medicine (NM) scans, magnetic resonance imaging (MRI), and ultrasonography (US) are relevant to the diagnostic evaluation of neurological emergencies in pregnancy. Either MRI or US should be used preferentially if they can provide the necessary information without a clinically relevant delay. Otherwise, the favorable risk-benefit profile of most X-ray and CT studies still supports their use during pregnancy [3].

Imaging modalities

Ionizing radiation exposure

Apprehension surrounding ionizing radiation-based imaging in pregnancy centers on four feared complications that can result at various time points along fetal development. Risks include fetal demise (0-2 weeks), malformation, developmental delay or intellectual disability (2-8 weeks), and increased life-time risk of cancer (anytime). The typical occupational limit for fetal radiation is 5 mGy and fetal risk is negligible up to 50mGy [4, 5•]. Carcinogenicity is a stochastic effect meaning no amount of radiation exposure is “safe”. However, the risk is often lower than daily background radiation exposure.

Roentgenogram

X-rays of structures remote from the gravid uterus carry very low radiation exposure to the fetus. Abdominal shielding can, albeit minimally, further reduce the exposure. Direct anterior-posterior (AP) X-ray of the abdomen has a dose exposure of < 9 mGy. While X-rays are safe in pregnancy, minimization of exposure is still warranted. Limiting X-rays to a single view or obtaining a single partial-chest/partial-abdomen film to confirm the positions of lines and tubes is prudent. Posterior-anterior (PA) views carry one-tenth of the dose

Table 1. Summary of safety concerns and costs of drugs reviewed. *ACE* acetylcholine esterase, *ARB* angiotensin renin blocker

Drug	Safety considerations	Crosses placenta?	Cost
Thrombolytics			
Alteplase	Recommend close monitoring for uterine bleeding after use in pregnant women	No	$$
Reteplase	Risk of bleeding increased in pregnant women; recommended close monitoring for uterine bleeding after use in pregnant women	No	$$
Tenecteplase	Recommend close monitoring for uterine bleeding after use in pregnant women	No	$$
Antiplatelets			
Acetylsalicylic acid (ASA)		Yes	$
Clopidogrel	ESC guidelines recommend limited use in pregnancy; black box warning of diminished platelet effect in patients with 2 loss-of-function alleles in CYP2C19 gene	Unknown	$$
Cangrelor		Unknown	$$$
Ticagrelor	Black box warning for bleeding risk may exacerbate bradyarrhythmias	Unknown	$$
Anticoagulants and reversals			
Enoxaparin	Black box warning for spinal/epidural hematomas with neuraxial intervention	No	$$-$$$
Heparin (unfractionated)	Some products use benzyl alcohol as preservative, which is contraindicated for use in pregnant females; if prescribing, use preservative-free formulation	No	$
Apixaban	Black box warning for spinal/epidural hematomas with neuraxial intervention and premature discontinuation	Yes	$$$
Rivaroxaban	Black box warning of spinal/epidural hematomas with neuraxial intervention and premature discontinuation	Yes	$$$
Warfarin	Black box warning about fatal bleeding	Yes	$
Andexanet alfa	Black box warning about risk of arterial and venous thrombotic events, cardiac arrest, and sudden death	Unknown	$$
Antihypertensives			
ACE inhibitor/ARB	Black box warning about fetal toxicity	Yes	$
Amlodipine		Yes	$
Clevidipine		Unknown	$
Clonidine	Black box warning against use as epidural agent for obstetric, postpartum, or perioperative pain management	Yes; amniotic fluid concentrations may be even higher than maternal serum	$$
Hydralazine		Yes	$
Esmolol		Yes	$
Labetalol		Yes	$
Nicardipine		Limited placental transfer	$
Nifedipine	Reports of prematurity, perinatal asphyxia, intrauterine growth retardation	Yes	$

Table 1. (Continued)

Drug	Safety considerations	Crosses placenta?	Cost
Nitroprusside	Black box warning for hypotension and cyanide toxicity	Yes	$-$$
Antiepileptic drugs			
Lamotrigine	Black box warning for serious skin rashes	Yes	$$
Levetiracetam		Yes	$-$$
Ketamine	Produces dose-dependent increase in uterine contractions; ketamine clearance reduced in pregnancy	Yes	$
Phenytoin	Black box for cardiovascular risk with rapid infusion	Yes	$
Phenobarbital		Yes	$
Valproic acid	Black box warning about fetal risk, hepatotoxicity, pancreatitis, and use in mitochondrial disease	Yes	$$
Immunomodulatory			
Azathioprine	Black box warning about malignancy	Yes	$-$$$
Intravenous immunoglobulin (IVIG)	Black box warning for risk of thrombosis, renal dysfunction and renal failure	Dependent on IgG subclass and gestational age, with more transfer later in pregnancy	$$-$$$
Tacrolimus	Black box warning for serious infections and malignancy; whole blood concentrations decreased in pregnancy, but unbound drug increases; consider measuring unbound drug in pregnant and postpartum	Yes	$-$$
Other			
Mannitol	May decrease amniotic fluid	Yes	$
Pyridostigmine		Yes	$-$$

exposure and therefore, when possible, sending a stable ICU patient for PA imaging in radiology may also be considered [6].

Computed tomography

Pregnancy should not affect the indications or timeliness of emergent CT imaging. For neuroimaging, non-contrast CT of the head (NCCT head) carries the lowest fetal dose exposure of 0.001 mGy. That from CT of the lumbar spine ranges from 2-20 mGy, with the remainder of CT-based neuroimaging ranging closer to NCCT head [7, 8]. The only exception is CT scanning of the abdomen and pelvis. With a dose exposure of 50mGy, every effort should be made to use an alternative modality such as ultrasound (US) or MRI [3, 5•, 7, 9]. Consultation with the radiologist should occur to ensure all options have been considered and the benefits of the study for the mother outweigh the risks to fetus.

With increasing availability of portable CT scanners, it is helpful to be aware of a change in practice away from abdominal shielding and to advocate against it. The practice has been called into question for two reasons. Radiation scatter for imaging

Table 2. Risk of fetal effects from medications

	Overall Major Congenital Malformations	Reported Malformations	Fetal Loss/ Spontaneous Abortions	Prenatal Growth Retardation	Premature Birth	Other
Anti-platelet/ Anticoagulant						
Aspirin	Variable reports, likely not	Gastroschisis	Unknown	Unknown	0.89 (0.81–0.98)	Neonatal Intracerebral Hemorrhage 9.66 (1.88–49.48)
Rivaroxaban	--	No specific malformation	2.70 (1.79–4.07)	Unknown	Unknown	--
Apixaban	--	No specific malformation	6.76 (2.99–15.25)	Unknown	Unknown	--
Warfarin	--	Craniofacial	Not significant when compared to heparin	Unknown	Unknown	--
Antihypertensives						
Angiotensin-converting-enzyme inhibitor/Angiotensin receptor blocker exposure in any trimester	2.16 (1.72–2.71)	Central Nervous System 2.02 (1.08–3.28) Cardiovascular 2.96 (2.57–3.39) Urogenital 4.57 (2.11–9.89)	Miscarriage 1.63 (1.30–2.05) Stillbirth 2.36 (1.17–4.76)	2.30 (1.20–4.41)	1.69 (1.04–2.76)	--
Angiotensin-converting-enzyme inhibitor/Angiotensin receptor blocker exposure in 1st trimester only	1.94 (1.71–2.21)	Central Nervous System 1.88 (0.73–4.83) Cardiovascular System 3.02 (3.60–3.51) Urogenital 3.60 (0.42–30.51)	Miscarriage 1.63 (1.30–2.05) Stillbirth 2.36 (1.17–4.76)	1.04 (0.59–1.81)	1.26 (0.84–1.91)	--

Table 2. (Continued)

	Overall Major Congenital Malformations	Reported Malformations	Fetal Loss/ Spontaneous Abortions	Prenatal Growth Retardation	Premature Birth	Other
Antiepileptic Drugs						
Levetiracetam	0.72 (0.43–1.16)	No specific malformation	2.47 (0.50–10.15)	1.27 (0.34–3.54)	0.87 (0.31–2.04)	--
Phenobarbital	1.83 (1.35–2.47)	Cleft lip/palate	0.90 (0.44–1.93)	1.88 (1.07–3.32)	1.59 (0.87–2.75)	--
Phenytoin	1.69 (1.3–2.17)	Cleft lip/palate Club foot	1.5 (0.85–2.91)	0.68 (0.37–1.21)	1.03 (0.55–1.82)	--
Valproic Acid	2.93 (2.36–3.69)	Cleft lip/palate Club foot Hypospadias	1.83 (1.04–3.54)	1.28 (0.86–1.95)	0.96 (0.65–1.37)	--
Immunomodulation						
Tacrolimus	--	No specific malformation	Unknown	Unknown	Unknown	Children with risk of hospitalization for infections in first 12 months 4.35 (1.02–18.45)

areas other than the abdomen and pelvis occurs almost completely through internal tissue transfer. Also, newer CT technology has safety mechanisms for gating exposure based on detected radiation. If that mechanism is interrupted by the lead shield, it could result in a paradoxically higher effective radiation dose experienced by the conceptus [2, 10]. In critically ill patients, the added weight of lead on the gravid uterus may contribute to further discomfort, increased intra-abdominal pressure translating to increased intracranial pressure (ICP), or hemodynamic compromise from IVC compression in the supine position.

Digital subtraction angiography

DSA carries the highest risk of fetal radiation exposure from 3 distinct sources which are fluoroscopy, cut film radiography, and digital subtraction angiography. During pregnancy, DSA should be limited to emergent intervention or diagnostic studies needed to inform emergent care. The operator can use a number of essential dose-reducing techniques including radial or carotid access [3, 8••, 12]. Of note, a recent case series estimated that cerebral angiography during mechanical thrombectomy via groin access that minimizeduse of biplane resulted in a fetal radiation exposure of only 0.024 μGy [4].

Nuclear medicine scans

The most relevant NM scan in the care of the pregnant patient in the neuro-intensive care unit (neuro ICU) is the Technitium-99m hexamethylpropylene-amine oxime (99mTc HMPAO) study for determination of death by neurologic criteria. If ancillary testing is required to diagnose brain death, this test is considered safe for the fetus and ongoing somatic support [5•].

Magnetic resonance imaging

Prior concerns over increased specific absorption rate (SAR) of energy by the fetus at 3 tesla (3 T) versus 1.5 tesla (1.5 T) and safety of MRI during the first trimester have been allayed in updated guidelines by both the American Colleges of Radiology (ACR) and Obstetrics and Gynecology (ACOG). Non-contrast MRI at 3 T or less is considered to be safe during any trimester of pregnancy by both colleges [3, 5•].

Ultrasound

Ultrasound imaging is safe in pregnancy. However, there is the potential for a rise in tissue temperature from absorption of soundwave energy. Epidemiological studies prior to 1992, when the US Food and Drug Administration (FDA) imposed a limit on spatial-peak temporal average intensity of ultrasound transducers of 720mW/cm2, reported a correlation of low birth weight, delayed speech, dyslexia, and non-right handedness with exposure to ultrasound in utero. At this limit, an increase in fetal tissue temperature of up to 2°C is still possible. With the rise in point-of-care ultrasound (POCUS) in ICUs, it is important to understand that the thermal effects are directly proportional to exposure and dwell times. Also, B-mode has the lowest risk of temperature elevation, while color and spectral Doppler have the highest. Lastly, when machines are calibrated for obstetric imaging, the thermal effects are minimized; thus, it is also important when using POCUS to use appropriate settings and pay attention to the thermal and mechanical indices (TI) and (MI) to

ensure safe imaging. Ultrasound imaging of the fetus should be performed efficiently by a trained operator and only when medically necessary [3, 5•].

Contrast

Iodinated agents

Modern low osmolality contrast media is classified as a category B drug by the FDA. Though it is both absorbed by the fetus and crosses the fetal blood-brain barrier, to date there are no known mutagenic effects, and the theoretical risk of hypothyroidism has not been reported [6]. When imaging is needed to guide emergency management, CT with contrast should be performed without delay. For less time-sensitive vessel imaging, non-contrast time-of-flight (TOF) MRI should be obtained instead; but only if it is already part of the center's existing protocols, possible to be performed without clinically significant delay, and adequate diagnostic information can be obtained [3, 5•].

Gadolinium-based contrast agents

Free gadolinium is toxic and is always administered with a chelating agent. It has been shown to be teratogenic in repeated high doses in animal studies. In humans, the duration of fetal exposure is unknown. Gadolinium-based contrast agents (GBCAs) readily cross the placenta. The fetus excretes it into the amniotic fluid from where it re-ingests and reabsorbs it. The longer the agent persists in amniotic fluid, the more likely it is to become unbound from the chelate raising concern for nephrogenic systemic fibrosis (NSF). A single cohort of 26 women received a clinically recommended dose of GBCA during the first trimester without any mutagenic effects noted. The complications that have been reported are from the retrospective analysis of a Provincial database from Ontario, Canada that reviewed MRI with GBCA exposure versus no MRI exposure during pregnancy in all live births (> 1.4 million) of 20-week gestation or more from 2003 to 2015. GBCA exposure was associated with an increase in NSF-like connective tissue disorders which was not statistically significant. It was also associated with an increased risk of a rheumatological, inflammatory, or infiltrative skin disorders and with still birth or neonatal death which did reach statistical significance [17•]. If performed, the ACR recommends formal documentation of a risk statement in the report. The report should include that the diagnostic question cannot be obtained without the use of IV contrast or another imaging modality, that the information needed affects the care of the mother or conceptus during the course of the pregnancy, and that discussion with the referring physician reveals that it would not be prudent to wait until after delivery [6]. The ACOG recommends that GBCA be limited to situations in which the benefits clearly outweigh the risks [3]. Breast feeding should not be interrupted following GBCA administration as only negligible amounts are excreted into breast milk [3].

Medical and surgical management

Cerebrovascular disease

Cerebrovascular diseases occur rarely in pregnancy, but pregnancy-induced hypercoagulable state and hypertensive diseases of pregnancy are risk factors. The incidences of CVD types in descending order during pregnancy and

puerperium are PAS (34/100,000), pICH (12.2/100,000), CVST (12/100,000 – highest during puerperium), and aSAH (10-58/100,000) [18–21].

PAS varies with gestational age and accounts for 15% of maternal mortality. The highest risk is in the third trimester and immediate postpartum period [22–24]. Risk factors include African American ethnicity, age over 35, and presence of autoimmune disease states including catastrophic antiphospholipid syndrome (CAPS), immune thrombocytopenia purpura (ITP), and other thrombotic microangiopathies of pregnancy [25–27]. Cesarean delivery is associated with increased likelihood of postpartum stroke though a causal relationship has not been well established [25, 28, 29]. Medical management of stroke is highly protocolized and PAS-specific medication considerations are necessary.

ICH is a devastating condition associated with grave prognosis, regardless of pregnancy status. pICH is associated with an in-hospital maternal mortality rate of nearly 20% [30, 31]. Approximately 50% of pICH occurs in the puerperal period, while 40% are reported close to delivery [31]. The cornerstone of medical management for pICH involves blood pressure control, reversal of coagulopathy, and management of mass effect individualized for maternal status, gestational age, and pregnancy-specific medication considerations.

CVST is estimated to affect 0.012% of deliveries during the puerperal period. This risk is increased by infection, instrumented delivery, cesarean section, increasing maternal age, increasing hospital size, hyperemesis gravidarum hemodynamic fluctuations, and hyperhomocysteinemia. Anticoagulation remains the mainstay of treatment for CVST. Despite increased choice of agent in the general population, available data on use of direct oral anticoagulants (DOACs) during pregnancy do not support this option [32–34].

Thrombolytics (alteplase, tenecteplase, reteplase, urokinase, streptokinase)

Intravenous (IV) and intraarterial (IA) thrombolytic therapies are cornerstones of management for acute ischemic stroke (AIS) and other life-threatening thrombotic events in non-pregnant patients. Concerns for potential fetal harm, life-threatening hemorrhage in the mother, and lack of evidence supporting the safety of its use resulted in including pregnancy as a relative contraindication to thrombolytic therapy. However, these large molecules do not cross the placenta. Neither concerns of direct effects of fetal hemorrhage nor teratogeneses are warranted. A review of existing literature found that complication rates for 141 pregnant women treated with IV thrombolysis were no higher than for non-pregnant patients. For PAS specifically, there were 15 articles with a total of 30 patients who received either IV or IA thrombolytics. Urokinase (UK) and alteplase (tPA) were the most frequent agents used. Again, there was no increased risk of complication in pregnancy when compared to non-pregnant women [3, 35••]. The potential does exist for increased uterine bleeding during pregnancy, which can be life-threatening in the 48hours postpartum. The risk of placental abruption exists in the setting of PAS with or without thrombolysis. The possibility of additional risk from this therapy is unknown. The AHA/ASA 2018 AIS Guidelines support consideration of IV tPA administration in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risk of uterine bleeding. This decision should be made based on maternal risk-benefit and personal values expressed by the patient or their designated healthcare proxy [8••, 36, IIb].

Mechanical thrombectomy

Mechanical thrombectomy (MT) became standard of care for acute ischemic stroke (AIS) resulting from anterior large vessel occlusions following the publication of a series of landmark trials in 2015 (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT). In all 5 trials, pregnancy was an exclusion criterion. Nevertheless, reports of MT in pregnant patients began in 2016 and a handful of cases have been published since [37–41]. All 4 of the initial cases resulted in excellent outcomes leading to the 2018 Canadian Best Practice Consensus Statement on Acute Stroke Management in Pregnancy to recommend that pregnancy not be considered a contraindication to angiography. Pregnant women should undergo angiography and MT for disabling stroke without delay [8••]. The hesitancy in widespread adoption of this practice recommendation is over undue concern for fetal radiation exposure which was recently estimated to be minimal [4]. There are also the risks of maternal arterial dissection and hemorrhagic complications. However, with potential for severe morbidity from stroke, the benefits are considered to outweigh the risks [8••].

Antiplatelets

Antiplatelet therapy is essential to both acute and long-term management of cerebrovascular disease. Safety data for low-dose acetyl salicylic acid (ASA) in pregnancy is extensive. Another benefit is that ASA is inexpensive compared to other common antiplatelet agents. There may be maternal factors that require either continuation of an alternative antiplatelet agent, dual antiplatelet therapy (DAPT), or intravenous infusion as bridge therapy. Familiarity with ASA, clopidogrel, ticagrelor, and cangrelor in the pregnant neuro ICU population is important.

Acetylsalicylic acid

Acetylsalicylic acid (ASA) is an irreversible non-selective cyclooxygenase inhibitor. Older studies raised concerns that ASA increased the risk of fetal malformations but multiple meta-analyses including over 31 studies failed to produce evidence of this for low-dose ASA (60-100 mg). Despite being expressed in breast milk, no associated reports of harm exist. ASA is assigned an FDA pregnancy category B. In fact, low-dose ASA may confer benefit by reducing preterm birth in women at risk for pre-eclampsia [42]. A secondary analysis of a randomized placebo-controlled trial for aspirin in pregnancy suggested aspirin reduced preterm birth before 3-week gestation in nulliparous healthy women [43]. The recent ASPIRIN study, a randomized double-blind trial, found low-dose aspirin reduced preterm birth and perinatal mortality in nulliparous women in low-income and middle-income countries [44]. However, aspirin may increase risk of neonatal intracranial hemorrhage [45]. Pregnant women should be prescribed ASA for PAS as per practice in the general population.

Clopidogrel

Clopidogrel is an irreversible adenosine diphosphate P2Y12 platelet receptor inhibitor (ADP-P2Y12). Despite less clinical observational data in humans compared to ASA, it is also an FDA pregnancy class B drug that does not affect

lactation. The only noted complication to date is increased intrapartum and postpartum bleeding. It is recommended to hold Plavix for 5–7 days prior to delivery [46]. While ASA is the preferred antiplatelet agent in pregnancy, clopidogrel may be used when maternal benefits outweigh the risks.

Ticagrelor

Ticagrelor is a reversible ADP-2PY12 inhibitor. It is currently an FDA pregnancy class C drug. Animal studies at doses 5–7 times higher than recommended did result in fetal structural abnormalities. To date there are 3 case reports of ticagrelor use in pregnancy. ST-elevation myocardial infarction (STEMI) with percutaneous coronary intervention (PCI) necessitating DAPT was the indication in 2 cases, while progressive CVST requiring DAPT in addition to LMWH was the third. In all 3 cases, ticagrelor was discontinued 5–7 days prior to uneventful delivery of health neonates [47–49]. Given limited experience with ticagrelor in pregnancy, it may be used in pregnancy if warranted by maternal risk-benefit ratio.

Cangrelor

Cangrelor is a continuous intravenous infusion formulation of a reversible ADP-2PY12 inhibitor. It is currently an FDA pregnancy class C drug. Animal studies at all doses demonstrated delayed fetal growth in both rats and rabbits. A single recent case report details its use for 5 days to bridge DAPT for cesarean delivery in a pregnant woman with recent intracranial stent for PAS secondary to middle cerebral artery (MCA) occlusion. Treatment with a reduced dose of 0.75mcg/kg/min resulted in an uneventful delivery of a healthy neonate with APGARS 9 and 9 [50]. Though cangrelor is not recommended in pregnancy, there may be unique situations in which the maternal benefits outweigh the risks.

Anticoagulants

Anticoagulation is the mainstay of treatment for PAS related to hypercoagulable state or embolic source, CVST, and other systemic thromboembolic events. Low-molecular weight heparin (LMWH) has long been the anticoagulant of choice in pregnancy owing to the known risk of fetal warfarin syndrome and association of unfractionated heparin with teratogenicity and increased fetal bleeding [51]. Enoxaparin, a low-molecular weight heparin, provides a good safety profile, does not cross the placenta, or enter breast milk at standard doses [52]. Also, recent meta-analysis of enoxaparin use in pregnancy found a lower rate of spontaneous abortions in treated women compared to controls [53]. Teratogenicity of the DOACs is unclear, but meta-analysis of case reports suggests an increased risk of miscarriage. Rivaroxaban is most reported in the literature ($n = 178$), and 4% had anomalies possibly related to rivaroxaban [55]. Through the World Health Organization database of direct oral anticoagulants (DOACs), a recent concern has emerged that both rivaroxaban and apixaban may have an increased risk of spontaneous abortion [56]. At this time, anticoagulation in pregnancy remains limited to LMWH and in rare cases unfractionated heparin.

Anticoagulant reversal agents

Reversal of iatrogenic coagulopathies may be required for hemorrhagic complications or invasive procedures. Prothrombin complex concentrates, fresh frozen plasma, vitamin K, and protamine sulfate are all FDA pregnancy category C. A new reversal agent, andexanet alfa that reverses direct factor Xa inhibitors, is currently an FDA category N drug (not yet classified). There is no clinical data on its use in pregnancy or lactation, and no recommendations can be made at this time.

Antihypertensives

Women with hypertensive disorders of pregnancy are considered to be at risk for stroke and seizures. There is little data to guide blood pressure (BP) goals for the various disease states in the neuro ICU during pregnancy. In general, the BP goals of pregnancy should be followed including when considering permissive or therapeutic hypertension whenever feasible. In pregnancy, severe hypertension is defined as > or = 160/110 mmHg and is considered and obstetric emergency requiring immediate inpatient care. Initial goal should be to lower BP < 160/110 mmHg. The Control of Hypertension in Pregnancy Study (CHIPS), an international multicenter randomized controlled trial, found that independent of pre-eclampsia (PE), pressures above this threshold were associated with increased maternal length of stay >10 days, pregnancy loss or high level of neonatal care for >48 h, increased risk of preterm birth at both <34-week and < 37-week gestation, low birth weight (<10th percentile), and low maternal platelets and elevate maternal liver enzymes (HELLP). The study also found that untreated BP of 140/90 mmHg or higher increased the incidence of severe hypertension (relative risk 1.8; 95% CI, 1.34–2.28). Therefore, once BP < 160/110 mmHg is achieved and neurological indication for hypertension has resolved, careful titration of medication should be made to achieve the goal of <140/90 mmHg. Close monitoring of the blood pressure is needed to avoid episodes of hypotension and low placental perfusion. Continuous fetal monitoring is required to identify early signs of fetal distress [8••, 57].

Until recently, the ACOG recommended use of IV labetalol or hydralazine as first-line therapy for hypertensive disorders in pregnancy. A recent systematic review and meta-analysis of hydralazine use in pregnancy revealed that mothers treated with hydralazine had a higher number of side effects (RR 1.21, 95% CI, 1.01–1.45) when compared to those treated with either labetalol, nifedipine, ketanserin, diazoxide, urapidil, isradipine, and epoprostenol. Also, infants of mothers treated with hydralazine had lower birth weights (WMD: −135.30, 95% CI: −260.95 to −9.65) [58]. Currently labetalol, methyldopa, long-acting nifedipine, and other beta blockers (BB) (metoprolol, pindolol, propranolol, acebutolol) are considered first-line agents, with hydralazine, clonidine, and thiazide diuretics considered second line. The limitation of long-acting nifedipine in the neurocritically ill is the frequent inability to administer medications via oral route. Blood pressure control is less consistent with shortacting nifedipine. Traditionally calcium channel blockers (CCBs) have been considered pregnancy category C. Amlodipine has a long duration of action but can be crushed and given via enteral tubes. Until recently, there were no studies assessing its safety in early pregnancy. Mito and colleagues

performed a retrospective review of 231 pregnant women of which 48 were treated with amlodipine during their first trimester. They found no association with first trimester exposure to amlodipine and increased rate of fetal malformations compared with other antihypertensives (54/231) or no medication (129/231) [59••, 60••]. Both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) remain contraindicated in pregnancy.

In the neuro ICU, continuous infusions are often used to maintain tight BP control and adjust BP goals in a controlled manner. Also, there may be the need for acute discontinuation of antihypertensive effects, not possible with oral medications. In pregnancy, labetalol infusion is considered first line and esmolol and nicardipine infusions, second line. With its risk of cyanide toxicity, nitroprusside should only be considered a last resort [61, 62]. Clevidipine is now considered a first-line antihypertensive infusion for acute ischemic and hemorrhagic stroke in the non-pregnant population [63]. However, it is designated a pregnancy class C drug, with no literature to date regarding its use in pregnancy. Nicardipine infusion has a rapid onset of action but a 4–6-h duration of action. Since clevidipine is both rapid in onset and elimination from the system (within minutes), it may be considered in rare instances where maternal benefits outweigh potential fetal risks, such as flowlimiting stenosis. Here, maternal cerebral hypoperfusion may occur requiring rapid reversal of antihypertensive effects. Prior to initiating this medication, discussion with the multi-specialty team is warranted.

Seizures and status epilepticus

Seizures and status epilepticus (SE) are frequently encountered in the neurocritically ill. In pregnancy, particular etiologies could include the eclamptic spectrum, medication non-compliance, changes in medication metabolism, acute symptomatic status epilepticus (from acute brain insult), or unprovoked new-onset refractory status epilepticus (NORSE). In addition to treatment of seizures, antiepileptic drugs (AEDs) are also used for seizure prophylaxis (for certain cerebrovascular accidents, trauma, or cranial surgery), headache, neuropathic pain, and behavior/agitation management. It has been known for decades that many of these medications are not without adverse fetal effects. Newer comparative data on toxicity is available to guide medical decision-making.

Antiepileptic drugs

Certain medication exposures in the first trimester place the fetus at risk for major congenital structural malformations. Indeed, much of the current literature for AEDs focus on women taking daily medication during the first trimester. Many AEDs cross the placenta including levetiracetam (LEV), phenytoin (PHT), and valproate (VPA) [64••]. In 2019, Tomson compared rates of major congenital malformations with individual AEDs as reported by the North American Antiepileptic Drugs and Pregnancy Registry (2012), UK and Ireland Pregnancy Registry, and the International Registry of Antiepileptic Drugs and Pregnancy (EURAP, 2018). VPA was associated with one of the highest prevalence rates of major congenital malformations (range 6.7-10.3%), while (LEV) had one of the lowest

(0.7-2.8%). In 2018, the EURAP registry reported a dose-dependent increase in risk of major malformations for VPA and phenobarbital (PHB), among others. The same study also included the largest reported cohort of in-utero LEV monotherapy exposure and found an overall similar risk profile to low-dose lamotrigine (LTG) exposure [65]. A recent study of 1547 pregnancies, 231 (14.9%) of which did not have AED exposure in the first trimester, demonstrated no significant change in the rate of major congenital malformations if AEDs were increased or added in the second or third trimester [66]. The study also found no statistically significant association between the infants' developmental quotient (DQ) at 1 year of age and AED usage outside of the first trimester, although there was a non-significant trend towards a lower DQ with higher doses or the addition of PHB, VPA, and LEV, among others. A recent systematic review and meta-analysis pooled 96 studies with a total of 58,461 patients and reported the odds ratios for overall major congenital malformations, combined fetal losses, prenatal growth retardation, preterm birth, and other specific malformations. Overall, VPA, PHB, and PHT were associated with higher risk for major congenital malformations but LEV was not [67]. Given the physiological changes during pregnancy, therapeutic drug level monitoring should guide dose optimization for all AEDs.

Myasthenia gravis

The incidence of myasthenia gravis (MG) complicating pregnancy is 1/68,000 and its clinical course varies. Approximately, one-third experience improvement, one-third no change or worsening, and one-third experience a myasthenic crisis (MC). First-line treatment during pregnancy is oral pyridostigmine [68, 69]. Intravenous acetylcholinesterase inhibitors should be avoided as they can induce uterine contractions. It is well established that plasma exchange and/or IVIG can be deployed for prompt, transient use in MC and both are safe in pregnancy [68, 69, 70•].

In patients with severe disease who are at higher risk of recurrent exacerbation during pregnancy, adjunct steroids and rituximab maybe started during their ICU course if prolonged hospitalization is expected and maternal benefit outweighs the risk. Steroids are associated with small (<1%) risk of cleft palate and rituximab with transient decline in B-cell counts, though data is very limited for rituximab and is generally not recommended [68, 71].

Epidural anesthesia is preferred over narcotics, neuromuscular blocking agents (NMBAs), and local anesthetics for pain management [68]. Though NMBAs should generally be avoided, a case report demonstrated the efficacy of sugammadex post-rocuronium in a compliant MG patient for a cesarean delivery [72].

Pre-eclampsia in myasthenia gravis

Pre-eclampsia (PE) presents a unique challenge in this population as magnesium, the treatments of choice for seizure prophylaxis in PE, is contraindicated in MG [71, 73]. Thus, levetiracetam, valproic acid, and diazepam have all been used for seizure prophylaxis in these mothers. Phenytoin may be used for refractory cases [74–75].

Also, BBs and CCBs which are first line for BP control in PE pose risk of precipitating a MC. These agents may be considered when BP is not responsive

to methyldopa or hydralazine which are considered safe in MG. If either BB or CCBs are needed, the patient should be monitored closely for signs or symptoms of decompensation [76].

Parturition in myasthenia gravis

Vaginal delivery is the preferred method to mitigate maternal risk. However, cesarean sections are indicated if there are obstetric complications to consider but may induce MC. Due to maternal fatigue during the second phase of delivery, MG patients still frequently undergo cesarean sections. Recently, a small, case-control (n = 10) study demonstrated that cesarean section can be avoided with epidural anesthesia and vacuum delivery in MG parturients, effectively reducing maternal fatigue without neonatal complications [77••].

Cerebral edema, space-occupying lesions, and intracranial hypertension

General measures to reduce intracranial hypertension (IH) include elevating the head of the bed to a 30-45° angle and midline head position. Hyperosmolar therapy should be avoided in pregnant patients, if possible, given the potential for severe fetal dehydration and electrolyte abnormalities. Hypertonic saline is a known abortifacient (first trimester) and should also be avoided if possible. Hyperventilation which is a temporizing measure for IH crises can reduce placental oxygen transfer [77••]. Thus, in pregnancy, decompressive craniectomy for malignant stroke, traumatic brain injury or craniectomy, and evacuation of space-occupying lesions falls higher in the algorithm for management than in non-pregnant patients.

With respect to mode of delivery, decision regarding when and how to plan the delivery should be a patient-centered collaborative multispecialty discussion. For women who have hemodynamic instability or IH, emergency cesarean section is most reasonable.

Emerging therapies

Hypothermia

Post-maternal cardiac arrest care

Cardiac arrest occurs in 1:12,000 admissions for delivery globally, with 800 pregnant women dying daily. A shift in the paradigm of post-maternal cardiac arrest (CA) care in pregnancy is needed to improve neurological outcomes in these young patients [79, 80]. Hypothermia is standard of care for supporting neurological recovery post cardiac arrest in the general population. There is no evidence to guide target temperature for hypothermia in neonates, pregnant or postpartum patients. Pre-clinical work, by Ikonomidou et al., suggests that mild, but not moderate, hypothermia significantly reduces neuronal and oligodendrocytic apoptosis following sevoflurane exposure in a macaque model [81]. Of the two human case reports of hypothermia following maternal CA, one resulted in fetal demise of unclear relation to hypothermia (prolonged downtime). The other had good maternal and fetal outcome. Despite absence of trial data, expert consensus recommends consideration of ultra-mild hypothermia (36°C) in post-maternal CA to avoid further impact on the coagulopathy of

pregnancy. The same protocol should be used as for non-pregnant patients [80, 82, IIb]. Typical fetal effects of hypothermia are decreased fetal heart rate and variability. Continuous fetal monitoring is needed [79]. With expansion of hypothermia as a treatment modality in post-maternal CA resuscitation, there is potential for this modality to be extended to other disease pathologies (TBI, stroke, SE) in pregnancy.

Ketamine

The effects of ketamine are myriad with widespread implications across multiple receptors and molecular pathways. There is a growing body of animal literature warning of the potential toxicity of in-utero exposure to ketamine. This includes disruption of a NOTCH signaling pathway in neural crest development that, in humans, increases the risk of congenital disorders including Hirschsprung disease, Treacher Collins syndrome, Waardenburg-Shah syndrome, DiGeorge syndrome, CHARGE syndrome, neuroblastoma, and melanoma [83]. One study postulated that midazolam co-administration with ketamine may mitigate ketamine-induced autophagy by reduction of reactive oxygen species [84]. In humans, APGAR scores were lower following in-utero exposure to ketamine versus thiopentone [85].

Status epilepticus

As in the general population, ketamine is emerging as a potential novel therapeutic for refractory status epilepticus in pregnant patients. This was highlighted in a recent case report of 7 days of in-utero exposure to ketamine for refractory status epilepticus in a 7-week-old fetus. Ketamine was started on day 3 of ongoing super refractory status epilepticus in a patient with known symptomatic epilepsy who was being weaned off of VPA. It was effective in arresting status epilepticus. The APGAR scores were 9 following cesarean delivery at 37-week and 5-day gestation. At 9-month follow-up, there were no negative outcomes noted and the baby met developmental milestones [86]. Despite the potential fetal risks, the morbidity and mortality to both mother and fetus of status epilepticus may justify the use of ketamine in pregnancy for this indication.

Pain management, analgesia, and opioid sparing

Ketamine has become an attractive alternative to opioid use in the treatment of pain. There is also the additional benefit of perioperative amnesia and lack of respiratory depression. Use of ketamine in pregnant patients for pain management is rare; however, with increasing use in the general population, the inference can be made that ketamine may be useful in managing postoperative pain after cesarean section, or in treatment of acute headache in disease states such as subarachnoid hemorrhage. There is report of two pregnant women for whom ketamine was used for sickle cell crisis pain, refractory to high-dose opioids. Decreases in opioid use were noted in the first patient, with complete pain relief experienced by the second. Ketamine was discontinued due to adverse side effects, including unknown contribution to preterm labor in the

first patient. There were no maternal or fetal complications for the second case [87].

The above discussion on implications for fetal development suggests that serious consideration of risk versus benefit be given when using ketamine for this indication. It also highlights the need for further research into the timing, dosing, and co-administration of other anesthetic medications in this population [88].

Immunomodulation/immunosuppression

There are multiple autoimmune diseases that can affect the critically ill pregnant patient at any point in their neuro ICU course including catastrophic antiphospholipid syndrome (CAPS), immune thrombocytopenic purpura (ITP), and other microangiopathies of pregnancy. These are rare entities lacking standard recommendations for duration and dosing of medication. Intravenous immunoglobulin (IVIG) presents a safe alternative with standard dosing. It is now a preferred treatment for these disorders due to its mitigation of inflammation without causing immunosuppression [27]. IVIG is well tolerated across a wide variety of disease states and may prove beneficial in the treatment of a number of conditions. Chen et al. highlight this prospect in their use of IVIG in their animal model of status epilepticus. They demonstrated decreased microglial activation, reduction in complement component 3 (C3) levels, breakdown of blood-brain barrier, and spontaneous seizures [89]. In humans, the current literature consists of retrospective case reports regarding the use of IVIG for status epilepticus in the general population [90, 91]. Despite the lack of literature in the pregnant population, its safety profile in pregnancy suggests there is no reason to withhold IVIG in pregnant patients in status epilepticus. Another fascinating investigational use of IVIG is as a potential therapeutic option to prevent TORCH syndrome in infants of mothers with a known TORCH infection [92••].

In pregnant patients who have undergone a solid organ transplant, recommendations favor use of azathioprine and tacrolimus which are fairly well tolerated, though tacrolimus is associated with an increased risk of hypertension, pre-eclampsia, preterm birth, and low birth weight. Small amounts of it are excreted in breast milk but no negative outcomes have been reported [92••].

Fetal considerations

Preterm delivery

Questions regarding benefits and risks of preterm delivery may become prominent, particularly when delivery may expand treatment options for the mother. A common example in the neuro ICU is identifying the optimum time for definitive treatment of a ruptured complex AVM in an expectant patient who has been stabilized but remains critically ill. If definitive care can be safely delayed, additional weeks in the ICU to facilitate maximum in utero fetal development can be of considerable benefit depending on gestation age (GA). This can also be applied to certain space-occupying lesions. A recent meta-analysis included 65 studies to determine mean survival rates and rates of survival with and without developmental

impairments of extremely premature infants. Mean survival rates increased from 24.1 to 90.2% for infants at 22-week and 27-week GA, respectively. The risk of severe impairment for surviving infants was 36.3% at 22, 14% at 25, and 4.2% at 27-week GA. Alternatively, the chance of survival without impairment for live-born infants increased from 1.2 to 40.6% and 64.2% at 22, 25, and 27-week GA, respectively [94]. Antenatal exposure to both corticosteroids and magnesium sulfate decreases risk of neurodevelopmental impairment or death in premature births 22–27 weeks [95].

Fetal somatic support in maternal death by neurologic criteria

Brain death during pregnancy is extremely rare, and support of the fetus requires highly complex decision-making within a multidisciplinary team. The literature cites case reports of the brain-dead maternal body being supported until the fetus is over 25-week gestation or has an acute deterioration mandating delivery. Determining the optimal gestational age for initiating support and the optimal time of gestation in the brain-dead patient are still to be determined [96, 97]. Other unanswered questions are the intricate ethical considerations as to rights and decisional authority over the maternal body. Typically, the main stakeholders in the decision-making include the prior known wishes of the brain-dead patient and their families or surrogates [97]. Other areas for consideration include topics that critical care teams tend to overlook, for example, the psychological impact when caring for the dying body of the brain-dead patient. Staff et al. include the nursing staff and midwives in their discussion of this topic. They point out that the physical description of the dying body is often excluded from research in this topic [97]. These previously poorly identified psychological constructs are becoming more apparent as medical teams are forced to confront issues surrounding burnout and compassion fatigue. As care of the critically ill patient becomes increasingly sophisticated, it is the ethical dilemmas that will continue to challenge and test the multispecialty medical professionals who continue to advance the science.

Conclusion

The complex physiological adaptations of pregnancy, myriad of fetal considerations, paucity of high-quality evidence to inform medical decision-making, and the need for constant care coordination among multiple subspecialties undoubtedly challenge any neurointensivist caring for pregnant patients inflicted by a neurological emergency. Neurocritically ill pregnant patients have the potential for remarkable recoveries and to live long and fulfilling lives as evidenced by growing interest and active research and publication on several of the topics discussed herein. Despite these efforts, several critical decisions continue to require multidisciplinary discussion. When management of a life-threatening emergency does not afford the time for this process, the neurointensivist must be prepared to treat based on maternal risk benefit, despite potential fetal harm, or even demise.

Compliance with Ethical Standards

Conflict of Interest

Deepa Malaiyandi declares that she has no conflicts of interest. Elysia James declares that she has no conflicts of interest. Lindsay Peglar declares that she has no conflicts of interest. Nurose Karim declares that she has no conflicts of interest. Nicholas Henkel declares that he has no conflicts of interest. Kristin Guilliams declares that she has no conflicts of interest.

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•• Of major importance

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