# Brain death in pregnancy: a systematic review focusing on perinatal outcomes



Maria Gaia Dodaro, MD; Anna Seidenari, MD; Ignazio R. Marino, MD; Vincenzo Berghella, MD; Federica Bellussi, MD, PhD

**OBJECTIVE:** Brain death (BD) during pregnancy might justify in select cases maternal somatic support to obtain fetal viability and maximize perinatal outcome. This study is a systematic review of the literature on cases of brain death in pregnancy with attempt to prolong pregnancy to assess perinatal outcomes.

**DATA SOURCES:** We performed a systematic review of the literature using Ovid MEDLINE, Scopus, PubMed (including Cochrane database), and CINHAIL from inception to April 2020.

**STUDY ELIGIBILITY CRITERIA:** Relevant articles describing any case report of maternal brain death were identified from the aforementioned databases without any time, language, or study limitations. Studies were deemed eligible for inclusion if they described at least 1 case of maternal brain death.

**METHODS:** Only cases of brain death in pregnancy with maternal somatic support aimed at maximizing perinatal outcome were included. Maternal management strategy, diagnosis, clinical course, fetal monitoring, delivery, and fetal and neonatal outcome data were collected. Mean, range, standard deviation, and percentage calculations were used as applicable.

**RESULTS:** After exclusion, 35 cases of brain death in pregnancy were analyzed. The mean gestational age at diagnosis of brain death was at 20.2±5.3 weeks, and most cases (68%) were associated with maternal intracranial hemorrhage, subarachnoid hemorrhage, and hematoma. The most common maternal complications during the study were infections (69%) (eg, pneumonia, urinary tract infection, sepsis), circulatory instability (63%), diabetes insipidus (56%), thermal variability (41%), and panhypopituitarism (34%). The most common indications for delivery were maternal cardiocirculatory instability (38%) and nonreassuring fetal testing (35%). The mean gestational age at delivery was 27.2±4.7 weeks and differed depending on the gestational age at diagnosis of brain death. Most deliveries (89%) were via cesarean delivery. There were 8 cases (23%) of intrauterine fetal demise in the second trimester of pregnancy (14–25 weeks), and 27 neonates (77%) were born alive. Of the 35 cases of brain in pregnancy, 8 neonates (23%) were described as "healthy" at birth, 15 neonates (43%) had normal longer-term follow-up (>1 month to 8 years; mean, 20.3 months), 2 neonates (6%) had neurologic sequelae (born at 23 and 24 weeks of gestation), and 2 neonates (6%) died (born at 25 and 27 weeks of gestation). Mean birth weight was 1,229 grams, and small for gestational age was present in 17% of neonates. The rate of live birth differed by gestational age at diagnosis of brain death: 50% at <14 weeks, 54.5% at 14 to 19 6/7 weeks, 91.7% at 20 to 23 6/7 weeks, 100% at 24 to 27 6/7 weeks, and 100% at 28 to 31 6/7 weeks.

**CONCLUSION:** In 35 cases of brain death in pregnancy at a mean gestation age of 20 weeks, maternal somatic support aimed at maximizing perinatal outcome lasted for about 7 weeks, with 77% of neonates being born alive and 85% of these infants having a normal outcome at 20 months of life. The data of this study will be helpful in counseling families and practitioners faced with such rare and complex cases.

**Key words:** brain death, fetal monitoring, pregnancy, somatic support, transplantation

## Introduction

The concept of brain death (BD) was first introduced by Mollaret and Goulon in 1959[1]; however, their hypothesis was not supported by scientific data. After the first human heart transplantation, performed by Christiaan Barnard in 1967, when a beating human heart was harvested from a donor diagnosed as brain dead, the need of scientific criteria was strongly perceived. The following year, 1968, a Harvard ad hoc committee in the United States defined the neurologic criteria for the diagnosis of BD.[2] BD was described as irreversible cessation of all functions of the entire brain[2] defined by the persistence of 4 signs: complete abolition of consciousness and of any movements, abolition of cranial nerves reactivity, abolition of spontaneous respiration (absence of respiratory movements in the presence of hypercapnia), and flat electroencephalogram (EEG). After 1968, most countries of the world adopted these criteria mainly to allow the withdrawal of unnecessary vital support (ie, ventilator support) after a diagnosis of BD and, in selected cases, organ donation for transplantation. In fact, it is considered unethical and futile to continue to support vital organ functions after the diagnosis of BD; however, during pregnancy, prolonged maternal somatic support might be justified to obtain fetal viability and good

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## AJOG at a Glance

### Why was this study conducted?

There are limited data on perinatal outcomes after brain death (BD) in pregnancy with maternal somatic support aimed at maximizing perinatal outcomes.

### Key findings

In this systematic review of literature, the mean gestational age of 35 cases of BD in pregnancy was 20 weeks; maternal somatic support lasted for 7 weeks, with 77% of neonates being born alive and 85% of these infants having a normal outcome at 20 months of life. The rate of live birth differed by gestational age at diagnosis of BD: 50% at <14 weeks of gestation, 54.5% at 14 to 19 6/7 weeks of gestation, 91.7% at 20 to 23 6/7 weeks of gestation, 100% at 24 to 27 6/7 weeks of gestation, and 100% at 28 to 31 6/7 weeks of gestation.

### What does this add to what is known?

As there is no systematic review on perinatal outcomes after BD in pregnancy with maternal somatic support, the data in this study will be helpful in counseling families and practitioners faced with such rare and complex cases.

perinatal outcome.[3,4] The complexity of BD in pregnancy requires a multidisciplinary approach, involving cooperation among obstetricians, neurosurgery or neurology, intensive care medicine, neonatology, anesthesiology, transplantation surgery, and ethics committee. To the best of our knowledge, there are limited data for prognosis and clinical guidance in maternal patients with BD. In this article, we reviewed the available cases of somatic support in pregnant women with BD, focusing on perinatal outcomes.

## Objective

This study aimed to evaluate by systematic review of literature all cases of BD during pregnancy with attempt at prolonging pregnancy with the aim of assessing perinatal outcomes.

## Methods

### Search strategy

This review was performed according to a protocol recommended for systematic review. The review protocol was designed a priori defining methods for collecting, extracting, and analyzing data. The search was conducted using Ovid MEDLINE, Scopus, PubMed, CINHAIL, and the Cochrane Library as electronic databases from inception to April 2020. Key words used in electronic searching included "maternal OR pregnancy AND brain death," "maternal OR pregnancy" AND "brain death," and "maternal OR pregnancy" AND "brain death" OR "brain death" (MeSH terms). No restriction for language or geographic location was applied. Reference lists of retrieved relevant articles were screened for finding additional studies.

### Study selection and outcomes

All studies that reported at least 1 case of maternal BD during pregnancy with an attempt at prolonging pregnancy after BD were eligible for inclusion. We excluded studies dealing with pregnancy in a persistent vegetative state. Furthermore, we excluded studies that only discussed ethical and legal issues or with no maternal and perinatal outcome data. The primary outcome was neonatal live birth, assessed by trimester of pregnancy in which diagnosis of BD was made. Secondary outcomes included latency from gestational age at diagnosis of BD to delivery (days), assessed by gestational age in which diagnosis of BD was made; the evaluation of fetal monitoring methods (eg, cardiotocography [CTG], biophysical profile [BPP], ultrasound, fetal growth monitoring, and Doppler assessment), medical treatments (eg, steroids for fetal maturity), maternal medical complications and somatic support procedures (eg, nutrition and ventilatory support, drugs infusion, organ procurement), pregnancy-specific issues (eg, tocolytic use, indication for delivery, delivery mode), and fetal and neonatal outcomes.

### Data extraction and analysis

All nonduplicate identified articles were independently reviewed by 2 authors (M.G.D. and A.S.), and relevant articles were selected by mutual agreement. Disagreement was resolved by discussion with a third reviewer (F.B. or V.B.). All articles were case reports or small series. Articles were deemed eligible for inclusion in our review if they described at least 1 case of maternal BD. There was no patient or public involvement in the study selection. There was no funding source involved in this study. For each case, we extracted maternal age, parity, cause of BD, diagnosis of BD, gestational age at diagnosis of BD, comorbidity before diagnosis of BD, maternal medical complications probably related and subsequent to BD, nutrition, and ventilatory support technique. In addition, we assessed fetal monitoring methods (CTG, BPP, ultrasound, biometry, and Doppler evaluation), use of steroids for fetal maturity and tocolytic use, medications used during life support, pregnancy outcomes (indication for delivery, gestational age of delivery, mode of delivery, organ procurement for transplantation), neonatal outcome (sex, weight, birthweight percentile, neonatal Apgar scores at 5 minutes, neonatal complications, and long-term outcomes). In our analysis, we particularly focused on the latency from diagnosis of BD to delivery, fetal monitoring, and pregnancy complications. We contacted available authors for additional information to try to get long-term neonatal outcomes. Means, standard deviations, ranges, and percentages were calculated using reported data points. Any data points that were not reported in case reports are explicitly stated in the tables below as NA (not available). This systematic review has been submitted to PROSPERO (identification number 218078).

## Results

Initially, 1045 manuscripts were identified; after exclusion, 35 cases of BD in

pregnancy from 35 manuscripts were included (Figure 1).[3–37] The mean age of the mothers was 27.8±5.8 years, and 55% of the patients were multiparous (Table 1). When reported (n=34), the main causes for the BD were intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), or hematoma (68%); trauma (12%); suicide attempt (9%); and cerebral tumor or mass (6%) (Table 1). Details on the diagnosis of BD were not reported in 66% of cases, with most cases (65%) reporting criteria for the diagnosis of BD listing EEG and clinical examination as criteria (Table 1). The diagnosis of BD was made at a mean gestational age of 20.2 ±5.3 weeks; among the cases, 11% were in the first trimester of pregnancy, 83% were in the second trimester of pregnancy, and 6% were in the third trimester of pregnancy (Table 1).

Comorbidities were reported in 14 of 22 cases (64%) reporting this variable. The most common complications possibly related to the BD in pregnancy were infections (69%) (eg pneumonia, urinary tract infection [UTI], sepsis), circulatory instability (63%), diabetes insipidus (DI) (56%), thermal variability (41%), and panhypopituitarism (34%) (Table 2). Nutrition was enteral (43%), parenteral (33%), or a combination of these 2 methods (24%). When reported in the papers, 80% of the cohort of patients with BD was ventilated via a tracheostomy, whereas 20% of the cohort of patients with BD was ventilated via orotracheal intubation (Table 2).

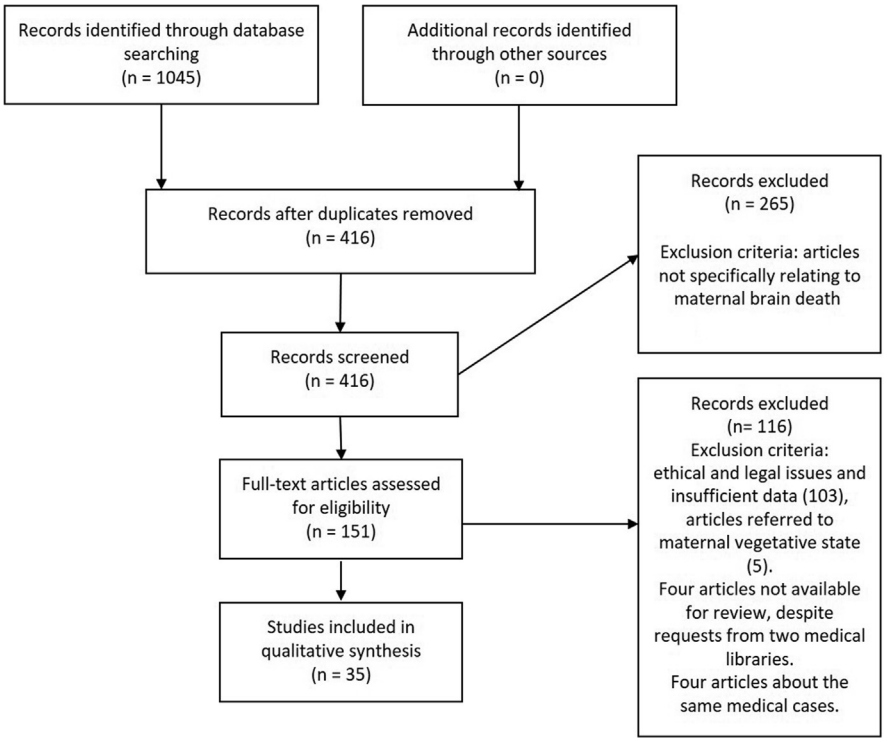
Fetal monitoring was done by a combination of CTG, BPP, and ultrasound biometry and Dopplers, often daily (Table 3). Tocolysis was reported in only 4 cases, whereas, when reported, steroids for fetal maturity were given in 61% of cases. Multiple medical therapies were necessary during life support, including treatment of DI (71%), antibiotics (71%), pharmacologic support of the cardiovascular system (64%), thyroxine (61%), corticosteroids (57%), blood transfusion (34%), treatment for temperature instability (32%), and insulin (25%) (Table 3).

The most common indications for delivery were maternal cardiocirculatory instability (38%), nonreassuring fetal testing (35%), fetal growth restriction (FGR) (12%), spontaneous labor (12%), and oligohydramnios (12%) (Table 3). Total days from diagnosis of BD to delivery were 48.9±38.8 days (approximately 7 weeks) and differed by trimester of pregnancy: 75±63 days (approximately 11 weeks) for first trimester of pregnancy, 48.5 ±33.2 days (approximately 7 weeks) for second trimester of pregnancy, and 2±0 days for third trimester of pregnancy (Table 3; Figure 2). Mean gestational age at delivery was 27.2±4.7 weeks and differed depending on gestational age at diagnosis of BD. When diagnosis of BD was made at <14 weeks of gestation, gestational age at delivery was 26.7±4.9 weeks; at 14 to 19 weeks of gestation, it was 26.5±4.8 weeks; at 20 to 23 weeks of gestation, it was 27.5±4.9 weeks; at 24 to 27 weeks of gestation, it was 29.5±6.2 weeks; and at 28 to 31 weeks gestation, it was 31.5±1.5 weeks (Figure 3). The rate of live birth rate differed by gestational age at diagnosis of BD: 50% at <14 weeks, 54.5% at 14 to 19 6/7 weeks, 91.7 % at 20 to 23 6/7 weeks, 100% at 24 to 27 6/7 weeks, and 100% at 28 to 31 6/7 weeks (Figure 4).

The number of births by gestational age was as follows: 8 of 35 cases (23%) at <24 weeks, 9 of 35 (26%) at 24 to 27 6/7 weeks, 12 of 35 (34%) at 28 to 31 6/7 weeks, and 6 of 35 (17%) at 32 to 35 6/7 weeks; furthermore, no woman with BD delivered at >36 weeks of gestation. Most deliveries (89%) were via cesarean delivery. Organ procurement occurred in 39% of cases reported (Table 4).

Perinatal outcome is described in Table 5. There were 8 cases (23%) of intrauterine fetal demise (IUFD) in the second trimester of pregnancy (14–25 weeks of gestation), and 27 neonates

**FIGURE 1**
**PRISMA flowchart of article identification, screening, review, and inclusion**




*PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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**TABLE 1**
**Characteristics of the reported cases of maternal BD: cause, diagnosis, and gestational age at diagnosis of BD**

| Study, year | Country | Age of mother (y) | Parity | Cause of BD | Diagnosis of BD | Gestational age at BD (wk) |
|---|---|---|---|---|---|---|
| Dillon et al,[4] 1982 | United States | 24 | 0 | Meningitis | Two EEG, 24 h apart, demonstrated no cerebral activity. Evoked brainstem showed no activity. | 23 |
| Friedman et al,[5] 1983 | Israel | 25 | NA | ICH; SAH | "A clinical state of brain death was diagnosed on basis of deep coma, generalized flaccidity, no reflexes, frozen eyes with maximally dilated pupils and no response to light or ice water introduced into the external meatus of the ear." | 33 |
| Heikkinen et al,[6] 1985 | Finland | 31 | 3 | ICH and SAH | All brainstem reflexes were absent.<br>EEG was performed.<br>Apnea test was not performed. | 21 |
| Shrader,[7] 1986 | United States | 27 | NA | NA | "Neurological examination shows no brain activity." | 22 |
| Field et al,[3] 1988 | United States | 27 | 0 | CNS mass | EEG was performed.<br>"Diagnosis of brain death was made using Harvard criteria." | 22 |
| Bernstein et al,[8] 1989 | United States | 30 | 3 | Traumatic brain injury | EEG was performed.<br>Maternal temperature=35.9°C.<br>Auditory and visual evoked responses were absent. | 15 |
| Antonini et al,[37] 1992 | Italy | 25 | 0 | ICH | EEG was performed. | 15 |
| Anstötz,[9] 1993 | Germany | 18 | NA | Car accident | NA | 13 |
| Nettina et al,[11] 1993 | United States | 31 | NA | ICH | NA | 27 |
| Béguin,[10] 1993 | Switzerland | 20 | NA | ICH | NA | 20 |
| Wuermeling,[12] 1994 | Germany | 18 | NA | Car accident | EEG was performed.<br>Doppler-sonography of the arteries supplying the brain was performed. | 14 |
| Iriye et al,[13] 1995 | United States | 35 | 2 | ICH after cocaine | EEG was performed. | 30 |
| Vives et al,[14] 1995 | Spain | 25 | 1 | Meningitis | EEG was performed. | 27 |
| Catanzarite et al,[15] 1997 | United States | 25 | 1 | ICH | NA | 25 |
| Lewis and Vidovich,[16] 1997 | United States | 20 | NA | ICH; SAH | "The patient was pronounced brain dead based on two clinical examinations done 6 hours apart." | 25 |

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**TABLE 1**
**Characteristics of the reported cases of maternal BD: cause, diagnosis, and gestational age at diagnosis of BD**
*(continued)*

| Study, year | Country | Age of mother (y) | Parity | Cause of BD | Diagnosis of BD | Gestational age at BD (wk) |
|---|---|---|---|---|---|---|
| Spike,[18] 1999 | United States | 20 | NA | ICH | EEG was performed. Blood flow scan showed no cerebral blood flow. | 16 |
| Beca et al,[17] 1999 | Chile | 26 | 0 | ICH | EEG was performed.<br>Apnea test was not performed. | 18 |
| Lane et al,[19] 2004 | Ireland | 26 | NA | Cerebral venous sinus thrombosis | Brainstem tests were performed. | 13 |
| Hussein et al,[20] 2006 | United Kingdom | 33 | 0 | ICH | NA | 26 |
| Souza et al,[21] 2006 | Brazil | 40 | 0 | ICH | Transcranial Doppler scan of the cerebral arteries was performed. | 25 |
| Hurtado et al,[22] 2007 | Mexico | 19 | 0 | Attempting suicide (gunshot) | NA | 19 |
| Mejía et al,[23] 2008 | Argentina | 29 | 0 | ICH | EEG was performed. Auditory and somatosensitive evoked responses were absent. | 17 |
| Yeung et al,[24] 2008 | United States | 26 | NA | Metastatic melanoma—hematoma in the right cerebellum | Evoked potentials were negative. | 15 |
| Woderska et al,[25] 2012 | Poland | 40 | 4 | ICH | NA | 22 |
| Said et al,[26] 2013 | United Arab Emirates | 35 | 2 | ICH | NA | 16 |
| Burkle et al,[27] 2015 | United States | 32 | NA | ICH | NA | 22 |
| Kinoshita et al,[28] 2014 | Japan | 32 | NA | Attempted suicide; cardiac arrest | "Standard brain death criteria of the Japanese Ministry of Health" | 20 |
| Wawrzyniak,[29] 2015 | Poland | 30 | 3 | ICH | Apnea test and instrumental examination were not performed. | 22 |
| Nishimura et al,[30] 2016 | Japan | 30 | 1 | Attempting suicide; cardiac arrest | NA | 23 |
| Gopčević et al,[31] 2017 | Croatia | 34 | 2 | ICH | "Clinical testing to confirm the diagnosis of maternal brain death was performed twice. Apnea test were not performed.<br>Confirmation of brain death by multi-slice computerized tomography contrast pan-angiography could only be confirmed after delivery." | 20 |

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**TABLE 1**
**Characteristics of the reported cases of maternal BD: cause, diagnosis, and gestational age at diagnosis of BD**
*(continued)*

| Study, year | Country | Age of mother (y) | Parity | Cause of BD | Diagnosis of BD | Gestational age at BD (wk) |
|---|---|---|---|---|---|---|
| Holliday and Magnuson-Woodward,[32] 2017 | United States | 36 | 4 | Anoxic brain injury secondary to cocaine | "Brain death testing was performed." | 19 |
| Piskorz and Jakubiec-Wisniewska,[35] 2019 | Poland | 29 | 0 | ICH | NA | 21 |
| Pikto-Pietkiewicz et al,[34] 2019 | Poland | 27 | NA | ICH | NA | 13 |
| Reinhold et al,[36] 2019 | German | 28 | NA | Traffic accident; ICH | Clinical examination was performed.<br>EEG was performed. | 9 |
| Boran et al,[33] 2019 | Turkey | 21 | NA | Intracranial mass; ICH | Apnea test.<br>Transcranial Doppler ultrasonography. | 19 |
| Total | | 27.8±5.8 y (25.0–31.5) | NA=15/35 (43%)<br>Multiparous=11/20 (55%)<br>Nulliparous=9/20 (45%) | NA: 1/35 (3%)<br>ICH, SAH, or hematoma: 23/34 (68%)<br>Trauma: 4/34 (12%)<br>Attempted suicide: 3/34 (9%)<br>Cerebral tumor or mass: 2/34 (6%)<br>Cocaine: 2/34 (6%)<br>Meningitis: 2/34 (6%)<br>Cardiac arrest: 2/34 (6%)<br>Cerebral venous sinus thrombosis: 1/34 (3%) | NA: 12/35 (34%)<br>Clinical examination: 8/23 (35%)<br>EEG+clinical examination: 7/23 (30%)<br>EEG: 4/23 (17%)<br>EEG+cerebral blood flow scan: 2/23 (9%)<br>Transcranial Doppler scan of the cerebral arteries: 1/23 (4%)<br>Apnea test+transcranial Doppler ultrasonography: 1/23 (4%). | 20.2±5.3 wk (16–23)<br>First trimester of pregnancy: 12.0±2.0 (4/35 [11%])<br>Second trimester of pregnancy: 20.6±3.8 (29 /35 [83%])<br>Third trimester of pregnancy: 31.5±2.2 (2/35 [6%]) |

*BD*, brain death; *CNS*, central nervous system; *EEG*, electroencephalogram; *ICH*, intracranial hemorrhage; *IQR*, interquartile range; *NA*, not available; *SAH*, subarachnoid hemorrhage; *SD*, standard deviation. Continuous data presented as mean ± standard deviation (interquartile range)

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(77%) were born alive. Of the 35 cases, 8 neonates (23%) were described as "healthy" at birth, 15 neonates (43%) had normal longer-term follow-up (>1 month to 8 years; mean, 20.3 months), 2 neonates (6%) had neurologic sequelae (probably from preterm births at 23 and 24 weeks of gestation), and 2 neonates (6%) died (possibly related to preterm births at 25 and 27 weeks of gestation). Mean birth weight was 1,229±476 grams, small for gestational age was present in 17% of neonates, with 40% of the neonates having Apgar scores of <7 at 5 minutes, possibly secondary to preterm birth (Table 5).

## Discussion

### Main results

This systematic review of literature focusing on perinatal outcome after somatic support for fetal reasons in pregnant women with BD identified 35 cases. The mean age of the mothers was 28 years; the main cause for BD was ICH,

**TABLE 2**
**Maternal complications and life support characteristics**

| Study, year | Comorbidity before diagnosis of BD | Maternal medical complications probably related and subsequent to BD | Nutrition | Ventilatory support |
|---|---|---|---|---|
| Dillon et al,[4] 1982 | Seizures | Thermal variability, DI | Total parenteral nutrition | Intubated |
| Friedman et al,[5] 1983 | No | NA | NA | NA |
| Heikkinen et al,[6] 1985 | No | Thermal variability, pneumonia, hypotension, DI, aspiration pneumonia (*Pseudomonas* bacteria), panhypopituitarism | E/P nutrition | Intubated |
| Shrader,[7] 1986 | NA | DI | Total parenteral nutrition | NA |
| Field et al,[3] 1988 | No | Thermal variability, panhypopituitarism, DI, ARDS, hypotension, UTI (*Klebsiella* infection) | Total parenteral nutrition | NA |
| Bernstein et al,[8] 1989 | NA | Thermal variability, panhypopituitarism, DI, pneumonia (*Pseudomonas*, *Acinetobacter*, *Haemophilus*) | Enteral nutrition | Tracheostomy |
| Antonini et al,[37] 1992 | NA | Panhypopituitarism, pneumonia (Pseudomonas), UTI, hemodynamic instability, hyperglycemia, anemia | Total parenteral nutrition | NA |
| Anstötz,[9] 1993 | NA | Severe infection | NA | NA |
| Nettina et al,[11] 1993 | NA | Hypothermia; hypotension | NA | NA |
| Béguin,[10] 1993 | NA | No complication | NA | NA |
| Wuermeling,[12] 1994 | NA | Infection | NA | NA |
| Iriye et al,[13] 1995 | Drugs abuse | Hypotension | NA | NA |
| Vives et al,[14] 1995 | UTI and acute sinusitis 1 week earlier | Hypotension, sepsis, DIC, cardiac arrhythmia | NA | NA |
| Catanzarite et al,[15] 1997 | NA | Hypotension, ARDS, DI, panhypopituitarism, aspiration pneumonia | E/P nutrition | NA |
| Lewis and Vidovich,[16] 1997 | History of trauma 11 mo earlier | Hypotension, DI, sepsis | Total parenteral nutrition | NA |
| Spike,[18] 1999 | NA | Panhypopituitarism, DI, thermal variability, hypotension | NA | NA |
| Beca et al,[17] 1999 | No | Hemodynamic instability | NA | NA |

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(continued)

**TABLE 2**
**Maternal complications and life support characteristics** *(continued)*

| Study, year | Comorbidity before diagnosis of BD | Maternal medical complications probably related and subsequent to BD | Nutrition | Ventilatory support |
|---|---|---|---|---|
| Lane et al,[19] 2004 | NA | DI, pneumonia, hyper- and hyponatremia | NA | NA |
| Hussein et al,[20] 2006 | No | Anemia, circulatory instability (hypertension, bradycardia, and hypotension), pneumonia, adrenal insufficiency, hyperglycemia, hypothermia | Total parenteral nutrition | NA |
| Souza et al,[21] 2006 | Metallic mitral valve prosthesis (childhood episode of rheumatic fever) in anticoagulant therapy | Panhypopituitarism, hyperglycemia, DI, hypotension, bradycardia, hypothermia, pneumonia | Enteral nutrition | Pressure-limited mechanical ventilation (first 10 d) Tracheotomy after ventilation-associated pneumonia |
| Hurtado et al,[22] 2007 | NA | NA | E/P nutrition | NA |
| Mejía et al,[23] 2008 | Acute otitis media treated with antibiotics | DI, panhypopituitarism, UTI, pneumonia, hemodynamic, instability | Enteral nutrition | NA |
| Yeung et al,[24] 2008 | Metastatic malignant melanoma | Panhypopituitarism, DI, adrenal insufficiency, hyperparathyroidism | Total parenteral nutrition | Tracheotomy |
| Woderska et al,[25] 2012 | Vascular malformation-related subarachnoid hemorrhage at 27 y | Circulatory failure, respiratory failure, respiratory, and UTI | NA | NA |
| Said et al,[26] 2013 | Gestational diabetes mellitus | Several hypotension, hypertension, DI, hypernatremia, panhypopituitarism, hypothermia, sepsis because of pneumonia, UTI, line infection, meningitis | Enteral nutrition | Pressure-limited mechanical ventilation (first 18 d) Tracheotomy |
| Burkle et al,[27] 2015 | NA | NA | NA | NA |
| Kinoshita et al,[28] 2014 | Hypothyroidism | DI, hypothyroidism, hypotension | Enteral nutrition | NA |
| Wawrzyniak,[29] 2015 | Hypertension, hypothyroidism, surgical intervention for cerebral aneurysm | Hypertensive crisis, hypotension, DI, hypothermia and hyperthermia, adrenal insufficiency, *Candida* sepsis, UTI, pneumonia | E/P nutrition | Pressure-limited mechanical ventilation (first 7 d) Tracheotomy |
| Nishimura et al,[30] 2016 | Depression | Refractory seizure, circulatory instability, aspiration pneumonia | NA | NA |

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*(continued)*

**TABLE 2**
**Maternal complications and life support characteristics** *(continued)*

| Study, year | Comorbidity before diagnosis of BD | Maternal medical complications probably related and subsequent to BD | Nutrition | Ventilatory support |
|---|---|---|---|---|
| Gopčević et al,[31] 2017 | No | Hypotension, DI, diabetes mellitus, hypothermia, pneumonia twice (*Haemophilus*, *Pseudomonas*), sepsis on 3 occasions (*Enterococcus*, *Acinetobacter*, *Pseudomonas*) | Enteral nutrition | Pressure-limited mechanical ventilation and then tracheotomy |
| Holliday and Magnuson-Woodward,[32] 2017 | Hepatitis C, asthma, sleep apnea, and gestational diabetes mellitus | Hyperglycemia, low potassium, DI, panhypothyroidism, hypothermia, hypotension, hospital-acquired pneumonia | Enteral nutrition<br>Percutaneous endoscopic gastrostomy tube | Tracheotomy |
| Piskorz and Jakubiec-Wisniewska,[35] 2019 | NA | Disruption of the hypothalamic pituitary axis<br>Disorder of water, electrolyte, and acid base balance | NA | NA |
| Pikto-Pietkiewicz et al,[34] 2019 | No | ACTH deficit, hypothyroidism, DI, acute pancreatitis, sepsis, UTI, and pneumonia | E/P nutrition | Pressure-limited mechanical ventilation (first 12 d)<br>Tracheotomy |
| Reinhold et al,[36] 2019 | No | Hypopituitarism, severe DI, hypothyroidism, recurrent bacterial pneumonia, and UTI | Enteral nutrition | NA |
| Boran et al,[33] 2019 | Gestational diabetes | Hypernatremia, pneumonia | Enteral nutrition | NA |
| Total mean value | NA: 13/35 (%) | NA: 3/35 (9%) | NA: 14/35 (40%) | NA: 25/35 (71%) |
| | No: 8/22 (%) | Infections: 22/32 (69%) | Enteral: 9/21 (43%) | Tracheotomy: 8/10 (80%) |
| | Gestational diabetes mellitus: 3/22 (14%) | Pneumonia: 8/22 (36%) | Parenteral: 7/21 (33%) | Intubated: 2/10 (20%) |
| | Hypothyroidism: 2/22 (9%) | Pneumonia+UTI: 4/22 (18%) | E/P: 5/21 (24%) | |
| | Infection: 2/22 (9%) | Sepsis: 2/22 (9%) | | |
| | Vascular malformation: 2/22 (9%) | UTI: 1/22 (5%) | | |
| | History of trauma: 1/22 (5%) | Pneumonia + sepsis: 2/22 (9%) | | |
| | Metallic mitral valve prosthesis: 1/22 (5%) | UTI+pneumonia+sepsis+meningitis: 1/22 (5%) | | |

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*(continued)*

**TABLE 2**
**Maternal complications and life support characteristics** *(continued)*

| Study, year | Comorbidity before diagnosis of BD | Maternal medical complications probably related and subsequent to BD | Nutrition | Ventilatory support |
|---|---|---|---|---|
| | Metastatic malignant melanoma: 1/22 (5%) | Pneumonia+ UTI+sepsis: 2/22 (9%) | | |
| | Hypertension: 1/22 (5%) | Circulatory instability: 20/32 (63%) | | |
| | Depression: 1/22 (5%) | DI: 18/32 (56%) | | |
| | Hepatitis C: 1/22 (5%) | Thermal variability: 13/32 (41%) | | |
| | Asthma: 1/22 (5%) | Panhypopituitarism: 11/32 (34%) | | |
| | Sleep apnea: 1/22 (5%) | Diabetes mellitus or hyperglycemia: 5/32 (16%) | | |
| | Seizure: 1/22 (5%) | Electrolytes disorders: 5/32 (16%) | | |
| | Drug abuse: 1/22 (5%) | Adrenal insufficiency: 4/32 (13%) | | |
| | | Hypothyroidism: 4/32 (13%) | | |
| | | ARDS or respiratory failure: 3/32 (9%) | | |
| | | Anemia: 2/32 (6%) | | |
| | | DIC: 1/32 (3%) | | |
| | | Hyperparathyroidism: 1/32 (3%) | | |
| | | Seizures: 1/32 (3%) | | |
| | | Acute pancreatitis: 1/32 (3%) | | |
| | | No complication: 1/32 (3%) | | |

Mother kept alive even after delivery for approximately 1 year: excluded from total duration of life support.

*ACTH*, adrenocorticotropic hormone; *ARDS*, respiratory distress syndrome; *DI*, diabetes insipidus; *DIC*, disseminated intravascular coagulation; *E/P*, enteral and parenteral nutrition; *IQR*, interquartile range; *NA*, not available; *UTI*, urinary tract infection.

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**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies**

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| Dillon et al,[4] 1982 | CTG | NA | Yes | NA | NA | NA | No | Phenytoin, diazepam, IV antibiotics, steroids, IV fluid, insulin, vasopressin, vasopressor |
| Friedman et al,[5] 1983 | CTG | NA | Yes | NA | NA | NA | No | Dexamethasone, mannitol, diphenylhydantoin, ampicillin |
| Heikkinen et al,[6] 1985 | FHR | FHR daily | Yes | Weekly | Biometry | NA | No, amniocentesis at 30 wk: immature pulmonary condition | Dexamethasone |
| | CTG | CTG weekly after 28 wk | | | | | | Piperacillin, albumin, whole blood weekly, hydrocortisone, thyroxine 0.05 mg, intranasal vasopressin, dopamine |
| Shrader,[7] 1986 | NA | NA | Yes | NA | Biometry | NA | NA | Vasopressin, heating and cooling blankets, antibiotics |
| Field et al,[3] 1988 | FHR | FHR at every shift | Yes | NA | Biometry | NA | After 26 wk weekly betamethasone sodium | Vasopressin |
| | CTG | CTG twice a week after 26 wk | | | | | phosphate injections (12 mg every 12 h for 2 doses) | Trimethoprim and sulfamethoxazole (UTI), heating and cooling blankets, thyroxine, cortisol, insulin infusion, ampicillin sodium and gentamicin sulfate (sepsis), piperacillin sodium, nafcillin sodium |

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*(continued)*

**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies** *(continued)*

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| Bernstein et al,[8] 1989 | CTG | CTG every 8 h for 30 min | NA | NA | NA | Yes, terbutaline | Betamethasone 26 wk and every 10 d, amniocentesis for fetal lung maturation every 2 wk beginning at 28 wk | Thyroid hormone |
| | BPP | BPP 3 times a week | | | | | | Corticosteroids, synthetic vasopressin, cooling and heating blankets for temperature instability, blood transfusion, subcutaneous heparin, insulin therapy |
| Antonini et al,[37] 1992 | FHR | FHR monitored daily | Yes | Weekly | Biometry | — | — | Dopamine, thyroid hormone, corticosteroids, vasopressin, temperature control, blood transfusion, albumin, antibiotics |
| Anstötz,[9] 1993 | NA | NA | NA | NA | NA | — | — | NA |
| Nettina et al,[11] 1993 | CTG | CTG daily | NA | NA | NA | NA | NA | Fluid volume replacement and vasopressors, hypothalamic dysfunction (DI) correction, hyperthermia blanket and warming lights IV fluids through a warmer, prophylactic broad spectrum antibiotics |
| Béguin,[10] 1993 | NA | NA | NA | NA | NA | — | — | NA |
| Wuermeling,[12] 1994 | NA | NA | NA | NA | NA | — | — | NA |
| Iriye et al,[13] 1995 | CTG | NA | Yes | NA | Biometry | Yes, magnesium sulfate | Yes | IV fluids, dopamine |
| Vives et al,[14] 1995 | CTG | NA | Yes | NA | Biometry | NA | No | Dopamine |

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*(continued)*

**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies** *(continued)*

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| | | | | | Doppler | | | Dobutamine, amiodarone |
| Catanzarite et al,[15] 1997 | CTG | NA | Yes | NA | Biometry | Yes, magnesium sulfate and indomethacin | No | Dopamine infusion, fluid, treatment for temperature instability, antibiotics, vasopressin, hydrocortisone and thyroxine replacement, insulin therapy, IV amphotericin B and vaginal terconazole |
| Lewis and Vidovich,[16] 1997 | NA | NA | NA | NA | NA | NA | No | Thyroxine, dopamine, norepinephrine bitartrate (Levophed), and desmopressin acetate, antibiotics |
| Spike,[18] 1999 | Fetal monitoring | Fetal monitoring every shift after 26 wk | Yes | NA | Biometry | NA | No | NA |
| Beca et al,[17] 1999 | NA | NA | NA | NA | NA | — | — | Dopamine, antibiotic therapy |
| Lane et al,[19] 2004 | NA | NA | Yes | Daily | NA | — | — | Pharmacologic support of the cardiovascular system, endocrine replacement therapy for pituitary failure, including corticosteroids and thyroid hormone, correction of hypernatremia and desmopressin therapy, antibiotic therapy for a pulmonary infection |

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*(continued)*

**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies** *(continued)*

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| Hussein et al,[20] 2006 | CTG | NA | Yes | NA | Doppler | Yes (nifedipine 20 mg, 3 times daily sublingually) | Yes | Blood transfusion, automatic rotating bed, amoxicillin, physiotherapy (pneumonia), desmopressin, Supplement of potassium, intramuscular hydrocortisone, insulin, warm air over blanket |
| Souza et al,[21] 2006 | CTG<br>BPP | NA | Yes | NA | Biometry<br>Doppler | NA | Yes | Prednisone<br>Continuous IV insulin, enteric desmopressin, crystalloid and colloid replacement+low doses of norepinephrine and dopamine, air heater and blankets, ceftriaxone |
| Hurtado et al,[22] 2007 | BPP<br>CTG after 22 wk | NA | Yes | NA | Biometry | — | — | NA |
| Mejía et al,[23] 2008 | NA | NA | NA | NA | NA | NA | Yes (24 wk) | Dopamine, desmopressin, ACTH, thyroid hormones, piperacillin-tazobactam+vancomycin (UTI), cephalosporin |
| Yeung et al,[24] 2008 | FH tones until 24 wk and modified BPP | Daily FH tones<br>Modified BPP weekly | Yes | NA | Biometry | NA | Yes (24 wk) | Thyroid hormones<br>Hydrocortisone, low-molecular-weight heparin |
| Woderska et al,[25] 2012 | NA | NA | NA | NA | NA | NA | NA | Dopamine |

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*(continued)*

**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies** *(continued)*

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| Said et al,[26] 2013 | "Heart rate monitoring" | NA | Yes | NA | Biometry | NA | Yes | Vasopressors |
| | | | | "Serial" | | | | Antihypertensives, vasopressin, antibiotics, meropenem and vancomycin (meningitis), thyroid hormone, steroids, passive rewarming and blankets |
| Burkle et al,[27] 2015 | NA | NA | NA | NA | NA | NA | NA | NA |
| Kinoshita et al,[28] 2014 | NA | NA | Yes | NA | Biometry | NA | No | Levothyroxine, continuous infusion of vasopressin nasal desmopressin, hydrocortisone |
| Wawrzyniak,[29] 2015 | NA | NA | Yes | NA | Biometry | NA | Yes (24 wk) | Methyldopa, verapamil, magnesium sulfate, urapidil, nitroglycerin, dopamine, norepinephrine, sublingual desmopressin, diuretic therapy, methylprednisolone, blood transfusion, antibiotics, antifungal medicines |
| Nishimura et al,[30] 2016 | NA | NA | Yes | NA | NA | NA | No | NA |
| Gopčević et al,[31] 2017 | CTG | CTG daily from 26 wk | Yes | Every 2 d | Doppler | NA | Yes | Norepinephrine |
| | BPP | | | | | | | Desmopressin, insulin, levothyroxine, antibiotics, heating blankets, heparin |

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*(continued)*

**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies** *(continued)*

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| Holliday and Magnuson-Woodward,[32] 2017 | CTG | NA | Yes | 20 wk, 26 wk, 29 wk, 30 wk, 31 wk | Biometry | NA | Yes (24 wk and 30 wk) | Furosemide, Medication for treatment DI, panhypothyroidism, hypothermia, and hypotension |
| Piskorz and Jakubiec-Wisniewska,[35] 2019 | FH | FHR daily | NA | NA | NA | NA | Yes (24 wk) | Hormone therapy, pentoxifylline infusion, DHA replacement |
| Pikto-Pietkiewicz et al,[34] 2019 | CTG | NA | Yes | NA | Biometry | NA | Yes (24 wk) | Levothyroxine, hydrocortisone, desmopressin, carbapenems and fluoroquinolones, ceftriaxone, piperacillin with tazobactam, ceftazidime, meropenem, and fluconazole |
| Reinhold et al,[36] 2019 | CTG | NA | Yes | NA | Biometry<br>Doppler | NA | Yes (24 wk and 30 wk) | Desmopressin<br>L-thyroxine, hydrocortisone, antibiotics |
| Boran et al,[33] 2019 | NA | NA | Yes | Daily | NA | NA | NA | Pharmacologic support of the cardiovascular system, endocrine replacement treatment (pituitary-thyroid), hypotonic fluid replacement, antibiotic therapy |

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.* *(continued)*

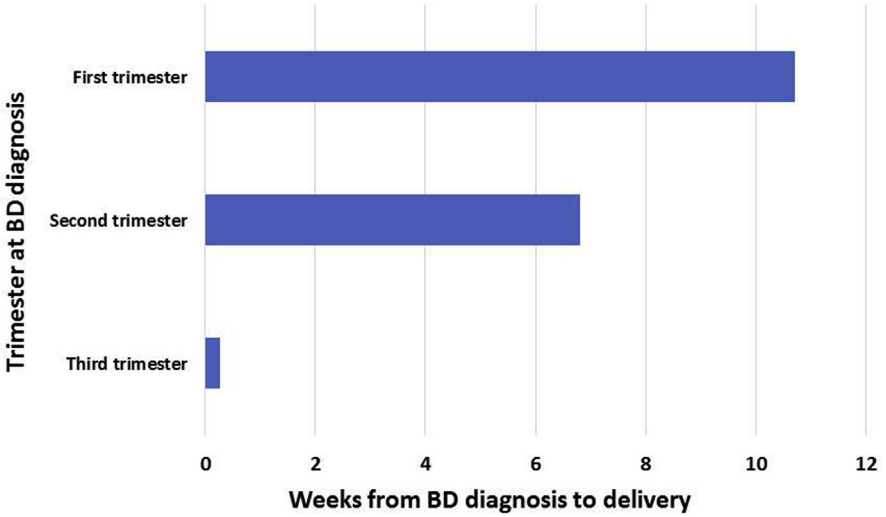
**TABLE 3**
**Fetal monitoring of the reported cases of maternal BD and life support medical therapies** *(continued)*

| Study, year | Fetal monitoring: CTG, BPP, or FHR | Frequency of CTG or BPP | US | Frequency of US | US biometry or Doppler | Tocolytic | Steroid for fetal maturity | Medications used during life support |
|---|---|---|---|---|---|---|---|---|
| Total mean value | NA: 14/35 (40%) | NA: 26/35 (74%) | NA: 11/35 (31%) | NA: 28/35 (80%) | NA: 16/35, (46%) | Yes: 4/28, (14%) | NA: 5/28 (18%) | NA: 7/35 (20%) |
| | CTG only: 10/21 (48%) | FHR daily: 2/9 (22%) | Yes: 24/24 (100%) | Daily: 2/7 (29%) | Biometry only: 14/19, (74%) | NA: 24/28, (86%) | Yes: 14/23 (61%) | Treatment of DI: 20/28 (71%) |
| | CTG and BPP: 4/21 (19%) | CTG daily: 2/9 (22%) | | Weekly: 2/7 (29%) | Doppler only: 2/19, (11%) | 7 IUFDs at <22 wk excluded | No: 9/23 (39%) | Pharmacologic support of the cardiovascular system: 18/28 (64%) |
| | CTG+FHR: 2/21 (10%) | FHR daily+CTG weekly: 1/9 (11%) | | Every 2 days: 1/7 (14%) | Both: 3/19, (16%) | | 7 IUFDs at <22 wk excluded | Antibiotics: 20/28 (71%) |
| | FHR: 2/21 (10%) | FHR at every shift+CTG twice a week: 1/9 (11%) | | Other: 2/7 (14%) | | | | Thyroxine: 17/28 (61%) |
| | Other: 2/21 (10%) | CTG every 8 hr+BPP 3 times a week: 1/9 (11%) | | | | | | Corticosteroids: 16/28 (57%) |
| | FHR+BPP: 1/21 (5%) | FHR daily+BPP weekly: 1/9 (11%) | | | | | | Treatment temperature instability: 9/28 (32%) |
| | | FHR at every shift: 1/9 (11%) | | | | | | Insulin: 7/28 (25%), fluid: 6/28 (21%), blood transfusion: 5/28 (18%), antiepileptic drugs: 3/28 (11%), heparin: 3/28 (11%), antimycotic: 3/28 (11%), diuretics: 3/28 (11%), albumin: 2/28 (7%), antihypertensive: 2/28 (7%), potassium replacement: 1/28 (4%), pentoxifylline: 1/28 (4%), antiarrhythmic drugs: 1/28 (4%), DHA replacement: 1/28 (4%), automatic rotating bed: 1/28 (4%), ACTH: 1/28 (4%) |

*ACTH*, adrenocorticotropic hormone; *BPP*, biophysical profile; *CTG*, cardiotocography; *DHA* docosahexaenoic acid; *DI*, diabetes insipidus; *FHR*, fetal heart rate; *IV*, intravenous; *IUD*, intrauterine death; *NA*, not available; *US*, ultrasound; *UTI*, urinary tract infection.

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.*

**FIGURE 2**
**Latency from BD to delivery (weeks) for gestational age at diagnosis of BD**




*BD*, brain death.

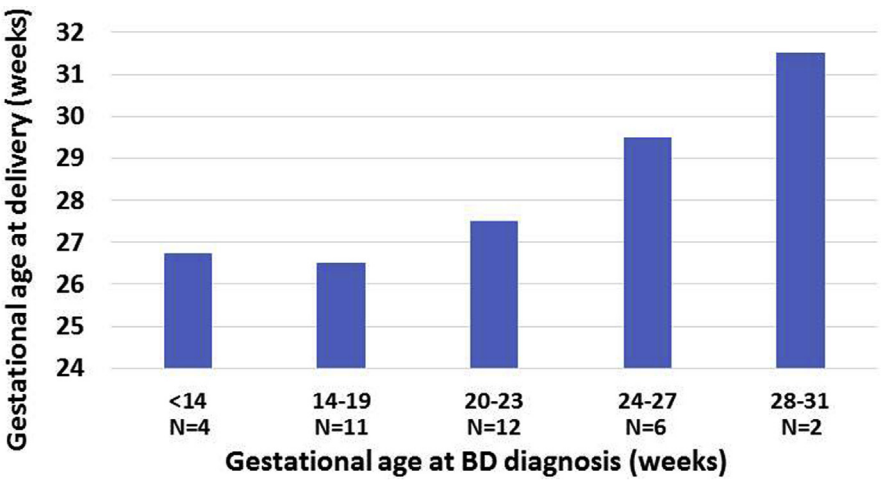
*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.*

SAH, or hematoma (68%); the most commonly diagnostic criteria for BD listed were EEG along with clinical examination; and diagnosis of BD was made at a mead gestational age of 20 weeks, mostly in the second trimester of pregnancy (83%) (Table 1).

Total days from diagnosis of BD to delivery were 48.9±38.8 days (approximately 7 weeks) and differed by trimester of pregnancy: 75±63 days in the first trimester of pregnancy, 48.5±33.2 days in the second trimester of pregnancy, and 2±0 days in the third trimester of pregnancy (Table 3; Figure 2). The most common complications were infections (69%) (eg, pneumonia, UTI, sepsis), circulatory instability (63%), DI (56%), thermal variability (41%), and panhypopituitarism (34%) (Table 2). Therefore, multiple medical therapies were necessary during life support (Table 3). The most common indications for delivery were maternal cardiocirculatory instability (38%) and nonreassuring fetal testing (35%). Mean gestational age at delivery overall was 27 weeks and differed depending on gestational age at diagnosis of BD: 26.7±4.9 weeks at <14 weeks of gestation, 26.5±4.8 weeks at 14 to 19 weeks of gestation, 27.5±4.9 weeks at 20 to 23 weeks of gestation, 29.5±6.2 weeks at 24 to 27 weeks of gestation, and 31.5±1.5 weeks at 28 to 31 weeks of gestation (Figure 3). Most deliveries (89%) were via cesarean delivery. Organ procurement occurred in 39% of cases reported (Table 4).

Regarding our main objective, there were 8 cases of IUFD (23%) in the second trimester of pregnancy (14−25 weeks of gestation), and 27 neonates (77%) were born alive. The rate of live birth differed by gestational age at diagnosis of BD: 50% <14 weeks, 54.5% at 14 to 19 6/7 weeks, 91.7% at 20 to 23 6/7 weeks, 100% at 24 to 27 6/7 weeks, and 100% at 28 to 31 6/7 weeks (Figure 4). Of the 35 cases of BD in pregnancy, 8 neonates (23%) were described as "healthy" at birth, 15 neonates (43%) had normal longer-term follow-up (>1 month to 8 years; mean, 20.3 months), 2 neonates (6%) had neurologic sequelae (born at 23 and 24 weeks of gestation), and 2 neonates (6%) died (born at 25 and 27 weeks of gestation). Mean birth weight was 1,229 grams, small for gestational age was present in 17% of neonates, with 40% of neonates having Apgar scores of <7 at 5 minutes (Table 5).

**FIGURE 3**
**Gestational age at delivery by gestational age at diagnosis of BD**




*BD*, brain death.

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.*

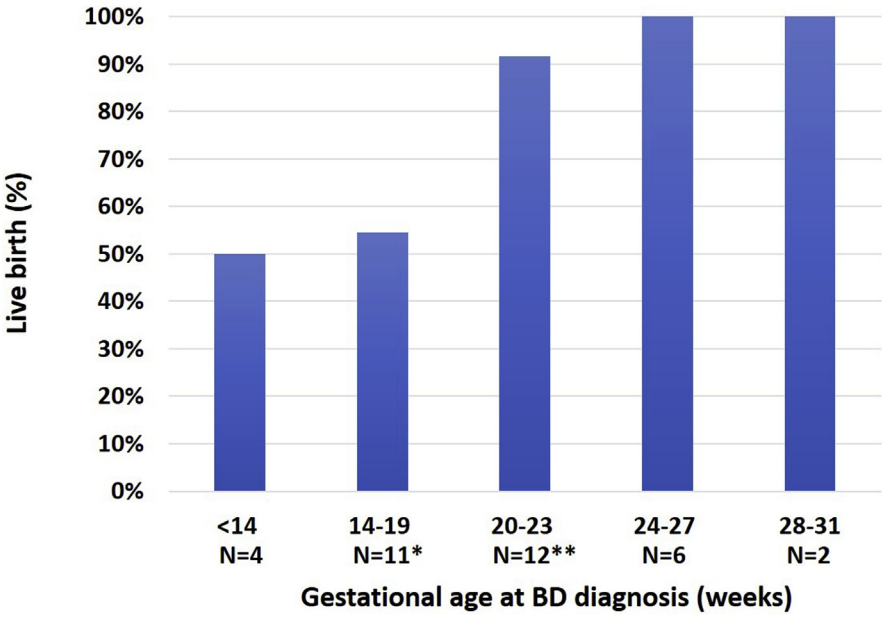
### Strengths and limitations

To the best of our knowledge, this is the largest systematic review on BD in pregnancy. Furthermore, this is the largest study that focused on perinatal outcome. However, we acknowledge the limitations associated within our systematic review regarding data extraction. For some variables (eg, diagnostic criteria for BD), several case reports lacked clinical details. Another

limitation was possible publication bias in favor of reporting good outcomes. It is also possible that many of the pregnancies the authors excluded because of missing clinical data might have had outcomes that were different. Moreover, important improvements in the quality of hospital care provided to mothers and preterm neonates have occurred over the years and might yield better perinatal outcomes.

In fact, 12 of the 35 cases of BD in this systematic review occurred in the last 10 years. Although all cases occurred well after the definition of BD per the Harvard 1968 committee, experts in the field continue to propose evolving criteria for BD, as science progresses. For example, in 2020, Truog et al[38] described BD as a state of 3 findings, that is, "irreversible apneic unconsciousness." Unconsciousness is diagnosed by absence of response to painful stimuli and absence of brainstem reflexes (eg, nonresponsive pupils), demonstrating that the brainstem is nonfunctional. Apnea is diagnosed by withholding ventilator support for a few minutes and demonstrating that the patient is not breathing despite a high level (eg, >60 mEq/L) of carbon dioxide in the blood ($PaCO_2$). This finding in a pregnant woman is incompatible with the survival of the fetus. This finding is unfeasible in a pregnant woman as such levels are harmful to the fetus. Irreversibility is assumed if the cause of the injury is known, no reversible causes can be identified, and the patient's condition does not change over several hours.[38] In addition, in 2020, Greer et al[39] similarly proposed that "determination of BD can be done with a clinical examination that demonstrates coma, brainstem areflexia, and apnea." This is seen when "(1) there is no evidence of arousal or awareness to maximal external stimulation, including noxious visual, auditory, and tactile stimulation; (2) pupils are fixed in a midsize or dilated position and are nonreactive to light; (3) corneal, oculocephalic, and oculovestibular reflexes are absent; (4) there is no facial movement to noxious stimulation; (5) the gag reflex is absent to bilateral posterior pharyngeal stimulation; (6) the cough reflex is absent to deep tracheal suctioning; (7) there is no brain-mediated motor response to noxious stimulation of the limbs; and (8) spontaneous respirations are not observed when apnea test targets reach pH <7.30 and PaCO2 >60 mm Hg. If the clinical examination cannot be completed (as is the case in pregnancy for the apnea test), ancillary testing may be considered with brain blood flow studies or electrophysiologic testing." By design, we did not report on ethical, cultural, family, and other issues and instead focused on maternal and perinatal medical issues and outcomes.

**FIGURE 4**
**Rate of live birth by gestational age at diagnosis of BD**




The *asterisk* indicates that 1 neonate died of necrotizing enterocolitis at several months of age and 1 neonate died at day 30. The *double asterisk* indicates that there are 2 neonates with neurologic sequelae.

*BD*, brain death.

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.*

## Comparison with previous literature

In 2010, Esmaeilzadeh et al[40] reported 30 cases of BD in pregnancy with an attempt at pregnancy prolongation; however, as Esmaeilzadeh's study included Suddaby et al's[41] 7 cases of BD in pregnancy, which lacked details and outcomes, it was excluded from other reviews and in our review. The rate of live birth reported in the study of Esmaeilzadeh et al[40] was 63%, which similar to our results (77%), with a postnatal follow-up up to 24 months available only for 50% of neonates, with all neonates having normal development. The last review on BD in pregnancy included 24 cases,[32,33] not including the Suddaby et al's[41] 7 cases; consequently, our reviewed cases increased by approximately 50% (n=35). Moreover, this review did not focus on perinatal outcome but on religious issues.[33] Boran et al[33] reported a live birth rate of 62%.[33] Definitions of outcomes (eg, FGR) were not always reported and might have differed among reports.

## Conclusion and implications

There are several complex implications regarding the clinical management of

**TABLE 4**
**Delivery characteristics and organ procurement**

| Study, year | Indication for delivery | Time from BD to delivery (d) | Gestational age at delivery (wk) | Mode of delivery (wk) | Organ procurement |
|---|---|---|---|---|---|
| Dillon et al,[4] 1982 | Fetal distress | 24 | 26 | CD | No |
| Friedman et al,[5] 1983 | Spontaneous labor, husband refused CD; late decelerations and meconium stained during labor | 2 | 33 | Vaginal delivery | NA |
| Heikkinen et al,[6] 1985 | Maternal blood pressure | 70 | 31 | CD | No |
| Shrader,[7] 1986 | Growth arrest | 63 | 31 | CD | NA |
| Field et al,[3] 1988 | Septicemia, growth restriction | 63 | 31 | CD | No |
| Bernstein et al,[8] 1989 | Possible fetal distress, premature uterine contractions | 107 | 32 | CD | No |
| Antonini et al,[37] 1992 | — | 49 | 22 | IUFD[a] | No |
| Anstötz,[9] 1993 | — | 42 | 19 | IUFD | No |
| Nettina et al,[11] 1993 | Maternal hypotension | 44 | 33 | CD | Yes |
| Béguin,[10] 1993 | — | 3 | 20 | IUFD | Yes |
| Wuermeling,[12] 1994 | — | NA | >14 | IUFD | NA |
| Iriye et al,[13] 1995 | Maternal blood pressure fluctuation, fetal distress | 2 | 30 | CD | No |
| Vives et al,[14] 1995 | Maternal hypotension, fetal distress | 1 | 27 | CD | No |
| Catanzarite et al,[15] 1997 | Fetal distress | 25 | 28 | CD | No |
| Lewis and Vidovich,[16] 1997 | Sufficient fetal lung maturity | 54 | 32 | CD | Yes |
| Spike,[18] 1999 | Unusual pattern of the placenta in ultrasound | 100 | 31 | CD | No |
| Beca et al,[17] 1999 | — | 5 | 18 | IUFD | NA |
| Lane et al,[19] 2004 | — | 8 | 14 | IUFD | Yes |
| Hussein et al,[20] 2006 | Progressive oligohydramnios Suspected placental insufficiency | 14 | 28 | CD (amniotic fluid meconium stained) | NA |
| Souza et al,[21] 2006 | Progressive oligohydramnios Suspected placental insufficiency | 25 | 29 | CD | Yes |
| Hurtado et al,[22] 2007 | Hypertensive disorder, abruptio placentae | 23 | 22 | IUFD | Yes |
| Mejía et al,[23] 2008 | Maternal hypotension and cardiac arrest | 56 | 25 | CD | No |
| Yeung et al,[24] 2008 | Hypotension, advancing tumor growth | 88 | 27 | CD | No |
| Woderska et al,[25] 2012 | Circulatory failure, respiratory failure, symptoms of respiratory and urinary tract infection | NA | 23 | CD | Yes |
| Said et al,[26] 2013 | IUGR | 110 | 32 | CD | NA |
| | Oligohydramnios | | | | |
| Burkle et al,[27] 2015 | NA | NA | 29 | CD | NA |
| Kinoshita et al,[28] 2014 | Spontaneous labor | 79 | 33 | Vaginal delivery | NA |
| Wawrzyniak,[29] 2015 | Bleeding from airways | 31 | 27 | CD | NA |

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.* *(continued)*

**TABLE 4**
**Delivery characteristics and organ procurement** *(continued)*

| Study, year | Indication for delivery | Time from BD to delivery (d) | Gestational age at delivery (wk) | Mode of delivery (wk) | Organ procurement |
|---|---|---|---|---|---|
| Nishimura et al,[30] 2016 | Circulatory instability | 8 | 24 | CD | NA |
| Gopčević et al,[31] 2017 | Fetal tachycardia and unreactive undulatory oscillations | 64 | 29 | CD | Yes |
| Holliday and Magnuson-Woodward,[32] 2017 | Bigeminy with frequent runs of premature ventricular contractions | 90 | 31 | CD | No |
| | Fetal distress | | | | |
| Piskorz and Jakubiec-Wisniewska,[35] 2019 | Circulatory instability | 38 | 27 | CD | NA |
| Pikto-Pietkiewicz et al,[34] 2019 | Fetal distress | 99 | 27 | CD | NA |
| Reinhold et al,[36] 2019 | Acute preeclampsia | 151 | 30 | Vaginal delivery | Yes |
| Boran et al,[33] 2019 | — | 28 | 25 | IUFD | No |
| Total | NA: 1/27 (4%)<br>Cardiocirculatory instability: 10/26 (38%)<br>Fetal distress: 9/26 (35%)<br>FGR: 3/26 (12%)<br>Spontaneous labor: 3/26 (12%)<br>Oligohydramnios: 3/26 (12%)<br>Suspected placental insufficiency: 2/26 (8%)<br>Hypertensive disorder: 2/26 (8%)<br>Septicemia: 1/26 (4%)<br>Sufficient fetal lung maturity: 1/26 (4%)<br>Unusual pattern of the placenta in ultrasound: 1/26 (4%)<br>8 IUFDs excludeda[a] | 48.9±38.8 d (20.7–72.2)<br>NA: 3/43, (9%)<br>First trimester of pregnancy: 75.0±63.0<br>Second trimester of pregnancy: 48.5±33.2<br>Third trimester of pregnancy: 2.0±0 | 27.2±4.7 wk (25–31)<br>(Wuermeling[12] excluded)<br><24 wk: 8/35 (23%)<br>24–27 6/7 wk: 9/35 (26%)<br>28–31 6/7 wk: 12/35 (34%)<br>32–35 6/7 wk: 6/35 (17%)<br>>36 wk: 0/35 (0%) | CD: 24/27 (89%)[a]<br>Vaginal delivery: 3/27 (11%)[a]<br>Excluded IUFD: 8/35 (23%)[a] | NA: 12/35 (34%)<br>Yes: 9/23 (39%)<br>No: 14/23 (61%) |

*CD*, cesarean delivery; *FGR*, feta; growth restriction; *ICH*, intracranial hemorrhage; *IUFD*, intrauterine fetal demise; *IUGR*, intrauterine growth restriction; *NA*, not available; *RDS*, respiratory distress syndrome; *SAH*, subarachnoid hemorrhage.

[a]IUFD at 22 weeks of gestation soon after maternal death because of cessation of cardiac activity.

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cases of BD in pregnancy. In medicine, making the right diagnosis is imperative. In pregnancy, although unconsciousness and irreversibility of BD can be ascertained, the apnea test should not be performed; other means, such as radiologic absence of cranial blood flow, should be utilized for the formulation of the diagnosis of BD.[38]

After the diagnosis of BD is made, pregnancy is possibly the only condition in which somatic support may be considered to continue support for the sake of the fetus.[39] Therefore, counseling must include some data on the prognosis if somatic support is considered as an option. Survival capacity inversely correlates with patient's age, and primary brain pathology is associated with longer survival than multisystem etiologies.[42] Nonpregnant adults with BD, especially if young (<35 years), can survive for years, even up to 20 years when the patient is <20 years old.[38,42] Nonetheless, these are outliers. This systematic review of cases of BD in pregnancy with somatic support to improve perinatal outcomes showed that, in most cases (66%), the neonate was born alive and did well at 20 months of follow-up. In addition, 6% of neonates had neurologic sequelae, and 6% of neonates died; this was probably secondary to the fact that all live neonates were born prematurely (overall mean age at birth, 27 weeks of gestation). Consequently, 23% of cases resulted in IUFD. Even cases with BD diagnosed at ≤14 weeks had a mean gestational age at delivery in the viability mean of 26.7 weeks of gestation. Perinatal outcome seemed to depend mostly on gestational age at delivery, as perinatal outcomes in

**TABLE 5**
**Perinatal outcomes and follow-up**

| Study, year | Gestational age at birth (wk)[a] | Sex | Weight (g) | Birthweight percentile | Apgar score at 5 min | Complications | Infant outcome and follow-up (mo) |
|---|---|---|---|---|---|---|---|
| Dillon et al,[4] 1982 | 26 | F | 930 | 81 | 8 | RDS, hydantoin syndrome | Born alive |
| Friedman et al,[5] 1983 | 33 | M | 1920 | 47 | 7 | NA | Normal at 6 mo |
| Heikkinen et al,[6] 1985 | 31 | M | 1600 | 57 | 7 | NA | Normal at 8 mo |
| Shrader,[7] 1986 | 31 | M | 1500 | 44 | NA | RDS | Born alive |
| Field et al,[3] 1988 | 31 | M | 1440 | 35 | 8 | RDS | Normal at 18 mo |
| Bernstein et al,[8] 1989 | 32 | M | 1555 | 27 | 9 | NA | Normal at 11 mo |
| Antonini et al,[37] 1992 | 22 | NA | IUFD | — | — | — | IUFD |
| Anstötz[9] 1993 | 19 | NA | IUFD | — | — | — | IUFD |
| Nettina et al,[11] 1993 | 33 | M | 2083 | 62 | 9 | NA | Born alive |
| Béguin,[10] 1993 | 20 | NA | IUFD | — | — | — | IUFD |
| Wuermeling,[12] 1994 | >14 | NA | IUFD | — | — | — | IUFD |
| Iriye et al,[13] 1995 | 30 | M | 1610 | 79 | 8 | NA | Born alive |
| Vives et al,[14] 1995 | 27 | M | 1150 | 84 | 10 | RDS | Normal at 14 mo |
| Catanzarite et al,[15] 1997 | 28 | M | 1315 | 85 | 7 | Fungemia and sepsis | Discharged on d 34 and has done well |
| Lewis and Vidovich,[16] 1997 | 32 | NA | NA | NA | NA | NA | Healthy infant |
| Spike,[18] 1999 | 31 | M | 1440 | 35 | 8 | NA | 8 wk in the NICU with no unusual complications |
| Beca et al,[17] 1999 | 18 | NA | IUFD | NA | NA | NA | IUFD |
| Lane et al,[19] 2004 | 14 | NA | IUFD | IUFD | — | — | IUFD |
| Hussein et al,[20] 2006 | 28 | M | 1285 | 82 | NA | RDS | Normal at 24 mo |
| Souza et al,[21] 2006 | 29 | M | 815 | <5 | 10 | NA | Normal at 3 mo |
| Hurtado et al,[22] 2007 | 22 | NA | 450 (IUFD) | IUFD | — | — | IUFD |
| Mejía et al,[23] 2008 | 25 | NA | 450 | <5 | NA | Premature birth complication, *Candida* infection | Died at d 30 |
| Yeung et al,[24] 2008 | 27 | F | 820 | 23 | 8 | NA | Died of necrotizing enterocolitis at several months of age |

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.*

(continued)

**TABLE 5**
**Perinatal outcomes and follow-up** *(continued)*

| Study, year | Gestational age at birth (wk)[a] | Sex | Weight (g) | Birthweight percentile | Apgar score at 5 min | Complications | Infant outcome and follow-up (mo) |
|---|---|---|---|---|---|---|---|
| Woderska et al,[25] 2012 | 23 | F | 600 | NA | 7 | RDS, IVH grade II, NEC grade I, *Klebsiella* pneumoniae, pneumothorax, anemia | Delay in speech development at 20 mo |
| Said et al,[26] 2013 | 32 | M | 750 | <5 | 7 | RDS | Born alive |
| Burkle et al,[27] 2015 | 29 | NA | NA | NA | NA | NA | Healthy child |
| Kinoshita et al,[28] 2014 | 33 | F | 2130 | 77 | 8 | RDS and infection | Discharged 40 d after birth and followed up regularly |
| Wawrzyniak,[29] 2015 | 27 | F | 680 | <10 | 6 | NA | Normal at 96 mo |
| Nishimura et al,[30] 2016 | 24 | M | 690 | 76 | NA | NA | Serious neurologic disorders at 24 mo |
| Gopčević et al,[31] 2017 | 29 | F | 1030 | 29 | 9 | ICU admission | Normal at 72 mo |
| Holliday and Magnuson-Woodward,[32] 2017 | 31 | M | 1635 | 72 | NA | RDS | Normal at 1 mo |
| Piskorz and Jakubiec-Wisniewska,[35] 2019 | 27 | NA | 1250 | 92 | 6 | NA | Born alive |
| Pikto-Pietkiewicz et al,[34] 2019 | 27 | F | 830 | 35 | 7 | RDS, retinopathy, infection | Normal at 36 mo |
| Reinhold et al,[36] 2019 | 30 | F | NA | NA | 8 | NA | Normal at 12 mo |
| Boran et al,[33] 2019 | 25 | NA | IUFD | NA | — | — | IUFD |
| Total | 27.2±4.7 d (25–31) (Wuermeling[12] excluded) <24 wk: 8/35 (23%) 24–27 6/7 wk: 9/35 (26%) | NA: 12/35 (34%) Male: 15/23 (65%) Female: 8/23 (35%) | NA: 3/27 (11%) 1229.5±475.6 Excluded 8 IUFDs[a] | IUFD: 8/35 (23%) NA: 4/35 (11%) Fetal weight<10%: 4/23 (17%) | NA: 7/27 (26%)[a] Apgar score of ≤7 at 5 min: 8/20 (40%) Excluded 8 IUFDs[a] | NA: 14/27 (52%)[a] RDS: 10/13 (77%) Infections: 5/13 (38%) ICU admission: 1/13 (8%) | IUFD at 14–25 wk: 8/35 (23%) Normal survival, >1 mo to 8 years: 15/35 (43%) Born alive and/or "healthy": 8/35 (23%) Neonatal death (25 and 27 wk): 2/35 (6%) |

*Dodaro. Brain death and pregnancy. Am J Obstet Gynecol 2021.*

*(continued)*

**TABLE 5**
**Perinatal outcomes and follow-up** *(continued)*

| Study, year | Gestational age at birth (wk)[a] | Sex | Weight (g) | Birthweight percentile | Apgar score at 5 min | Complications | Infant outcome and follow-up (mo) |
|---|---|---|---|---|---|---|---|
| | 28–31 6/7 wk: 12/35 (34%)<br>32–35 6/7 wk: 6/35 (17%)<br>>36 wk: 0/35 (0%) | | | | | IVH grade II, NEC grade I, pneumothorax, or anemia: 1/13 (8%)<br>Hydantoin syndrome: 1/13 (8%)<br>Prematurity complications: 1/13 (8%)<br>Excluded 8 IUFDs[a] | Neurologic sequelae (23 and 24 wk): 2/35 (6%) |

*F*, female; *ICU*, intensive care unit; *IUFD*, intrauterine fetal demise; *IVH*, intraventricular hemorrhage; *M*, male; *NA*, not available; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit; *RDS*, respiratory distress syndrome.

[a] Birthweight percentile and other outcomes.

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our systematic review on BD were similar to perinatal outcomes for neonates born at a mean gestational age of 27 weeks.

For fetal benefit, the goal for gestational age at delivery should be ≥32 weeks; aiming to ≥36 weeks for delivery seems unreasonable given previous literature not showing any case delivered so late after the diagnosis of BD (Tables 4 and 5). The corollary is that if diagnosis of BD is made at ≥32 weeks of gestation, delivery is probably indicated without prolonged somatic support, unless it is necessary to make appropriate organ donation arrangements. The critical care interventions which best prolonged pregnancy to 32 weeks of gestation, keeping the baby safe in utero, have been described in detail.[39] Unfortunately, of 317 institutional protocols for care of patients with BD from US hospitals, only 8 (2.5%) noted that a pregnant patient could not be evaluated for BD if the fetus could be preserved. Of the protocols that permitted evaluation of BD, 94% did not include guidance about fetal management after maternal diagnosis of BD, and 99% did not indicate who was responsible for making decisions for the fetus.[43] Guidance for the complex care of BD in pregnancy should be included in all protocols for BD. ■

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