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Review Article

Targeted Temperature Management in Pregnant Patients after Cardiac Arrest: A Systematic Review

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Abstract

Background: Targeted temperature management (TTM) is a standard care intervention following resuscitation, known to improve neurological outcomes in patients. However, there is a lack of comprehensive studies on the application of TTM, specifically therapeutic hypothermia, in pregnant patients. Considering the critical importance of maternal and fetal health, this study aimed to investigate the use of TTM in pregnant women following cardiac arrest.

Methods: This systematic review was conducted by searching multiple databases, including Web of Science, PubMed Central, MEDLINE, Scopus, EMBASE, and Cochrane, up to October 2024. The search was conducted with no restrictions on time, place, or language. Articles were selected based on predefined inclusion criteria, which included case reports detailing the use of TTM in pregnant women after cardiac arrest. The quality of the included studies was assessed using the Jonna Briggs Institute (JBI) checklist for case reports.

Results: A total of nine articles met the inclusion criteria. Among the reported cases, there was 1 (11.1%) case of maternal death and 2 (22.2%) cases of fetal death, neither of which appeared to be directly attributable to the use of hypothermia. Neurological outcomes were favorable for all surviving mothers and fetuses following the application of TTM. The most common maternal complications during hypothermia for mothers were decreased blood pressure and heart rate, occurring in 2 (22.2%) cases. For the fetuses, bradycardia was the most frequently reported complication, occurring in 5 (55.5%) cases.

Conclusion: The use of TTM in pregnant patients following cardiac arrest might be considered on a case-by-case basis with the involvement of a multidisciplinary team. Pregnancy does not appear to be an absolute contraindication for TTM. However, close fetal monitoring is essential to ensure fetal well-being during the procedure.

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Keywords ● Cardiopulmonary resuscitation ● Cardiac arrest ● Hypothermia ● Hypothermia, induced ● Pregnancy

What's Known

- The 2015 American Heart Association guidelines for Cardiac Arrest in Pregnancy indicated that pregnancy is not an absolute contraindication for targeted temperature management (TTM). However, most randomized controlled trials (RCTs) published since 2002 have excluded pregnant patients, leading to ongoing controversy and limited evidence in this field.

What's New

- Targeted temperature management (TTM) during pregnancy can be considered on a case-by-case basis with a multidisciplinary team approach. Pregnancy does not appear to be a contraindication for TTM.
- Fetal bradycardia was the most commonly reported complication during hypothermia. Therefore, continuous fetal monitoring is recommended during TTM to ensure fetal well-being.

Introduction

Cardiac arrest is a leading cause of cardiovascular disease-related deaths and is associated with a significant risk of neurological damage and poor quality of life among survivors.[1-3] The overall prognosis for these patients largely depends on the extent of initial

neurological damage.[4] Despite advancements in cardiac arrest response systems and post-resuscitation guidelines, survival rates and neurological outcomes remain suboptimal.[5]

Targeted temperature management (TTM) is a critical component of post-resuscitation care, as it has been shown to mitigate neurological damage and improve its outcomes.[6] The American Heart Association (AHA) 2020 Cardiopulmonary Resuscitation (CPR) guidelines recommend maintaining TTM between 32 °C and 36 °C for at least 24 hours in patients with out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA), regardless of the initial cardiac rhythm.[7] Similarly, the 2021 European Resuscitation Council (ERC) guidelines recommend TTM for adults who remain unresponsive after the return of spontaneous circulation (ROSC) following OHCA or IHCA.[4]

Cardiac arrest during pregnancy represents one of the most challenging clinical scenarios. Although most features of resuscitation of a pregnant woman align with standard adult resuscitation protocols, there are unique considerations due to the presence of two patients: the mother and the fetus.[8] According to a study analyzing inpatient data from the United States, cardiac arrest during delivery was approximately 1 in 12,000 admissions for delivery, highlighting the need for prompt recognition and treatment in this population.[9] Globally, an estimated 800 women die every day due to pregnancy-related complications,[10] and maternal mortality rates in the United States, as reported by the National Vital Statistics System, have risen steadily from 17.4 deaths per 100,000 live births in 2018 to 32.9 deaths per 100,000 live births in 2021, the highest rate since 1964.[11]

The 2022 TTM2 Trial study found that the use of hypothermia therapy is generally safe for patients surviving cardiac arrest, with few contraindications, primarily related to the exclusion criteria of previous randomized controlled trials (RCTs), such as active bleeding, severe clinical scenarios, and known coagulopathy. However, pregnancy has consistently been an exclusion criterion in most RCTs conducted since 2002.[12-23] The 2015 AHA guidelines for Cardiac Arrest in Pregnancy stated that pregnancy is not an absolute contraindication for TTM. However, its use should be individualized, particularly in the context of antenatal cesarean delivery and coagulation disorders.[8]

Possible adverse effects of hypothermia include electrolyte imbalances, intravascular volume changes, cardiac arrhythmias, immunosuppression, and alterations in coagulation profiles. While these complications are typically manageable in an intensive care setting, they may pose significant risks to both the mother and fetus during pregnancy.[6] Despite the widespread acceptance of TTM as an evidence-based intervention for improving neurological outcomes in non-pregnant patients, there remains a significant knowledge gap regarding its use in pregnant women following cardiac arrest. The present practice relies heavily on individualized decision-making and anecdotal evidence.

Given the growing emphasis on maternal health and the persistently high rates of maternal mortality even with advances in medical technology, there is an urgent need to evaluate the safety and efficacy of TTM in pregnant patients. This systematic review aimed to synthesize the existing literature on the use of TTM in pregnant women following cardiac arrest, with a focus on evaluating the benefits, risks, and outcomes of this intervention. The findings of this study could contribute to evidence-based revisions of clinical protocols and guidelines for CPR and post-resuscitation care in pregnant patients.

Materials and Methods

Study Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[24] and was approved by the ethics committee of Jahrom University of Medical Sciences (Jahrom, Iran), (approval code: IR.JUMS.REC.1402.077s). Two researchers (S.A. and R.Z.) independently performed all steps of the study, including database searching, study selection, quality assessment, and data extraction. Disagreements between the researchers were resolved through discussion or by consulting a third researcher (M.O). The primary outcome of this review was to evaluate the mortality rate, neurologic outcomes, and complications associated with hypothermia therapy in pregnant women following cardiac arrest. The secondary outcome focused on the mortality rate, neurologic outcomes, and complications of hypothermia for the fetuses.

Searching Strategy

A comprehensive search was conducted across multiple databases, including Web of Science, PubMed Central, MEDLINE, Scopus, EMBASE, and Cochrane, from their inception through October 30, 2024. Keywords and their synonyms related to cardiac arrest, hypothermia, and pregnancy, were used to identify relevant studies (table 1). The detailed search strategy is presented in the Appendix file (table S1).

Table 1: Search strategy for systematic review of targeted temperature management in pregnant patients following cardiac arrest

Keywords		Synonymous
Population	Pregnant women	Pregnancy* OR "Pregnant" OR "Maternal"
Intervention	Hypothermia	Hypothermia* OR "Targeted Temperature Management" OR "Therapeutic hypothermia"
Outcomes	Cardiac Arrest	Cardiac Arrest* OR "Cardiopulmonary Arrest" OR "Arrest" OR "Cardiopulmonary resuscitation"

The search methodology initially employed PICO; however, due to limited research in this area and the potential for excluding relevant studies based solely on PICO criteria, the search approach was ultimately refined to focus on PIO parameters.

Study Selection

The search was conducted without restrictions on time, location, or language. Duplicate articles were removed using EndNote software (version 20, Clarivate Analytics, USA). If the articles met our inclusion criteria, they entered the analysis stage. Titles and abstracts of the retrieved articles were screened for relevance to the study objectives. If necessary, full-text articles were reviewed to confirm eligibility based on the inclusion criteria.

Inclusion Criteria:

- Case reports detailing the use of hypothermia therapy or TTM in pregnant women following successful resuscitation from cardiac arrest.
- Given the absence of clinical trials in this field, case reports were selected for evaluation and analysis.

Exclusion Criteria:

- Studies published only as abstracts without full-text availability.
- Review articles, books, and studies of low methodological quality.

Quality Assessment

The quality of the included studies and the risk of bias were evaluated using the Jonna Briggs Institute (JBI) case report checklist.[25] This checklist consisted of eight questions, each question scored as "Yes," "No," "Unclear," or "Not applicable", with a maximum score of 8. Studies were classified as follows:

-Low risk of bias: >70% of questions answered "Yes."
-Medium risk of bias: 50–70% of questions answered "Yes."
-High risk of bias: <50% of questions answered "Yes."

Data Extraction and Synthesize

Relevant data were extracted from the selected articles using a standardized checklist. The extracted data included:

-Study title, publication date, study location
-Target population details (maternal age, gestational age, race)
-Maternal medical history and cause of cardiac arrest
-Duration of resuscitation, and post-resuscitation Glasgow Coma Scale (GCS) score,
-Hypothermia induction protocol,
-Outcomes and complications of hypothermia for mother and fetus.

Statistical Analysis

Descriptive data analysis was performed using Excel software, version 2016 (Microsoft, USA). Continuous variables with non-normal distributions were presented as median (range), and categorical variables were expressed as frequency and percentage.

Results

Descriptive Characteristics

A systematic review of the databases (Appendix file, table S1) identified 420 records, of which 163 duplications were removed. After screening titles and abstracts, 239 articles were excluded. The full text of the remaining 18 articles was reviewed, and 9 case-report studies meeting the inclusion criteria were selected for analysis (figure 1).[26-34]

Quality assessment using the JBI checklist revealed that 8 (88.8%) articles scored between 7 and 8, indicating a low risk of bias, while 1 (11.1%) article scored 4, indicating medium risk of bias. According to the country of the research, 7 (77.7%) studies were conducted in the United States of America, 1 (11.1%) study in Japan, and 1 (11.1%) study in Italy. The median age of the women in the case reports was 31 years (range: 20-44 years), with the median gestational age at the time of cardiac arrest of 20 weeks (range: 13-36 weeks), and median gestational age at delivery of 39 weeks (range: 31-40 weeks) (table 2).

History of Maternal Diseases

Among the reported cases, 3 (33.3%) involved healthy mothers with no history of underlying diseases. High blood pressure, arrhythmia, depression, heart palpitations, long QT syndrome, and drug addiction were each reported in 1 (11.1%) case. In 1 (11.1%) case, the maternal medical history was not mentioned (table 2).

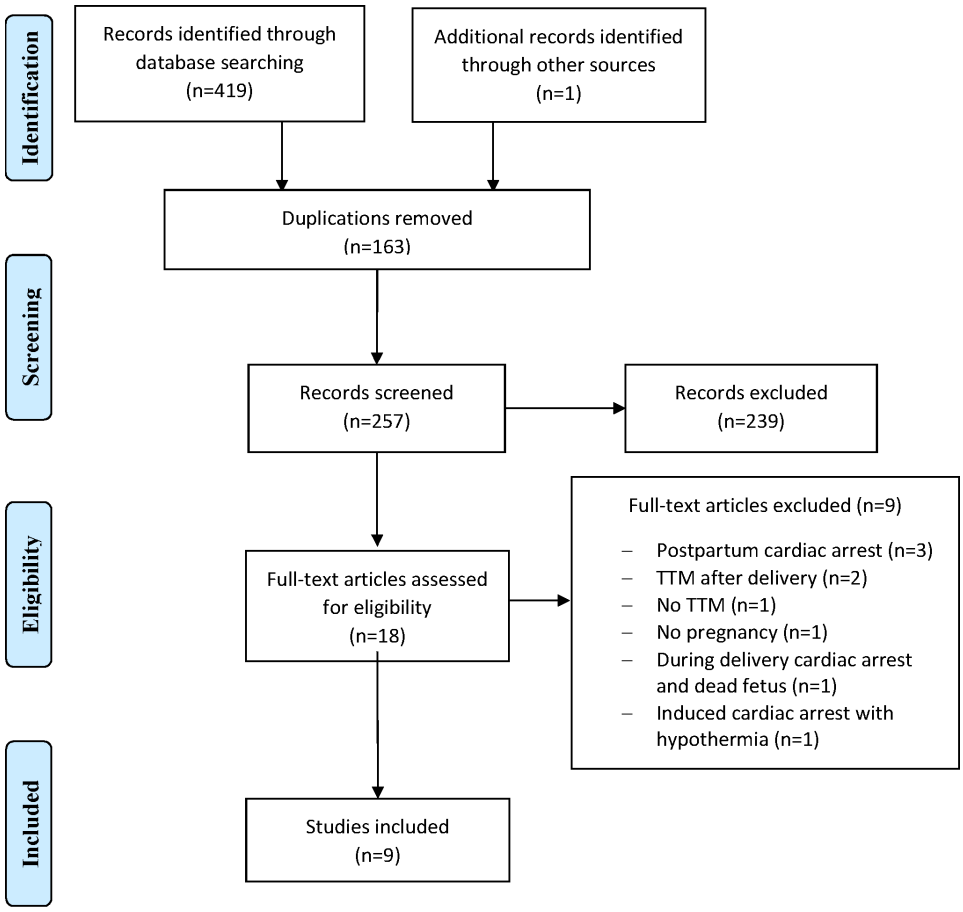

Figure 1: The flow diagram shows the study selection strategies according to PRISMA guidelines.

Table 2: Characteristics of the included studies

Reference	Year of publication	Study location	Maternal age (years)	Gestational age at cardiac arrest (weeks)	Gestational age at delivery (weeks)	Race	Maternal medical history	Risk of bias score
Rittenberger et al.[33]	2008	USA	35	13	39	NM	Hypertension	8
Wible et al.[34]	2010	USA	44	20	Fetal demise	NM	NM	8
Chauhan et al.[26]	2012	USA	33	20	39	White	Healthy	7
Oguayo et al.[32]	2015	USA	20	18	40	Black	Healthy	8
De Santis et al.[28]	2016	Italy	31	13	39	NM	Long QT syndrome	7
Oami et al.[31]	2018	Japan	37	23	Fetal demise	NM	Healthy	8
Hogg et al.[29]	2020	USA	28	Second trimester	39	Caucasian	Arrhythmia	4
McMillan et al.[30]	2020	USA	30	31.4	31.4 (3 days post-CPR)	NM	Substance abuse	8
Conrad et al.[27]	2021	USA	31	36	36 (36 hours post-CPR)	NM	Depression and palpitations	8

CPR: Cardiopulmonary resuscitation; NM: Not mentioned

Cause of Cardiac Arrest

The most common cause of cardiac arrest was ventricular fibrillation, occurring in 6 (66.6%) cases. Other causes included long QT syndrome type II with ventricular tachycardia (1 case, 11.1%), pulmonary embolism (1 case, 11.1%), and drug overdose (1 case, 11.1%) (table 3).

Actions Related to the Resuscitation and Induction of Hypothermia

Ventricular fibrillation was the initial electrocardiogram rhythm in 6 (66.6%) cases,

asystole in 1 (11.1%) case, and 2 (22.2%) cases were not reported (table 3). The median of the resuscitation time was 12 min (min=4, max=25 min). The median GCS of mothers after resuscitation was 3 (min=3, max=5).

For 6 (66.6%) mothers, the target hypothermia temperature was 33 °C to 34 °C within 24 hours. After that, gradual warming reached 36.5 °C to 37.5 °C during 24 hours. In 1 (11.1%) case, normothermia was maintained for 48 hours after hypothermia induction. In another case 1 (11.1%), the target temperature was 36 °C, initiated 12 hours after cardiac arrest and maintained for at least 3 days. One (11.1%) case involved a four-phase hypothermia protocol: (1) cooling to 33 °C within 4 hours, (2) maintaining 35 °C for 24 hours, (3) gradual rewarming in 16 hours, (4) maintaining 37 °C for 24 hours. The method of hypothermia induction was not reported in 1 (11.1%) case. The median time interval from cardiac arrest to the hypothermia induction was 2.5 hours (min=1, max=12 hours). The median duration of the maternal hospitalization was 10 days (min=6, max=42 days), and the median follow-up period was 9 months (min=2, max=36) (table 4).

Maternal Outcomes and Complications

Maternal survival was reported in 8 (88.8%) cases, while 1 (11.1%) case resulted in maternal death. Neurological outcomes were favorable, with 3 (33.3%) cases reporting no neurological deficits, and 5 (55.5%) cases reporting mild neurological deficits or memory loss related to cardiac events (table 5).

No complications during hypothermia were reported in 5 (55.5%) cases. In the remaining 4 (44.4%) cases, reported complications included decreased blood pressure and heart rate, persistent clonus, shivering, and hyperglycemia. Other maternal complications are detailed in table 6.

The deceased mother, with a gestational age of 31 weeks and four days, experienced cardiac arrest due to drug overdose and eclampsia. She gave birth on the 3rd day of hospitalization. While the baby survived, the mother passed away on the 6th day following organ donation due to post-anoxic myoclonus and diffuse brain damage. Hypothermia induction was initiated 12 hours after cardiac arrest, with a target temperature of 36 °C, which was maintained until the 3rd day. Maternal side effects during hypothermia included decreased blood pressure, heart rate, and SpO_2, along with stable clonus.

Fetus/Infant Outcomes and Complications

Live births were reported in 7 (77.7%) cases. Apgar scores at 1 min were 3 in 2 (22.2%) infants and 8 in 5 (55.5%) infants. At 5 min, Apgar scores were 4 in 2 (22.2%) infants and 9 in 5 (55.5%) infants. No neurological sequelae were reported in surviving infants (table 5). Fetal bradycardia was the most common complication occurring in 5 (55.5%) cases (table 6).

Fetal death was reported in 2 (22.2%) cases. A 23-week fetus died 10 days after cardiac arrest due to pulmonary embolism. The time interval between cardiac arrest and hypothermia induction was 2 hours.

Table 3: The clinical characteristics of pregnant patients related to cardiac arrest and resuscitation

Reference	Cause of cardiac arrest	Initial cardiac rhythm	OHCA or IHCA	Witnessed or unwitnessed cardiac arrest	Time from cardiac arrest to CPR initiation (min)	Duration of CPR (min)	Time from cardiac arrest to ROSC (min)
Rittenberger et al.[33]	Ventricular fibrillation due to coronary artery disease	Ventricular fibrillation	OHCA	Witnessed	0 (Immediate)	21	21
Wible et al.[34]	Ventricular fibrillation due to suspected cocaine-induced myocardial infarction	Ventricular fibrillation	OHCA	Witnessed	0 (Immediate)	NM	NM
Chauhan et al.[26]	Ventricular fibrillation due to peripartum cardiomyopathy	Ventricular fibrillation	OHCA	Witnessed	0 (Immediate)	25	25
Oguayo et al.[32]	Ventricular fibrillation	Ventricular fibrillation	OHCA	Witnessed	5	8	13
De Santis et al.[28]	Ventricular fibrillation	Ventricular fibrillation	OHCA	Witnessed	NM	NM	20
Oami et al.[31]	Pulmonary embolism	Asystole	IHCA	Witnessed	0 (Immediate)	4	4
Hogg et al.[29]	Long QT syndrome type 2 and ventricular tachycardia	NM	OHCA	Unwitnessed	NM	NM	NM
McMillan et al.[30]	Opioid overdose	NM	OHCA	Unwitnessed	NM	NM	NM
Conrad et al.[27]	Ventricular fibrillation and mitral valve prolapse	Ventricular fibrillation	OHCA	Witnessed	0 (Immediate)	12	12

CPR: Cardiopulmonary resuscitation; ROSC: Return of spontaneous circulation; OHCA: Out-of-hospital cardiac arrest; IHCA: In-Hospital Cardiac Arrest; NM: Not mentioned

Table 4: Post-resuscitation characteristics of pregnant patients and targeted temperature management

Reference	Maternal GCS after resuscitation	Time from cardiac arrest to cooling initiation (hours)	Hypothermia induction protocol	Hospitalization period of mothers (days)	Follow-up period (months)
Rittenberger et al.[33]	5	1	24 hours with a mean temperature of 33 °C, followed by gradual rewarming over the next 24 hours to 37.5 °C	6	2
Wible et al.[34]	5	6	24 hours with a temperature of 33 °C, followed by slow rewarming to 36.5 °C during 24 hours, and then, maintenance of normothermia with surface cooling for the next 48 hours	42	12
Chauhan et al.[26]	3	3	24 hours with a mean temperature of 33 °C, followed by gradual rewarming over the next 24 hours	10	36
Oguayo et al.[32]	3	3	24 hours with a mean temperature of 33 °C, followed by gradual rewarming over the next 24 hours to 37 °C	NM	NM
De Santis et al.[28]	3	2	24 hours with a mean temperature of 34 °C, followed by slow rewarming over the next 24 hours	NM	6
Oami et al.[31]	3	2	24 hours with a mean temperature of 34 °C, followed by slow rewarming over the next 24 hours	23	NM
Hogg et al.[29]	NM	NM	NM	NM	6
McMillan et al.[30]	NM	12	Hypothermia with a target temperature of 36 °C from 12 hours after arrest, continued until day 3 of hospitalization (duration not specified)	Mother deceased	12
Conrad et al.[27]	3	1	Phase 1: Cooling to 33 °C within 4 hours; Phase 2: Cooling to 35 °C for 24 hours; Phase 3: Gradual rewarming over 16 hours; Phase 4: Maintenance of 37 °C for 24 hours	9	NM

GCS: Glasgow coma scale; NM: Not mentioned

Table 5: The clinical outcomes of mother and fetus after targeted temperature management

Reference	Outcome of hypothermia in mother	Outcome of hypothermia in fetus/infant	Apgar (1 min)	Apgar (5 min)	Neurological outcomes in the mother	Neurological outcomes in infants
Rittenberger et al.[33]	Alive	Alive	8	9	Mild neurological impairment at the time of discharge (cerebral performance category 2)	Normal
Wible et al.[34]	Alive	Fetal demise (28 hours after cardiac arrest and during hypothermia)	Dead fetus	Dead fetus	Failure to recall hospitalization in 1 year following assessment	Dead fetus
Chauhan et al.[26]	Alive	Alive	8	9	Mild neurological deficit with retrograde memory loss from a few minutes before arrest to the first 2 days of hospitalization (post-anoxic encephalopathy)	Normal
Oguayo et al.[32]	Alive	Alive	8	9	Mild short-term memory loss	Normal
De Santis et al.[28]	Alive	Alive	8	9	Normal	Normal
Oami et al.[31]	Alive	Fetal demise (on day 10 due to hydrops)	Dead fetus	Dead fetus	Normal	Dead fetus
Hogg et al.[29]	Alive	Alive	8	9	Normal	Normal
McMillan et al.[30]	Mother deceased (organ donation)	Alive	3	4	Deceased mother	Normal
Conrad et al.[27]	Alive	Alive	3	4	Mild neurological deficit around the cardiac event	Normal

Table 6: Reported complications in mothers and fetus/infants

Reference	Complications reported during hypothermia in the mother	Complications reported during hypothermia in the fetus	Other complications reported in the mother	Other complications reported in fetus/infant
Rittenberger et al.[33]	Shivering (before muscle relaxant administration)	Fetal bradycardia (FHR: 90-100 bpm)	Decreased protein S activity	NM
Wible et al.[34]	Hyperglycemia	Fetal demise	Acute kidney failure, pulmonary edema, deep vein thrombosis, and heparin-induced thrombocytopenia	Fetal demise
Chauhan et al.[26]	NM	Fetal shivering and bradycardia (FHR: 90-100 bpm)	Pulmonary edema (before hypothermia induction)	NM
Oguayo et al.[32]	NM	NM	NM	NM
De Santis et al.[28]	NM	Fetal bradycardia (FHR: 90-100 bpm)	NM	NM
Oami et al.[31]	Hypotension (requiring dopamine to maintain SBP>100 mmHg)	Fetal bradycardia (requiring dopamine to maintain FHR>100 bpm)	NM	Fetal bradycardia (FHR 60 bpm) after the second dose of rtPA and before TTM initiation- Hydrops and fetal demise
Hogg et al.[29]	NM	NM	NM	NM
McMillan et al.[30]	Hypotension, bradycardia, and decreased SpO_2- Persistent clonus	Decreased FHR (105 bpm) with minimal variability	Hypoxic-ischemic encephalopathy, anaphylaxis, preeclampsia/ eclampsia, and hyperglycemia (before hypothermia induction)- post-anoxic myoclonus and diffuse brain injury leading to organ donation	NM
Conrad et al.[27]	NM	NM	NM	NM

SBP: Systolic blood pressure; FHR: Fetal heart rate; TTM: Targeted temperature management; NM: Not mentioned

The hypothermia protocol aimed to achieve a target temperature of 34 °C within 24 hours, followed by gradual rewarming. Fetal bradycardia occurred after the administration of the second thrombolytic dose and prior to the initiation of TTM. The fetus died on the 10th day due to hydrops.

The second case of fetal death occurred at a gestational age of 20 weeks. Cardiac arrest was caused by ventricular fibrillation following a heart attack and cocaine use. Hypothermia induction began 6 hours after cardiac arrest, with a protocol targeting a body temperature of 33 °C for 24 hours, followed by gradual rewarming over 24 hours to 36.5 °C, and then maintaining normothermia for 48 hours. The fetus died 28 hours after cardiac arrest, during the hypothermia phase.

Discussion

The findings of this study suggested that the TTM was not contraindicated during pregnancy and might be considered a treatment option for pregnant patients after cardiac arrest. However, its use should be individualized, with careful consideration of the risks and benefits for both the mother and the fetus, and implemented by a multidisciplinary team comprising an intensivist, cardiologist, gynecologist, and neurologist. Historically, pregnancy was considered a contraindication for hypothermia therapy in clinical trials. However, there is no evidence to support this exclusion.[35]

The maternal mortality rate in the present study was 11.1%. All survived mothers demonstrated favorable neurological outcomes by the end of the follow-up period. A favorable neurological outcome was defined as a cerebral performance category (CPC) score of 1 or 2, and according to the data reported in the selected articles, all surviving mothers achieved this outcome.[36] In comparison, the TTM2 trial reported that mortality rates following hypothermia therapy in non-pregnant patients ranged from 27% to 81.3% in RCTs, with favorable neurological outcomes ranging from 10.2% to 69%.[6] The improved survival rate in the present study might be attributed to the younger age and clinical characteristics of pregnant patients, such as initial shockable rhythm, witnessed cardiac arrest, immediate initiation of CPR, and relatively short CPR duration.

Only one maternal death was reported in this study. In this case, the baby survived, but the mother passed away on the 6th day of hospitalization following organ donation. The deceased mother had pre-existing

conditions, including hypoxic-ischemic encephalopathy, anaphylaxis, preeclampsia/eclampsia, and hyperglycemia. Hypothermia induction was initiated 12 hours after cardiac arrest, which might have been delayed. Despite this, care teams hypothesized that this method could protect the fetus and concluded that it remains a reasonable treatment option to consider during pregnancy.[30]

Among the complications reported during TTM, hypotension, and bradycardia were the most common in mothers. Hypothermia might exacerbate hypotension, which could be managed with inotropic or vasopressor drugs. Recent studies supported the use of phenylephrine as the vasopressors of choice during pregnancy, while dopamine and dobutamine were safely used for inotropic support in pregnant women.[6, 37, 38] Another complication reported during hypothermia induction was shivering, which reduced the rate of body temperature reduction due to increased heat generation and oxygen consumption. Repeated use of pethidine (meperidine) to control shivering could lead to significant fetal exposure and respiratory depression in newborns. Non-depolarizing neuromuscular blocking agents, such as vecuronium, are preferred to prevent shivering, as they have minimal placental transfer, and are less likely to cause fetal muscle weakness.[39]

The results of this study showed that most fetuses survived hypothermia therapy following maternal cardiac arrest. The survival rate of fetuses in the present study was 77.7%, and all surviving fetuses demonstrated normal neurological outcomes. A favorable neurological outcome was defined as a pediatric cerebral performance category (PCPC) score of 1 or 2. Although there is no long-term data on neonatal and childhood neurodevelopment, and there are some problems with using this scale in infants, fetuses appear to remain neurologically intact following therapeutic hypothermia.[40] In the cardiac arrest in pregnancy study (CAPS), the survival rate and favorable neurologic outcome following maternal cardiac arrest (without hypothermia therapy) were 79% and 84%, respectively. Although the survival rates were similar, the neurological outcomes of fetuses were better potentially due to the neuroprotective effect of hypothermia and a higher maternal survival rate (88.8% vs 58%). Maternal survival is the strongest predictor of fetal survival.[41, 42]

Prolonged hypothermia (72 hours) has been successfully used in infants with hypoxic encephalopathy.[43] Additionally, several studies have reported the safe use of hypothermia during pregnancy, in various clinical scenarios, including aortic repair, sepsis, hypermagnesemia, and cardiopulmonary bypass, with both maternal and fetal survival. However, fetal bradycardia during hypothermia was reported in some cases.[44-53]

In the present study, fetal bradycardia was the most common complication during hypothermia, occurring in 55.5% of cases. Therefore, fetal bradycardia is a potential adverse event associated with hypothermia and should be continuously monitored in pregnant patients undergoing hypothermia. Fetal bradycardia with a fetal heart rate (FHR) of ≥60 beats per minute (bpm) as reported in our study cases typically does not require intervention. However, an FHR of ≤55 bpm might necessitate preterm delivery and the use of drugs with positive chronotropic effects, such as isoproterenol. For fetal support, dobutamine might be preferred due to its beneficial effects on placental vascular resistance.[54, 55]

Two cases of fetal death were reported in the reviewed case reports. In one case, the mother was 23 weeks pregnant and experienced cardiac arrest due to pulmonary embolism. Fetal bradycardia developed after the administration of the second dose of thrombolytic therapy and before the initiation of TTM. The fetus died on the 10th day due to hydrops. In this case, the fetus showed signs of hydrops despite careful monitoring and management to maintain the FHR during TTM. Although it remains unclear whether thrombolytic treatment or TTM contributed to the development of hydrops fetalis, it is worth noting that TTM has been safely used in some cases of neonatal hypoxic-ischemic encephalopathy. In addition, no significant hemodynamic disturbances were observed during TTM in this case. Therefore, the harmful effects of cardiac arrest were most likely the primary cause of fetal hydrops. The researchers believed that maternal survival should be prioritized in such critical situations.[31, 56]

In the second case of fetal death, the gestational age at the time of cardiac arrest was 20 weeks, and the cardiac arrest was caused by ventricular fibrillation following heart attack and cocaine use. Fetal death occurred approximately 28 hours after cardiac arrest during hypothermic therapy. Factors such as cardiac arrest itself, prolonged spontaneous recirculation time, cocaine-induced vasoconstriction, and general myocardial hypokinesia, might have impaired uterine blood flow, contributing to fetal death. Therefore, the role of hypothermia in this case remained unclear.[34]

While the effects of hypothermic therapy on the fetus are not fully understood, in

life-threatening situations such as cardiac arrest, the priority is to save the mother's life. In these cases, hypothermic therapy might be used despite potential fetal risks, as it has been shown to reduce maternal mortality and neurological complications. Furthermore, therapeutic hypothermia might indirectly benefit the fetus by increasing the mother's chances of survival, which in turn might enhance fetal outcomes.[34, 57]

Maternal cardiac arrest leads to the cessation of uterine perfusion. However, the extent of fetal damage varies with the duration of nonperfusion. A longer duration of ROSC was associated with poorer outcomes for both the mother and fetus.[58] Notably, in 3 (33.3%) of the reviewed cases, resuscitation efforts lasted 20 min or longer, yet the mother and infant were discharged with favorable outcomes due to prompt resuscitation and early initiation of TTM.[26, 28, 33] The success of this approach depends on several factors, including timely therapeutic interventions, effective multidisciplinary coordination, and adequate infrastructure and resources.

There is a possibility of publication bias, as most studies reported the successful outcomes of hypothermia. Heterogeneity exists in the methods of hypothermia induction and outcome evaluation. However, the protocols for hypothermia in surviving mothers aligned with the AHA guidelines for non-pregnant patients.[7] In the case of the deceased mother, the protocol's consistency with AHA guidelines could not be confirmed due to unspecified hypothermia duration. Therefore, it is reasonable to follow the same TTM protocol for pregnant patients as for non-pregnant patients.

Although the neurological outcomes in surviving mothers and fetuses were appropriate, there was heterogeneity in how these outcomes were evaluated and reported across studies, as well as in follow-up durations. This could be due to the lack of appropriate assessment scales in most reports. Future studies should use scales such as the Adult/Pediatric Cerebral Performance Category to ensure consistency.[36, 40]

The most important strength of this study was its use of the systematic review method to synthesize findings from all primary studies. However, considering the limited number of primary studies, variability in hypothermia management methods, and differences in outcome evaluation for pregnant women with cardiac arrest, there is still insufficient evidence regarding the implementation of this method in pregnant women and its associated complications. As a result, the generalization of these findings should be made with caution. Some studies lacked detailed information, and attempts to contact the authors for clarification were unsuccessful. Although the risk of bias was low in 88.8% of the selected articles, according to the JBI checklist, the overall quality of the evidence was limited. Future studies are necessary to evaluate the positive and negative effects of using TTM during pregnancy on both mothers and fetuses. Additionally, research should investigate the long-term effects of hypothermia on a child's development and outcomes.

Conclusion

Pregnancy does not appear to be a contraindication for TTM. With prudent clinical judgment, TTM could be safely implemented in pregnant patients following cardiac arrest. In clinical practice, it is recommended to adhere to the AHA guidelines for TTM in non-pregnant patients, while tailoring treatment to individual cases and employing a multidisciplinary team approach. Additionally, continuous fetal monitoring, including regular ultrasound assessments and cardiotocography, is essential during TTM to ensure fetal well-being.

In this study, the majority of mothers and fetuses survived and were discharged with favorable neurological outcomes following successful resuscitation and the application of hypothermia. However, the evidence remains limited due to the case-report nature of the included studies, resulting in low-quality evidence. Future research should incorporate standardized neurological outcome evaluation scales to better understand the maternal and fetal complications associated with TTM and to establish evidence-based best practices for its use in pregnancy.

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Authors' Contribution

All authors were involved in the study's concept, design, data acquisition, interpretation, analysis, and manuscript drafting and reviewing, either fully or partially. They have read and approved the final manuscript and agree to be accountable for all aspects of the work, ensuring

that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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