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Review

Maternal Brain Death and Somatic Support

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Abstract

Brain death is a concept used in situations in which life-support equipment obscures the conventional cardiopulmonary criteria of death, and it is legally recognized in most countries worldwide. Brain death during pregnancy is an occasional and tragic occurrence. The mother and fetus are two distinct organisms, and the death of the mother mandates consideration of the well-being of the fetus. Where maternal brain death occurs after the onset of fetal viability, the benefits of prolonging the pregnancy to allow further fetal maturation must be weighed against the risks of continued time *in utero*, and preparations must be made to facilitate urgent cesarean section and fetal resuscitation at short notice. Where the fetus is nonviable, one must consider whether continuation of maternal organ supportive measures in an attempt to attain fetal viability is appropriate, or whether it constitutes futile care. Although the gestational age of the fetus is central to resolving this issue, there is no clear upper physiological limit to the prolongation of somatic function after brain death. Furthermore, medical experience regarding prolonged somatic support is limited and can be considered experimental therapy. This article explores these issues by considering the concept of brain death and how it relates to somatic death. The current limits of fetal viability are then discussed. The complex ethical issues and the important variations in the legal context worldwide are considered. Finally, the likelihood of successfully sustaining maternal somatic function for prolonged periods and the medical and obstetric issues that are likely to arise are examined.

Key Words: Mother; brain injury; brain death; fetus; ethics; legal.

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Introduction

"Brain death" describes the irreversible loss of brainstem function in a patient receiving artificial organ support that delays the onset of cardiac arrest and somatic death *(1)*. It is considered futile and therefore unethical to continue to support vital organ function once a diagnosis of brain death has been made *(2)*. A potential exception is maternal brain death, where a live fetus is present. The mother and fetus are two distinct organisms, and the death of the mother mandates consideration of the appropriateness of continuing maternal somatic support to prolong gestation to attain fetal viability. Current advances in critical care medicine enable prolonged maternal organ support and continuation of the pregnancy to maximize the chances of an optimal fetal outcome. The key issue is whether continuing maternal organ supportive measures in an attempt to attain fetal viability is an appropriate option, with a reasonable likelihood of success, or

whether it constitutes futile "experimental" care with no hope of success.

A substantial number of cases of maternal brain death have been reported in recent years *(3–9)* and have generated considerable public interest in several countries *(10–13)*. The potentially divisive nature of these issues was demonstrated by the "Erlanger Baby" controversy, which arose after the brain death of a pregnant female in Germany in 1992 and divided public opinion *(8)*. One side denounced prolonged somatic support as medical experimentation and demanded that the young woman and her child be left to "die in dignity." The other side referred to the unborn child's "right to life" and therefore wanted the maternal somatic support continued until the fetus could be born *(8)*. The potential for discord in this context highlights the need to carefully dissect the issues raised by these tragic occurrences.

Brain Death Versus Somatic Death

The irreversible cessation of brainstem function implies death of the brain as a whole *(1,14–17)*. This concept is used to determine when death has occurred in cases in which the provision of "life support" obscures the conventional cardiopulmonary criteria of death *(14–16)*. It is an irremediable event that heralds the permanent loss of consciousness and is ultimately followed by circulatory arrest. This concept provides the basis for cadaveric "beating heart" organ donation. Brain death is internationally recognized as being equivalent to somatic death in the medical field *(18)* and is legally recognized in most, although not all, countries worldwide. However, there remain significant differences worldwide in the diagnostic criteria used for determination of brain death *(18)*. In addition, some debate does exist in the medical literature regarding the equivalence of traditional "somatic" and "brain" death *(19–22)*. What is not in dispute is the fact that brain death is a totally irreversible, irremediable, and final event. There is no recorded case of recovery after the diagnosis of brainstem death. These findings form the basis for the concept of the equivalence of somatic and brain death.

Brain death ultimately is followed by somatic death, often within days, despite meticulous supportive care *(23)*. Although there are rare and exceptional case reports in the literature of survival for longer durations, it is generally considered unethical and futile to continue to support vital organ function once a diagnosis of brain death has been made *(2)*. However, in the tragic situation of maternal brain death, attempts have been made to sustain maternal somatic function with the aim of allowing the pregnancy to continue until the fetus has attained viability. This situation is not maternal life support *per se* given that maternal brain death, and therefore legal death, has occurred.

Fetal Maturation and the Limits of Fetal Viability

Where maternal brain death occurs after the threshold of fetal viability, i.e., 24 weeks' gestation, the continuation of the pregnancy facilitates fetal maturation *in utero* and increases the prospects of a good fetal outcome without neurological or other sequelae *(24)*. Although some have advocated cesarean delivery of a fetus of 28 weeks' gestation after maternal brain death *(24)*, an alternative strategy of *in utero* maintenance of the fetus until 32 weeks seems to offer the best hope for an optimal fetal outcome. However, in each case, the benefits of further fetal maturation to optimize fetal outcome must be weighed against the risks of continued time *in utero*. The potential for sudden maternal hemodynamic compromise must be borne in mind. Accordingly, a cesarean section emergency kit must be available at the bedside at all times to effect immediate delivery in such an event or where fetal deterioration is detected.

Where the fetus is clearly nonviable, i.e., before 22 weeks' gestation, the central question becomes whether continuing maternal organ supportive measures in an attempt to attain fetal viability is appropriate, or whether it constitutes futile care. The key determinant of success in attempts to sustain maternal somatic function is the duration of time required for the fetus to develop to the stage at which a good fetal outcome is likely. In this regard, it is useful to consider the data on premature delivery in the general population as a reference point in determining the limits of fetal viability in the setting of maternal brain death. Recent authoritive reviews on this subject report that a fetus born before 24 weeks has little prospect of surviving *(25,26)*. At 24 weeks, a fetus has approximately a 20–30% likelihood of survival with a 30–50% chance of suffering from severe handicap if born alive *(25,26)*. At 28 weeks, there is an approximately 80% chance of survival and a 10% risk of severe handicap. A gestational age of 32 weeks has generally been considered the earliest time at which delivery can be made with the best chance of survival and the least chance of handicap. At that stage there would be a 98% chance of survival with a less than 2% risk of handicap *(25)*.

There are insufficient data regarding the effects of maternal brain death on fetal well-being. Although the aforementioned outcome figures relate to the general population, it seems prudent to exercise caution in extrapolating from these data to the context of maternal brain death. The physiological alterations and therapeutic interventions necessary to sustain maternal somatic function (e.g., the effects of vasopressor therapy on utero-placental blood flow) and complications of prolonged maternal support (e.g., sepsis) are likely to impact adversely on the onset of fetal maturity, although these effects cannot be accurately quantified.

The data on fetal outcome after prolonged somatic support of a brain dead mother are limited; however, they demonstrate the potential for a favorable fetal outcome in his context. Table 1 details fetal outcome in all cases reported to date. Of 12 published cases describing prolonged maternal somatic support after brain death, six cases report normal infant follow-ups at varying durations (3–18 months) after birth *(2,24,27–30)*. In four cases, no information is available regarding neonatal outcome *(31–34)*, whereas two cases reported fetal demise *in utero (3,8,35)*. Of particular importance, there is no report of unfavorable outcome in infants born alive to brain dead mothers, for which follow-up details are provided. However, it must be emphasized that, due to issues such as publication bias, the true frequency of unfavorable fetal outcomes after prolonged somatic support in pregnant mothers who are brain dead is not known.

The health of the fetus must be considered in making the decision to prolong maternal somatic support. The mechanism of maternal death may be a key determinant of fetal outcome for several reasons. If the initiating pathophysiological process leading to maternal brain death involved a severe hypoxic or metabolic insult, then the fetal central nervous system is likely

to be similarly damaged. Also, the underlying maternal pathological process leading to maternal brain death may be present in the fetus or may critically compromise placental function (e.g., maternal thrombocytosis), and result in fetal death *(3)*. Furthermore, drug therapy given to the mother in the interval between onset of the fatal illness and maternal brain death may compromise fetal outcome. Examples might include antiviral therapies for encephalitis or meningitis. Fetal neurological function may usefully be assessed in the third trimester via determination of fetal heart rate variability and biophysical profile assessment. Persistent decreased or absent fetal heart rate variability is a bad prognostic sign and may indicate fetal brain death *(36)*. Severe neurological injury also may manifest as early intrauterine growth retardation, microcephaly, and ventriculomegaly. Where there is clear evidence of fetal compromise, there is little likelihood of a successful fetal outcome.

Successful Maternal Somatic Support: Probabilities and Limits

Determining the likelihood of successfully maintaining maternal somatic function for a prolonged duration after brain death is of central importance. The rarity of prolonged maintenance of somatic function after brain death is clear from previous studies reporting the ventilation of patients following brain death until cardiac arrest supervened. In their series of 1200 brain dead patients, Jennett and Hessett were unable to find a single case of somatic survival beyond 14 days *(37)*. Hung and Chen, in a prospective study of 73 patients who met the clinical criteria for brainstem death, found that 97% developed cardiac asystole within 7 days, despite continued full cardiorespiratory support *(38)*. Jorgensen reported that of 63 patients diagnosed as brain dead, 100% developed asystole within 9 days *(39)*. Median time to cardiac arrest after brain death was 3.5–4.5 days in a UK study *(40)*. Shewmon, in his meta-analysis of somatic survival after brain death, did report multiple cases of prolonged maintenance of somatic function after brain death, but he acknowledged that finding was the exception *(41)*.

The longest duration for which successful support of maternal organ function after maternal brain death has been achieved to date is 107 days *(28)*. The woman involved was a 30-year-old who suffered a massive brain injury at 15 weeks' gestation. She was declared brain dead 10 days later, i.e., at 16.5 weeks. Vital organ support was provided for 15 weeks and 2 days (i.e., 107 days), and a live infant was delivered at approximately 32 weeks' gestation. Maternal somatic function remained relatively stable up until organ support was discontinued after delivery of the infant. This situation raises the potential that support of maternal function could have been prolonged for longer had it been necessary in this case.

It is possible, therefore, at least in theory, to sustain maternal somatic function for extended periods. Although it is clear that the nearer the pregnancy is to term, the more likely that there can be a successful fetal outcome, the outer limits of successfully maintaining a body on life support in the absence of brainstem function are unclear. Each case must be considered individually because there will frequently be clear reasons, such as evidence of fetal compromise, that will strongly influence the decision to attempt to prolong maternal somatic function and that must be given precedence.

We suggest that, at present, attempts to prolong maternal somatic function are futile in all cases where the pregnancy is of less than 16 weeks' gestation at the time of maternal brain death. Several lines of reasoning support this outer limit to attempts to extend maternal somatic function. First, this duration is the maximal duration for which maternal somatic function has been sustained to date *(28)* (Table 1). This duration of maternal somatic support has not been extended in 15 years, despite dramatic advances in organ support therapies in the interim. Second, although a gestational age of 32 weeks is considered the optimal stage for fetal delivery in this context, there are many successful reports of fetal survival at 24 weeks of gestation. These advances in neonatal medicine may reduce the duration that maternal somatic function needs to be prolonged to produce a successful fetal outcome. Third, the literature demonstrates that failure to maintain maternal somatic support is not the key limiting factor in attempts to attain fetal viability. Actually, the two reported cases in which attempts to attain fetal viability failed were due to fetal compromise *in utero (3,8,35)* (Table 1). Finally, as is discussed in the previous section, reports to date of successful maternal somatic support attest that neonatal outcome in this setting is generally very good, which lends support to efforts to prolong fetal gestation *in utero* to attain viability.

Ethical Issues

Maternal brain death raises difficult ethical issues. The central question is whether providing extended maternal somatic support after brain death, for the benefit of the fetus, is ethical. A key issue is an examination of whose interest takes primacy, i.e., the interests of the fetus or those of the mother. The right of a person to die with dignity, and a person's right to autonomy and bodily integrity are frequently cited as issues deserving consideration in this context *(8,42)*. However, by definition, the pregnant mother is already dead, and these issues are not of relevance. Although there is a need to respect a body after death, it is not clear that discontinuing somatic support to allow immediate somatic death and subsequent decomposition is more respectful or dignified than continuing support for the benefit of the fetus *(8)*.

Balanced against these considerations regarding the mother are the ethical issues that center on the fetus. The provision of extended maternal somatic support for the benefit of the fetus can be considered ethical provided there is a reasonable, albeit poorly quantified, hope of success. Where the fetus nears viability, the process is not unlike the somatic support provided for the purposes of organ donation after brain death *(21)*. This situation is widely recognized legally, and in the United States it is governed by the provisions of the Uniform Anatomical Gift Act *(21)*. Under this legislation, physicians would be justified in providing prolonged somatic support if the woman had previously indicated a wish to donate her organs. In this setting, the issue of whether the pregnancy was a "wanted" pregnancy may then be considered. It is particularly important to determine the existence of any previously expressed maternal opinions (e.g., advanced directive, living wills, and discussion with family). However, if the mother's wishes were not clear, the consent of the next of kin would be required to proceed with maternal somatic support.

Substantial difficulties arise in regard to providing maternal somatic support where the pregnancy is in its early stages,

Table 1
Maternal Details and Fetal Outcome in Reported Cases of Maternal Brain Death to Date

Case report	*Etiology of maternal Brain death*	*Gestation at presentation*	*Duration of somatic support*	*Gestation at delivery*	*Fetal/neonatal outcome*
Dillon et al. *(24)*	Meningo-encephalitis	23 weeks	24 days	26 weeks	Live infant born Birthweight 930 g Borderline microcephaly Fetal hydantoin syndrome RDS requiring IPPV for 5 weeks Discharged from NICU at 3 months of age weighing 2 kg
Heikkinen et al. *(27)*	Subarachnoid and intracerebral hemorrhage	21 weeks	70 days	31 weeks	Live infant born Birthweight 1600 g Apgar scores 6 at 1 minute and 7 at 5 minutes Developing normally at 8 months
Field et al. *(2)*	Intracranial mass lesion	22 weeks	63 days	31 weeks	Live infant born Birthweight 1440 g Mild RDS developed Growing and developing normally at 18 months
Bernstein et al. *(28)*	Motor vehicle accident	15 weeks	107 days	32 weeks	Live infant born Birthweight 1555 g No respiratory difficulties Developing normally at 11 months
Nettina et al. *(34)*	Intracerebral hemorrhage	27 weeks	6 weeks	33 weeks	Live infant born Birthweight 2084 g Infant did not require mechanical ventilation. No follow-up reported
Wuermeling *(35)* Anstoz *(8)*	Motor vehicle accident	13 weeks	6 weeks	N/A	Spontaneous abortion at 19 weeks gestation
Iriye et al. *(31)*	Intracerebral hemorrhage	30 weeks	2 days	30 weeks	Live infant born Birthweight 1610 g Apgar scores 7 at 1 minute and 8 at 5 minutes Further data regarding neonatal outcome not presented
Vives et al. *(29)*	Pneumococcal meningitis	27 weeks	36 hours	27 weeks	Live infant born RDS requiring IPPV and surfactant therapy Discharged at 2 months Follow-up at 14 months; normal growth and development
Catanzarite et al. *(30)*	Intracerebral hemorrhage	25 weeks	25 days	28.5 weeks	Live infant born Birthweight 1315 g Apgar scores 3 at 1 minute and 7 at 5 minutes Discharged day 34 "Follow-up normal" is all that is mentioned
Lewis et al. *(32)*	Subarachnoid hemorrhage	25 weeks	54 days	31 weeks	Live infant born Follow up not available
Spike *(33)*	Intracranial hemorrhage	16 weeks	100 days	31 weeks	Live infant born Birthweight 1440 g Apgar scores 8 at 1 minute and 8 at 5 minutes Further follow-up not available
Lane et al. *(3)*	Cerebral venous sinus thrombosis	13 weeks	8 days	N/A	Intrauterine death at 14 weeks gestation

RDS, respiratory distress syndrome; IPPV, intermittent positive pressure ventilation; NICU, neonatal intensive care unit; N/A, not applicable.

because attempts to attain fetal maturation have much less likelihood of success. In addition, the measures required to provide extended maternal somatic support are much more extensive and prolonged than those required in the setting of organ donation. The absence of a proven management strategy to maintain prolonged maternal somatic function means that this support constitutes experimental therapy, which has important implications. Accordingly, there is no moral imperative to provide a therapy that is considered experimental *(42)*. Furthermore, the wishes of the mother in regard to the fetus in such cases are rarely known, given the limited duration of the pregnancy. The need for fully informed consent from the next of kin is of paramount importance where experimental therapies are being considered. An alternative viewpoint, perhaps most widely expressed during the Erlanger Baby controversy, is that this therapy constitutes medical experimentation with little or no hope of success *(8)*.

A wider ethical issue that should be considered concerns the concept of distributive justice. This concept concerns our obligation to society at large to make the best uses of the resources available to maximize overall benefit. The cost of maternal somatic support, both in terms of direct financial cost and the extended use of scarce critical care facilities, is considerable. Where a fetus is potentially viable, a cogent argument can be made for prolonging somatic support given that one is essentially trading time in an adult critical care unit for time that would be required caring for a severely premature infant in a neonatal critical care unit. This support is justifiable on a purely financially basis alone and should greatly improve the likelihood of a good fetal outcome. However, the lower the likelihood of a successful fetal outcome, the greater the need to consider the wider implications of a decision to proceed with prolonged maternal somatic support.

The interests and concerns of other family members, particularly the next of kin, are of central importance. The immediate family must be involved in decision making, be offered counseling, and be made aware of their right to independent legal and medical advice. Because the newly bereaved family will bear the emotional and financial consequences of the birth of an infant with severe neurodevelopmental or other disabilities, it is essential to give the family clear information regarding the risks and benefits of prolonged somatic support to achieve fetal maturation. The risks of the delivery of an infant with severe disability should be specifically addressed where consent is being sought from the next of kin to provide maternal somatic support. Significant problems arise where the interested parties disagree regarding maintaining somatic support. Further difficulties arise where the next of kin is a husband who prefers that the fetus not be born. If the woman is not married to the father of the fetus, then this person is not the next of kin. The importance of a consensus-building approach, in which the immediate family is centrally involved, cannot be overstated. In situations where agreement cannot be reached, the intervention of the courts may be necessary.

Legal Issues

The legal rights conferred on the fetus are closely linked to the maternal right to therapeutic abortion. These rights generally depend on gestational age and vary considerably worldwide. Countries that confer the greatest legal protection to the fetus either do not permit therapeutic abortion in any circumstances (e.g., Egypt, Chile, Malta, Iran, and The Philippines) or permit abortion only in circumstances where a pregnancy threatens the mother's life (e.g., Ireland, Nigeria, Mexico, Paraguay, and Venezuela). Many countries balance the legal rights of the fetus against the risk of serious damage to the mother's physical (e.g., Argentina, Ethiopia, Pakistan, Poland, and Thailand) and/or mental (e.g., Israel, Jamaica, Malaysia, New Zealand, Portugal, and Spain) health. In countries in which the rights of the fetus are more limited, the fetus is generally accorded increasing legal protection as gestational age progresses. Accordingly, the fetus may be accorded legal protection at 14 weeks (e.g., Austria, Belgium, Cambodia, France, Germany, and Romania), 18 weeks (e.g., Sweden), or 24 weeks (e.g., Singapore and United States) gestational age, depending on the jurisdiction. Finally, a number of countries explicitly recognize three other grounds for therapeutic abortion: when pregnancy results from rape, when pregnancy results from incest, and when there is a high probability of fetal impairment.

Given that the mother is legally dead, restrictions on the rights of the fetus based on its potential to pose a threat to her life, or to her physical or mental health, are no longer of relevance to the decision to prolong maternal somatic support. Therefore, in any given country, an obligation to maintain a fetus to a viable gestational age may exist where (1) the legal rights conferred on the fetus are independent of gestational age or (2) the fetus has exceeded the gestational age beyond which therapeutic abortion is permitted *(4,43)*. In these circumstances, it seems likely that a court would consider that removal of life support would not be justified when that would inevitably result in ending the life of the fetus, provided it could be demonstrated that there exists a realistic prospect of delivery of a live baby.

In contrast, if a careful consideration of the available medical evidence clearly suggested that the fetus could not be successfully maintained *in utero*, then therapy would be considered futile and would not be permitted *(43)*. Therefore, even in countries where the fetus has considerable legal rights, there seems to be no legal imperative to continue maternal somatic support where there is little likelihood of a successful fetal outcome. However, this issue remains controversial and would be open to legal challenge. Indeed, resort to the legal process may well result in different decisions based on the jurisdiction in which the court operates and therefore should be reserved as the final option in situations where agreement between the interested parties regarding maternal somatic support cannot be reached.

Support of Maternal Somatic Function

As already stated, there is no medical therapy or management strategy that prolongs maternal somatic function for prolonged durations after brain death. The intensive care physician is faced with extrapolating from the experience of sustaining organ function after brain death to allow for organ donation and with consulting case reports *(2,3,5,6,28)* and reviews *(9)* in the literature. A relatively predictable picture involving loss of cardiovascular stability, complete pituitary failure, loss of temperature regulation, sepsis, and bradyarrythmias resulting in eventual cardiac arrest emerges.

Support of multiple organ systems, including the respiratory, cardiovascular, and endocrine systems are universal requirements. Nutritional support should be instituted early, preferably by the enteral route. Specific invasive procedures may be necessary, including surgical placement of a tracheostomy to facilitate long-term mechanical ventilation, and placement of invasive lines, including a central venous pressure line and an arterial line to facilitate management of cardiovascular instability. Cardiovascular instability resulting in hypotension mandates optimization of intravascular volume status and vasopressor support. The presence of hypotension unresponsive to these measures raises the possibility of adrenocortical failure, and a trial of corticosteroids is indicated.

Pituitary failure is likely, mandating hormonal replacement with thyroid hormone, corticosteroids, and vasopressin, and management of diabetes insipidus. Glucose intolerance is frequently described and may require insulin therapy. The corticosteroids prednisone and methylprednisone have been recommended because they are inactivated by the placenta and their use will minimize exposure of the fetus to glucocorticoids. After maternal administration of prednisone, the fetal concentration of active drug is less than 10% of that in the mother *(9)*. Thermovariability may be particularly difficult to manage and may require heating and cooling blankets and repeated septic screens. Blood transfusion may be required for management of persistent anemia. The efficacy of erythropoietin in this context is not known. Maternal thromboembolism must be considered a high risk, mandating prophylaxis with fractionated or unfractionated heparins.

Sepsis, in the absence of hemodynamic collapse, constitutes the greatest risk to maternal somatic function. Repeated episodes of sepsis, including recurring (ventilator-associated) pneumonias and (urinary catheter-associated) bladder and kidney infections are likely. Bloodstream infections are particularly likely, due to the presence of artificial lines in the vascular system. Bacterial infections are likely to become increasingly resistant to antibiotic therapy over a time period of several months in the intensive care unit (ICU). Systemic fungemia and fungal-induced amnionitis, which precipitated delivery of the infant, have been described in this context *(30)*. Strict asepsis, if possible involving isolation of the maternal body, within the ICU, is necessary to reduce the likelihood of developing sepsis. Consideration should be given to strategies to reduce the incidence of catheter-associated sepsis, although unproven in this context, including the use of antibiotic- or bactericide-coated catheters and/or tunneled central venous lines.

Fetal Effects of Drugs Used During Maternal Somatic Support

The provision of prolonged maternal somatic support mandates the use of multiple drugs to maintain somatic stability and treat complications. The use of these drugs, particularly during the early-to-middle stages of gestation, has clear potential to harm the fetus. However, the complexity of the physiology of the maternal-fetal unit, and the preeminent ethical need to avoid potential fetal harm, limit the data available on the safety of drugs in pregnancy. Reliance is placed on data derived from animal studies, incidental observations on individual women treated with an agent, or longitudinal tracing of groups of women who required treatment with the agent. It is therefore difficult to provide conclusive evidence of safety for any drug in pregnancy. It is necessary to weigh the risks and benefits of any drug use and to consider the potential risks to the fetus if the condition goes untreated.

Maternal bacterial sepsis is a common complication. Penicillins, cephalosporins, and erythromycins have long been used in pregnant women; are safe for the fetus; and are those most favored for use for susceptible infections *(44,45)*. Although aminoglycosides have known toxic effects on the fetus, including ototoxicity and nephrotoxicity, they may be used in severe infection and are safe, provided maternal serum levels are carefully monitored and doses are adjusted to avoid toxicity *(44,46)*. The use of tetracyclines during pregnancy has been linked with fetal dental staining and interference with bone growth *(44,46)*. The folate inhibitors trimethoprim and sulfonamides are best avoided, due to the risk of fetal neural tube defects, especially in the first trimester *(44,46)*. Fluoroquinolones have been demonstrated to cause fetal arthropathy in animals *(46)*. The first-line agents for the treatment of tuberculosis (i.e., isoniazid, rifampin, and ethambutol) are considered safe in pregnancy, but in the era of multidrug-resistant mycobacterial isolates, agents with known or suspected fetal toxicity may need to be used *(44)*. In regard to newer agents, such as the new macrolides azithromycin and clarithromycin, the data are limited *(44)*. However, it is important to effectively treat the infection, by prescribing an agent that the causative bacterium is sensitive to, rather than by using a perceived "safer" option that may not effectively treat the infection *(45)*.

Fungal infection may complicate prolonged maternal somatic support *(30)*. Topical antifungal agents are commonly used in pregnancy; do not seem to be teratogenic *(47)*, and when used vaginally to treat candida vulvovaginitis, they may reduce the incidence of premature delivery *(48)*. However, there is a substantial risk of fetal toxicity with the use of systemic antifungals, and their use during pregnancy must be limited to life-threatening infections. The systemic antifungal drug with which there has been the most experience in pregnancy is amphotericin B, and it remains the drug of choice. Although there no reports of teratogenesis attributed to this agent, it does cross the placenta and has produced fetal adverse effects, including low birthweight and microcephaly *(47)*. There is evidence to suggest that fluconazole exhibits dose-dependent teratogenic effects; however, it seems to be safe at lower doses (150 mg/day). Ketoconazole, flucytosine, and griseofulvin have been shown to be teratogenic and/or embryotoxic in animals *(47)*.

The potential for certain steroids to cross the placenta, whereas others are inactivated by the placenta, has practical applications. Steroids that cross the placenta relatively easily and are not inactivated by the placenta, such as β- and dexamethasone, are used in situations where fetal transfer is desirable, such as to accelerate fetal lung maturation. In contrast, steroids that are inactivated by the placenta, such as prednisone and methylprednisone, are used for maternal indications (e.g., steroid replacement therapy and asthma).

There exists a near universal need for drugs to maintain hemodynamic stability, such as inotropic and/or pressor agents, and antihypertensive agents, in this context. The commonly used pressor agents, such as epinephrine norepinephrine and dopamine, are endogenously produced and are safe in pregnancy. Vasopressin has been successfully used to maintain

hemodynamic stability in nonpregnant brainstem-dead patients *(49)*. However, caution is warranted when considering its use in the setting of maternal brain death, because it may adversely affect uterine blood flow *(50)*. Of concern, one report of prolonged maternal somatic support found that intramuscular vasopressin, used to treat diabetes insipidus, initiated premature uterine contractions *(24)*. Of interest, intranasal desmopressin is the treatment of choice for diabetes insipidus. Labetalol and methyldopa have been recommended as first line for the control of hypertension in pregnancy, with β-blockers and prazosin and hydralazine as alternatives *(51)*. Angiotensin-converting enzyme inhibitors should be avoided because they may cause multiple adverse effects, including fetal renal tubular dysgenesis resulting in neonatal renal insufficiency *(51)*.

Several other drugs deserve specific mention due to their potential for fetal toxicity. Anticonvulsants are commonly required to control maternal seizures before brainstem death. Phenytoin is a proven teratogen and may result in fetal hydantoin syndrome, growth retardation, and central nervous system defects, and it should be avoided. In the case reported by Dillon et al. *(24)*, the infant manifested the stigmata of fetal hydantion syndrome due to long-term maternal phenytoin therapy. Valproic acid and carbamazepine cause neural tube defects and also should be avoided *(51)*. Warfarin should be avoided due to the risk of skeletal and central nervous system defects, including Dandy-Walker syndrome *(51)*, and heparin should be used instead for thromboembolic prophylaxis.

Maintenance of Fetal Health and Obstetric Management

The effects of prolonged maternal critical illness on fetal physiology are largely unknown. Because the central objective of prolonged maternal somatic support is to maximize the likelihood of a good fetal outcome, every effort must be made to promote a favorable intrauterine environment. This strategy mandates an awareness of the normal pregnant physiological variables as opposed to the nonpregnant state. In this regard, normal pregnancy is associated with a chronic respiratory alkalosis, which creates a diffusion gradient for carbon dioxide across the placenta, facilitating the elimination of CO_2 from the fetus. However, prolonged mechanical hyperventilation to produce hypocapnia may produce maternal lung damage and reduce placental perfusion *(52)*. Therefore, it seems prudent to target ventilation to achieve maternal arterial CO_2 levels at the low-to-normal range (30–35 mmHg). Maternal hypothermia may direct fetal energy away from growth and development of the fetus, and therefore aggressive efforts at maintaining maternal normothermia are recommended.

The preservation of uteroplacental blood flow is an important priority. The placental vasculature is not autoregulated, and maternal hypotension rapidly results in placental hypoperfusion and fetal hypoxia. This situation can lead to permanent neurological injury in the absence of rapid correction or prompt delivery. Vasoactive agents that may cause uteroplacental vasoconstriction should be reserved for maternal hypotension unresponsive to intravascular volume loading and agents such as dobutamine or dopamine. In later pregnancy, the risk of aortocaval compression by the gravid uterus in the supine position mandates measures to ensure lateral displacement of the uterus.

Fetal surveillance should be initiated in the form of modified nonstress tests and interval assessment of fetal growth from the time of fetal viability onward. Amniocentesis has been used to assess fetal lung maturity and determine optimal timing of cesarean delivery *(9)*. Evidence suggests that fetal heart rate monitoring is predictive of fetal health between 27 and 30 weeks' gestation. Aggressive tocolytic therapy may be required for threatened preterm labor, with one report of the successful use magnesium sulfate and indomethacin to prolong pregnancy *(30)*. Where premature delivery is anticipated despite tocolysis, prophylactic antenatal corticosteroids should be given.

Once fetal monitoring is instituted, a cesarean section emergency kit must be available at all times at the mother's bedside for immediate use, because speed is essential once the decision has been made to deliver the fetus. Data from perimortem caesarean sections indicate that fetal neurological outcome is much improved if fetal delivery can achieved within 5 minutes of maternal cardiovascular compromise *(53)*. A neonatal incubator and warmer and neonatal resuscitation equipment are required, and immediate access to a neonatal intensive care unit may be required. These issues may mandate transfer of the brain dead mother to a tertiary facility.

Conclusions

Maternal brain death raises difficult ethical and legal issues. The key issue in determining whether to provide extended maternal somatic support to facilitate fetal maturity *in utero* remains the fetal gestational age at the time of maternal brain death. Although it is clear that there is no theoretical limit to the duration of time for which maternal somatic function may be sustained, successful prolonged maintenance of maternal somatic function is rare. The legal rights conferred on the fetus vary depending on jurisdiction; however, these rights may only be usefully exercised if there exists some expectation of successful delivery of a live baby. If no realistic prospect of success exists, then maternal somatic support would be considered futile and should not be permitted. At present, attempts to prolong maternal somatic function seem to be futile if the pregnancy is of less than 16 weeks' gestation at the time of maternal brain death, given the absence of reports of successful delivery of a live fetus in these pregnancies. This point might be an appropriate cut-off in this context. However, that this point is an arbitrary cut-off point must be emphasized.

A consensus-building approach that involves broad-based consultation including the immediate family, appropriate legal advice, and external medical experts is central to resolving the issues raised after maternal brain death. The immediate family must be centrally involved in this process, and the wishes of the mother, whether expressed or implied, should be determined. The cultural, social, and legal differences that exist worldwide may make it necessary for each country or institution treating these patients to develop their own guidelines.

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