Standardized Management of the First Hour of Premature Infants: A Meta-Analysis

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abstract

CONTEXT: The postnatal management of preterm infants at birth may influence their clinical course in the short, medium, and long term. The concept of the "Golden Hour" (GH) has emerged in neonatology, aiming to standardize this management.

OBJECTIVE: We conducted a meta-analysis to assess GH's impact on early clinical outcomes and on the comorbidities of prematurity.

DATA SOURCES: Pubmed, Embase, Scopus, and Cochrane Library were searched without any restriction.

STUDY SELECTION: We included randomized, prospective, and retrospective studies comparing periods with and without the application of a GH protocol for preterm birth.

DATA EXTRACTION: Two independent reviewers screened titles and abstracts and assessed full texts for eligibility.

RESULTS: Twelve prospective and 6 retrospective studies were included, for a total of 5104 patients. There was a significant reduction in hypothermia both on admission and at 1 hour (odds ratio [OR], 0.40 [95% CI, 0.27–0.60] and OR 0.39 [95% CI, 0.18–0.85]), with increased temperature (mean difference [MD], +0.57 °C [95% CI, 0.07–1.07]). Mean blood glucose and hypoglycemia rates on admission were not statistically affected. However, time to intravenous infusion was reduced (MD, −27.51 minutes [95% CI, −49.40 to −5.56]). There was a significantly lower rate of severe intraventricular hemorrhage (OR, 0.65 [95% CI, 0.47–0.89]) and a trend toward decreased bronchopulmonary dysplasia (OR, 0.69 [95% CI, 0.47–1.02]). Time to administration of surfactant was statistically reduced (MD, −23.6 minutes [95% CI, −42.2 to −5]). Mortality and other comorbidities of prematurity were not different.

LIMITATIONS: Four studies were judged to be of poor quality, and certainty for evidence was graded as low or very low.

CONCLUSIONS: The application of a GH at birth reduced the rate of hypothermia and the time required for intravenous infusion without statistically significant impact on glycemic control.

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Dr Tribolet conceptualized and designed the search strategy, data selection, and analysis and drafted and revised the manuscript. Dr Dénes contributed to the search strategy, data selection, and analysis. Dr Rigo contributed to data interpretation, writing, and editing the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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INTRODUCTION

The postnatal management of preterm infants at birth has significant impact on short-, medium-, and long-term outcomes. Stabilizing preterm infants right after birth is a complex process,[1,2] given the challenges of adapting to the extrauterine environment, including respiratory, circulatory, and thermal transitions as well as the sudden interruption of nutrient supply from the placenta. During their first hour of life, preterm infants are at heightened risk of hypothermia,[1,3] hypoglycemia,[4] and infection.

In adult intensive care, consistency in management is a quality indicator and has enhanced patient safety.[5,6] However, the impact of such consistency in management of resuscitation at birth remains uncertain. In recent years, the concept of the "Golden Hour" (GH) has emerged in neonatology, aiming to standardize the management of the first hour of life of preterm infants and focusing on evidence-based stabilization approaches.

The key elements of these protocols include anticipation and effective communication mainly to prevent hypothermia and hypoglycemia. A recent international survey highlighted great diversity of practices for neonatal GH procedures. Local protocols for small infants were implemented in 78% of units resuscitating preterm from 22 to 23 weeks of gestation (wGA) and in 69% units starting at 24 to 25 wGA. Thermoregulation protocols were available in 91% and 89% of cases, respectively.[7]

The first aim of this systematic review is to identify specific components of GH protocols for management of preterm infants at birth.

Secondary, this meta-analysis aims to evaluate the impact of GH protocols on the immediate clinical course and on the comorbidities of prematurity.

METHODS

Research Protocol

The systematic review and meta-analysis were conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for meta-analysis in health care interventions.[8] The protocol was registered with the Prospective Register of Systematic Reviews (registered December 20, 2021; CRD42021292379).

Criteria of Eligibility

Studies evaluating a protocol for the management of premature infants during their first hour of life, compared with standard care, were deemed eligible. Randomized control trials (RCTs) and prospective and retrospective cohorts were included. The latter 2 designs were included because RCTs are deemed less efficient to study interventions involving complex behavioral aspects. If a study reported several groups of "GH protocol patients" compared with baseline, only the last one was included in the meta-analysis. Mannikin studies and case reports were excluded.

Search Strategy

Medline via Ovid, Embase, Scopus, and Cochrane Library of Trials were searched between inception and August 7, 2023 without language restriction, filter, or limit. The search included Mesh/Emtree terms and free language. Search strategies are available in online supplementary material (eFigure 1). References from publications eligible for full-text review and systematic reviews allowed for an additional "snowball search."

Study Selection

Rayyan QCRI web app was used for a 2-step study selection. After exclusion of duplicates, 2 independent reviewers screened titles and abstracts for potentially relevant studies.

Full texts were then independently assessed for eligibility. Conflicts at any step of the selection process were resolved through discussion with a third reviewer.

OUTCOMES

To evaluate the implemented management strategies, we extracted the method practices from each study to determine the objectives and means to achieve GH.

Time to close the incubator, as a proxy for admission completion, was the main procedural outcome.

Mortality, occurrence of hypoglycemia (within 1 hour and 24 hours), and hypothermia (temperature on admission and within 1 hour) were selected as the main clinical outcomes, with the thresholds for hypoglycemia and hypothermia being specific to the included studies.

Time to secure intravenous (IV) access was evaluated as a secondary procedural outcome.

Markers of cardiorespiratory stability (incidence of desaturation or bradycardia, hypotension, intubation rate, surfactant requirement) during the procedure were assessed as secondary clinical outcomes. Comorbidities commonly associated with very preterm birth (patent ductus arteriosus [PDA] requiring surgery, bronchopulmonary dysplasia [BPD; all grades (need for oxygen at 28th day of life) and severe (need for supplemental oxygen ≥30% or positive pressure at 36 weeks' postmenstrual age [PMA] or discharge)], severe intraventricular hemorrhage [IVH], cystic periventricular leukomalacia [cPVL], severe retinopathy of prematurity [ROP; requiring treatment], and necrotizing enterocolitis [NEC; Bell stage 2 or 3]) were evaluated.

Data Extraction and Analysis

Data were independently extracted on a prespecified form by 2 reviewers and discussed with a third when discordant. Authors were contacted to provide additional data for

unreported information. Review Manager software (RevMan 5.4; The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data analyses.

Given the heterogeneity of study designs and GH protocols, we calculated odds ratios (ORs) and 95% CI with a random-effect model because it allows for generalization inference.[9]

For continuous outcomes, mean differences (MDs) and 95% CI were computed. When data were communicated in median and IQR, means and SD were mathematically estimated.[10,11]

Numbers needed to treat were computed for statistically significant results.[12]

Heterogeneity was assessed with I^2 statistic. In case of high heterogeneity, we considered exploring explanatory factors with subgroup analyses according to study settings, gestational age (GA) strata, or study quality.

Bias, Quality, and Grading of Recommendations, Assessment, Development, and Evaluation Assessment

Two independent authors evaluated risks of bias (RoB) and assessed quality in individual studies using the Revised Cochrane Risk-of-Bias for randomized trials (RoB2) or the Newcastle-Ottawa Scale (NOS) for cohort studies with a rating of studies ranging from "poor quality" to "good quality" as detailed in eFigure 2.[13] For cohort studies, quality of selection, comparability, and outcomes were evaluated.

All studies were to be included regardless of their quality.

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method[14] was used to assess the strength of evidence across studies for outcomes with significant difference. The importance of each outcome was assigned consistently with the International Liaison Committee on Resuscitation (ILCOR) rating when available.[15]

RESULTS

Literature Search and Study Selection

The search strategy identified 834 records, 227 of which were duplicates. Screening of 607 titles and abstracts led to the selection of 49 articles. Among these, 18 studies met the inclusion criteria (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart, Figure 1—exclusion criteria details in eTable 1).

Study Characteristics

Studies' characteristics are summarized in Table 1.

No RCT was found. All included studies were cohort studies: 12 prospective studies[16–27] and 6 retrospective studies.[28–33] The comparative arm was prospective in Lambeth et al and Herath et al[18,19] and retrospective in 16 other studies.[16,17,20–33] Two studies targeted specific outcomes: Dylag et al evaluated the reduction in BPD[26] while Chiriboga et al focused on IVH.[23] One study was multicentric.[33]

Patient Characteristics

Patient's characteristics are described in Table 2.

In total, 5104 newborns were included. Studies recruited between 24 and 868 infants. Four studies focused on extremely preterm infants,[16,22,24,30] 2 focused on preterm infants younger than 29 wGA,[17,29] and 1 focused on infants younger than 30 wGA.[23] Eight studies included infants younger than 32 wGA or with a birth weight (BW) of 1500 g or less.[18,19,21,25–28,33] Two extended inclusions to age less than 33 wGA[20,32] and 1 to age less than 35 wGA.[31]

In most studies, groups were matched in terms of GA, BW, and sex.[16–21,23,24,26–30,32] Dixon et al reported a significant difference in mean BW ($P = .03$) and a difference in GA ($P = .06$) between groups,[25] while both median BW and GA differed in Hemingway et al.[33] The study populations were not described in 2 studies.[20,31]

RoB and GRADE Assessment

The quality of 14 studies was evaluated as good according to the NOS criteria. Four studies were judged to be of poor quality given insufficient study population description in 2 studies,[20,31] and, in 2 others, differences between groups reduced their comparability.[25,33]

Assessments are summarized in eFigure 2.

Certainty of evidence was graded as low for time to completion and as very low for occurrence of hypothermia and hypoglycemia at admission, mortality, BPD, IVH, and time to surfactant administration (eFigure 3).

Outcome Analysis

Review of Practices

The interventions in each study are summarized in Table 3.

In most studies, a multidisciplinary team designed a GH protocol[16–18,21,23–29,33] sometime after a review of their process outcomes.[18,20,21,23–28,30–32] Simulation trainings were performed to implement protocols.[16,17,19–21,24,25,28]

Maternal history was reviewed,[17,21,25,29,30] and special considerations for each infant were anticipated.[29,30] Resuscitation equipment was verified prior to birth,[16–21,23–26,28,30,32] mostly with checklists.[16,18–23,27] Some studies designed carts with specific materials for GH protocols. Nine included setting up incubator, IV pumps, and ventilator.[16,17,19,24–26,29,30,32]

Communication was emphasized through assignation of specific team roles and responsibilities[16,17,19–30] and reinforced with posters and checklists.[16,23–26,28,30]

Multiples studies emphasized the importance of team debriefing.[17,19,28,30,31] Family inclusion was also supported by most studies.[16–18,21,25,30]

To prevent hypothermia, several interventions have been implemented: maintaining delivery room (DR) temperature

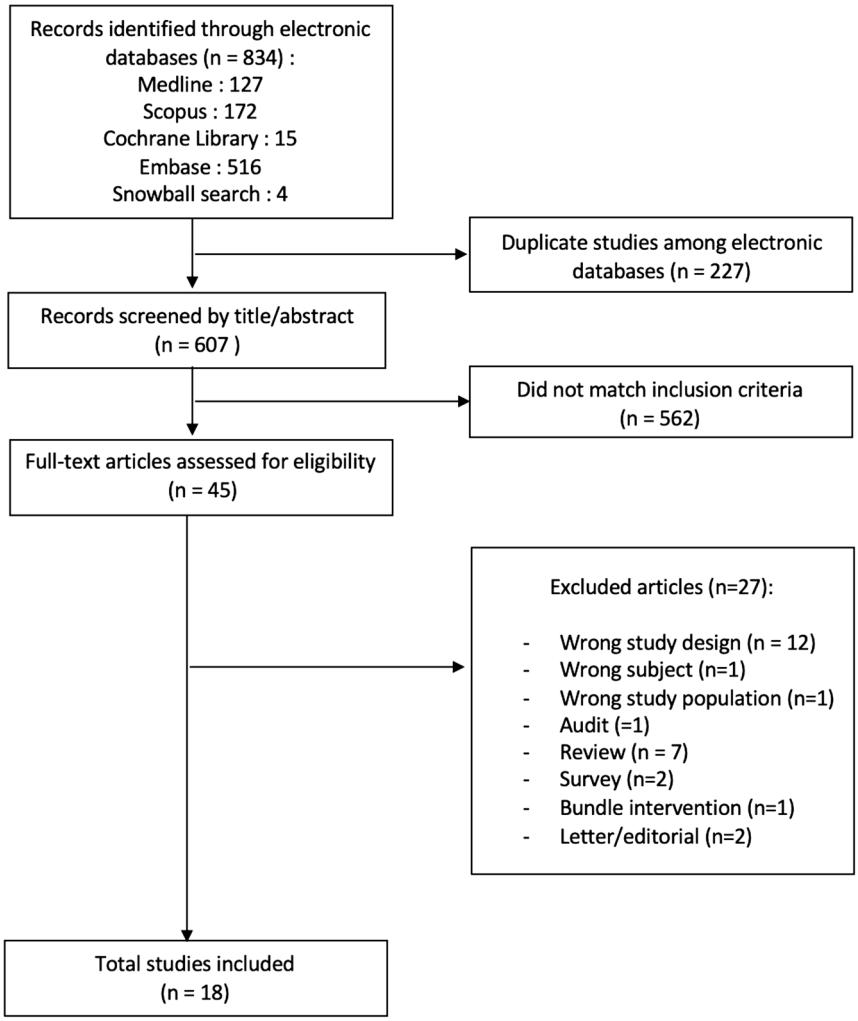

FIGURE 1.
PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

between 26 and 28 °C,[16,17,19–21,23–26,28–32] use of radiant warmers,[16,17,21,24–26,28–32] chemical warming devices,[16,21,24,28–30] thermal mattress,[17,20,23–26,28,31] warm and humidified ventilation gases,[30,31] polyethylene bags[16–21,23–31] or warm blankets[19–21,25,28,31] and hat.[16–18,20,24,25,28,30,31] Infants were transported in a prewarmed incubator[16,17,19,20,24,28,31,32] or a thermal mattress.[26] On neonatal intensive care unit (NICU) admission, a preheated incubator[16,19,20,28,31] or a radiant warmer[17,18] was used. Early temperature measurement was considered crucial.[17–19,21,23,25,26,28,29,32]

In 7 studies, electrocardiogram leads were applied in DR.[17,21,24,25,28–30]

In most cases, fraction of inspired oxygen was adjusted according to pulse oximetry[16–18,20,21,25,26,28,30,31] with oxygen titration[16–18,20,21,24–26,28,30] starting from different levels. Twelve studies used a T-piece resuscitator for positive pressure ventilation.[16–21,23–26,28,29,32] Intubation was systematic for extremely preterm infants in 6 studies.[16,19,24,26,29] Some studies required prophylactic surfactant administration,[16,18,19,24,26,28,29] while others used it as a rescue treatment.[17,20,26,30] Three studies included an early loading dose of caffeine.[24,26,29]

Nine studies anticipated infusion fluids and parental nutrition (PN).[16,17,19,25–27,29,30,32] Umbilical veinous catheter (UVC) was rapidly placed.[16–21,23–26,29,30,32] Peripheral venous access was initiated in 6 studies pending central venous access (CVA)[19,21,24,25,31,32] or if CVA was not established within 25 minutes of life.[17,18,26] Ten studies initially infused dextrose 10%.[16,17,19,21,24–27,30,31] Early PN was initiated in some studies[18,20,29] or pending radiograph confirmation of UVC position.[21,24,25,31] Most studies stressed early blood glucose measurement.[17–21,24,25,27,31]

Delayed cord clamping (DCC) was recommended by 5 studies.[23,24,26,27,30] Two studies suggested using cord blood for initial laboratory workup as a blood-sparing

TABLE 1. Characteristics of Included Studies

Author, Year, Country	Study Design	Multi- or Single-Center	Comparative Arm	Inclusion Criteria	Outcomes
Vergales et al[16] 2015 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Infants <27 wGA	- clinical outcomes: IVH, BPD - normothermia at admission - time to admission - MBP - length of stay: PMA at discharge - survival/death - composition and experience of the team - satisfaction of the staff (DR and NICU admission)
Ashmeade et al[17] 2016 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants ≦28 wGA or BW ≦1000 g	- time to surfactant administration - time to dextrose then amino acid infusions - blood glucose on admission - temperature on admission - chronic lung disease, ROP, NEC, IVH, late-onset sepsis, death
Lambeth et al[18] 2016 US	Prospective cohort	Single	Prospective cohort (without protocol)	Inborn infants <1500 g	- temperature on admission - blood glucose on admission - time to IV fluids and antibiotics - proportion of infants receiving surfactant within 2 h after birth
Herath et al[19] 2016 Sri Lanka	Prospective cohort	Single	Prospective cohort (without protocol)	Infants <32 wGA	- resuscitation and respiratory support: availability of prechecked equipment, attendance of senior medical staff, adherence to NLS guidelines, SpO_2 >85% at 10 min of life - temperature on admission, warming methods - glycemia >2.6 mmol/L at 1 h of life - administration of IV fluids, antibiotics, vitamin K within 1 h - admission completed within 60 min
Peleg et al[20] 2018 Israel	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants ≦$32^{6/7}$ wGA Exclusion criteria: - major congenital malformations - infants not treated in the dedicated area	- temperature on admission - first blood glucose - blood transfusion within 72 h of life - respiratory distress syndrome, mechanical ventilation, BPD, postnatal steroid - late-onset sepsis - IVH, cPVL, NEC - death
Harriman et al[21] 2018 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <32 wGA	- axillary temperature on admission and at 1 h of life - time to IV fluids - time to antibiotics - time to incubator closure
Habib et al[22] 2018 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Extremely preterm infants	- time to normothermia - time to antibiotics - time to IV fluids - death
Chiriboga et al[23] 2019 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <30 wGA Exclusion criteria: - outborn infants - congenital anomalies - extremely preterm infants not actively resuscitated - death before ultrasonography cranial screening	- mortality - severe IVH - BPD, NEC, RDS - need for surfactant - admission temperature - time to admission - glucose concentration

(Continued on next page)

TABLE 1. Characteristics of Included Studies (Continued)

Author, Year, Country	Study Design	Multi- or Single-Center	Comparative Arm	Inclusion Criteria	Outcomes
Croop et al[24] 2020 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <27 wGA	- axillary temperature on admission to the NICU - hypoglycemia (<45 mg/dL) on admission - completion of admission stabilization - adherence to the intended interventions - IVH grade 3 or 4, BPD, ROP - length of stay - death, death, or BPD
Dixon et al[25] 2020 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <32 wGA or <1500 g	- normothermia on admission and within 1 h - adherence with the use of increased temperature in DR - adherence with the use of polyethylene bags and thermal mattresses
Dylag et al[26] 2021 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <30 wGA or <1500 g	- BPD - adherence with DR surfactant - adherence with extubation guidelines
Welch et al[27] 2023 US	Prospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <32 wGA	- time to infusion, antibiotics, and incubator closure - hypothermia on admission and at 1 h - hypoglycemia on admission and at 1 h
Reynolds et al[28] 2009 US	Retrospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <32 wGA or BW <1500 g	- temperature on admission
Reuter et al[29] 2014 US	Retrospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <29 wGA or BW <1000 g	- BPD, IVH - time to intubation, surfactant, umbilical line placement, NICU admission - death - cPVL, PDA, NEC - duration of invasive and noninvasive ventilation - minimal temperature during resuscitation
Castrodale et al[30] 2014 US	Retrospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <28 wGA	- axillary temperature on admission - admission glycemia - time to UVC and UAC - time to glucose and amino acid infusion
Herranz et al[31] 2018 Spain	Retrospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <35 wGA	- temperature on admission
Jeong et al[32] 2022 Korea	Retrospective cohort	Single	Retrospective cohort (without protocol)	Inborn infants <33 wGA Exclusion: - congenital malformations	- time to admission, respiratory support, peripheral access, catheter insertion, antibiotics, and incubator closure - hypothermia on admission and at 1 h - hypoglycemia on admission and at 1 h - CRP 1 wk after admission - cPVL, PDA, NEC, sepsis, IVH grade 3 or 4, BPD, ROP, death
Hemingway et al[33] 2023 US	Retrospective cohort	Multiple	Retrospective cohort (without protocol)	Inborn infants <32 wGA	- surfactant administration and timing - temperature on admission - glycemia - need for vasopressors - comorbidities: IVH, NEC, BPD, ROP - length of stay

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; cPVL, cystic periventricular leukomalacia; CRP, C-reactive protein; DR, delivery room; IV, intravenous; IVH, intraventricular hemorrhage; MBP, mean blood pressure; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NLS, newborn life support; PDA, patent ductus arteriosus; PMA, postmenstrual age; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; SpO_2, pulsed capillary oxygen saturation; UAC, umbilical arteriosus catheter; UVC, umbilical veinous catheter; wGA, wk of gestational age.

TABLE 2. Patient's Characteristics of Included Studies

Author	Number of Participants	Gestational Age (Mean ± SD) or (Median [Range] or [P25–P75]), wk	Birth Weight (Mean ± SD) or (Median [Range] or [P25–P75]), g	Male Sex, n (%)	Cesarean Delivery, n (%)	Apgar Score at 5 min (Mean ± SD or Median [Range] or [P25–P75])
Vergales et al[16]	I: 90 C: 62	I: 24.9 ± 1.1 C: 25.1 ± 1.1 *P* = .37	I: 746 ± 185 C: 745 ± 165 *P* = .95	I: 48 (55) C: 34 (55) *P* = .87	I: 48 (53) C: 38 (61) *P* = .40	I: 6.5 ± 1.9 C: 6.4 ± 2.1 *P* = .7
Ashmeade et al[17]	I: 122 C: 173	I: NR C: NR *P* = .712	I: 840 ± 252 C: 834 ± 217 *P* = .848	I: 60 (50) C: 77 (45)	I: 84 (69) C: 122 (71)	I: 7 (1–9) C: 7 (2–9) *P* = .044
Lambeth et al[18]	I: 105 C: 50	I: 26.2 ± 1.2 C: 26.5 ± 4.2 *P* = .931	I: 985 ± 276 C: 1040 ± 566 *P* = .913	I: 54 (51) C: 26 (52) *P* = .947	NR	NR
Herath et al[19]	I: 64 C: 58	I: 30.0 ± 1.8 C: 29.9 ± NR *P* = .708	I: 1190 ± 232 C: 1168 ± 251 *P* = .627	I (n = 61): 31 (51) C: 38 (48) *P* = .239	I: 24 (37.5) C: 16 (27.6) *P* = .244	NR
Peleg et al[20]	I: 194 C: 194	I: 30.2 (24–32.6) C: 30.2 (24.2–32.6) *P* = .834	I: 1326 (380–2538) C: 1334 (500–2177) *P* = .478	NR	NR	NR
Harriman et al[21]	I: 7 C: 17	I: 29.1 ± 2.8 C: 29.1 ± 2.6 *P* = .96	I: 1309 ± 448 C: 1130 ± 393 *P* = .34	I: 3 (43) C: 9 (53) *P* = .99	NR	NR
Habib et al[22]	NR	NR	NR	NR	NR	NR
Chiriboga et al[23]	I: 281 C: 117	I: 27 (25–28) C: 27 (25–28) *P* = .34	I: 910 (760–1130) C: 880 (732–1040) *P* = .08	I: 144 (51) C: 56 (48) *P* = .54	NR	NR
Croop et al[24]	I: 92 C: 80	I: 25 (23–26) C: 25 (24–26) *P* = .44	I: 670 (580–805) C: 705 (607–854) *P* = .13	I: 20 (48) C: 42 (52) *P* = .66	I: 57 (62) C: 53 (66) *P* = .56	I: 6 (3–7) C: 5 (3–7) *P* = .56
Dixon et al[25]	I: 13 C: 54	I: 30.3 ± 1.3 C: 29.3 ± 2.5 *P* = .06	I: 1512 ± 420 C: 1234 ± 409 *P* = .032	I: 7 (54) C: 31 (57) *P* = .99	NR	NR
Dylag et al[26]	I: 466 C: 322	GA <30 wk: I: 65.5% C: 63.7% *P* = .61	NR	I: 223 (47.9%) C: 172 (53.4%) *P* = .12	NR	NR
Welch et al[27]	I: 314 C: 181	I: 28.4 C: 28.2 *P* > .05	NR	I: 168 (53) C: 87 (48) *P* > .05	I: 235 (75) C: 131 (72) *P* > .05	NR
Reynolds et al[28]	I: 103 C: 245	I: 27.5 ± ? C: 27.5 ± 2.4 *P* = NR	I: 1022 ± 382 C: 989 ± 287 *P* = NR	NR	NR	NR
Reuter et al[29]	I: 40 C: 32	I: 25.7 (24.7–27.4) C: 26 (24.6–27.4) *P* = .489	I: 875 (690–1080) C: 857 (649–1148) *P* = .414	I: 19 (48) C: 15 (47) *P* = 1	NR	I: 7 (5–7) C: 7 (6–8) *P* = .114
Castrodale et al[30]	I: 119 C: 106	I: 26 (IQR 2) C: 26 (IQR 3) *P* = .338	I: 830 (IQR 299) C: 778 (IQR 300) *P* = .187	NR	NR	NR
Herranz et al[31]	I: 438 C: 430	NR	NR	NR	NR	NR
Jeong et al[32]	I: 117 C: 81	I: 28.5 C: 28.3 Ranges with *P* = .77 – .953 and .751	Ranges with *P* = .94 – .956 – .967 and .853	I: 69 (59) C: 40 (49) *P* = .183	I: 89 (76) C: 54 (67) *P* = .197	NR
Hemingway et al[33]	I: 158 C: 179	I: 29 (27–31) C: 28 (26–30) *P* = .03	I: 1350 (1060–1630) C: 1120 (800–1510) *P* = .0006	I: 87 (55) C: 75 (42) *P* = .01	I: 109 (69) C: 132 (74) *P* = .39	I: 8 C: 8 *P* = .2

Abbreviations: C, control; I, intervention; GA, gestational age; NR, not reported; P25, 25th percentile; P75, 75th percentile.

strategy.[20,24] Four studies included vitamin K administration in their protocol.[17–19,21]

Twelve studies advocated for early antibiotic administration.[17–22,24–26,29,30,32]

Meta-analysis

The results of the meta-analysis are detailed below and summarized in Figures 2 and 3. All forest plots and subgroup analyses are available in supplemental material (eFigures 4, 5 and 6).

Times to procedure completion were reported in 2 studies, with a significant improvement in admission care completion within 1 hour of life (OR, 2.35 [95% CI, 1.38–3.98]).[19,32]

Reported in 8 studies, mortality rates did not appear to be influenced by GH protocols (OR, 0.80 [95% CI, 0.50–1.28] – $I^2 = 56\%$).[16,17,20,23,24,29,32,33]

Hypoglycemia

There was no difference in mean glycemia on admission in 4 studies[17,23,30,33] (MD, –0.16 mg/dL [95% CI, –4.16 to 3.84]). In 6 other studies, rates of hypoglycemia (<40 mg/dL,[17,18] <45 mg/dL,[21,24,30] or <50 mg/dL[28]) were not statistically different, but we observed a trend toward reduction (OR, 0.59 [95% CI 0.33–1.07]).[19,20,24,27,30,32] Heterogeneities were high for both outcomes. No additional data on the evolution of glycemia during the first day were reported.

Hypothermia

Occurrences of hypothermia (defined as temperature <36.5 °C in most studies and <36.0 °C in the last two[15,16]) both on admission and at 1 hour were significantly reduced (OR, 0.40 [95% CI, 0.27–0.60][16,17,19,24,27,30–32] and OR, 0.39 [95% CI, 0.18–0.85],[21,25,32] respectively) with different heterogeneity ($I^2 = 76\%$ and 0%). Mean temperatures on admission improved (MD +0.57 °C [95% CI, 0.07–1.07] – $I^2 = 99\%$).[23,28,30,31,33]

Secondary Outcomes

The time to obtain IV access evaluated per se or according to IV infusion start was statistically shorter in the GH groups (MD −27.51 minutes [95% CI, −49.4 to −5.56]).[17,21,29,32] Achievement of IV access within the first hour was more frequent (OR, 12.77 [95% CI, 8.33–19.57]).[19,27,30]

Cardiorespiratory stability during the procedure was difficult to assess given the diversity of protocols, with variable practices of prophylactic intubation and surfactant administration.

The incidence of desaturation or bradycardia was not reported. Hypotension reported in Vergales et al only was reduced (OR, 0.42 [95% CI, 0.21–0.85] – $P = .02$).[16]

When not mandated in procedures, intubation rates[20,29] and surfactant needs[23,24] did not statistically differ between groups (OR, 0.84 [95% CI, 0.58–1.22] and OR, 0.82 [95% CI, 0.35–1.96], respectively). Time to surfactant administration was significantly decreased (MD −23.6 minutes [95% CI, −42.2 to −5]).[17,29,33] Although not a predefined outcome, time to antibiotic administration was also reduced in most studies (MD between 14.6 and 97.5 minutes).[18,19,21,27,32]

Severe IVHs were significatively reduced in GH groups (OR, 0.65 [95% CI, 0.47–0.89]) with a low heterogeneity ($I^2 = 14\%$).[16,17,20,23,24,29,32,33] Trends were found for reductions in both all grades of BPD (OR, 0.69 [95% CI, 0.47–1.02])[16,17,20,23,24,26,29,32,33] and severe BPD (OR, 0.58 [95% CI, 0.33–1.02]).[16,20,21,31] Severe ROP,[17,24,32,33] NEC,[17,20,23,29,32,33] sepsis,[17,20,32] PDA,[29,32] and cPVL[20,29,32] did not differ between groups (OR, 0.58 [95% CI, 0.20–2.01]; OR, 0.95 [95% CI, 0.65–1.38]; OR, 0.69 [95% CI, 0.36–1.32]; OR, 0.95 [95% CI, 0.50–1.83]; and OR, 0.90 [95% CI, 0.35–2.30], respectively).

Subgroups Analysis (eFigure 5 and 6)

When focusing on study design, we found no difference between prospective and retrospective studies except for time to surfactant administration ($I^2 = 92\%$).

Subgroup analysis according to the quality of study only revealed a high heterogeneity between groups for the outcomes "hypothermia on admission" ($I^2 = 96\%$) and "mortality" ($I^2 = 82.5\%$). Excluding studies of poor quality from the analysis led to results similar to those of the overall analysis.

To perform subgroup analysis by GA stratum, we stratified studies according to inclusion criteria: less than 28 wGA, less than 32 wGA, and less than 35 wGA. For the outcome "mean temperature on admission," differences between groups were high ($I^2 = 94\%$), with more improvement for studies including older GAs.

Hypoglycemia on admission was affected by GA ($I^2 = 88\%$), with variable ORs.

Mortality also appeared to be influenced by GA ($I^2 = 62\%$), with the OR in favor of controls in less than 28 wGA (OR, 1.71 [95% CI, 0.92–3.19]), in contrast to less than 32 wGA (OR, 0.63 [95% CI, 0.33–1.21]). BPD analysis gave results with similar discrepancies (OR, 1.22 [95% CI, 0.76–1.97] in <28 wGA; OR, 0.64 [95% CI, 0.39–1.04] in <32 wGA; and OR, 0.68 [95% CI, 0.47–0.99] in <35 wGA), as did severe BPD and severe ROP.

DISCUSSION

This meta-analysis of 18 studies, consisting of 5104 newborns, highlights the benefits of GH procedures on thermoregulation, early start of fluid administration with a trend to lower rates of hypoglycemia, and important comorbidities of prematurity, including severe IVH and potentially BPD, although with low or very low quality of evidence. No difference in mortality was found.

Only 2 studies reported the incubator closing time, with a significant reduction in stabilization time, suggesting an improved and more efficient workflow during admission.

TABLE 3. Management Strategies Implemented

	Golden Hour Procedure	Vergales[16]	Ashmeade[17]	Lambeth[18]	Herath[19]	Peleg[20]	Harriman[21]	Chiriboga[23]	Croop[24]	Dixon[25]	Reynolds[28]	Habib[22]	Dylag[26]	Jeong[32]	Welch[27]	Reuter[29]	Castrodale[30]	Herranz[31]	Hemmingway[33]
	Creation of a multidisciplinary team	x	x	x			x	x	x	x	x		x		x	x			x
	Review of literature		x	x	x	x	x	x	x	x	x		x		x				
	Review of department's results			x		x	x	x	x	x	x		x	x	x		x	x	
	Presurvey of member knowledge	x							x	x									
	Discussion with radiology staff			x			x		x			x							
	Creation of a dedicated DR					x										x			
	Education of members	x	x	x	x	x	x		x	x	x	x	x						
	Training by simulation	x	x		x	x	x		x	x	x								
	Training of UVC placement			x															
Anticipation	Review maternal history		x				x			x						x	x		
	Discuss special considerations															x	x		
	Request additional help		x		x	x		x	x					x	x		x		
	DR equipment check	x	x	x	x	x	x	x	x	x	x		x	x			x		
	Use of checklist	x		x	x	x		x				x			x				
	Setting up incubator, perfusion, IV pump, and ventilator	x	x		x				x	x			x	x		x	x		
	Prewarming of DR	x	x		x	x	x	x	x	x	x		x	x		x	x	x	
Communication	Team roles attribution	x	x		x	x	x	x	x	x	x	x	x		x	x	x		
	Team leader (± hands-on)	x	x			x			x	x	x					x			
	Poster to remind roles	x						x	x	+/−	x		x				x		
	Documentation form in DR	x	x				x		x	x	x		x			x			
	Button on uniform/visual material			x															
	Team debriefing		x		x						x						x	x	
	Family inclusion	x	x	x			x			x							x		

(Continued on next page)

TABLE 3. Management Strategies Implemented (Continued)

		Vergales[16]	Ashmeade[17]	Lambeth[18]	Herath[19]	Peleg[20]	Harriman[21]	Chiriboga[23]	Croop[24]	Dixon[25]	Reynolds[28]	Habib[22]	Dylag[26]	Jeong[32]	Welch[27]	Reuter[29]	Castrodale[30]	Herranz[31]	Hemmingway[33]
Thermoregulation	Prewarming operating room	x	x		x	x	x	x	x	x	x		x	x		x	x	x	
	Preheated radiant warmer bed	x	x				x		x	x	x		x	x		x	x	x	
	Chemical warming mattress	x					x		x		x					x	x		
	Thermal mattress		x			x		x	x	x	x		x					x	
	Warm and humidified ventilator gases															x		x	
	Plastic bag	x	x	x	x	x	x	x	x	x	x		x		x	x	x	x	
	Blankets warmed				x	x	x			x	x							x	
	Hat(s)	x	x	x		x			x	x	x						x	x	
	Prewarmed transport incubator	x	x		x	x			x		x			x				x	
	Radiant in NICU		x	x															
	Early temperature probe		x	x	x		x	x		x	x		x	x		x			
	No transport if <36.5 °C							x											
	Dedicated member for thermoregulation									x									
	Automated door closing systems																	x	
	Avoidance of touch skin with metal																	x	
Cardiorespirator	EKG leads		x				x		x	x	x					x	x		
	Use of pulse oxymeter	x	x	x	x	x	x			x	x		x				x	x	
	Oxygen titration	x	x	x		x	x		x	x	x		x				x		
	Use of PEEP/T-piece	x	x		x	x	x	x	x	x	x		x	x		x			
	Prophylactic intubation	a			b				c				b			b			
	Prophylactic surfactant	a		x	b				b		d		d			b			
	Therapeutic surfactant		x		e	x			e				f				x		
	Early extubation												x						
	Caffeine								x				x			x			
	Orogastric tube insertion in DR		x																
	Intubation by most experimented							x	x										

(Continued on next page)

TABLE 3. Management Strategies Implemented (Continued)

		Vergales[16]	Ashmeade[17]	Lambeth[18]	Herath[19]	Peleg[20]	Harriman[21]	Chiriboga[23]	Croop[24]	Dixon[25]	Reynolds[28]	Habib[22]	Dylag[26]	Jeong[32]	Welch[27]	Reuter[29]	Castrodale[30]	Herranz[31]	Hemmingway (27)
IV and fluids	Early UVC	X	X	X	[g]	X	X	X	[g]	X			X	X	X	X	X		
	Attempt PIV	[a]	[h]	[h]	[i]	X	X		[i]	X			[g]					X	
	Early D10	X	X		X		[i]		[i]	[g]			X		X		X	[i]	
	Early parenteral nutrition			X		X	[g]		[g]	[i]						X		[g]	
	Early glycemia		X	X	X	X	X		X	X					X			X	
	Arterial line							X	X							X			
	Enteral hydration before IV													X					
Miscellaneous	Delayed cord clamping							X	X				X		X		X		
	Cord blood sampling					X			X										
	Early vitamin K		X	X	X		X												
	Antibiotics <1 h		X	X	X	X	X		X	X		X	X	X		X	X		
	Weight and length at 10 MOL		X		X						X					X	X		
	Erythromycin eye ointment		X				X												
	Limit assessment/examen												X						
	Blood pressure after procedure																X		
	Vitamin A								X										
	Prophylactic indomethacin	X											X						
	Bed elevation at 30°							X											
	Minimal stimulation							X											
	Avoidance of cuffed blood pressure measurement							X											
	Avoidance of skin-to-skin first 72 h							X											
	Head midline							X											

Abbreviations: D10, dextrose 10%; DR, delivery room; EKG, electrocardiogram; IV, intravenous; MOL, min of life; NICU, neonatal intensive care unit; PEEP, positive end-expiratory pressure; PIV, peripheral intravenous; UVC, umbilical venous catheter.

[a] <27 wGA.
[b] <26 wGA.
[c] ≤24 wGA.
[d] <28 wGA.
[e] ≥26 wGA.
[f] ≥28 wGA.
[g] in second time.
[h] if no UVC at M20–25.
[i] in first intention.

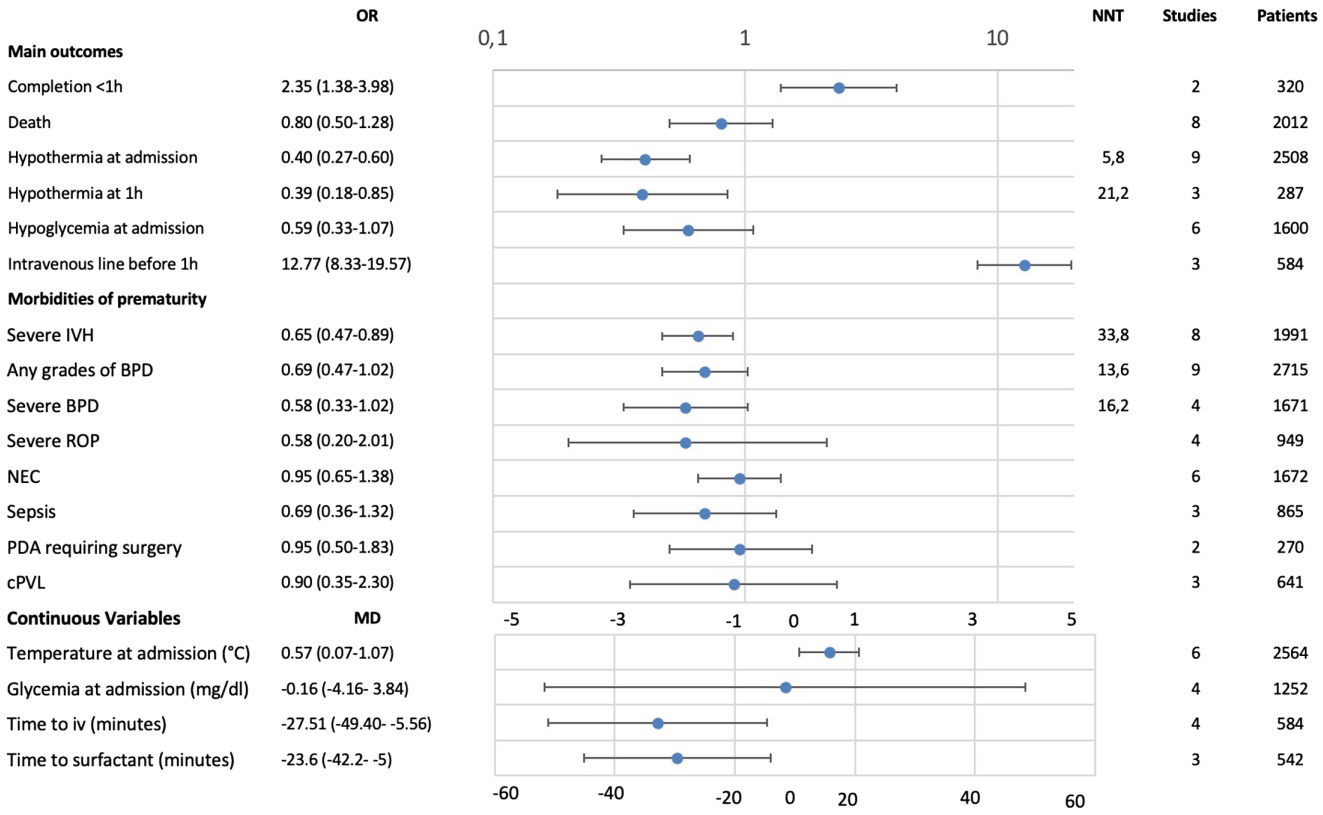

FIGURE 2.
Forest plot overview. BPD, bronchopulmonary dysplasia; cPVL, cystic periventricular leukomalacia; iv, intravenous; IVH, intraventricular hemorrhage; MD, mean difference; NEC, necrotizing enterocolitis; NNT, number needed to treat; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity.

This aligns with key aims of the GH, which promotes anticipation through equipment preparation and effective communication.

Avoiding early hypothermia is important for preterm infants' evolution. The literature reports rates of hypothermia on NICU admission between 32% and 85%,[33] which is consistent with the 61% rate found before implementation of GH in included studies. GH protocols led to higher mean temperatures on admission and to a 27% (from 61% to 34%) reduction in the incidence of hypothermia. In a detailed systematic review, ILCOR reviewers reported increased risks of neonatal mortality and morbidities related with hypothermia at NICU admission.[34] In some studies, hypothermia has been independently associated with higher rates of IVH and neurologic injury, respiratory disease and BPD, or late-onset sepsis.[33,34] This improvement in thermoregulation in GH groups could potentially contribute to the reductions in IVH and BPD.[33]

Worsening respiratory outcomes have been described with hypothermia, possibly through alteration of pulmonary mechanics, of surfactant distribution, and through modulated pulmonary vascular changes.[33] Less-invasive surfactant administration failure has been shown to be more frequent in infants with lower admission temperature.[35] Included studies spanned more than 10 years and attempted to implement contemporary guidelines that evolved rapidly. This led to very heterogenous approaches for respiratory care, including intubation and indications for surfactant administration. Respiratory outcomes were therefore difficult to analyze. Reducing the time to therapeutic surfactant administration should be beneficial for infants as administration within the 2 first hours of life compared with late administration decreases mortality, BPD at 36 wGA, BPD or death at 36 wGA, and risk of air leak.[36]

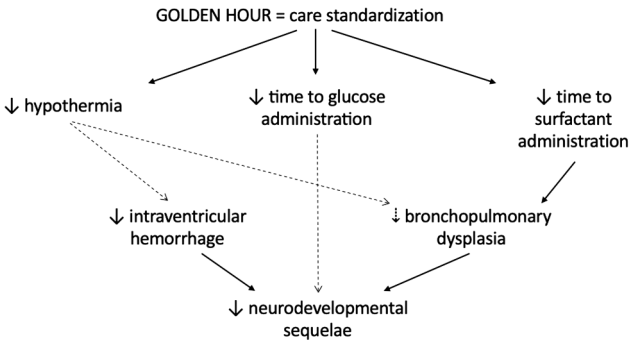

FIGURE 3.
Potential pathways explaining the benefits of Golden Hour protocols.

Hypoglycemia is a common occurrence in preterm populations, affecting 34% of the infants born before 33 wGA.[37] In the studies included, implementation of GH procedures reduced rates of hypoglycemia on admission from 30% to 23%. The time required for IV carbohydrates infusion was also significantly reduced, suggesting more rapid normalization of glycemia when required. This earlier treatment of hypoglycemic newborns is likely beneficial.[37] Many authors agree that severe and persistent hypoglycemia can cause seizure and brain injury. The prognosis of transient and mild hypoglycemia remains unclear, but an increased risk of low executive and visual motor functions has been reported.[37] Earlier initiation of glucose infusion could also reduce bolus glucose administration, which may exacerbate oxidative stress and lead to glucose reperfusion injury.[37]

This systematic review was conducted with some methodological strengths. Following a predefined protocol registered in PROSPERO, we searched 4 databases with indexing terms as well as free language. There was no language restriction for inclusion.

However, some limitations remain. The primary aims of the studies were diverse, with some focusing on thermoregulation and prevention of BPD or IVH. In addition, heterogeneity in hypothermia and hypoglycemia thresholds and reporting decreases comparability.

It is also important to note that more than 10 years elapsed between the first and last included studies. Neonatology is a medical discipline with rapidly evolving practices. This complicates comparison of GH protocols with each other as well as their outcomes.

To account for those, a more conservative random-effect analysis was computed in the overall analysis.[9] However, we found a high heterogeneity in most analyses. To address it and explore potential explanations, we performed subgroup analyses. Race and ethnicity were not addressed in the studies. Most studies were conducted in the US, 2 were conducted in Asia, and 1 was conducted in Israel. Only the study by Herath et al was carried out in a developing country. Analyses according to study design did not explain the heterogeneity.

Heterogeneity of hypothermia on admission and mortality outcomes seemed impacted by quality of study, but results remained similar after excluding poor-quality studies. Other outcomes were unaffected.

What seemed to have the greatest influence on the heterogeneity of studies is the variability of GAs included. Indeed, subgroups analysis according to category of GA inclusions led to significant subgroup heterogeneity in outcomes such as temperature on admission, hypoglycemia, BPD (any grades and severe), and severe ROP. It is well known that incidences of comorbidities of prematurity differ widely according to the population studied and that their physiopathology is multifactorial.

Although not significantly higher rates of death, BPD, and ROP were observed in the subgroup of studies including only infants younger than 28 wGA, it is difficult to attribute this effect solely to the GH intervention. Additionally, this subgroup comprised results from only 2 studies. Vergales et al partially attributed the higher mortality rate to the absence of data on infants who were resuscitated in DR but died before NICU admission in the control group.[15] Their protocol required intubating all infants younger than 27 wGA, while it has since been shown that stabilization with continuous positive airway pressure in the DR, rather than intubation, improves survival without BPD.[38] An additional analysis including studies with infants younger than $28^{6/7}$ wGA (5 studies[15–17,21,27]) did not confirm these unfavorable trends. While this reassuring finding may be due to the larger sample size, it could also be related to the inclusion of slightly older infants. It is important to highlight the need for further studies in this particularly vulnerable population.

Finally, certain components of the GH (such as DCC, use of T-pieces, thermoregulation devices, etc), when considered individually, have demonstrated significant reductions in prematurity-related comorbidities. Therefore, it is difficult to determine with certainty whether the standardized approach of the GH alone is responsible for the positive outcomes observed in this meta-analysis.

CONCLUSION

GH procedures, by systematically applying the latest resuscitation and management recommendations, appear to improve thermal and glycemic stability and could improve respiratory transition. This meta-analysis found a significant reduction in severe IVH and a trend toward a reduction of BPD, however, with very low certainty of evidence. This should encourage the creation and application of GH protocols for preterm infants. While evidence-based guidelines for resuscitation at birth are well established, research supporting recommendations for the management of the first few hours of life remain limited. Summarizing components and outcomes of GH procedures is a first step in this direction and should improve comparability in future studies.

The results of this meta-analysis seemed less significant in the subgroup analyses of studies focusing on extremely preterm infants, which should lead to further studies in this vulnerable population. Such standardized management procedures could also be adapted and evaluated for other acute situations at birth, including hypoxic-ischemic anoxia and diaphragmatic hernia.

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
BW: birth weight
cPVL: cystic periventricular leukomalacia
CRP: C-reactive protein
DCC: delayed cord clamping
DR: delivery room
GA: gestational age
GH: Golden Hour
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
ILCOR: International Liaison Committee on Resuscitation
IV: intravenous
IVH: intraventricular hemorrhage
MBP: mean blood pressure
MD: mean difference
NEC: necrotizing enterocolitis
NICU: neonatal intensive care unit
NLS: newborn life support
NOS: Newcastle-Ottawa Scale
OR: odds ratio
PDA: patent ductus arteriosus
PMA: postmenstrual age
PN: parental nutrition
RCT: randomized controlled trial
RoB: risk of bias
ROP: retinopathy of prematurity
SpO_2: pulsed oxygen saturation
UAC: umbilical arteriosus catheter
UVC: umbilical veinous catheter
wGA: weeks of gestational age

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