28

Intensive Care Management of the Pregnant Patient after Cardiac Arrest

Markus B. Skrifvars

Bullet Points

- Cardiac arrest is uncommon in pregnant patients. Therefore, few intensivists have experience with post-cardiac arrest care in pregnancy.
- Pregnant post-cardiac arrest patients should receive tailored intensive care considering the state of pregnancy, general principles of post-cardiac arrest care and the disease causing the arrest.
- Cardiac causes commonly lead to ventricular fibrillation or ventricular tachycardia and may result from a myocardial infarction, cardiomyopathy or myocarditis.
- Non-cardiac causes such as hypovolemia related to bleeding, hypoxia, thromboembolism, maternal fluid embolism and air embolism as well as intracranial bleeding are possible causes of cardiac arrests with a non-shockable rhythm such as pulseless electrical activity or asystole.
- Immediately after return of spontaneous circulation, the patient should be assessed according to an ABCD approach.
- The airway should be secured in all patients after cardiac arrest unless they are conscious and have stable vital signs. Endotracheal intubation may be difficult and should be done with diligence.
- Hypoxia, extreme hyperoxia as well as hypo- and hypercarbia should be avoided. Mechanical ventilation should be undertaken utilising a lung-protective strategy.
- Blood pressure may be high immediately after return of spontaneous circulation if the patient has received adrenaline during cardiopulmonary resuscitation but afterwards patients may require intravenous fluid and/or vasopressors. The blood pressure target should be between 65 and 70 mmHg.
- Manage patient temperature targeting to 33–36 °C. In patients with bleeding or severe shock, targeting to 36° may be preferable.
- Use short-acting sedative agents such as propofol and remifentanil to facilitate early extubation in the neurologically improving patient.

M. B. Skrifvars (✉)
Department of Emergency Care and Services, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
e-mail: markus.skrifvars@hus.fi

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- Avoid hyper- and hypoglycaemia using insulin if needed. If the patient is not arousable within 48–72 h, a multimodal approach should be used to determine prognosis and guide future care. Include a thorough neurological examination, electroencephalography, a computed tomography of the brain, somatosensory evoked potentials and biomarkers.
- Recovery from cardiac arrest takes time and may require rehabilitation and support for both patient and family.

28.1 Introduction and Epidemiology

Given the rarity of cardiac arrest in pregnancy, most intensivists will have limited practical experience in post-cardiac arrest care of maternal patients. The United Kingdom cardiac arrest in pregnancy study (CAPS) published in 2017 identified 66 maternal deaths occurring in 1 year, equalling an incidence of 2.78 cases per 100,000 maternities [1]. Most of these deaths occurred in the hospital, and many were related to an anaesthetic procedure. The 12-month FINNRESUSCI study conducted in Finland (two large emergency medical systems and all Finnish intensive care units) identified no pregnant women among the 548 cardiac arrest patients who survived to intensive care unit (ICU) admission [2, 3]. In the United States, related at least in part to the opioid crisis, critical cardiovascular events such as cardiac arrests are increasing during pregnancy [4]. This trend may lead to a rise in the number of pregnant women with cardiac arrest who will require ICU care in the future.

All randomised controlled trials on post-resuscitation care have excluded pregnant patients [5–8]. Thus, the discussion regarding management of pregnant patients after cardiac arrest in this chapter is based on interpretation of the applicability, benefits and possible harms of the available therapeutic interventions given the state of the pregnancy, as well as on generally accepted principles of critical care management of the pregnant patient.

28.2 Pathophysiology of the Post-Cardiac Arrest Syndrome

Non-pregnant patients who initially survived cardiac arrest to be admitted to an ICU die mostly due to brain injury and less commonly due to cardiac injury [9, 10]. The main cause of brain injury is global hypoxia, which initiates a series of events that result in various degrees of hypoxic-ischaemic brain injury (HIBI) or hypoxic-ischaemic encephalopathy (HIE) [11, 12]. The damage occurring after cardiac arrest is usually described as a ‘two-hit model’. The primary injury occurs during cardiac standstill and is highly dependent on both the no-flow time (the period the patient is in cardiac arrest and does not receive any basic life support) and the low-flow time (the period of chest compression, during which there is some circulation) [13]. The development of HIBI appears to be predominantly related to the length of the no-flow state, accentuating the importance of immediate basic life support. The magnitude of pre-arrest hypoxia and hypotension also seem to be important [14]. Patients with cardiac arrest related to hypoxia (suffocation, hanging) appear to develop a severe form of HIBI and have a worse prognosis [15]. There are limited data about the cause of death in pregnant patients treated in the ICU after cardiac arrest, and there is little likelihood of data on this topic forthcoming soon. At this time, it is therefore reasonable to assume that these findings may be relevant in the pregnant population as well.

If return of spontaneous circulation (ROSC) is achieved, the second hit develops over the following 24–48 h [16]. The pathophysiology behind the second hit neurological injury is complex but includes reperfusion injury, disturbed autoregulation, local brain hypoxia and brain tissue oedema [11, 17]. Fever is a common feature and multiple studies have suggested harm from fever after cardiac arrest. During the first 24 h, cerebral blood flow decreases and oxygen deficit develops [18, 19]. In severe cases, catastrophic cerebral oedema may develop, leading to brain death. Patients may also develop a generalised systemic inflammatory response similar to that observed in sepsis, with elevation of inflammatory marker and cytokine levels [20, 21]. This

inflammatory response tends to manifest in patients who also develop extracranial organ failure [22, 23]. Myocardial dysfunction, which typically occurs during the first 24 h following ROSC and then tends to abate, is probably an important cause of this organ failure [24]. Treatment in cases with an evolving inflammatory response remains mainly supportive [22]. High-volume haemofiltration has been tried as a means of reducing inflammatory cytokine levels with inconclusive results [25].

28.3 Stage of Pregnancy and Change in Physiology Relevant to the ICU Physician

The stage of pregnancy will influence the type of ICU care provided after cardiac arrest [26]. During early pregnancy (up to a gestational age of 20 weeks), post-resuscitation treatment of the pregnant woman should adhere to the principles of post-resuscitation management for the general population [12]. At this time, the most profound physiological changes of pregnancy have yet to occur, and the fetus is not viable. Thus, the strategy should be to maximise the likelihood of benefit for the mother and, by proxy, that of the fetus. After 20 weeks of gestation, the physiological changes of pregnancy become more apparent and therefore merit greater consideration when planning care.

28.4 Immediate Management after Return of Spontaneous Circulation

Immediately after return of spontaneous circulation (ROSC) the woman should be surveyed according to an ABCD type approach.

Airway: Evidence shows that most women undergoing in-hospital resuscitation are intubated during the cardiac arrest [27]. However, the importance of intubation during CPR has recently been challenged [27]. Therefore, more patients may undergo cariopulmonary resuscitaiton (CPR) with only bag-valve-mask ventilation or airway devices in the future. After ROSC, the airway must be secured, with the sole exception of the completely conscious patient who has experienced a very brief cardiac arrest. Pregnant women also have an increased risk of regurgitation, placing even greater importance on securing of the airway with an endotracheal tube (ETT). Since endotracheal intubation is more difficult in pregnant women than in the general population, this should be performed in a controlled manner. Ideally, an airway checklist should be used (Table 28.1) [28]. Correct placement of the endotracheal tube is best confirmed by combining visual inspection of chest rise, fogging of the tube, continuous capnography and assessment of tube location by auscultation (i.e. absence of auditory sound over the stomach indicating oesophageal intubation followed by auditory signs indicating entry to air into the lungs during inspirium) [29]. Initially the tube should be placed and secured at a depth of 21–23 cm. Placement at the correct depth is then verified by chest radiography or direct fiberoscopy (see also Chap. 21).

Breathing: Most pregnant/post-partum women after cardiac arrest will likely require ventilator support. While there is no direct evidence to support this assumption, controlled mechanical ventilation may be less damaging than manual ventilation with unknown and probably dynamic parameters. Thus, mechanical ventilation is best initiated early after ROSC. Minute ventilation increases up to 50% during pregnancy [30]. Initial ventilation settings should take this change into consideration. As a rule of thumb, the aim should be for 14–16 breaths per minute, a tidal volume of between 400 and 500 mL (6–8 mL/kg ideal body weight) and a positive end-expiratory pressure (PEEP) of 6 cmH_2O.

During CPR, all patients receive 100% oxygen, and there is no accurate way to monitor the adequacy of oxygenation. After ROSC, oxygenation should be monitored using pulse oximetry (peripheral oxygen saturation) and by sampling of arterial blood gases. The fraction of inspired oxygen (FiO2) should be titrated to achieve an oxygen saturation of 94–98% [29]. If the woman is still undergoing bag-valve-mask ventilation, FiO2 may be adjusted by regulating fresh oxygen flow [31]. The FiO2 achieved will depend on minute

Table 28.1 Checklist to be used for safe management of the airway outside the operating room. All parts of the list are addressed by the whole team prior to initiating the procedure (modified from a list used since 2011 in the ED of Helsinki University Hospital and developed by RN M Kemppainen, RN A Rantanen, MD S Urtamo, MD J Puolakka)

Aim	Action
Preoxygenation	O_2 flow of >15 L, ensure the reservoir bag of the bag-valve-mask is full
Intravenous access	Ideally two iv lines with fluid running
Patient monitoring	1. Peripheral oxygenation saturation 2. Electrocardiography 3. Invasive blood pressure if possible, or non-invasive measurement set to measure every 2 min 4. Capnography connected to the bag-valve-mask with curve shown on screen (ensure it functions by using it during preoxygenation) 5. Assign one person to follow vital signs during the procedure
Medications	1. Anesthetic drugs 2. Norepinephrine infusion prepared and connected to an intravenous line 3. A bolus of vasopressor (diluted norepinephrine or diluted epinephrine) prepared in a 5 ml syringe
Airway equipment	1. Endotracheal tube - prepare two sizes and a 10 ml syringe for filling cuff 2. Laryngoscope ready and checked 3. Stylet or bougie ready to be used with lubricant 4. Tape or lace for securing the endotracheal tube 5. Suction ready and checked 6. Plan for difficult intubation. Consider and prepare a videolaryngoscope and an supraglottic airway
Prepare the patient	1. Optimise patient positioning, use the 'sniffing position' 2. Optimise work conditions for the person performing intubation 3. Clarify the person allocated to each of the following roles: (a) Performance of cricoid pressure (if required) (b) Moving the larynx into an optimal position (c) Positioning the side of the patients' mouth to facilitate tube insertion 4. Decide on a strategy of there is a circulatory collapse and the patient requires cardiopulmonary resuscitation

ventilation; with an oxygen flow of 4 L/min, the FiO2 approximates 50% [31]. Most women will not require prolonged ventilation with 100% oxygen. However, if arrest had occurred secondary to hypoxia (e.g. suffocation, acute asthma, pulmonary embolism or aspiration), ongoing treatment with high FiO2 may be required to maintain appropriate oxygen saturation. If the cause of the arrest was cardiac and CPR was promptly initiated, less oxygen will probably be required. In this situation, prolonged use of 100% oxygen will result in extreme hyperoxia [32].

Ventilation should be adjusted to achieve a PaCO2 of around 32–34 mmHg, which is normal during pregnancy [30]. Hyperventilation (PaCO2 < 32 mmHg) is harmful both during and after cardiac arrest in the non-pregnant patient [33, 34]. In pregnant women, hyperventilation may also cause vasoconstriction with a resultant decrease in uterine blood flow, which may lead to foetal distress [35]. End-tidal CO2 level monitored by capnography may provide some guidance for setting ventilation after the woman has stabilised. However, in the first hours after cardiac arrest, there may be a large arterial-alveolar difference due to faulty tissue perfusion (including the lungs). Thus, setting the correct minute ventilation requires frequent arterial blood gas sampling in the first hours of ventilation [36]. This will also aid in adjusting FiO2.

28.4.1 Circulation

During the first 20 min after ROSC, the risk of re-arrest is high. Efforts should be invested in ensuring adequate monitoring of patient vital signs. This should include continuous

electrocardiography (ECG), blood pressure and capnography. A sudden drop in end-tidal CO2 suggests impending re-arrest; this can be verified by identifying lack of a palpable pulse and loss of an organised cardiac rhythm on the ECG. The treating staff should be prepared to identify and rapidly manage re-arrest should this occur. If the woman had a shockable initial rhythm and sequences of shock-resistant ventricular fibrillation/tachycardia (VF/VT), these arrhythmias may recur. In such cases, a defibrillator must remain available nearby. If the woman was resuscitated from a non-shockable rhythm such as pulseless electrical activity (PEA) or asystole, recurrent PEA or severe hypotension are more likely. These can only be identified if blood pressure is measured continuously parallel to monitoring of electrocardiography. A high-monitoring environment and invasive blood pressure measurement are preferred as these will facilitate the response to possible maternal re-arrest.

Adrenaline received during resuscitation can sometimes greatly elevate systemic blood pressures. The half-life of adrenaline approximates 5 min, therefore the treating clinician should be alert to the option of hypotension occurring shortly (within 5–10 min) after ROSC [12]. The likelihood of such occurrence may even be higher in women whose cause of arrest was hypovolemia (e.g. hemorrhage).

Disability: A brief neurological examination should be undertaken after ROSC. If the woman has received adrenaline or atropine her pupils may be dilated. If the patient is restless or combative, a sedative agent or opiate should be administered. Generally, extubation should not be performed shortly after ROSC; the added work of spontaneous breathing may augment post-arrest intracellular energy deficit, and the patient may not be able to protect her airway, resulting in gastric aspiration. Sedation must be tailored first and foremost to maternal condition, as foetal well-being hinges on maternal well-being. Additional considerations affecting the choice of sedation are the stage of pregnancy and the pregnancy management plan. If immediate delivery is planned, an obstetric anaesthesiologist and a neonatologist should be involved in the decision-making process at this stage. For example, if caesarean delivery is being planned, sedation should be kept to a minimum in order to diminish the likelihood of neonatal respiratory depression. See below the discussion regarding sedation options.

28.5 Logistics of ICU Care

Comatose post-ROSC patients commonly require intensive care for a minimum of 48–72 h. Observational data from non-pregnant out of hospital cardiac arrest patients suggests that transfer from the scene of the arrest to a specialised cardiac arrest centre may be associated with better outcomes than transfer to the nearest hospital [37–39]. Pregnant and peripartum women who have arrested outside the hospital, and achieved ROSC should be transferred to a hospital with both intensive care and obstetric expertise. The details of the arrest and the clinical condition of the patient after ROSC should be ascertained from the emergency medical service (in case of out-of-hospital arrest) or the resuscitation team (in case of in-hospital arrest) and diligently documented. These details are of paramount importance for decisions at a later stage of intensive care (Table 28.1). A protocol should ideally be used in all intensive care units when managing patients after cardiac arrest [40]. This is particularly true for pregnant women, as care is being delivered to two patients rather than one.

28.6 Determining the Cause of the Arrest

Important information regarding cardiac arrest management will provide clues on arrest cause, and should be collected from the CPR providers, either the emergency medical service providers or members of the in-hospital cardiac arrest team (Table 28.2). Acute myocardial infarction is the most common cause for cardiac arrest in non-pregnant patients, but it is less common in pregnant patients [41]. In pregnant women, heart failure due to exacerbation of pre-existing heart

Table 28.2 Pre- and intra-arrest factors that should be ascertained from the emergency medical service (in case of out-of-hospital arrest) or the resuscitation team (in case of in-hospital arrest) and diligently documented. These details are of paramount importance for decisions at a later stage of intensive care

Factor	Relevance and how to avoid pitfalls
Relevant symptoms prior to the arrest	May provide insight regarding the etiology of the arrest Headache may suggest an intracranial process. Dyspnea may suggest heart failure or pulmonary embolism. Chest pain may suggest myocardial infarction or arterial dissection
Clinical status prior to the arrest	Seizure in late pregnancy is most commonly pre-eclampsia. Other possible causes are intracranial pathologies such as subarachnoid hemorrhage, other forms of intracerebral hemorrhage or sinus vein thrombosis. Cardiac arrest in such cases may be related to a sudden increase in intracerebral pressure or severe hypoxia due to respiratory depression
Was the arrest witnessed?	Unwitnessed arrest has a much worse prognosis both in and out of hospital
Did the patients receive bystander-initiated life support?	Chest compression is pivotal for survival and may not have been delivered in a timely manner. Even in-hospital cardiac arrest may not be recognised or responded to appropriately. Obstetric department staff rarely encounter patients in cardiac arrest
Initial rhythm	May suggest the most likely cause of arrest and is also an important predictor of survival. The reported initial rhythm is best verified against real-time pre-hospital/event electrocardiography printouts
Duration of the arrest	The actual time of the arrest may be difficult to ascertain. It is therefore common practice to use the time the call was placed to the dispatch centre or to the cardiac arrest team as “time zero”
Clinical findings after return of spontaneous circulation	Persistent hypertension (notwithstanding intra-arrest use of adrenaline) suggests eclampsia or an intracranial process Ongoing hypotension suggests bleeding Ongoing hypoxia suggests pulmonary embolisms or massive aspiration

disease, cardiomyopathy or myocarditis are more common [42] and may cause a primary cardiac arrhythmia. However, myocardial infarction has also been reported during pregnancy [43]. Ventricular fibrillation may also be related to certain electrolyte disturbances and intoxications [44].

The diagnostic workup of patients resuscitated from a shockable rhythm should start with a 12-lead ECG. In cases of prolonged CPR with use of adrenaline, changes suggesting ischaemia may be seen immediately after ROSC. Therefore decisions should be made based on the findings of an ECG obtained 20 min from ROSC [42].

If ongoing ST-segment elevation is observed, additional investigations should be undertaken without delay regardless of pregnancy [43, 45]. The value of measuring cardiac enzyme levels early after cardiac arrest remains unclear even in the general population [46]. An echocardiogram (ECHO) may reveal regional wall motion abnormalities, valvular abnormalities (e.g. aortic stenosis, mitral regurgitation), cardiomyopathy or severe cardiac failure. Computed tomography may be required to rule out alternative causes (e.g. aortic or coronary dissection). If indicated, iodinated contrast media may be used despite ongoing pregnancy. To date, no teratogenic effects have been clearly attributed to exposure to the newer generation of low-osmolality contrast media during pregnancy [47].

The option of coronary artery disease as the cause of cardiac arrest is commonly overlooked even in non-pregnant women [48]. While pregnant women are younger, aortic dissection, coronary artery dissection and clinically significant atherosclerotic coronary artery disease have all been described during pregnancy [49]. Maternal mortality from myocardial infarction ranges between 5% and 37% even in developed countries [47, 50, 51]. Therefore, regardless of pregnancy, the mother should receive appropriate workup and treatment. In the presence of ongoing ST-elevation (and in some cases with non-ST elevation myocardial infarction), early coronary angiography may be indicated [52].

Coronary rupture has been reported during performance of coronary angiography in pregnant women, and foetal exposure to ionising radiation should be minimised, therefore such catheterisation should only be performed by an experienced invasive cardiologist. In such cases, the risk-benefit ratio must always be weighed together with the family on an individual basis, the understanding being that the benefit of the mother comes before that of the fetus.

Subarachnoid hemorrhage (SAH) may also cause ventricular fibrillation in rare instances. If the ECG and ECHO results are normal, computed tomography imaging of the brain is indicated. The presence of a headache preceding the arrest is often described in SAH-related cardiac arrest. However, the absence of a pre-arrest headache does not rule out SAH [53].

For pregnant women with PEA as their initial non-perfusing rhythm, the mnemonic BEAUCHOPS (bleeding, embolism, anaesthetic complications, uterine atony, cardiac disease, hypertension due to eclampsia, other causes and sepsis) summarises the etiological factors that should be considered (Table 28.3) [54]. Efforts should be made to identify and treat these causes as well as the causes of PEA observed in the general population even during resuscitation [55]. If this has not been completed before ROSC, the likely etiology should be ascertained with further

Table 28.3 Identifying the cause of the arrest and tailoring investigations and management in the ICU according to the mnemonic 'BEAUCHOPS'

Cause of the arrest	Diagnostic considerations	Management priorities immediately after ROSC	Management priorities during the first 24–48 h
Bleeding	Hemoglobin level, coagulation status, focused assessment with s*onography* for trauma (FAST), whole body computed tomography, temperature, arterial blood gases and electrolytes	Identify active bleeding identify and control the source of bleeding, correct coagulation profile, transfuse, warm the patient and correct acid-base and electrolyte disorders throughout surgery/ radiological intervention	Identify possible rebleeding. Manage coagulation and venous thromboembolism prophylaxis
Embolism	Echocardiography Computed tomography coronary angiography Duplex ultrasound of the lower limbs	Thrombolysis/surgical embolectomy and/or extracorporeal membrane oxygenator	Anticoagulation with heparin infusion or low molecular weight heparin
Anaesthetic complications	Identify possible trigger and Document the relevant clinical details of the event	Stabilisation	Stabilisation
Uterine atony	Obstetric consultation, vaginal ultrasound, clinical examination	Immediate surgery	Stabilisation
Hypertension due to eclampsia	Clinical history, urinary screening for protein, electroencephalography, kidney and liver function tests	Computed tomography of the brain to rule out complications, managment of convulsions and blood pressure stabilization	Identify relevant organ failure (liver, kidneys), infuse magnesium, control blood pressure
Other cause	Clinical history suggesting overdose, drug screen. In case of trauma appropriate CT scan (head, neck, thorax, abdomen, pelvis)	Relevant antidote if such exists (e.g. naloxone) arterial blood gas (seek findings suggestive of intoxications), anion gap calculation Identify active bleeding in trauma patients	Stabilisation. Renal replacement in certain intoxications Trauma treatment according to standard management strategies
Sepsis	Blood, sputum and urinary cultures, cerebrospinal fluid in specific cases, chest radiography, targeted computed tomography scan	Antibiotics	Antibiotics and obtain source control

investigations after ROSC and treatment should be targeted accordingly (Table 28.2). Initial workup should include 12-lead ECG, arterial blood gas analysis with lactate, haemoglobin and electrolytes and chest radiography. A computed tomography scan of the brain, thorax, abdomen, and pelvis should be considered. CT angiogram must be undertaken if pulmonary embolism or arterial dissection is suspected and in select cases with suspected coronary heart disease. A drug and toxicology screen is in order when there is reason to suspect drug abuse or foul play and when no other obvious cause of arrest has been identified.

The circumstances surrounding the arrest will also be important for prognostication purposes (Table 28.2) [56] and must therefore be accurately documented in the hospital charts. If the CA occurs in the hospital during delivery (either vaginal or C-section), hemorrhage, eclampsia and maternal fluid and air embolism need to be kept in mind. Maternal amniotic fluid embolism is a dramatic event which occurs most commonly immediately after delivery of the placenta [57].

28.7 Mechanical Ventilation

Most patients with cardiac arrest who have been admitted to intensive care remain ventilated for 24–72 h [58]. The goals of positive pressure mechanical ventilation are to provide stable oxygenation and ventilation while protecting the lungs from secondary damage [59].

Oxygenation targets: Maternal hypoxemia (PaO2 < 75 mmHg) should be avoided by means of moderate PEEP and, if required, increased FiO2 [32]. Maternal arterial oxygen in the range of 75–100 mmHg appears to suffice for fetal oxygenation [60, 61]. Retrospective studies have associated extreme hyperoxia (PaO2 > 300 mmHg) in the first days after ROSC with higher death rates and poorer neurological outcomes [62, 63]. Hyperoxia is most commonly observed with inadvertent prolonged use of 100% oxygen [32]. Whether targeting moderate hyperoxia is protective or harmful in cardiac arrest patients is currently unclear [58]. Therefore, until more data is forthcoming. Hyperoxia should be avoided after cardiac arrest.

Ventilation targets: In late pregnancy (>28 weeks), the normal PaCO2 is in the range of 30–32 mmHg, which is lower than in the non-pregnant patient [26]. This is multifactorial, but is in part related to hyperventilation induced by progesterone and beginning after the first trimester. In cardiac arrest patients, the evidence is conflicting regarding optimal PaCO2 targets. It is generally accepted that hyperventilation should be avoided as it can induce arterial vasoconstriction in the brain [58, 64, 65]. As noted above, in pregnant women, hyperventilation may also cause uterine artery vasoconstriction, thereby decreasing blood flow to the fetus [26]. Mild hypercapnia has been shown to increase brain oxygenation [66, 67]. Current investigations in non-pregnant patients after ROSC are therefore focusing on the option of targeting mild hypercapnia. However, in the pregnant patient, even mild hypercapnia may cause acidosis which may be harmful for the fetus and cannot be recommended for pregnant patients at the present time [54, 60]. As there is no conclusive evidence regarding carbon dioxide targets, targeting normoventilation is likely most safe.

Lung protection: Lung-protective ventilation with avoidance of excessive tidal volumes is recommended in patients with ARDS. One study showed an increase in mortality with tidal volumes (TV) exceeding 8 mL/kg (predicted ideal body weight) [68]. Thus, in general, TVs of 5–6 mL/kg should be used and the frequency titrated to achieve the desired PaCO2. This might be slightly more challenging in the pregnant patient than in the general population given the metabolic increase. The indications for and method of lung-protective ventilation are discussed in greater detail in Chap. 23.

28.8 Targeted Temperature Management

Targeting of systemic temperatures to 33–36 °C for at least 24 h is recommended in non-pregnant cardiac arrest patients [12]. Recent evidence support the use of TTM also in patients resuscitated from non-shockable and in-hospital CA [69].

However, all clinical trials thus far have focused mainly on patients with an assumed cardiac cause for the arrest and have excluded pregnant women. There is little or no data on whether targeted temperature management (TTM) is efficacious in arrests occurring due to non-cardiac causes (e.g. pulmonary embolism, hypoxia, hemorrhage), although the ultimate mechanism of brain injury is likely to be similar (hypoperfusion mixed with increasing hypoxemia over time). In addition, the evidence suggests TTM may be beneficial mainly for patients resuscitated from a shockable initial rhythm [70].

TTM in pregnant and peripartum women: The two main concerns regarding the use of TTM in pregnant and peripartum women after ROSC are the risk of maternal hemorrhage and the potential for fetal damage especially if targeting 33 °C. Nonetheless, case reports have come out in recent years describing successful treatment of pregnant women with TTM which have suggested feasibility and lack of side effects [71]. Cardiac conduction may be modified during hypothermia with prolongation of the QT interval, QRS and PR segments all being observed. This reduction in heart rates usually only occurs within the lower range of temperatures used for TTM [72]. One case reported appearance of maternal bradycardia at 33 °C accompanied by signs of fetal distress [73]. Therefore, TTM of pregnant women must be accompanied by close monitoring and controlling of maternal heart rate and continuous monitoring of fetal heart rate. The decision as to which temperature (33 or 36 degrees) to target should be made on a case-by-case basis while taking into account the possible benefits and risks.

Systemic temperatures below 32 °C may also affect the coagulation cascade and platelet function [74]. This issue is of concern particularly in the peripartum period when there is an increased risk of maternal bleeding regardless of the mode of delivery. Theoretically, the risk of bleeding increases as systemic temperatures decrease. In non-pregnant patients after ROSC, there do not appear to be major differences in outcome when treated with 33 °C versus 36 °C. Therefore, in women after ROSC who are at risk of hemorrhage, a temperature of 36 °C should be targeted. At this time the literature describes only two women who arrested post-partum and were treated with TTM after achieving ROSC; of these, one exhibited coagulopathy [75]. However, the characteristics of the case were suggestive of amniotic fluid embolism which may itself be accompanied by coagulopathy. TTM after cardiac arrest is generally not associated with an increased risk of bleeding [5, 6]. Therefore, this treatment should be provided if it may improve maternal outcome. However, more attention should be directed towards selection of the individuals for treatment and to monitoring to prevent bleeding complications.

Pre-hospital induction of hypothermia with cold fluids during the arrest [76] or after ROSC is not beneficial [77, 78]. Targeted temperature management should therefore be started in the ICU and should continue for at least 24 h (Table 28.3). Outcomes are not better with treatment for 48 h compared to 24 h [5]. At the end of the TTM treatment period, the woman should be rewarmed slowly to 36.5–37 °C. Fever occurs commonly and may be treated with paracetamol. Any rebound hyperthermia may be treated invasively or non-invasively [5]. Temperatures exceeding 38.5 °C should be prevented especially in the comatose patients with signs of hypoxic-ischaemic brain injury.

28.9 Sedation

In the first 24 h after ROSC, sedation should be kept deep in most cases; waking the patient up in order to perform neurological assessment is best avoided [79]. Most patients are encephalopathic, and the lack of a positive neurological response does not influence treatment decisions. A wake-up test may cause hypertension and arrhythmias and increase intracerebral pressure. Exceptions to this rule include patients with a very brief cardiac arrest, cases with alcohol intoxication or drug overdose, or those needing frequent clinical neurological assessments when findings may change immediate clinical management (e.g. when there are focal findings on the brain CT

scan). After 24 h, sedation should be titrated using a sedation scale [80, 81].

Traditionally patients treated with TTM after ROSC were sedated using continuous infusions of midazolam and fentanyl [8]. At this time, short-acting agents such as propofol and remifentanil are preferred as they have been shown to shorten the time to extubation in this population [82]. Propofol is more likely to cause hypotension than midazolam [83, 84]. Thus, despite literature associating this drug with delirium and poorer outcomes, midazolam remains favoured by some for haemodynamically unstable patients [79]. Dexmedetomidine is another option for pregnant post-cardiac arrest women. Dexmedetomidine causes less hypertension and tachycardia than midazolam and has therefore been used in women with eclampsia for control of hypertension [85, 86]. However, in non-pregnant patients undergoing TTM (33 °C), the use of dexmedetomidine has been associated with bradycardia [87]. Dexmedetomidine has also been proposed for sedation during rewarming as shivering may occur at this stage of treatment, although conclusive evidence to support such practice is still lacking [88]. The metabolism of many sedative drugs (e.g. propofol, midazolam, morphine) is prolonged at systemic temperatures below the norm, therefore dosing may require adjustment dependent on the temperatures targeted and the phase of treatment [83].

28.10 Blood Pressure Management

The optimal blood pressure after cardiac arrest is not well defined. Studies have shown that disturbed cerebral autoregulation and decreases in cerebral blood flow contributes to poor outcome in patients post cardiac arrest [84]. Especially in patients with chronic hypertension, the autoregulation curve is shifted to the right, and patients could benefit from higher blood pressure [89]. Patients with eclampsia also appear to have disturbed autoregulation [90]. Nonetheless recent evidence does not support targeting mean arterial blood pressures higher than 65–70 mmHg after return of spontaneous circulation [91–93]. Marked hypotension with blood pressure less than 60 mmHg appears harmful [94] and should be avoided during the first 48 h. Signs of adequate blood pressure include adequate urinary output and decreasing lactate [12]. The one exception to this rule may be the woman with active bleeding where there is some evidence to support carefully monitored hypotensive resuscitation until bleeding has been controlled [94, 95].

Hypotension should generally be treated with either intravenous fluids or vasopressors, depending on the possible cause of the arrest. Hypovolemic shock (i.e. if the cause of arrest was hemorrhage or loss of intravascular volume for any other reason) should continue to be treated with fluids or blood products. Cardiogenic shock (i.e. infarction, arrhythmia, myocarditis) should be treated with vasopressors. Distributive shock (sepsis, anaphylaxis) may require treatment with both. In obstructive shock (e.g. pulmonary embolism, pneumothorax, tamponade), the woman will be less responsive to treatment with either fluids or vasopressors. In this situation the cause of the arrest must be reversed rapidly to maintain circulation, this may include thrombolysis or insertion of a chest drain.

There is limited evidence to direct the choice of vasopressors after cardiac arrest. However, vasoplegia is often seen after ROSC, particularly in patients who have entered the metabolic stage of cardiac arrest (i.e. in prolonged resuscitation). Norepinephrine is a good treatment option, but large amounts of fluid may also need to be infused. Norepinephrine increases mean arterial blood pressure without resulting in tachycardia [91, 92]. Based on data from patients with cardiogenic shock, treatment with norepinephrine is preferred over treatment with epinephrine which may cause severe tachycardia and recurrent shock [96]. Also see Chap. 38 regarding drug treatment during pregnancy. The response to treatment is best judged by lactate clearance and urinary output (0.5–1 mL/kg) [93, 97, 98]. The possibility of recurring cardiac ischemia should be kept in mind and serial echocardiography imaging to assess cardiac and valve function and left ventricular filling pressures may be indicated. Anecdotal evidence supports the short-term use

of inhaled nitric oxide and milrinone in the patient treated after cardiac arrest related to maternal fluid embolism [56].

28.11 Fluid and Glucose Management

Extrapolation from non-pregnant patients suggests that hypotonic fluids should be avoided during the first 24–48 h unless the patient has documented hypernatremia, and fluids containing glucose should be avoided unless the patient has a documented hypoglycaemia [99–102]. Apart from these two specific situations, there is limited evidence regarding the choice of fluid after cardiac arrest (see also Chap. 7 regarding fluid therapy). If there is clear evidence of cerebral edema, targeting a blood sodium level of 140–145 mmol/L appears well justified [17]. Hypertonic saline or mannitol may also be used in severe brain edema cases, although conclusive evidence of their benefit is lacking [17].

Hyperglycemia is commonly found in patients admitted after cardiac arrest and is associated with worse outcomes [103]. Lenient normoglycemia (i.e. blood glucose <10 mmol/L) is best targeted [104, 105]. Strict normoglycemia increases the likelihood of iatrogenically induced hypoglycemia without increasing benefit [7, 105].

28.12 Management of Seizures

Ideally, patients after cardiac arrest should be monitored with continuous electroencephalography (EEG) to allow early identification of epileptic activity. When such monitoring is unavailable, intermittent EEG is also an option. Seizures (and more often myoclonus) often occur in non-pregnant patients after ROSC and are usually related to HIBI [106]. In pregnant or peripartum women, the possibility of pre-eclampsia and eclampsia should also be kept in mind [26]. Differentiating between these two conditions may be difficult. However, HIBI usually occurs after prolonged CPR and tends to appear more than 24 h after ROSC. Epileptic activity and seizures related to HIBI are strongly associated with no- and low-flow times [106].

There is no evidence to support prophylactic seizure prevention after ROSC [12, 107, 108]. The presence of epileptic activity is associated with a poor prognosis, but some patients are amenable to treatment once such activity has appeared. Phenytoin is not particularly effective in treatment of myoclonus or more severe epileptic activity related to HIBI [109]. Sodium valproate is contraindicated in pregnancy given the risk of birth defects. Therefore, in pregnant women with seizure activity after ROSC, levetiracetam is probably the drug of choice [110, 111]. Levetiracetam is eliminated by the kidneys and has linear pharmacokinetics and low protein binding, all of which increase its safety profile for both mother and fetus. Seizures related to eclampsia should also be treated with magnesium and strict control of blood pressure (See also Chap. 16).

28.13 General Intensive Care Management

If the gestational age is greater than 20 weeks, and the fetus is still in situ, placing the woman in the supine position is accompanied by the risk of aortocaval compression. Aortocaval compression may decrease venous return, causing hypotension and even shock or re-arrest. Therefore, after ROSC, the pregnant woman should be placed in a left lateral tilt position. Because of the option of inferior cava compression, central venous lines should be placed above the diaphragm [26, 54]. The risk of thrombosis is increased in pregnancy. However, coagulation disturbances have been described after cardiac arrest and have been associated with worse outcome [112]. Whether these coagulation disturbances require correction and to what degree such correction is possible and/or may change outcome remains unclear [113]. It is therefore wise to test coagulation periodically in order to balance the risk of administering prophylaxis for deep vein thrombosis with the need to correct coagulation abnormalities on an individual basis.

Aspiration may occur both during and after cardiac arrest, especially with prolonged periods of bag-valve-mask ventilation. Although gastric content may be sterile in non-hospitalised patients, treatment with an antibiotic is justified. In general in patients undergoing TTM after cardiac arrest, prophylactic uses of antibiotics has been shown to decrease the incidence of ventilator associated pneumonia [114]. The antibiotic chosen should depend on the cause of the arrest (e.g. hemorrhage vs. pneumonia) as well as local practices and bacterial resistance patterns. If the cause of arrest was not infectious, a second generation cephalosporin (e.g. cefuroxime) has been shown to suffice in unconscious traumatic brain injury patients [115]. Although there is limited evidence to support such practice, if the woman remains hypoxemic and aspiration is suspected, fiberoptic bronchoscopy and pulmonary lavage may be considered in order to remove residual gastric content and/or sputum[116].

Gastric ulcer prophylaxis is commonly used in intensive care, although conclusive evidence to support such practice is lacking [117]. Pregnant and peripartum women also have an increased risk of regurgitation, the symptoms of which may be alleviated with proton-pump inhibitors. Comatose hemodynamically unstable patients have a higher risk of developing gastrointestinal hemorrhage. Patients after myocardial infarction and/or percutaneous coronary intervention commonly receive antiplatelet agents and anticoagulants, further increasing the risk gastrointestinal hemorrhage.

28.14 Extracorporeal Membrane Oxygenation (ECMO) and Mechanical Assist Devices

The role of ECMO in management of cardiac arrest is unclear, especially in pregnant patients [118]. One centre has reported good results with the use ECMO in pregnant patients but only half of the women described were placed on ECMO during or immediately after CPR (see also Chap. 14). In the patient with extreme shock or hypoxia after return of spontaneous circulation, consideration should be given to treatment in an ECMO center (so-called ECMO watch) [56]. In non-pregnant patients, there is some evidence supporting the use of an intra-aortic balloon pump (IABP) [119–121], but there is no data on its applicability in pregnant patients. Furthermore, in late pregnancy, placing the patient in a lateral decubitus position may be difficult with an IABP. Caesarean section may also be considered if there is a chance that surgery will facilitate rather than complicate further care of the mother.

28.15 Prognostication

Patients after ROSC are usually kept sedated for 24–36 h, after which sedation is stopped, provided patient condition so allows. Continued sedation may be required in severe hypoxia, severe disseminated intravascular coagulopathy with ongoing hemorrhage or when brain edema or other pathological intracranial processes have been diagnosed [12, 79]. Ongoing coma or partial consciousness after termination of sedation suggests hypoxic-ischaemic encephalopathy (HIE). Factors increasing the risk of HIE are the absence of bystander-initiated life support and prolonged delays to return of spontaneous circulation [29]. HIE in general does not occur with ROSC delays briefer than 5 min.

If the patient fails to awaken, consultation with a neurologist is warranted and a multimodal prognostication approach should be applied [122]. Based on test results, the family can be approached with recommendations for further treatment, or in some cases, treatment withdrawal. All unconscious patients should undergo a thorough clinical examination. Important features include the presence/absence of brainstem reflexes (e.g. pupil size and reactivity, gag reflex) and cortical responses. An electroencephalography should again be obtained, as at this time it may identify more severe forms of HIE. Computed tomography of the brain is warranted to rule out intracranial pathology (e.g. severe brain oedema in HIE, hemorrhage). In some cases, magnetic resonance imaging of the brain may provide additional information on the severity of HIE and on the presence of lesions in areas of the brainstem which are seen less clearly in computed tomogra-

phy. Blood levels of specific brain biomarkers may also be used for prognostication after cardiac arrest. In non-pregnant patients, neuron-specific enolase (NSE) is most widely used and has been validated [123–125]; an increase in NSE between 24 and 48 h and elevated NSE 48 h after ROSC suggest severe HIE [125]. At a gestational age of 37 weeks, healthy pregnant women have normal NSE levels. However, NSE levels are physiologically elevated in the early weeks of pregnancy (up to 10 weeks) due to extracerebral sources (e.g. the corpus luteum). Women developing pre-eclampsia have ongoing elevated levels of NSE throughout pregnancy and up to a year later, whereas in healthy women, the levels tend to decline to normal during pregnancy [126, 127]. Furthermore, hemolysis causes elevation of NSE levels [128, 129]. Therefore, NSE should not be used for prognostication in early pregnancy, in women with pre-eclampsia, or in pregnant or post-partum women with disseminated intravascular coagulation, amniotic fluid embolism or those who have undergone massive transfusion due to bleeding.

28.16 Further Care and Rehabilitation

Recovery after cardiac arrest can take time [130, 131]. Data on long-term survival varies greatly, but survival to hospital discharge is generally higher in pregnant patients than in non-pregnant patients [132, 133]. Beyond somatic recovery, psychological symptoms and even post-traumatic stress disorder are not uncommon after cardiac arrest [134–137]. Patients may feel guilt, bewilderment and depression. The possible addition of having lost a child or having to care for a child after severe illness is likely to make things even more difficult. Follow-up and counselling is therefore much needed.

28.17 Conclusions

Care of the pregnant patient after cardiac arrest is challenging. Maternal cardiac arrest during pregnancy, and the peripartum period is fortunately rare. However, this rarity makes it difficult for clinicians and staff to attain clinical experience with this condition. Adequate preparation, education, simulation-based training and adherence to a high standard of intensive care are likely to facilitate efficient performance when needed.

References

1. Beckett VA, Knight M, Sharpe P. The CAPS study: incidence, management and outcomes of cardiac arrest in pregnancy in the UK: a prospective, descriptive study. BJOG. 2017;124(9):1374–81.
2. Vaahersalo J, Hiltunen P, Tiainen M, Oksanen T, Kaukonen KM, Kurola J, et al. Therapeutic hypothermia after out-of-hospital cardiac arrest in Finnish intensive care units: the FINNRESUSCI study. Intensive Care Med. 2013;39(5):826–37.
3. Hiltunen P, Kuisma M, Silfvast T, Rutanen J, Vaahersalo J, Kurola J, et al. Regional variation and outcome of out-of-hospital cardiac arrest (ohca) in Finland—the Finnresusci study. Scand J Trauma Resusc Emerg Med. 2012;20:80.
4. Salihu HM, Salemi JL, Aggarwal A, Steele BF, Pepper RC, Mogos MF, et al. Opioid drug use and acute cardiac events among pregnant women in the United States. Am J Med. 2018;131(1):64–71.
5. Kirkegaard H, Soreide E, de Haas I, Pettila V, Taccone FS, Arus U, et al. Targeted temperature management for 48 vs 24 hours and neurologic outcome after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA. 2017;318(4):341–50.
6. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. N Engl J Med. 2013;369(23):2197–206.
7. Oksanen T, Skrifvars MB, Varpula T, Kuitunen A, Pettila V, Nurmi J, et al. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. Intensive Care Med. 2007;33(12):2093–100.
8. Hypothermia after Cardiac Arrest Study G. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346(8):549–56.
9. Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004;30(11):2126–8.
10. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche JD, et al. Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med. 2013;39(11):1972–80.
11. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care. 2017;21(1):90.

12. Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VR, Deakin CD, et al. European resuscitation council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med. 2015;41(12):2039–56.
13. Adrie C, Cariou A, Mourvillier B, Laurent I, Dabbane H, Hantala F, et al. Predicting survival with good neurological recovery at hospital admission after successful resuscitation of out-of-hospital cardiac arrest: the OHCA score. Eur Heart J. 2006;27(23):2840–5.
14. Skrifvars MB, Nurmi J, Ikola K, Saarinen K, Castren M. Reduced survival following resuscitation in patients with documented clinically abnormal observations prior to in-hospital cardiac arrest. Resuscitation. 2006;70(2):215–22.
15. Penney DJ, Stewart AH, Parr MJ. Prognostic outcome indicators following hanging injuries. Resuscitation. 2002;54(1):27–9.
16. Sekhon MS, Griesdale DE. Individualized perfusion targets in hypoxic ischemic brain injury after cardiac arrest. Crit Care. 2017;21(1):259.
17. Hayman EG, Patel AP, Kimberly WT, Sheth KN, Simard JM. Cerebral Edema after cardiopulmonary resuscitation: a therapeutic target following cardiac arrest? Neurocrit Care. 2017;28(3):276.
18. Edgren E, Enblad P, Grenvik A, Lilja A, Valind S, Wiklund L, et al. Cerebral blood flow and metabolism after cardiopulmonary resuscitation. Resuscitation. 2003;57(2):161–70.
19. Buunk G, van der Hoeven JG, Meinders AE. Prognostic significance of the difference between mixed venous and jugular bulb oxygen saturation. Resuscitation. 1999;41(3):257–62.
20. Adrie C, Laurent I, Monchi M, Cariou A, Dhainaou JF, Spaulding C. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? Curr Opin Crit Care. 2004;10(3):208–12.
21. Vaahersalo J, Skrifvars MB, Pulkki K, Stridsberg M, Rosjo H, Hovilehto S, et al. Admission interleukin-6 is associated with post resuscitation organ dysfunction and predicts long-term neurological outcome after out-of-hospital ventricular fibrillation. Resuscitation. 2014;85(11):1573–9.
22. Roberts BW, Trzeciak S. Systemic inflammatory response after cardiac arrest: potential target for therapy? Crit Care Med. 2015;43(6):1336–7.
23. Roberts BW, Kilgannon JH, Chansky ME, Mittal N, Wooden J, Parrillo JE, et al. Multiple organ dysfunction after return of spontaneous circulation in postcardiac arrest syndrome. Crit Care Med. 2013;41(6):1492–501.
24. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol. 2002;40(12):2110–6.
25. Laurent I, Adrie C, Vinsonneau C, Cariou A, Chiche JD, Ohanessian A, et al. High-volume hemofiltration after out-of-hospital cardiac arrest: a randomized study. J Am Coll Cardiol. 2005;46(3):432–7.
26. Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med. 1995;152(2):427–55.
27. Andersen LW, Granfeldt A, Callaway CW, Bradley SM, Soar J, Nolan JP, et al. Association between tracheal intubation during adult in-hospital cardiac arrest and survival. JAMA. 2017;317(5):494–506.
28. Djabatey EA, Barclay PM. Difficult and failed intubation in 3430 obstetric general anaesthetics. Anaesthesia. 2009;64(11):1168–71.
29. Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, et al. European resuscitation council guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation. 2015;95:100–47.
30. Elkus R, Popovich J Jr. Respiratory physiology in pregnancy. Clin Chest Med. 1992;13(4):555–65.
31. Young P, Pilcher J, Patel M, Cameron L, Braithwaite I, Weatherall M, et al. Delivery of titrated oxygen via a self-inflating resuscitation bag. Resuscitation. 2013;84(3):391–4.
32. Nelskyla A, Parr MJ, Skrifvars MB. Prevalence and factors correlating with hyperoxia exposure following cardiac arrest--an observational single Centre study. Scand J Trauma Resusc Emerg Med. 2013;21:35.
33. Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, von Briesen C, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. Circulation. 2004;109(16):1960–5.
34. Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med. 2004;32(9 Suppl):S345–51.
35. Levinson G, Shnider SM, DeLorimier AA, Steffenson JL. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. Anesthesiology. 1974;40(4):340–7.
36. Roberts BW, Kilgannon JH, Chansky ME, Trzeciak S. Association between initial prescribed minute ventilation and post-resuscitation partial pressure of arterial carbon dioxide in patients with post-cardiac arrest syndrome. Ann Intensive Care. 2014;4(1):9.
37. Elmer J, Rittenberger JC, Coppler PJ, Guyette FX, Doshi AA, Callaway CW, et al. Long-term survival benefit from treatment at a specialty center after cardiac arrest. Resuscitation. 2016;108:48–53.
38. Soholm H, Wachtell K, Nielsen SL, Bro-Jeppesen J, Pedersen F, Wanscher M, et al. Tertiary centres have improved survival compared to other hospitals in the Copenhagen area after out-of-hospital cardiac arrest. Resuscitation. 2013;84(2):162–7.
39. Spaite DW, Stiell IG, Bobrow BJ, de Boer M, Maloney J, Denninghoff K, et al. Effect of transport interval on out-of-hospital cardiac arrest survival in the OPALS study: implications for triaging patients to specialized cardiac arrest centers. Ann Emerg Med. 2009;54(2):248–55.
40. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, et al. Implementation of

a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. Resuscitation. 2007;73(1):29–39.
41. Yannopoulos D, Bartos JA, Raveendran G, Conterato M, Frascone RJ, Trembley A, et al. Coronary artery disease in patients with out-of-hospital refractory ventricular fibrillation cardiac arrest. J Am Coll Cardiol. 2017;70(9):1109–17.
42. Lellouche N, Sacher F, Jorrot P, Cariou A, Spaulding C, Aurore A, et al. Sudden cardiac arrest: ECG repolarization after resuscitation. J Cardiovasc Electrophysiol. 2011;22(2):131–6.
43. Dumas F, Cariou A, Manzo-Silberman S, Grimaldi D, Vivien B, Rosencher J, et al. Immediate percutaneous coronary intervention is associated with better survival after out-of-hospital cardiac arrest: insights from the PROCAT (Parisian Region Out of hospital Cardiac ArresT) registry. Circ Cardiovasc Interv. 2010;3(3):200–7.
44. Kontio T, Salo A, Kantola T, Toivonen L, Skrifvars MB. Successful use of therapeutic hypothermia after cardiac arrest due to amitriptyline and venlafaxine intoxication. Ther Hypothermia Temp Manag. 2015;5(2):104–9.
45. Spaulding CM, Joly LM, Rosenberg A, Monchi M, Weber SN, Dhainaut JF, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med. 1997;336(23):1629–33.
46. Dumas F, Manzo-Silberman S, Fichet J, Mami Z, Zuber B, Vivien B, et al. Can early cardiac troponin I measurement help to predict recent coronary occlusion in out-of-hospital cardiac arrest survivors? Crit Care Med. 2012;40(6):1777–84.
47. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. Obstet Gynecol. 2005;105(3):480–4.
48. Winther-Jensen M, Hassager C, Kjaergaard J, Bro-Jeppesen J, Thomsen JH, Lippert FK, et al. Women have a worse prognosis and undergo fewer coronary angiographies after out-of-hospital cardiac arrest than men. Eur Heart J Acute Cardiovasc Care. 2017:2048872617696368.
49. Pierce T, Hovnanian M, Hedgire S, Ghoshhajra B. Imaging of cardiovascular disease in pregnancy and the peripartum period. Curr Treat Options Cardiovasc Med. 2017;19(12):94.
50. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. Circulation. 2006;113(12):1564–71.
51. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. J Am Coll Cardiol. 2008;52(3):171–80.
52. Dumas F, Bougouin W, Geri G, Lamhaut L, Rosencher J, Pene F, et al. Emergency percutaneous coronary intervention in post-cardiac arrest patients without ST-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv. 2016;9(10):1011–8.
53. Skrifvars MB, Parr MJ. Incidence, predisposing factors, management and survival following cardiac arrest due to subarachnoid haemorrhage: a review of the literature. Scand J Trauma Resusc Emerg Med. 2012;20:75.
54. Jeejeebhoy FM, Morrison LJ. Maternal cardiac arrest: a practical and comprehensive review. Emerg Med Int. 2013;2013:274814.
55. Saarinen S, Nurmi J, Toivio T, Fredman D, Virkkunen I, Castren M. Does appropriate treatment of the primary underlying cause of PEA during resuscitation improve patients' survival? Resuscitation. 2012;83(7):819–22.
56. Bernstein SN, Cudemus-Deseda GA, Ortiz VE, Goodman A, Jassar AS. Case 33-2019: a 35-year-old woman with cardiopulmonary arrest during Cesarean section. N Engl J Med. 2019;381(17):1664–73.
57. Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. Am J Obstet Gynecol. 2009;201(5):445 e1–13.
58. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest: associations with long-term neurologic outcome. Crit Care Med. 2014;42(6):1463–70.
59. Herlitz J, Castren M, Friberg H, Nolan J, Skrifvars M, Sunde K, et al. Post resuscitation care: what are the therapeutic alternatives and what do we know? Resuscitation. 2006;69(1):15–22.
60. Hill CC, Pickinpaugh J. Physiologic changes in pregnancy. Surg Clin North Am. 2008;88(2):391–401. vii
61. Catanzarite V, Willms D, Wong D, Landers C, Cousins L, Schrimmer D. Acute respiratory distress syndrome in pregnancy and the puerperium: causes, courses, and outcomes. Obstet Gynecol. 2001;97(5 Pt 1):760–4.
62. Kilgannon JH, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. Circulation. 2011;123(23):2717–22.
63. Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303(21):2165–71.
64. Falkenbach P, Kamarainen A, Makela A, Kurola J, Varpula T, Ala-Kokko T, et al. Incidence of iatrogenic dyscarbia during mild therapeutic hypothermia after successful resuscitation from out-of-hospital cardiac arrest. Resuscitation. 2009;80(9):990–3.
65. Pynnonen L, Falkenbach P, Kamarainen A, Lonnrot K, Yli-Hankala A, Tenhunen J. Therapeutic hypothermia after cardiac arrest—cerebral perfusion and metabolism during upper and lower threshold normocapnia. Resuscitation. 2011;82(9):1174–9.
66. Eastwood GM, Tanaka A, Bellomo R. Cerebral oxygenation in mechanically ventilated early car-

diac arrest survivors: the impact of hypercapnia. Resuscitation. 2016;102:11–6.
67. Eastwood GM, Schneider AG, Suzuki S, Peck L, Young H, Tanaka A, et al. Targeted therapeutic mild hypercapnia after cardiac arrest: a phase II multicentre randomised controlled trial (the CCC trial). Resuscitation. 2016;104:83–90.
68. Beitler JR, Ghafouri TB, Jinadasa SP, Mueller A, Hsu L, Anderson RJ, et al. Favorable neurocognitive outcome with low tidal volume ventilation after cardiac arrest. Am J Respir Crit Care Med. 2017;195(9):1198–206.
69. Lascarrou JB, Merdji H, Le Gouge A, Colin G, Grillet G, Girardie P, et al. Targeted temperature management for cardiac arrest with nonshockable rhythm. N Engl J Med. 2019;381:2327.
70. Freund B, Kaplan PW. A review of the utility of a hypothermia protocol in cardiac arrests due to nonshockable rhythms. Cardiol J. 2017;24(3):324–33.
71. Rittenberger JC, Kelly E, Jang D, Greer K, Heffner A. Successful outcome utilizing hypothermia after cardiac arrest in pregnancy: a case report. Crit Care Med. 2008;36(4):1354–6.
72. Chavez LO, Leon M, Einav S, Varon J. Editor's choice—inside the cold heart: a review of therapeutic hypothermia cardioprotection. Eur Heart J Acute Cardiovasc Care. 2017;6(2):130–41.
73. Wible EF, Kass JS, Lopez GA. A report of fetal demise during therapeutic hypothermia after cardiac arrest. Neurocrit Care. 2010;13(2):239–42.
74. Stockmann H, Krannich A, Schroeder T, Storm C. Therapeutic temperature management after cardiac arrest and the risk of bleeding: systematic review and meta-analysis. Resuscitation. 2014;85(11):1494–503.
75. Song KH, Lee BK, Jeung KW, Lee SM. Safely completed therapeutic hypothermia in postpartum cardiac arrest survivors. Am J Emerg Med. 2015;33(6):861 e5–6.
76. Bernard SA, Smith K, Finn J, Hein C, Grantham H, Bray JE, et al. Induction of therapeutic hypothermia during out-of-hospital cardiac arrest using a rapid infusion of cold saline: the RINSE trial (rapid infusion of cold normal saline). Circulation. 2016;134(11):797–805.
77. Kim F, Nichol G, Maynard C, Hallstrom A, Kudenchuk PJ, Rea T, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. JAMA. 2014;311(1):45–52.
78. Bernard SA, Smith K, Cameron P, Masci K, Taylor DM, Cooper DJ, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010;122(7):737–42.
79. Dell'Anna AM, Taccone FS, Halenarova K, Citerio G. Sedation after cardiac arrest and during therapeutic hypothermia. Minerva Anestesiol. 2014;80(8):954–62.
80. Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond agitation-sedation scale (RASS). JAMA. 2003;289(22):2983–91.
81. De Jonghe B, Cook D, Appere-De-Vecchi C, Guyatt G, Meade M, Outin H. Using and understanding sedation scoring systems: a systematic review. Intensive Care Med. 2000;26(3):275–85.
82. Bjelland TW, Dale O, Kaisen K, Haugen BO, Lydersen S, Strand K, et al. Propofol and remifentanil versus midazolam and fentanyl for sedation during therapeutic hypothermia after cardiac arrest: a randomised trial. Intensive Care Med. 2012;38(6):959–67.
83. Bjelland TW, Klepstad P, Haugen BO, Nilsen T, Dale O. Effects of hypothermia on the disposition of morphine, midazolam, fentanyl, and propofol in intensive care unit patients. Drug Metab Dispos. 2013;41(1):214–23.
84. Ameloot K, Genbrugge C, Meex I, Jans F, Boer W, Vander Laenen M, et al. An observational near-infrared spectroscopy study on cerebral autoregulation in post-cardiac arrest patients: time to drop 'one-size-fits-all' hemodynamic targets? Resuscitation. 2015;90:121–6.
85. Rashid MR, Najeeb R, Mushtaq S, Habib R. Comparative evaluation of midazolam, dexmedetomidine, and propofol as intensive care unit sedatives in postoperative electively ventilated eclamptic patients. J Anaesthesiol Clin Pharmacol. 2017;33(3):331–6.
86. Esmaoglu A, Ulgey A, Akin A, Boyaci A. Comparison between dexmedetomidine and midazolam for sedation of eclampsia patients in the intensive care unit. J Crit Care. 2009;24(4):551–5.
87. Tobias JD. Bradycardia during dexmedetomidine and therapeutic hypothermia. J Intensive Care Med. 2008;23(6):403–8.
88. Callaway CW, Elmer J, Guyette FX, Molyneaux BJ, Anderson KB, Empey PE, et al. Dexmedetomidine reduces shivering during mild hypothermia in waking subjects. PLoS One. 2015;10(8):e0129709.
89. Ameloot K, Meex I, Genbrugge C, Jans F, Boer W, Verhaert D, et al. Hemodynamic targets during therapeutic hypothermia after cardiac arrest: a prospective observational study. Resuscitation. 2015;91:56–62.
90. Jones-Muhammad M, Warrington JP. Cerebral blood flow regulation in pregnancy, hypertension, and hypertensive disorders of pregnancy. Brain Sci. 2019;9(9):224.
91. Jakkula P, Pettila V, Skrifvars MB, Hastbacka J, Loisa P, Tiainen M, et al. Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med. 2018;44(12):2091–101.
92. Ameloot K, De Deyne C, Eertmans W, Ferdinande B, Dupont M, Palmers PJ, et al. Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the

Neuroprotect post-cardiac arrest trial. Eur Heart J. 2019;40(22):1804–14.
93. Dell'Anna AM, Sandroni C, Lamanna I, Belloni I, Donadello K, Creteur J, et al. Prognostic implications of blood lactate concentrations after cardiac arrest: a retrospective study. Ann Intensive Care. 2017;7(1):101.
94. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma. 2002;52(6):1141–6.
95. Sapsford W. Should the 'C' in 'ABCDE' be altered to reflect the trend towards hypotensive resuscitation? Scand J Surg. 2008;97(1):4–11. discussion 2-3
96. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol. 2018;72(2):173–82.
97. Taccone FS, Donadello K, Dell'Anna AM. Lactate measurement after cardiac arrest: tissue hypoxia or adaptive response?*. Crit Care Med. 2014;42(8):1942–3.
98. Vincent JL, Quintairos ESA, Couto L Jr, Taccone FS. The value of blood lactate kinetics in critically ill patients: a systematic review. Crit Care. 2016;20(1):257.
99. Olson JE, Banks M, Dimlich RV, Evers J. Blood-brain barrier water permeability and brain osmolyte content during edema development. Acad Emerg Med. 1997;4(7):662–73.
100. Olson JE, Evers JA, Banks M. Brain osmolyte content and blood-brain barrier water permeability surface area product in osmotic edema. Acta Neurochir Suppl (Wien). 1994;60:571–3.
101. D'Alecy LG, Lundy EF, Barton KJ, Zelenock GB. Dextrose containing intravenous fluid impairs outcome and increases death after eight minutes of cardiac arrest and resuscitation in dogs. Surgery. 1986;100(3):505–11.
102. Peng TJ, Andersen LW, Saindon BZ, Giberson TA, Kim WY, Berg K, et al. The administration of dextrose during in-hospital cardiac arrest is associated with increased mortality and neurologic morbidity. Crit Care. 2015;19:160.
103. Skrifvars MB, Pettila V, Rosenberg PH, Castren M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. Resuscitation. 2003;59(3):319–28.
104. Investigators N-SS, Finfer S, Chittock DR, Su SY, Blair D, Foster D, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
105. Investigators N-SS, Finfer S, Liu B, Chittock DR, Norton R, Myburgh JA, et al. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367(12):1108–18.
106. Moonen C, Lemmens R, Van Paesschen W, Wilmer A, Eertmans W, Ferdinande B, et al. The impact of global hemodynamics, oxygen and carbon dioxide on epileptiform EEG activity in comatose survivors of out-of-hospital cardiac arrest. Resuscitation. 2018;123:92–7.
107. Longstreth WT Jr, Fahrenbruch CE, Olsufka M, Walsh TR, Copass MK, Cobb LA. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Neurology. 2002;59(4):506–14.
108. Brain Resuscitation Clinical Trial ISG. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. N Engl J Med. 1986;314(7):397–403.
109. Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol. 2004;3(10):598–607.
110. Wyszynski DF, Nambisan M, Surve T, Alsdorf RM, Smith CR, Holmes LB, et al. Increased rate of major malformations in offspring exposed to valproate during pregnancy. Neurology. 2005;64(6):961–5.
111. Alsdorf R, Wyszynski DF. Teratogenicity of sodium valproate. Expert Opin Drug Saf. 2005;4(2):345–53.
112. Kim J, Kim K, Lee JH, Jo YH, Kim T, Rhee JE, et al. Prognostic implication of initial coagulopathy in out-of-hospital cardiac arrest. Resuscitation. 2013;84(1):48–53.
113. Skrifvars M, Pettila V. Disseminated intravascular coagulation is bad news for patients following cardiac arrest. Resuscitation. 2013;84(1):9–10.
114. Francois B, Cariou A, Clere-Jehl R, Dequin PF, Renon-Carron F, Daix T, et al. Prevention of early ventilator-associated pneumonia after cardiac arrest. N Engl J Med. 2019;381(19):1831–42.
115. Esnault P, Nguyen C, Bordes J, D'Aranda E, Montcriol A, Contargyris C, et al. Early-onset ventilator-associated pneumonia in patients with severe traumatic brain injury: incidence, risk factors, and consequences in cerebral oxygenation and outcome. Neurocrit Care. 2017;27:187.
116. Loftus TJ, Lemon SJ, Nguyen LL, Voils SA, Brakenridge SC, Jordan JR, et al. Early bronchoalveolar lavage for intubated trauma patients with TBI or chest trauma. J Crit Care. 2017;39:78–82.
117. Krag M, Perner A, Wetterslev J, Moller MH. Stress ulcer prophylaxis in adult neurocritical care patients—no firm evidence for benefit or harm. Crit Care. 2016;20:22.
118. Biderman P, Carmi U, Setton E, Fainblut M, Bachar O, Einav S. Maternal salvage with extracorporeal life support: lessons learned in a single center. Anesth Analg. 2017;125(4):1275–80.
119. Fengler K, Fuernau G, Desch S, Eitel I, Neumann FJ, Olbrich HG, et al. Gender differences in patients with cardiogenic shock complicating myocardial infarction: a substudy of the IABP-SHOCK II-trial. Clin Res Cardiol. 2015;104(1):71–8.
120. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK

II): final 12 month results of a randomised, open-label trial. Lancet. 2013;382(9905):1638–45.
121. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med. 2012;367(14):1287–96.
122. Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European resuscitation council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85(12):1779–89.
123. Cronberg T, Rundgren M, Westhall E, Englund E, Siemund R, Rosen I, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology. 2011;77(7):623–30.
124. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H. Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation. 2009;80(7):784–9.
125. Oksanen T, Tiainen M, Skrifvars MB, Varpula T, Kuitunen A, Castren M, et al. Predictive power of serum NSE and OHCA score regarding 6-month neurologic outcome after out-of-hospital ventricular fibrillation and therapeutic hypothermia. Resuscitation. 2009;80(2):165–70.
126. Bergman L, Akerud H. Plasma levels of the cerebral biomarker, neuron-specific enolase, are elevated during pregnancy in women developing preeclampsia. Reprod Sci. 2016;23(3):395–400.
127. Bergman L, Akerud H, Wikstrom AK, Larsson M, Naessen T, Akhter T. Cerebral biomarkers in women with preeclampsia are still elevated 1 year postpartum. Am J Hypertens. 2016;29(12):1374–9.
128. Geisen U, Benk C, Beyersdorf F, Klemm R, Trummer G, Ozbek B, et al. Neuron-specific enolase correlates to laboratory markers of haemolysis in patients on long-term circulatory support. Eur J Cardiothorac Surg. 2015;48(3):416–20. discussion 20
129. Gao F, Harris DN, Sapsed-Byrne S, Sharp S. Neurone-specific enolase and Sangtec 100 assays during cardiac surgery: part III—dose haemolysis affect their accuracy? Perfusion. 1997;12(3):171–7.
130. Mateen FJ, Josephs KA, Trenerry MR, Felmlee-Devine MD, Weaver AL, Carone M, et al. Long-term cognitive outcomes following out-of-hospital cardiac arrest: a population-based study. Neurology. 2011;77(15):1438–45.
131. Cowan MJ, Pike KC, Budzynski HK. Psychosocial nursing therapy following sudden cardiac arrest: impact on two-year survival. Nurs Res. 2001;50(2):68–76.
132. Balki M, Liu S, Leon JA, Baghirzada L. Epidemiology of cardiac arrest during hospitalization for delivery in Canada: a Nationwide study. Anesth Analg. 2017;124(3):890–7.
133. Mhyre JM, Tsen LC, Einav S, Kuklina EV, Leffert LR, Bateman BT. Cardiac arrest during hospitalization for delivery in the United States, 1998–2011. Anesthesiology. 2014;120(4):810–8.
134. Cronberg T, Lilja G, Horn J, Kjaergaard J, Wise MP, Pellis T, et al. Neurologic function and health-related quality of life in patients following targeted temperature management at 33°C vs 36°C after out-of-hospital cardiac arrest: a randomized clinical trial. JAMA Neurol. 2015;72(6):634–41.
135. Israelsson J, Bremer A, Herlitz J, Axelsson AB, Cronberg T, Djarv T, et al. Health status and psychological distress among in-hospital cardiac arrest survivors in relation to gender. Resuscitation. 2017;114:27–33.
136. Lilja G. Follow-up of cardiac arrest survivors: why, how, and when? A practical approach. Semin Neurol. 2017;37(1):88–93.
137. Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, et al. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation. 2015;97:68–75.