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Maternal Critical Illness

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Abstract
Purpose of Review The purpose of this study was to define maternal critical illness (MCI) and outline its causes, the tools used to identify it, and current treatment recommendations.
Recent Findings Although MCI is uncommon, it comprises >10% of intensive care (ICU) admissions in women aged <50 years. Of critically ill mothers, 1:20 die. Almost half these deaths are preventable. Monitoring should follow convention, yet MCI is often treated outside ICUs. Patient youth and the relative rarity of MCI often lead to underestimation of risk and delays in care. Imaging is underutilized. There is no information regarding mechanical ventilation targets. Data regarding drug safety is derived from non-critically ill pregnant women and from retrospective case-control studies which often overestimate risk.
Summary MCI is accompanied by significant excess mortality. Imaging studies, treatments, or medication should not be withheld from cases of MCI solely due to concerns regarding fetal outcome. There remain important knowledge gaps in both diagnosis and treatment of MCI.

Keywords Pregnancy complications · Peripartum · Critical care · Pregnancy · Hemorrhage · Postpartum hemorrhage · Eclampsia · Pre-eclampsia · Sepsis

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Introduction

Maternal critical illness (MCI) is a relatively new field of intensive care. Like other rare diseases, MCI is difficult to study. Hesitance to include pregnant women in clinical trials has delayed research on this population; in response, the National Institutes Health Office of Research on Women's Health has begun to encourage inclusion of pregnant women in clinical trials [1]. Recent years have seen a surge of interest in the health of pregnant women and, within this framework, in MCI. This review discusses the definitions of MCI, its causes, and the tools used to identify it; it summarizes current information regarding monitoring and treatment of this population and points to existing knowledge gaps that require attention in future research.

Definition of Maternal Critical Illness

Maternal critical illness can be described using disease-specific criteria (e.g., hemorrhage, pre-eclampsia), organ-specific criteria (e.g., renal failure, heart failure), or treatment criteria (e.g., the need for ventilation, the need for ICU admission).

Epidemiology

Inconsistent definition is a major obstacle when determining the epidemiology of MCI [2•, 3•]. Maternal ICU admission (which differs from MCI) occurs in approximately 1:300 deliveries (290–330:100,000) (Table 1). While these rates are not particularly high, this cohort represents 12.1% of the women aged 16–50 years admitted to adult general ICUs [4••]. In developed countries, the rate of peripartum maternal death approximates 8.5–14:100,000 deliveries [5–7•]; therefore, one maternal death occurs approximately among every 20 maternal ICU admissions (Table 1).

The young age of the population suffering from MCI and the relative rarity of MCI often lead to underestimation of risk. "Approximately one quarter of women requiring high dependency unit care 'lie beneath' the criteria for near miss or severe maternal complications" [8]. As a result, treatment that would normally have been provided in an ICU is often provided elsewhere. When cases treated outside the ICU are included in MCI cohorts, the true proportion of mothers at risk rises to 1200/100,000 deliveries (1.2%) [9].

The definition of the "peripartum" period is an additional confounder. Many population-based studies of maternal death, for example, describe only cases occurring during admission for delivery [6, 7•]. Pregnancy-related diseases are not necessarily associated with delivery and may even manifest outside arbitrarily defined "peripartum" time frames after pregnancy. For example, postpartum cardiomyopathy was defined in the past as heart failure developing between the last month of pregnancy and the first 5 months after delivery [10]. Concerns regarding possible under-diagnosis even within this broad time frame led to a change in definition to include the

Table 1 Epidemiology of maternal ICU admission

Author	Journal, year of publication	Country	Data source	Incidence of maternal ICU admissions per deliveries	Proportion of maternal ICU admissions among all ICU admissions
ICNARC report	Ref 4.	England, Wales, and Northern Ireland	214 general ICUs	0.3% (290:100,000)	0.0015% (6793/468,668)
Zswart JJ et al.	Intensive Care Med. 2010 Feb.;36 (2):256–63.	The Netherlands	National database	0.24% (847/358,874)	No data
Richa F et al.	J Med Liban. 2008 Oct-Dec;56 (4):215–9.	Lebanon	Single hospital	0.24%	0.43%
Leung NY et al.	Hong Kong Med J. 2010 Feb.;16 (1):18–25.	Hong Kong	Single hospital	0.13% (50/37,505)	0.65% (50/7692)
Vasquez DN et al.	Chest. 2007 Mar;131 (3):718–24.	Spain	Single hospital	0.7% (161/23,044)	10% (161/1571)
Bandeira AR et al.	Int J Gynaecol Obstet. 2014 Jan.;124 (1):63–6.	Brazil	Single hospital	No data	No data
Selo-Oieme DO et al.	Arch Gynecol Obstet. 2005 Sep.;272 (3):207–10.	England	Single hospital	0.11%	0.81%
Anwari JS et al.	Saudi Med J. 2004 Oct;25 (10):1394–9.	Saudi Arabia	Single hospital	0.2%	1.6%
Mahutte NG et al.	Obstet Gynecol. 1999 Aug;94 (2):263–6.	Canada	2 hospitals	0.3% (131/43667)	No data
Rios FG et al.	Int J Gynaecol Obstet. 2012 Nov;119 (2):136–40.	Argentina	4 hospitals	0.8% (242/30,053)	3.8% (242/6271)

more lenient period "from the end of pregnancy to the months following delivery" [11]. Expanding the peripartum period to pregnancy "within the past year" has almost doubled the captured incidence of maternal mortality [12].

Identifying the Women at Risk

Most maternal deaths during the peripartum period occur due to intrapartum and postpartum hemorrhage, complications of hypertensive disease of pregnancy, infections, and exacerbation of pre-existing medical conditions (e.g., heart disease) [7•, 13••]. Reports of peripartum maternal complications show a similar case mix [9, 14•]. Several risk factors have been associated with these complications, including pregnancy at a later age [15, 16], multiparity [15, 17] assisted conception [17, 18], obesity [19], and possibly cesarean delivery [20].

Almost 40% of pregnancy-related deaths are potentially preventable [13••, 21, 22]. Worldwide, the most striking finding in reports of MCI is the presence of delays in care [23–26]. Apparently, identifying the risk factors associated with maternal complications in clinical studies is much easier than identifying deterioration in a specific parturient.

During hemorrhage, for example, patient vital signs are the tools used to determine patient condition. However, apart from the normal variability in the physiological response to hemorrhage, several physiological changes of pregnancy render the consequences of hemorrhage even more unpredictable during pregnancy. These include increased blood volume and decreased hematocrit yielding baseline anemia, decreased systolic blood pressure accompanied by increased heart rate secondary to reduced systemic vascular resistance, and increased respiratory rate [27]. The presence of maternal comorbidities such as diabetes and hypertension complicate diagnosis even further.

Maternal sepsis remains a lead cause of maternal mortality worldwide [5, 28]. The incidence of severe maternal sepsis seems to be on the rise [29, 30]. However, most tools fail to identify sepsis in obstetric populations [31, 32]. A meta-analysis of the physiological indicators commonly used to diagnose the presence of sepsis demonstrated that current knowledge regarding the normal range of these parameters during pregnancy and the peripartum period is based on observations from only a handful of studies. Furthermore, values considered normal during pregnancy and the peripartum period thoroughly overlap with the values normally used to diagnose the presence of sepsis [33••] (Table 2). This overlap precludes the use of standard early warning scores (EWS) for alerting medical staff to the presence of sepsis in the peripartum period.

This problem has prompted the development of modified early warning scores (MEWS) for the pregnant population [35•]. However, the MEWS was derived retrospectively from the vital signs of ICU obstetric admissions rather than prospectively from a full cohort of pregnant and peripartum cases. Furthermore, at this time, only one study has actually demonstrated a reduction in severe maternal morbidity after implementing the use of a MEWS [36••]; it is unclear whether this study was confounded by the Hawthorne effect.

Table 2 Data in pregnant women regarding the five parameters which comprised the systemic inflammatory response (SIR) preceding sepsis until recently [33]

Physiological parameter	SIRS criteria	No. of studies that have described this parameter during pregnancy	No. of women included in the studies altogether	1 SD above/below the norm	2 SDs above/below the norm
Temperature	>38 °C (100.4 °F) or <36 °C (96.8 °F)	10	2367	>38 °C (throughout pregnancy)	>38.1 °C (highest in the third trimester)
$PaCO_2$	<32 mmHg	12	441	No data. Average $PaCO_2$ throughout pregnancy is about 32 mmHg	No data
Respiratory rate	>20	9	312	>20 breaths per minute	>25 breaths per minute (during third trimester and delivery)
Heart rate beats per minute	>90 BPM	39	1374	No data	>90 BPM (throughout pregnancy and until 48 h after delivery)
White blood cell count ($\times 10^3/mm^3$)	>12,000/mm^3, <4000/mm^3, or >10% bands	23	4553	No data	17,500–23,000/mm^3 (during and immediately after delivery)

More recent consensus definitions suggest that the quickSOFA score (qSOFA) be used on wards to recognize patient deterioration from suspected infection. The qSOFA includes respiratory rate (≥22/min), altered mentation, and systolic blood pressure (≤100 mmHg). The presence of ≥2 criteria is associated with more than 10% mortality [34]

Pre-Emptive Treatment

Most causes of maternal death and critical illness are amenable to treatment even before ICU admission. In case of hemorrhage, early identification of ongoing bleeding is crucial. Uterotonic agents must be administered immediately postpartum to all women regardless of route of delivery or parturient location. [37]. Oxytocin (intravenous or intramuscular) is the drug of choice. Ongoing hemorrhage beyond 30 min calls first for addition of synthetic PGE2, then for other medical treatments [e.g., carboprost (15-methyl PGF2), methylergometrine, misoprostol (PGE1)] in parallel to other definitive treatments of hemorrhage. Hemorrhage must be treated aggressively with blood (in accordance with massive transfusion protocols), non-surgical interventions (e.g., uterine packing, balloon tamponade, angio-embolization), and timely definitive surgery when required [38•]. Several guidelines have been published for treatment of maternal hemorrhage.

Women with severe hypertensive disease of pregnancy or pre-eclampsia should be tightly monitored and their blood pressure kept below 160/100 mmHg [39]. Severely elevated blood pressures have been associated with increased risk of end organ damage (e.g., stroke, myocardial infarction, renal failure) and death [40]. Antihypertensive medications such as specific beta and calcium channel inhibitors, diazoxide, and sodium nitroprusside may assist in blood pressure control [41]. Magnesium sulfate remains a mainstay of treatment for seizure prophylaxis [42]; two controlled trials have established its superiority in reducing the risk of eclampsia compared to anticonvulsants [43, 44]. Atypical eclampsia, development of focal neurologic signs, and/or prolonged unconsciousness require urgent neuroimaging [45].

Diagnosis of peripartum infection demands a high index of suspicion. However, "[a]ntibiotic prescription for pregnant or postpartum women with suspected infection does not necessarily prevent progression to severe sepsis, which may be rapidly progressive." [46]. Therefore, once infection is suspected, the threshold for ICU admission should be low, and monitoring and supportive care should be initiated as soon as possible.

A similarly high index of suspicion is required to diagnose cardiomyopathy of pregnancy. Maternal prognosis has been associated with the severity of heart failure [47]. Depending on underlying etiology, it is thus reasonable to assume that commencing treatment of heart failure early (and thereby unloading the strain on the left heart) may be associated with better maternal outcome. Pre-existing heart disease often exacerbates during pregnancy. Appropriate cardiac care throughout pregnancy and timely anesthesia assessment and preparation may result in better management of delivery and a smaller number of complications, although this has yet to be proven.

Finally, guidelines for venous thromboprophylaxis may easily be implemented and have been shown to systematically reduce maternal death rates [48••].

Monitoring

Once MCI has been identified, hemodynamic monitoring should generally follow convention. When in doubt, the clinician should prioritize the balance between the potential risk and the benefit to the mother, rather than the potential risk to the fetus versus the benefit to the mother.

Central Venous Pressure The value of central vein monitoring for guiding fluid therapy remains questionable in most patients [49] and is no different in pregnancy. Early studies showing poor correlation between central venous and pulmonary capillary wedge pressures have led to disenchantment with both these tools for assessing fluid responsiveness in pre-eclampsia [50, 51]. Although standard operating procedures often recommend insertion of a CVP for guiding fluid management in pre-eclampsia, most professionals treating this population do not consider this tool particularly useful [52•].

Pulmonary Capillary Wedge Pressure Monitoring There is a relatively high complication rate among women undergoing pulmonary artery catheterization in the peripartum period (~4%), probably due to increased hypercoagulability and susceptibility to infection [53]. Insertion of a pulmonary artery catheter should therefore be restricted to specific cases of severe maternal hypertension, pulmonary vascular disease, and/or heart failure.

Dynamic Measures of Fluid Responsiveness There is little to no literature regarding the value of using dynamic measures (e.g., pulse pressure variation, stroke volume variation) to guide fluid therapy in the peripartum period. A search of the literature disclosed only one study comparing goal-directed fluid therapy using the LiDCO system during elective Caesarian delivery in 100 parturients with hypertensive disease. The control (unmonitored) group received less fluids and more phenylephrine and had somewhat poorer neonatal outcomes [54].

Impedance Cardiography This tool has been proposed for hemodynamic measurement during pregnancy because it is non-invasive, user-friendly, and requires little training. However, the accuracy of impedance cardiography in measuring cardiac output and stroke volume remains controversial even in non-pregnant populations. The few studies that have examined the validity of impedance cardiography during the paripartum period present conflicting results; some show good correlation between impedance measurements and other traditional measurement methods [55, 56] and others do not [57,

58]. Therefore, at this point, there is insufficient data to recommend this monitoring technique.

Echocardiography Bedside transthoracic echocardiography (TTE) has become entrenched in the management of critically ill patients and is similarly valuable in pregnancy [59•]. It may be used to identify the presence of pulmonary hypertension and/or right ventricular failure in pulmonary embolism (i.e., venous thromboembolic phenomena, amniotic fluid embolism), to differentiate between cardiomyopathy and severe hypertensive disease of pregnancy with left ventricular heart failure [60], to assess fluid responsiveness in the presence of severe pre-eclampsia [61], and to detect poor ventricular filling in septic or hemorrhagic shock. A meta-analysis of data from a prospective study and the existing literature comparing cardiac output measured by TTE with that measured using the pulmonary artery catheter in pregnant women with complications demonstrated excellent agreement [62].

Imaging Due to their low risk profile, ultrasonography and magnetic resonance imaging (MRI) are preferred over imaging techniques requiring ionizing radiation, provided they are sufficiently informative. However, if indicated, there is no justification for withholding diagnostic imaging from the mother due to concerns regarding their safety for the fetus. One study recently demonstrated that only 18.8% of obstetric patients admitted after involvement in high-risk motor vehicle accidents underwent appropriate imaging studies [63•].

Fetal risk from ionizing radiation depends on the dose of radiation and the gestational age of the fetus at the time of exposure [64]. Low-exposure imaging radiography tests include cervical spine and extremity radiography (about 0.001 mGy each) and chest radiography (0.01 mGy). Medium-exposure imaging includes computed tomography (CT) of the chest (0.66 mGy) and high-exposure tests include lumbar spine imaging and CT of the head or neck (about 10 mGy), abdomen (>35 mGy), and pelvis (50 mGy) [65].

Maternal exposure to radiation is accompanied by three types of risk: miscarriage, fetal growth retardation, and fetal teratogenesis. Teratogenesis is by far the greatest concern and occurs mainly during the first trimester of pregnancy. In general, exposure to <0.5 Gy is accompanied by a very small risk of teratogenicity in early pregnancy. Doses >0.5 Gy require risk assessment. Still, in absolute terms, the overall risk remains low (1:250) [65].

General Treatment Principles

Several principles should underlie any decision made by clinicians concerning treatment of critically ill pregnant women. First, maternal welfare must be prioritized over that of the fetus. Thus, no imaging study, treatment, or medication should be withheld from the pregnant ICU patient if it is necessary for her well-being [66].

The second principle is that pregnancy is not the same throughout the trimesters. Embryogenesis is mostly complete by the end of the first trimester. Therefore, malformations are significantly less likely to occur after this period. Information regarding the safety profile of some medications during pregnancy (e.g., antibiotics, antihypertensive medications, and magnesium sulfate) is mostly derived from women who were not critically ill. Retrospective case-control studies, which are most commonly used to asses maternal exposure, tend to overestimate the risk of malformation [67]. Information regarding the risk of drug administration is best derived from prospective registries when available [e.g., the Norwegian Mother and Child registry (MoBa), Swedish Medical Birth Register and Danish National Birth Cohort (DNBC)].

Finally, most treatment provided in the ICU is supportive (i.e., intended to prevent injury and sustain basic life functions rather than treat the underlying cause of disease). Therefore, the benefit provided by any treatment should surpass the damage it may incur.

Airway Management and Ventilation The rate of ventilator support among women admitted to an ICU in the peripartum period ranges between 13.6 and 58%, probably reflecting variability in case mix as well as practice [68, 69]. Some claim that non-invasive ventilation is generally not recommended during pregnancy due to an increased risk of aspiration in the presence of delayed gastric emptying [70]. However, among the pregnant patients who needed assisted ventilation in an ICU, one fourth to one fifth have received non-invasive ventilation with no untoward effect [71].

Intubation of a pregnant woman should be approached as if it were a known difficult intubation [72•, 73, 74]. Pregnancy is accompanied by increased airway edema and weight gain, both of which obscure the view of the vocal cords. This is further complicated by a lower functional residual capacity, relative dyspnea, and an increase in oxygen consumption, which lead to shorter times to desaturation in pregnancy [27]. If the patient is a priori hypoxemic or in shock, this leaves no leeway for mistakes. Precisely for this reason, intubation should not be unnecessarily postponed—it is best performed under controlled conditions by an experienced operator.

After intubation, debate surrounds target respiratory endpoints. Normal pregnancy is accompanied by tachypnea and respiratory alkalosis. Some recommend that minute ventilation be adjusted to maintain $PaCO_2$ between 30 and 32 mmHg. However, this recommendation is not supported by evidence and must therefore be weighed against the potential damage caused by cerebral vasoconstriction.

Regarding oxygenation, the maternal oxyhemoglobin dissociation curve shifts to the right during pregnancy (P_{50}

increases from 27 to 30 mmHg). A higher partial pressure of oxygen is therefore required to achieve the same maternal oxygen saturation. While there is no justification for administration of more oxygen than recommended for most critically ill patients, it is imperative to tightly follow maternal blood gases and lactate levels to ensure the presence of adequate tissue perfusion and oxygenation.

Conversely, the fetal oxyhemoglobin dissociation curve shifts to the left (P_{50} is 19 mmHg), conferring relative resilience to hypoxia. Because both utero-placental circulation and pre-fetal oxygen consumption by the placenta may limit the availability of oxygen to the fetus, this increase in fractional extraction during acute hypoxia creates a reserve capacity, allowing the fetus to tolerate up to a 50% reduction in oxygen delivery. During sustained hypoxia (e.g., severe maternal hypoxemia), this mechanism will lead to slowing of fetal growth, as oxygen consumption remains unchanged when corrected for fetal mass [75].

Medications The drugs administered to women admitted to the ICU in the peripartum period are intended to prevent complications or treat the underlying cause of admission.

- Vasopressors and inotropes: Norepinephrine and epinephrine are endogenous catecholamines, which make any relationship between exogenous administration of these drugs and adverse pregnancy outcomes difficult to determine. Furthermore, both drugs are used only during severe MCI, which in itself is associated with fetal risk. Norepinephrine is classified as FDA category C, the assumption being that the detrimental effect of placental vasoconstriction may be balanced by the benefit of decreasing hypoperfusion. Both epinephrine and norepinephrine cross the placenta, but controversy remains regarding their effect on the fetus. The clinician must judge whether maternal condition requires administration of these drugs or if an equally effective treatment alternative exists.

Data regarding ephedrine and phenylephrine (both second-line drugs for hemodynamic support in MCI) are mostly derived from their use during regional anesthesia for cesarean delivery. Ephedrine does not decrease the utero-placental circulation [76] but may be associated with fetal acidosis [77•]. Phenylephrine has been associated with increased maternal bradycardia [77•].

Dopamine, another endogenous catecholamine (classified as FDA category C), has been used in low doses (1–5 mcg/kg/min) to increase urine output women with oliguria and pre-eclampsia without untoward effects [78]. However, dopamine has been associated with more adverse events (particularly maternal arrythmias) than noradrenalin when used to treat septic shock in the general population [79].

- Pain control and sedation: Maternal pain thresholds are significantly increased during pregnancy [80]; even more so during labor in term pregnancy [81]. Although maternal blood volume is increased [27], so is maternal sympathetic tone and venous return to the heart [82]. This combination may result in an increased susceptibility to the hemodynamic side effects of analgesic drugs.

Opioids generally cross the placenta; nonetheless, they remain the mainstay of sedation and pain treatment in pregnancy. Remifentanyl is the analgesic of choice for long-term sedation due to its ultra-short metabolism. Natural opiates (e.g., morphine, codeine) have safety risk profiles in terms of teratogenicity. Some uncertainty still exists regarding whether synthetic opioids (e.g., fentanyl, tramadol) are associated with cardiovascular and neural tube defects [83]. Should delivery occur during critical illness, it is important to remember that opioids used in proximity to delivery may cause fetal respiratory depression; the presence of a neonatologist on location is thus crucial. Benzodiazepines should only be considered in unique circumstances given the overall increasing preference towards use of drugs other than benzodiazepines in the ICU as well as the controversy regarding the association of drugs from this family with congenital anomalies [84, 85].

The concentration of albumin is lower in fetal than in maternal serum during the first half of pregnancy. Propofol binds almost completely to albumin. Moreover, the pharmacodynamics of propofol are stable throughout pregnancy [86]; during brief exposure to propofol, the fluid cavities surrounding the developing embryo do not act as a reservoir for this drug; thus, maternal serum concentration of propofol is always higher than fetal serum concentration [87]. Although data regarding longer sedation periods with propofol is limited to case reports, the FDA final rule does not forbid the use of this drug.

Non-steroidal antiinflammatory drugs (NSAIDs) should be avoided during the first and third trimester of pregnancy. During the first trimester, use of NSAIDs has been associated with fetal congenital heart defects and increased risk of miscarriage. During the third trimester, NSAID use may cause premature closure of the ductus arteriosus and fetal distress [88].

- Muscle relaxants: Muscle relaxants are used to overcome patient-ventilator asynchrony in severely hypoxemic patients. Indications for administration of neuromuscular blockers in critically ill pregnant women are similar to those in the general population. In the presence of convulsions (e.g., eclampsia), the use of muscle relaxants is not recommended; there is significant concern that the presence of ongoing convulsions will be masked, leading to risk of increased neurological damage.

Short-acting muscle relaxants (e.g., Rocuronium, Atracurium) are generally preferred over long-acting muscle relaxants. Muscle relaxants may cause relatively prolonged maternal neuro-muscular blockade at term or in the postpartum period [89]. Muscle relaxants also partly cross the placenta which may induce neuromuscular blockade in the neonate [90].

- Stress ulcer prophylaxis: Administration of therapy for prevention of stress ulcers is one of the less controversial recommendations for critically ill patients [91]. Proton pump inhibitors (PPIs) are preferred as they significantly reduce the risk of both clinically important and overt GI bleeding compared to histamine-2-receptor antagonists (H2RA) [92]. Both PPIs and H2RAs are considered safe throughout pregnancy [93, 94].
- Prophylaxis of deep venous thrombosis (VTE): Women who are admitted to the ICU should be considered candidates for VTE prophylaxis [95, 96]. Apart from the increased risk of hypercoagulability inherent to pregnancy [27], most maternal ICU admissions occur postpartum [4••] and many arrive after cesarean delivery. Both of these are significant risk factors for occurrence of VTE [97, 98].

Anticoagulation therapy may consist of either unfractionated heparin or low-molecular weight heparin. Neither crosses the placenta nor enters breast milk and both are considered safe [99•]. There is limited evidence regarding the safety of newer anticoagulants, and they should therefore be avoided during pregnancy unless alternative; safer options are contraindicated (e.g., in the presence of heparin-induced thrombocytopenia).

- Antibiotic therapy: penicillins, cephalosporins, and macrolides have been used for decades and are classified as FDA pregnancy category B. Trimethoprim-sulfamethoxazole and tetracyclines are classified as FDA category D drugs and should therefore be avoided during pregnancy unless there is no other treatment choice (i.e., maternal benefit overshadows fetal risk). Both have been associated with teratogenicity and neonatal morbidity. Fluoroquinolones have been associated with fetal cartilage damage and arthropathies but are classified nevertheless as category C based on accumulating evidence from both animal studies and clinical experience of safety during pregnancy [100].

Unique Obstetric Considerations

Nutrition The caloric requirements of the human fetus is about 90–100 kcal/kg/day at term [101]. There is therefore no need to increase the caloric intake of the critically ill pregnant patient by more than 500 kcal/day, unless the patient was undernourished prior to ICU admission. Lactation is associated with an increase in energy expenditure of approximately 10–15% [102]. The energy loss incurred by lactation is met mostly by fat loss rather than protein loss [102, 103]. However, maternal high-fat diet has recently been associated with worse neurological outcomes in animal models of hypoxic-ischemic encephalopathy [104] and may affect the microbiome of the neonate [105]. Maternal glucose supplementation is also damaging, leading to fetal programming towards metabolic syndrome [106]. To conclude, pregnancy and lactation require little caloric expenditure. Maternal overfeeding and/or supplementation of maternal diet with specific nutritional components may be accompanied by a range of adverse fetal effects. Nutrition of the critically ill mother should not deviate from standard practice in terms of both total caloric intake and composition.

Breast Engorgement Postpartum breast engorgement may occur despite the presence of MCI. Symptoms include tight, painful breasts, and elevated body temperature, usually occurring on postpartum days 2–5. Treatment of breast engorgement has been anecdotal thus far; there is insufficient evidence to justify widespread implementation of any intervention for either preventing or treating breast engorgement [107].

Delivery Planning Mode and timing of delivery should both be determined by maternal benefit and relevant obstetrical indications. Almost half of the pregnancies involving MCI result in preterm delivery (gestational age <37 weeks) [108]. If the pregnancy endangers the mother, her well-being should be prioritized and delivery should occur regardless of gestational age. Otherwise, if possible, the pregnancy may be carried to term. Ideally, early preterm delivery (gestational age <34 weeks) should occur in a tertiary care center with expertise in maternal-fetal medicine, obstetric anesthesia, and neonatal intensive care.

The accepted limit of neonatal viability describes the period between 20 + 0/7 weeks and 25 + 6/7 weeks of gestation [109], prior to which neonatal monitoring is not indicated. Once gestational age has progressed beyond 24 weeks, monitoring per obstetrician recommendation (e.g., with non-stress test or ultrasound and biophysical profile) should be performed. Neonatal outcome may be improved by antenatal maternal administration of corticosteroids and/or magnesium sulfate for fetus' <34 weeks gestation. A 2-day antenatal corticosteroid course effectively promotes fetal lung maturation (betamethasone 12 mg ×1/day or dexamethasone 6 mg ×4/day) [109]. Neonatal benefit from such treatment must always be weighed against the risk of increased maternal susceptibility to infection. At a gestational age <30 weeks, antenatal

maternal treatment with magnesium sulfate within 6 h of delivery may also improve neonatal neurological outcome [109].

Conclusion

The definition of MCI must be standardized to elucidate the prevalence of this clinical condition and its causes. MCI is accompanied by significant excess mortality, perhaps in part due to differential treatment of MCI compared to critical illness in other populations (e.g., within versus outside the ICU). No imaging study, treatment, or medication deemed necessary for the mother's safety or well-being should be withheld in MCI due to concerns regarding fetal outcome. When deciding on treatment, the good of the mother should always outweigh any considerations regarding pregnancy outcome. There remain important knowledge gaps regarding identification and treatment (e.g., mechanical ventilation, drugs) of MCI.

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Compliance with Ethical Standards

Conflict of Interest Sharon Einav, Ruben Bromiker, and Hen Y. Sela declare that they have no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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