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Monitorização contínua da glicemia em recém-nascidos pré-termo/ Continuous Glucose Monitoring in Preterm infants- A Systematic Review

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E sob a Coorientação de:

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

Eu, Tiago Jorge Cardoso Pinto Ribeiro, abaixo assinado, nº mecanográfico 201503210, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

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Medicina Clínica

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Continuous Glucose Monitoring in Preterm Infants – A Systematic Review

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ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 29/03/2021

Assinatura conforme cartão de identificação: Tiago Jorge Cardoso Pinto Ribeiro

À minha família e aos meus amigos.

Continuous Glucose Monitoring in Preterm Infants – A Systematic Review

Abstract

Introduction: Dysglycemic events are common occurrences in preterm infants. This imbalance of blood glucose levels could lead to an increased risk of death, sepsis, neurosensorial impairment, retinopathy of prematurity, among other unfavorable consequences. Continuous glucose monitoring (CGM) allows for an early detection of dysglycemic events. This systematic review aims to assess the impact of CGM in glycemic values of preterm infants. **Methods:** We thoroughly searched several electronic databases from August 2020 to February 2021, we included reports based on inclusion/exclusion criteria. Primary outcomes were percentage of time spent in euglycemic range, number of dysglycemic episodes and mortality. **Results:** Three studies were included after screening, comprising a combined total of 278 preterm newborns. There were limitations in study design of included studies. CGM was compared with intermittent methods of blood glucose measurement (capillary test). Interventions and outcomes evaluated differed between included studies. **Conclusions:** CGM allows for better glycemic control, reduces number of painful readings, allows for early detection of dysglycemic events and reduces time spent in dysglycemic states (both hyperglycemia and hypoglycemia) when combined with corrective measures. Further research needs to be conducted to evaluate the long-term impact of CGM in neurosensorial and physical development of preterm infants.

Key words: Continuous glucose monitoring (CGM); Very Low Birth Weight Newborns (VLBW); Hyperglycemia; Hypoglycemia; Blood Glucose Measurements.

Resumo

Introdução: Os eventos disglicémicos são relativamente comuns em recém-nascidos pré-termo. Esta variação de glicemia pode levar a um aumento do risco de morte, sépsis, problemas no desenvolvimento neurossensorial, retinopatia do prematuro, entre outras consequências. A monitorização contínua da glicemia (CGM) permite a deteção precoce de eventos disglicémicos. Esta revisão sistemática tem como objetivo avaliar o efeito da CGM em recém-nascidos pré-termo. **Métodos:** Foram pesquisadas bases eletrónicas de agosto de 2020 até fevereiro de 2021, incluímos artigos baseados em critérios de inclusão/exclusão. Os outcomes primários avaliados foram: percentagem de tempo em euglicemia, número de episódios de disglicemias e mortalidade. **Resultados:** Apenas 3 estudos foram incluídos após pesquisa, um total combinado de 278 recém-nascidos pré-termo foi incluído nestes artigos. O risco de viés dos estudos incluídos variou desde baixo a intermédio. CGM foi comparada com métodos intermitentes de medição de glicose (testes capilares). As intervenções e outcomes medidos variaram entre estudos. **Conclusões:** CGM permite um melhor controlo glicémico, reduzindo o número de procedimento dolorosos, permitindo uma deteção mais precoce de eventos disglicémicos e reduzindo o tempo passado em estados disglicémicos (em hiperglicemia ou hipoglicemia), quando usado em conjunto com medidas de correção da glicemia. É necessária pesquisa adicional para avaliar o impacto a longo termo de CGM no desenvolvimento neurossensorial e físico de recém-nascidos pré-termo.

Palavras-Chave: Monitorização Contínua de Glicemia; Recém-nascidos com Muito Baixo Peso; Hiperglicemia; Hipoglicemia; Medição de glicemia.

1. Introduction

Preterm newborns often experience dysglycemic events, undergoing extensive periods of hyperglycemia or hypoglycemia. Included in this demographic are very low birth weight infants (VLBW). These neonates were born with birth weight <1500g and, due to glucose instability, can easily develop significant variations on blood glucose levels in a short amount of time (1), (2), (3).

There is a high level of uncertainty regarding the best approach when dealing with these events. It remains unclear what is the ideal target for blood glucose levels right after birth (4). It is uncertain if a rapid or a slow rate of recovery is preferable when treating dysglycemic events, and the potential neurosensorial outcomes that could derive from this adjustment (5). Additionally, it is unclear if tight glycemic control is beneficial in early life (6). It is, so far, not well-established if hyperglycemia and/or hypoglycemia, can cause long term effects in neurological and physical devolvement (7), (8), (9), (10), (11).

1.1 Background

Hyperglycemia may occur due to a variety of reasons, ranging from insulin resistance (12) and deficit, clinical stress (hypoxia, sepsis) (13), drug treatment (i.e., steroid treatment) (14) high glucose infusion rates, among others. It is estimated that around 20 to 88% of all preterm infants may experience hyperglycemia, at some point in early life, with more recent studies pointing to a percentage of around 30% (1), (2) . This condition is linked with increased mortality (more than double) (1), associated with neurosensorial impairment, retinopathy of prematurity (15), (16) and increased risk of intraventricular hemorrhage (17). To treat this disorder, there are two options: reducing

glucose infusion rates (lowering available energy) or increasing insulin infusion (that could lead to more hypoglycemic events, and a need for tighter glycemic control) (18).

On the other hand, hypoglycemia can affect up to 50% of all preterm infants (3). It may occur due to a depletion of fat and glycogen reserves that build up during 3º trimester of pregnancy. In addition, preterm infants need a steady glucose supply of 6-8 mg/kg/min, compared with 2-3 mg/Kg/day for term infants (19). From the available energy to the preterm infants, about 90% of all available glucose will be used to fuel the high-level brain activity. This high demand and relatively low supply can easily cause hypoglycemic events and can potentially lead to neurological complications (20), (21).

We can ascertain that dysglycemic events are common and associated with poorer outcomes for VLBW infants. Early detection of these events is key to ensure better long-term outcome and survivability. Despite this, there are few recommendations regarding glucose monitoring in VLBW infants (22).

In most NICU (newborn intensive care units) blood glucose is measured punctually (intermittent methods), using heel prick tests or, in occasion, venipuncture. These methods only provide with a singular measurement on an exact point in time. As such, dysglycemic events may linger unnoticed for long periods or even remain undetected. This could, in turn, lead to increased time spent in hypoglycemic and/or hyperglycemic states (23), (24).

In addition, these tests are associated with increased levels of pain endured by the newborn and can represent an additional stress for the infant (25), (23).

Real time continuous glucose measurement (RT-CGM) provides an influx of blood glucose values that could prove to be very helpful in monitoring and preventing extreme

blood glucose variations. CGM devices are already in widespread use for insulin delivery when treating diabetes, in both children and adults (26).

And, despite similar accuracy when compared with heel prick tests, and relative safety (27), these devices are not regularly used in NICU context (22).

1.2 Description of the intervention

Real time continuous glucose monitoring technology (RT-CGM) allows its users or caregivers to evaluate, in real time, blood glucose concentrations (28).

This device utilizes sensor electrodes and small filaments inserted into subcutaneous tissue. The electrodes measure glucose concentration through a glucose oxidase reaction. The signal is then transformed into a glucose reading and conveyed wirelessly to a matching device (28). Alerts can be customized for low or high glucose values.

These devices have only been deemed harmless for use in children age 2 or more, by USA authorities (29).

CGM has been used in some studies to guide glucose infusion rates, or insulin administration, integrated in computer guided algorithms for optimal glycemic control (24). This automatization is further discussed in the next section.

1.3 How the intervention might work

Studies demonstrate the feasibility, safety and potential advantages (better glycemic control) of using these devices in preterm infants, compared with more standard methods such as capillary blood glucose measure (23), (24), (30), (31).

CGM reduces the number of heel prick tests necessary for better control glucose in neonatal setting (23), and the subcutaneous insertion of CGM system is associated with lower distress and pain when compared with heel prick tests (25).

In addition, CGMD could also provide these readings in real time, allowing caregivers to decide adjustments based on protocols, algorithms, or based on professional experience (24). CGMD could also be associated with computer guided algorithms for an independent, automated, and reliable way to ensure that blood glucose stays between preset interval ranges (24), (32).

CGMD provides a continuous influx of data on blood glucose concentration, that could then be analyzed and processed by computer-based algorithms, who in turn could independently perform real time adjustments. These adjustments could be simple variations in parenteral feeding and/or insulin infusion, done in a short amount of time and completely automated. This could reduce the number and time spent in dysglycemic states (24).

In an increasingly automated health care services, CGMD could prove essential in the management of preterm infants.

1.4 Why is it important to conduct this review?

CGM is a growing field of research, several reports have been published, and many others are in development. Studies have showed that these devices are capable of accurate readings and can contribute to a better and safer blood glucose control, both in children and adults (26), (27).

However, little evidence is available on the advantages or disadvantages of using CGMD in preterm infants on a NICU context (22).

Thus, some questions arise: are CGMD safe for use in NICU context? Does CGMD detect significantly more dysglycemic events than traditional methods of blood glucose measurement (such as heel prick tests)? Is tight glycemic control beneficial for newborn infants? What are the long-term effects of CGM in neurodevelopment and physical outcomes?

Some recent systematic reviews and clinical trials have tackled these questions. Reilly C. *et al* intended to evaluate the impact of CGM on glucose stability in preterm infants. The study was conducted in 2019, and included studies published until January 2019. They concluded that, quote: "*The potential of CGM is significant although more research is required as little is definitively known about short- and long-term benefits and risks regarding its use in the preterm population*" (33).

More recently, Galderisi A. *et al* evaluated the impact of CGM in the neurodevelopment of preterm infants. It was conducted in 2020, and included studies published until September 2020. None of the included studies reported on long term neurological outcomes. The impact of CGM on mortality remains unclear, concluding that, quote: "*There is insufficient evidence to determine if CGM improves preterm infant mortality or morbidity. Long-term outcomes were not reported*" and "*Further research is needed*" (34).

Since then, new studies, involving a sizable number of newborns, were published. This could bring new insights and conclusions about these topics (30). In addition, several ongoing clinical trials are being conducted (35), (36), (37), and are soon to be published. In this review we analyzed all the available information about short- and long-term benefits from CGM use in preterm infants.

1.5 Objectives

1.5.1 Primary objectives

Systematic review that aims to assess the feasibility and safety of continuous glucose monitoring when compared with other methods of intermittent glucose measure (i.e., capillary blood glucose or central line testing).

To assess the effect of continuous glucose monitoring systems (CGMS) or CGMD in very low birth weight newborn infants, specific interventions were reviewed:

I) CGM using CGMS/CGMD compared with methods of intermittent glucose measure (capillary blood glucose or central line testing), in detecting **hyperglycemic events**.

II) CGM using CGMS/CGMD compared with methods of intermittent glucose measure (capillary blood glucose or central line testing), in detecting **hypoglycemic events**.

III) Safety of CGMS/CGMD compared with methods of intermittent glucose measure (capillary blood glucose or central line testing).

IV) Feasibility of CGMS/CGMD use in a neonatal intensive care unit environment.

2. Methods

2.1 Inclusion criteria

We reviewed studies that abided by the following criteria:

2.1.1 Types of studies

Randomized controlled trials or quasi-randomized controlled trials with randomized individual participants in parallel groups. We excluded feasibility and pilot studies. In this

review we included unpublished trials or trials reported solely in abstract, only if appraisal of study quality was feasible.

2.1.2 Types of participants

Newborn infants with birth weight <1500g, gestational age <37 weeks and postnatal life <28 days.

2.1.3 Types of interventions

I) CGM using CGMS/CGMD, compared with intermittent methods of glucose measure (capillary blood glucose or central line testing), both interventions utilizing the same methods to correct hyperglycemia and/or hypoglycemia. Corrective measures relevant for this review included:

I) **Computer-based algorithms** (using a combination of glucose rate infusion and insulin rate infusion variations, delivered automatically).

II) **Pre-defined guidelines** based on literature or clinical experience (using a combination of glucose rate infusion and insulin rate infusion variations).

III) **Glucose infusion rate adjustments** (increases or decreases).

IV) **Insulin infusion rate adjustments** (increases or decreases).

We included studies where corrective measures were identical in both groups. We planned on comparing between corrective measures to determine the most optimal for use, as we further explain in the subgroup analysis.

When intermittent glucose measure is associated with masked CGM (to preserve blinding), it was considered as intermittent glucose measure readings. This was done to, posteriorly, provide improved data analysis.

2.1 Types of outcome

2.2.1 Primary Outcomes

1- **All case mortality**: mortality before discharge, mortality at 28 days or as defined by the authors.

2- **Median time to correct hypoglycemia**, specified as hours to reach euglycemic concentration between 50 and 150 mg/dl or as defined by the authors.

3- **Median time to correct hyperglycemia**, specified as hours to reach euglycemic concentration between 50 and 150 mg/dl or as defined by the authors.

4- **Number of hyperglycemic events per individual**, defined as the mean number of episodes of hyperglycemia (>150 mg/dl) per individual included in both groups, or as defined by the authors.

5- **Number of hypoglycemic events per individual**, defined as the mean number of episodes of hypoglycemia (<50mg/dl) per individual included in both groups or as defined by the authors.

6- **Median time spent in euglycemic range**, defined as blood glucose levels between 50 and 150 mg/dl or as defined by the authors.

2.2.2 Secondary Outcomes

1- **Severe intraventricular hemorrhage** (IVH) grade III or IV.

2- **Skin lesions, skin infection or other adverse effects** attributed to CGMS/CGMD.

2- **Retinopathy of prematurity** (ROP).

3- **Late onset of sepsis**, described as a positive culture for bacteria in blood (recorded after 72 hours of life) up to 28 days of life.

4- **Growth impairment**, defined as weight, height, head circumference and BMI, or as determined by the authors.

5- **Neurodevelopmental outcome**, defined as cerebral palsy, significant mental developmental delay, or as defined by the authors.

6- **Percentage of weight loss** during study.

7- **Bronchopulmonary dysplasia**, defined as the necessity for respiratory support at 36 weeks corrected for gestational age.

2.3 Search methods

The following sources were searched:

2.3.1 Electronic searches

We searched electronic databases that included: MEDLINE (1966- February 2021, via PubMed), The Cochrane Central Register of Controlled trails (CENTRAL- until February 2021) and Clinicaltrails.gov.

We applied no language restriction. The search started in September 2020 and concluded in February of 2021.

I) Query used in the online search (CENTRAL and PubMed) was the following: (blood glucose sensor OR blood glucose analyzer OR continuous glucose monitoring OR CGM OR self-monitoring OR glucose monitor measurements OR tight glucose control OR tight glucose monitoring) AND (low blood sugar OR hypoglycemia OR hypoglycemics OR hyperglycemia OR hyperglycemic OR high blood sugar OR glucose intolerance OR glucose metabolism OR euglycemia OR euglycemic OR normal blood glucose OR

dysglycemia OR glycemia) AND (infant, very low birth weight OR very low birth weight OR VLBW OR extremely low birth weight OR ELBW OR preterm OR extremely low birth weight infants).

II) Query used in online search of Clinicaltrails.gov was the following: (hypoglycemia OR hyperglycemia OR dysglycemia) AND (newborn OR infants) AND (continuous glucose monitoring OR CGM OR self-monitoring).

Search and subsequent selection of reports were documented in a flowchart, following PRISMA recommendations. The flowchart is presented in **Fig. 1.**

2.3.2 Searching other resources

We reviewed the reference list of included studies, systematic reviews focused on this demographic group, and other relevant papers, in search of pertinent reports that were not identified in initial electronic search. If relevant studies were found they were included in the initial search results and reviewed following the method subsequently depicted. The number of included studies can be consulted in **Fig. 1.**

2.4 Data collection and analysis

Standard methods of Cochrane were applied, as described below.

2.5 Study selection

Selection process was conducted independently by two authors.

After applying the search terms and retrieving initial report yield, we proceeded to removed duplicate reports.

Subsequently, titles and abstracts of detected studies were assessed and reviewed, only retaining those relevant to this review.

Studies were then read in full, and carefully chosen based on selection criteria previously listed under “Inclusion criteria”. We removed all reports from the same studies, only retaining those with the most complete data.

If there was uncertainty regarding inclusion or exclusion of a particular study, the full report was assessed for eligibility.

Management of this process was performed using EndNote X9. Additionally, this program was used in citation managing.

All steps were documented in a flowchart according with Prisma recommendations, in **Fig.1**. Excluded studies can be consulted on supplemental material, under “**Characteristics of excluded studies”, Table 1** to **3** (38).

2.6 Data extraction

Included studies were reviewed in a comprehensive analysis. Data was collected regarding relevant information such as: author, date of publication, study design, geographic location, clinical features of population (birth weight, gestational age, maternal diabetes, sex male/female) sample size, interventions (type of CGMS, duration), outcomes, data analysis, among others.

This was done using data collecting forms designed for this review, that can be consulted as a supplemental material.

Ongoing studies were evaluated and if sufficient data was available, they were included in this review. If additional data was required, we planned to contact the authors of the reports for additional information.

2.7 Assessment of risk of bias

Every trial was evaluated for: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other form of bias. Each category was classified as High, Low or Unclear, with explanation for each point. This was done using the Cochrane "Risk of Bias tool" (39)

Tables regarding this assessment can be consulted under supplemental material, in "Risk of Bias", **Table 1** to **3**.

2.8 Measure of treatment effect

For every trial, we planned on using risk ratio (RR), odds ratio (OR), absolute risk difference (RD), number needed to treat (NNT), when dealing with categorical variables. For continuous variables we planned on using mean differences (MD). If size measurement varied across trials, we used standardized mean difference (SMD), each with 95% CI.

If meta-analysis was possible, we planned on utilizing OR for categorical variables, with 95% CI. For continuous variables we calculated weighted mean difference (WMD) with 95% CI.

2.9 Dealing with missing data

An effort was made to try and get the most complete data stets possible. If there was incomplete or unreported data on a study outcome or the dropout rate was too high (>20%), we would try to contact the primary investigator.

If data outcome was still unavailable despite efforts to acquire full data sets, an available-case analysis based on available data would be carried out.

If an important portion of data were missing, despite efforts to obtain full information, the study would be excluded.

2.10 Assessment of heterogeneity

We planned to present results of this review using meta-analysis. Before doing any meta-analysis, we decided that if there was enough similarity between studies, we would compare study design and clinical features such as population, type of intervention and outcome evaluated. We assessed statistical heterogeneity by calculating I^2 statistic. Additional Chi^2 test will be used to determine if heterogeneity was statistical significative.

After this assessment, if enough similarity were found between studies, we would perform meta-analysis. If not, each study results were described separately, analyzing it accordingly with criteria defined in “types of interventions” and “types of outcomes”.

2.11 Assessment of reporting bias

We expected a relatively small number of included reports (<10), as such, it would be difficult to perform funnel plots to assess any possible publication bias. If number of clinical trials were superior to 10, we would present a funnel plot.

We searched for included trials on PubMed, ClinicalTrials.gov and WHO ICTRP. We compared primary and secondary outcomes in the final report, with the outcomes submitted in trials registration, and evaluated if reporting outcomes were complete.

2.12 Data synthesis

Statistical analysis was performed using RevMan 5, a statistic tool provided by Cochrane. For meta-analysis data would be presented utilizing RR; RD; NNT; MD all with an 95% CI. If meta-analysis were deemed to be unsuitable, we would interpret the reports individually.

2.13 Subgroup analysis and investigation of heterogeneity

Subgroup analysis was planned with the subsequent order:

- Blood glucose levels, time spent in hypoglycemia, euglycemia, hyperglycemia in the subsequent subgroups
    - Birth weight <1000g, 1000g -1200g, 1200g -1500g.
    - Gestational age: <30 wks, 30-32 wks, 32-35 wks
- CGM with **computer algorithms** to control hyperglycemia and/or hypoglycemia.
- CGM with **pre-defined guidelines** to control hyperglycemia and/or hypoglycemia.
- CGM with **glucose infusion rate** increases (hypoglycemia)/decreases (hyperglycemias).
- CGM with **insulin infusion rates** increases (hyperglycemia)/decreases (hypoglycemias).

3. Results

3.1 Search Results

19 studies were eligible for full appraisal. 16 of those were excluded, the reasons for exclusion can be consulted in supplemental material under “Excluded Studies”, **Table 4**. Three studies were eligible for this review: (23) Uetwiller F. *et al*, from 2015; (24) Galderisi A. *et al,* from 2017 and (30) Beardsall K. *et al*, from 2021.

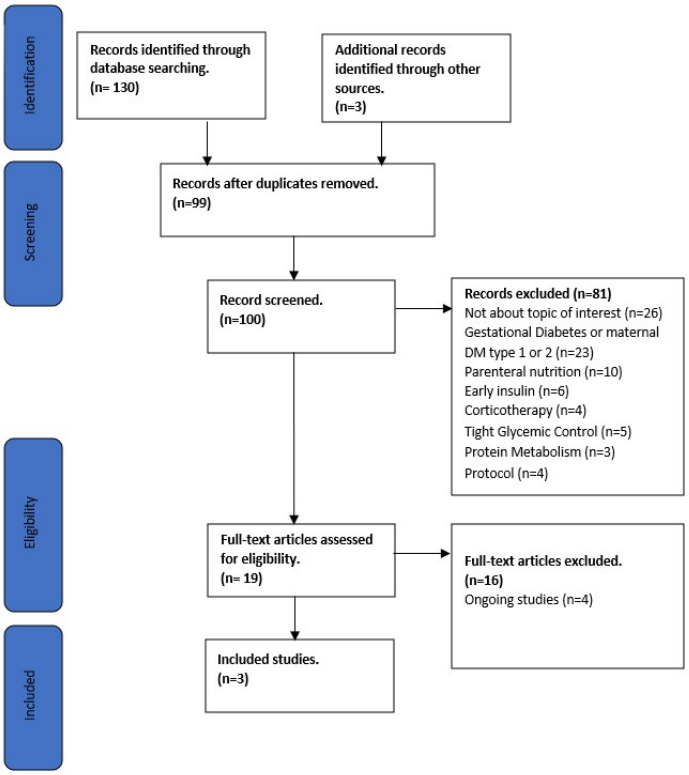


Figure 1: Flow diagram

3.2 Included studies

All 3 studies included in this review compared CGM vs intermittent methods of glucose measurement.

While Uetwiller F. *et al* evaluated the effects of CGM on time spent in hypoglycemic states, Galderisi A. *et al* documented the impact CGM on time spent in both

hyperglycemic and hypoglycemic states. More recently, Beardsall K. *et al* compared CGM with intermittent methods of blood glucose measurement in a large multinational study. Interventions slightly differed between included studies. We further analyzed each trial in more detail and accordingly with types of interventions that were previously defined.

3.3 Interventions

3.3.1 Comparison 1: Comparing CGM with intermittent methods using **computer-based algorithms** to correct Hyperglycemia/Hypoglycemia

Galderisi A. *et al* compared CGMS with intermittent methods of glucose measurement, both paired with **computer-based algorithms** for titration of glucose infusion to adjust blood glucose levels. Fifty newborn infants were enrolled in this study, inclusion criteria were: gestational age <32 weeks or birth weight <1500g.

The goal of this study was to maintain blood glucose levels on an euglycemic range (between 72-144 mg/dl).

Participants were divided into two groups. Unblinded group CGM (UB-CGM), where PID (proportional–integral–derivative) control algorithm adjustments were driven by CGMS. In the blinded CGM (B-CGM) group PID control algorithm adjustments were driven using standard of care glucometer based on blood glucose determinations. Outcomes stated in this trial encompassed: percentage of time spent in euglycemic range (72-144mg/dl), secondary outcomes were percentage of time in mild hypoglycemia (47-71 mg/dl), percentage of time spent in severe hypoglycemia (<47mg/dl), percentage of time in mild hyperglycemia (145-180 mg/dl) and percentage of time in severe hyperglycemia (>180mg/dl).

Further information about this trial can be consulted in supplementary material under "Characteristics of included studies", **Table 1.**

3.3.2 Comparison 2: Comparing CGM with intermittent methods using **pre-defined guidelines** to correct Hyperglycemia/Hypoglycemia

Beardsall K. *et al* performed a randomize controlled trial, parallel-group, multi-center and multinational (UK, Spain, Netherlands). 180 newborns were arbitrarily allocated (1:1) (in 24 hours after birth) to receive glucose and/or insulin infusion guided by CGM, or standard care (intermittent methods of glucose measure). Inclusion criteria were newborns ≤ 33 weeks gestation, birth weight ≤1200g, <24h after birth and written consent from parent or guardian**.** From this study, newborns with congenital malformations and newborns with congenital metabolic disorders were excluded.

In the intervention group (CGM), real time blood glucose values were accessible to the clinical team and guided glucose or insulin administration accordingly with **previously defined guidelines**. On the control group (intermittent blood glucose measurement), blood glucose was managed according with standard methods. In this group, CGMS was used but data collected was masked to the clinical team.

The primary outcome was percentage of time spent in euglycemic (target) range (2,6-10 mmol/L). Secondary outcomes involved proportion of time spent in dysglycemic states and several relevant clinical outcomes to this review. Additional data can be consulted in supplementary material under "Characteristics of included studies", **Table 2**.

3.3.3 Comparation 3: Comparing CGM with intermittent methods using **glucose infusion adjustments** to correct Hyperglycemia/Hypoglycemia

No study was found that compared this intervention to correct both hyperglycemia and hypoglycemia.

Uetwiller F. *et al* compared CGMS with intermittent methods of glucose measurement, both combined with glucose infusion rate increases to solely correct hypoglycemia. 48 newborns participated in this study. Inclusion criteria were gestational age ≤32 weeks and birth weight ≤1500g.

The aim of this study was maintaining blood glucose above 50 mg/dl.

Participants were distributed into two groups. In the CGM-group, blood glucose levels were measured using CGM, glycemic values ≤60 mg/dl were signaled by an alarm. Capillary blood testing was carried out to verify these indications. In IGM-group, standard methods (intermittent capillary blood glucose testing) were carried out every 4 hours.

Hypoglycemia events, defined as <50 mg/dl, were handled by an intravenous bolus of 10% dextrose, and tested 30 to 60 min later.

Outcomes reported in this trial include number and duration of hypoglycemic events per patient detected by CGMS.

Further information about this trial can be consulted in supplementary material under "Characteristics of included studies", **Table 3.**

3.3.4 Comparation 4: Comparing CGM with intermittent methods using **insulin infusion adjustments** to correct Hyperglycemia/Hypoglycemia

No trial tested this intervention isolated. Both Beardsall K. *et al* and Galderisi A. *et al* used insulin and blood glucose infusion rates to correct dysglycemic events.

3.4 Excluded studies

Studies that were reviewed in full, but later excluded. We documented the reasons for exclusion that can be consulted in supplementary material, under "Characteristics of excluded studies", **Table 4.**

3.5 Ongoing studies

4 studies were found. The summary of each clinical trial can be found under "Characteristics of ongoing studies", **Table 5.**

3.6 Risk of bias in included studies

Risk of bias was evaluated, as previously discussed, under "Assessment of risk of bias". After appraisal, Galderisi A. *et al* and Beardsall K. *et al* presented with a low risk of bias in most parameters evaluated, but it was discovered that there was a high risk of bias regarding blinding of personnel.

Uetwiller F. *et al* was discovered a high risk of bias regarding blinding of personnel, unclear risk regarding allocation concealment, and low risk in the remaining parameters.

Each study and each parameter can be view in detail, in Supplemental material, "Risk of bias", **Table 1** to **3.**

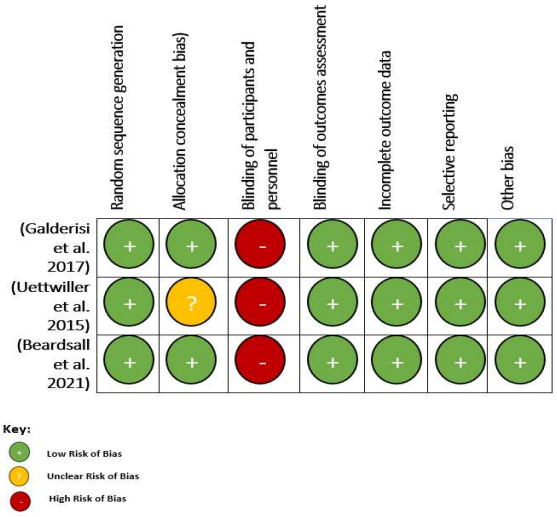


Figure 2: Risk of Bias

3.7 Effects of interventions

In the following section, for each comparation, we discussed the impact of each intervention on the outcomes previously defined in "types of outcomes".

3.7.1 CGM vs intermittent methods using computer guided algorithms (comparison 1) or guidelines (comparison 2) to correct Hyperglycemia/Hypoglycemia

Due to low number of included studies, subgroup analysis was not performed.

We decided to compare CGM vs intermittent methods, we compared Galderisi A. *et al* and Beardsall K. *et al,* summarizing relevant results and comparing reported outcomes.

3.7.1.1 Primary outcomes

Mortality before discharge

Galderisi A. *et al* reported 1 death in the B-CGM (blinded continuous glucose measurement) group and 0 deaths in the UB-CGM (unblinded continuous glucose measurement) group, with a p value of 0.99. No significant difference was found in mortality before discharge.

Beardsall K. *et al* reported no significant difference in mortality rate, with 6% (6/95) in the control group, and 2% (2/84) in the CGM group, with adjusted (for gestation and center) odds ratio of 0,263 CI of [0,0353, 1,3] and p value <0,13.

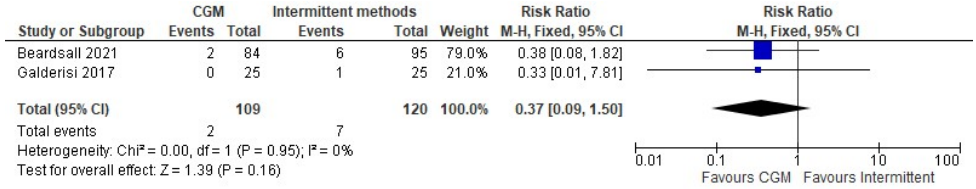


Figure 3: Mortality before discharge

Mortality at 28d

Galderisi A. *et al* reported no deaths in both groups.

Beardsall K. *et al* did not report this outcome.

Mean time spent in euglycemic level

Galderisi A. *et al* reported significantly more time spent in glycemic target range in the CGM (UB-CGM) group when compared with B-CGM, with the UB-CGM reporting 83% (95% CI, 79-87), compared with 71% (95% CI, 67-76%) in the B-CGM group, with a P value of <0,001.

Beardsall K. *et al* reported significant difference in mean time spent in euglycemic range, with 84% in the control group, and 94% in the CGM group, with adjusted (for gestation and center) mean difference of 8,9 CI 95% of (3,4 to 14,4) and p value of 0,005.

Time to resolve hypoglycemia

Galderisi A. *et al* did not report this outcome.

Beardsall K. *et al* did not report this outcome.

Time to resolve hyperglycemia

Galderisi A. *et al* did not report this outcome.

Beardsall K. *et al* did not report this outcome.

Number of recurring hyperglycemic events per individual or per proportion

Galderisi A. *et al* stated a substantial reduction in the number of episodes of hyperglycemia in the UB-CGM when compared with B-CGM group, with the UB-CGM reporting 0.8 ± 1.6 episodes per individual, compared with 2,2± 3.3 in the B-CGM group, with a P value of 0.04.

Beardsall K. *et al* did not report this outcome.

Number of episodes of recurrent hypoglycemia per individual or per proportion

Galderisi A. *et al* stated a substantial reduction in the number of episodes of hypoglycemia in the UB-CGM when compared with B-CGM group, with the CGM reporting 1.4 ± 2 episodes per individual, compared with 4.7 ± 6.2in the B-CGM group, with a P value of 0.01.

Beardsall K. *et al* did not report this outcome.

3.7.1.2 Secondary Outcomes

Percentage of weight loss

Galderisi A. *et al* reported that in the B-CGM group 7,6 % (1.9-10,3%) and 9,9% (5,0-12.9) in the UB-CGM, with a p value of 0.22. Weight loss between groups was not statistically significant.

Beardsall K. *et al* reported no significant difference between weight at 7 days with mean (SD) CGM -1,26 (0,79) and control group -1,3 (0,75) with adjusted (for gestational and center) mean difference of 0,05 (-0,19; 0,28), p=0,69.

Neurodevelopmental outcome

Galderisi A. *et al* did not report this outcome.

Beardsall K. *et al* did not report this outcome.

Severe intraventricular hemorrhage (IVH)

Galderisi A. *et al* reported no significant difference between CGM group compared with B-CGM, with the CGM reporting 0 cases, compared with 2 cases in the B-CGM group, with a P value of 0.49.

Beardsall K. *et al* reported no significant difference between both groups, with CGM reporting 33% (25/75) and control group 32% (27/4), with an adjusted ((for gestation and center) odds ratio of 1,02 [0,51, 2,1], p=0,95.

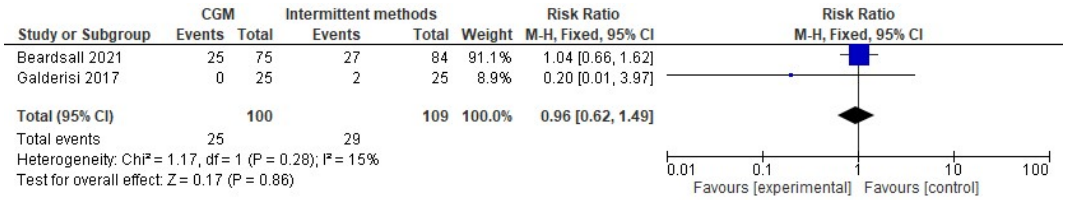


Figure 4: Intraventricular hemorrhage

Growth impairment

Galderisi A. *et al* did not report this outcome.

Beardsall K. *et al* reported no significant difference on body length SDS at day 7 between both groups, with CGM reporting mean (SD) -1,81 (1,07) and control group -1,78 (0,87), with an adjusted (for gestation and center) mean difference of -0,02 (-0,36, 0,31), p=0,89.

Skin lesions or skin infection

Galderisi A. *et al* did not report this outcome.

Beardsall K. *et al* did not report this outcome.

Number of episodes of retinopathy of prematurity (ROP)

Galderisi A. *et al* did not report this outcome.

Beardsall K. *et al* reported only the maximum grade across all examinations (2).

Late onset of sepsis

Galderisi A. *et al* reported no significant difference between CGM group compared with B-CGM, with the CGM reporting 0 cases, compared with 2 cases in the B-CGM group, with a P value of 0,49.

Beardsall K. *et al* did not report this outcome.

Bronchopulmonary dysplasia

Galderisi A. *et al* stated no substantial difference between the two groups. On the CGM group 0 cases were reported, and intermittent group reported 1 case out of 25 newborns.

Beardsall K. *et al* stated no major difference on Bronchopulmonary dysplasia between the two groups, with CGM reporting 45 episodes out of 75 and control group 56 of 85 newborns, with an adjusted (for gestation and center) odds ratio of 1.2 (0.52,2.8), p=0,66.

Figure 5: Bronchopulmonary dysplasia

3.7.2 CGM vs intermittent methods of glucose measurement, both groups using glucose infusion rate increases to correct Hypoglycemia/Hyperglycemia (comparison 3)

Only Uetwiller F. *et al* compared this intervention, just evaluating hypoglycemic events.

3.7.2.1 Primary outcomes

Mortality before discharge

Uetwiller F. *et al* did not report this outcome.

Mortality at 28d

Uetwiller F. *et al* did not report this outcome.

Median time spent in glycemic target range

Uetwiller F. *et al* did not report this outcome.

Time to resolve hypoglycemia

Uetwiller F. *et al* did not report this outcome.

Time to resolve hyperglycemia

Uetwiller F. *et al* did not report this outcome.

Number of episodes of recurrent hyperglycemia per individual or per proportion

Uetwiller F. *et al* did not report this outcome.

Number of recurring hypoglycemic events per individual or per proportion

Uetwiller F. *et al* reported a significant difference between CGM group with B-CGM, with the CGM reporting 1.2 ± 0.4 episodes per individual, compared with 0.4 ± 0.2 (while blinded episodes per patient was 1.2 ± 0.4) in the B-CGM group, with a P value <0.01.

Galderisi A. *et al* also reported this outcome, already summarized previously.

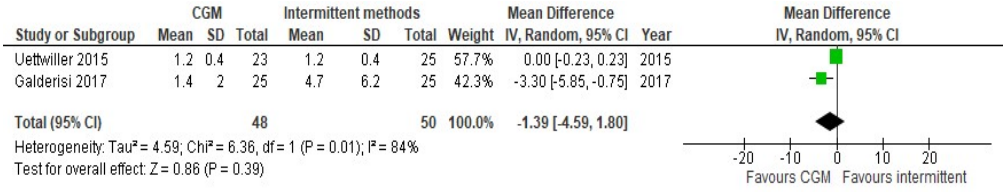


Figure 6: Number of recurring hypoglycemic events per individual or per proportion

3.7.2.2 Secondary Outcomes

Severe intraventricular hemorrhage (IVH)

Uetwiller F. *et al* did not report this outcome.

Neurodevelopmental outcome

Uetwiller F. *et al* did not report this outcome.

Growth impairment

Uetwiller F. *et al* did not report this outcome.

Skin lesions or skin infection

Uetwiller F. *et al* did not report this outcome.

Retinopathy of prematurity (ROP)

Uetwiller F. *et al* did not report this outcome.

Late onset of sepsis

Uetwiller F. *et al* did not report this outcome.

Bronchopulmonary dysplasia

Uetwiller F. *et al* did not report this outcome.

4. Discussion

4.1 Summary of evidence

4.1.1 Review Results

Three trials were eligible for this review: Galderisi A. *et al*, Uetwiller F. *et al* and Beardsall K. *et al*.

Galderisi A. *et al* compared CGM vs intermittent methods of glucose measurement while utilizing, in both groups, **computer-based algorithms** to correct hyperglycemia and/or hypoglycemia.

On the other hand, Uetwiller F. *et al* compared CGM vs intermittent methods of glucose measurement utilizing increases in **glucose infusion rates** to correct hypoglycemia. Lastly, Beardsall K. *et al* compared CGM vs intermittent methods utilizing **predefined guidelines** (variation in insulin and glucose infusion rates) to treat dysglycemic events.

No trials were found that compared CGM vs intermittent methods of blood glucose measurement, employing only: **insulin increases or decreases** to correct hyperglycemia/ hypoglycemia, or utilizing **glucose infusion rate** decreases to correct hyperglycemia.

The main objective of this review was to determine the impact of CGMS on dysglycemic events (hypoglycemia/hyperglycemia), access short- and long-term mortality in both groups, as well as evaluate the feasibility and safety of utilizing CGMS in the context of NICU.

4.1.2 Primary outcomes

From the primary outcomes analyzed in this review, time spent in euglycemic range was significantly increased in newborns assigned to CGM groups in the Galderisi A. *et al* and Beardsall K. *et al* studies.

No significant difference was found in terms of short-term mortality in the Galderisi A. *et al* and Beardsall K. *et al* studies.

Regarding dysglycemic events per individual, we can compare Galderisi A. *et al* and Uetwiller F. *et al* regarding the number of hypoglycemic episodes per individual. Uetwiller F. *et al* detected significantly more hypoglycemic events per individual in the CGM group, 1.2 ± 0.4, than in the control group, 0.4 ± 0.2 (with a real value of 1.2 ± 0.4), while Galderisi A. *et al* reported significantly less episodes (1.4 ± 2) in the CGM group than in the control group (4.7 ± 6.2). This could be attributed to the different interventions evaluated. Excluding intervention, we can infer that CGM detects more episodes than intermittent methods of glucose measurement.

4.1.3 Secondary Outcomes

Regarding secondary outcomes, Uetwiller F. *et al* did not report outcomes relevant to this review. Galderisi A. *et al* and Beardsall K. *et al* only reported on percentage of weight loss, severe intraventricular hemorrhage, and late onset of sepsis, with no substantial difference between groups.

While not considered in this review, Uetwiller F. *et al* also conluded that, by reducing the number of heel prick testes by 25% in CGM group, the pain experienced by newborns was reduced.

4.2 Review limitations

We performed an extensive research method and we believe that we identified all relevant studies for this review. We applied no language barrier. We excluded pilot studies and feasibility studies (33) and (34), only including randomized clinical trials.

However, the number of included trials was relatively small and this impacted the quantitative analyses of this review. In addition, included studies had differences regarding the tested interventions, using different methods to resolve dysglycemic events.

Only 3 studies, with a combined total of 278 enrolled newborns, were found. These trials reported on limited outcomes relevant to this review, and none evaluated the long-term effects of CGM in physical and neurological development.

4.3 Future considerations

CGM is a promising field, and it can be successfully used to improve glycemic control in preterm newborns. Despite this, some questions remain unanswered, such as what are the best glycemic targets to ensure proper physical and neurosensorial development, what is the cost-benefit of CGM, or what are the potential long-term outcomes of such interventions.

Therefore, and due to limitations present in this systematic review, we believe that further investigation needs to be conducted to properly answer relevant matters in this important medical field.

Larger studies need to be performed, and long-term outcomes (neurological and physical) need to be evaluated. It is important to understand the real impact of tight

glycemic control, and the ideal range for blood glucose values that allows for optimal development of preterm infants.

The use of automated glucose and insulin delivery needs to be further explored, as it is being done in some studies, to improve glycemic control (24), (32).

4.4 Conclusion

CGM clearly offers advantages in terms of time spent in euglycemic range (when combined with methods glucose correction).

Although the potential of CGM is high, new studies need to be conducted to ensure the safety and cost-benefit of such intervention, as well as long term outcomes and best glycemic target range for ideal neonatal development.

4.5 Declaration of competing interest

None.

5. References

1. Zamir I, Tornevi A, Abrahamsson T, Ahlsson F, Engström E, Hallberg B, et al. Hyperglycemia in Extremely Preterm Infants-Insulin Treatment, Mortality and Nutrient Intakes. J Pediatr. 2018;200:104-10.e1.

2. Sabzehei MK, Afjeh SA, Shakiba M, Alizadeh P, Shamshiri AR, Esmaili F. Hyperglycemia in VLBW infants; incidence, risk factors and outcome. Arch Iran Med. 2014;17(6):429-34.

3. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr. 2012;161(5):787-91.

4. van Kempen A, Eskes PF, Nuytemans D, van der Lee JH, Dijksman LM, van Veenendaal NR, et al. Lower versus Traditional Treatment Threshold for Neonatal Hypoglycemia. N Engl J Med. 2020;382(6):534-44.

5. Burakevych N, McKinlay CJD, Harris DL, Alsweiler JM, Harding JE. Factors influencing glycaemic stability after neonatal hypoglycaemia and relationship to neurodevelopmental outcome. Sci Rep. 2019;9(1):8132.

6. Tottman AC, Alsweiler JM, Bloomfield FH, Gamble G, Jiang Y, Leung M, et al. Long-Term Outcomes of Hyperglycemic Preterm Infants Randomized to Tight Glycemic Control. J Pediatr. 2018;193:68-75.e1.

7. Alsweiler JM, Harding JE, Bloomfield FH. Tight glycemic control with insulin in hyperglycemic preterm babies: a randomized controlled trial. Pediatrics. 2012;129(4):639-47.

8. McKinlay CJD, Alsweiler JM, Anstice NS, Burakevych N, Chakraborty A, Chase JG, et al. Association of Neonatal Glycemia With Neurodevelopmental Outcomes at 4.5 Years. JAMA Pediatr. 2017;171(10):972-83.

9. McKinlay CJ, Alsweiler JM, Ansell JM, Anstice NS, Chase JG, Gamble GD, et al. Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years. N Engl J Med. 2015;373(16):1507-18.

10. Tottman AC, Alsweiler JM, Bloomfield FH, Pan M, Harding JE. Relationship between Measures of Neonatal Glycemia, Neonatal Illness, and 2-Year Outcomes in Very Preterm Infants. J Pediatr. 2017;188:115-21.

11. Goode RH, Rettiganti M, Li J, Lyle RE, Whiteside-Mansell L, Barrett KW, et al. Developmental Outcomes of Preterm Infants With Neonatal Hypoglycemia. Pediatrics. 2016;138(6).

12. Salis ER, Reith DM, Wheeler BJ, Broadbent RS, Medlicott NJ. Hyperglycaemic preterm neonates exhibit insulin resistance and low insulin production. BMJ Paediatr Open. 2017;1(1):e000160.

13. Kao LS, Morris BH, Lally KP, Stewart CD, Huseby V, Kennedy KA. Hyperglycemia and morbidity and mortality in extremely low birth weight infants. J Perinatol. 2006;26(12):730-6.

14. Onland W, Cools F, Kroon A, Rademaker K, Merkus MP, Dijk PH, et al. Effect of Hydrocortisone Therapy Initiated 7 to 14 Days After Birth on Mortality or Bronchopulmonary Dysplasia Among Very Preterm Infants Receiving Mechanical Ventilation: A Randomized Clinical Trial. Jama. 2019;321(4):354-63.

15. Garg R, Agthe AG, Donohue PK, Lehmann CU. Hyperglycemia and retinopathy of prematurity in very low birth weight infants. J Perinatol. 2003;23(3):186-94.

16. Ertl T, Gyarmati J, Gaál V, Szabó I. Relationship between hyperglycemia and retinopathy of prematurity in very low birth weight infants. Biol Neonate. 2006;89(1):56-9.

17. Hays SP, Smith EO, Sunehag AL. Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. Pediatrics. 2006;118(5):1811-8.

18. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, Palmer CR, van Weissenbruch M, et al. Early insulin therapy in very-low-birth-weight infants. N Engl J Med. 2008;359(18):1873-84.

19. Hay WW, Jr., Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr. 2009;155(5):612-7.

20. Ferriero DM. The Vulnerable Newborn Brain: Imaging Patterns of Acquired Perinatal Injury. Neonatology. 2016;109(4):345-51.

21. Wong DS, Poskitt KJ, Chau V, Miller SP, Roland E, Hill A, et al. Brain injury patterns in hypoglycemia in neonatal encephalopathy. AJNR Am J Neuroradiol. 2013;34(7):1456-61.

22. Beardsall K. Real time continuous glucose monitoring in neonatal intensive care. Early Hum Dev. 2019;138:104844.

23. Uettwiller F, Chemin A, Bonnemaison E, Favrais G, Saliba E, Labarthe F. Real-time continuous glucose monitoring reduces the duration of hypoglycemia episodes: a randomized trial in very low birth weight neonates. PLoS One. 2015;10(1):e0116255.

24. Galderisi A, Facchinetti A, Steil GM, Ortiz-Rubio P, Cavallin F, Tamborlane WV, et al. Continuous Glucose Monitoring in Very Preterm Infants: A Randomized Controlled Trial. Pediatrics. 2017;140(4).

25. Galderisi A, Lago P, Steil GM, Ghirardo M, Cobelli C, Baraldi E, et al. Procedural Pain during Insertion of a Continuous Glucose Monitoring Device in Preterm Infants. J Pediatr. 2018;200:261-4.e1.

26. DeSalvo DJ, Miller KM, Hermann JM, Maahs DM, Hofer SE, Clements MA, et al. Continuous glucose monitoring and glycemic control among youth with type 1 diabetes: International comparison from the T1D Exchange and DPV Initiative. Pediatr Diabetes. 2018;19(7):1271-5.

27. Perri A, Giordano L, Corsello M, Priolo F, Vento G, Zecca E, et al. Continuous glucose monitoring (CGM) in very low birth weight newborns needing parenteral nutrition: validation and glycemic percentiles. Ital J Pediatr. 2018;44(1):99.

28. Olczuk D, Priefer R. A history of continuous glucose monitors (CGMs) in self-monitoring of diabetes mellitus. Diabetes Metab Syndr. 2018;12(2):181-7.

29. U.S. Food and Drug.

30. Beardsall K, Thomson L, Guy C, Iglesias-Platas I, van Weissenbruch MM, Bond S, et al. Real-time continuous glucose monitoring in preterm infants (REACT): an international, open-label, randomised controlled trial. Lancet Child Adolesc Health. 2021.

31. Thomson L, Elleri D, Bond S, Howlett J, Dunger DB, Beardsall K. Targeting glucose control in preterm infants: pilot studies of continuous glucose monitoring. Arch Dis Child Fetal Neonatal Ed. 2019;104(4):F353-f9.

32. Beardsall K, Thomson L, Elleri D, Dunger DB, Hovorka R. Feasibility of automated insulin delivery guided by continuous glucose monitoring in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2020;105(3):279-84.

33. Reilly C, Moore Z, Patton D, O'Connor T, Nugent L. The impact of continuous blood glucose monitoring on glucose stability in the preterm infant; A systematic review. Journal of Neonatal Nursing. 2020;26(3):136-41.

34. Galderisi A, Bruschettini M, Russo C, Hall R, Trevisanuto D. Continuous glucose monitoring for the prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2020;12:Cd013309.

35. Efficacy of Continuous Glucose Monitoring in Neonates With Hypoglycemia. https://ClinicalTrials.gov/show/NCT02300285.

36. Can a glucose sensor improve control of sugar levels of premature babies in intensive care? : https://doi.org/10.1186/ISRCTN12793535.

37. Continuous Glucose Monitoring and Cerebral Oxygenation in Preterm Infants. https://ClinicalTrials.gov/show/NCT04347590.

38. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.

39. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.

40. Alessandro Perri LG, Mirta Corsello, Francesca Priolo, Giovanni Vento, Enrico Zecca, Eloisa Tiberi. Continuous glucose monitoring (CGM) in very low birth weight

newborns needing parenteral nutrition: validation and glycemic percentiles. Ital J Pediatr. 2018.

41. Neonatal hypoglycemia continuous glucose monitoring: a randomized controlled trial in preterm infants. https://doi.org/10.1089/dia.2016.2525.

42. Real-time Continuous Glucose Monitoring in Very Low Birth Weight Neonates. https://ClinicalTrials.gov/show/NCT01942239.

43. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, Vanhole C, VanWeissenbruch M, Midgley P, et al. Validation of the continuous glucose monitoring sensor in preterm infants. Arch Dis Child Fetal Neonatal Ed. 2013;98(2):F136-40.

44. Saw HP, Yao NW, Chiu CD, Chen JY. The value of real-time continuous glucose monitoring in premature infants of diabetic mothers. PLoS One. 2017;12(10):e0186486.

45. Nally LM, Bondy N, Doiev J, Buckingham BA, Wilson DM. A Feasibility Study to Detect Neonatal Hypoglycemia in Infants of Diabetic Mothers Using Real-Time Continuous Glucose Monitoring. Diabetes Technol Ther. 2019;21(4):170-6.

46. Continuous Glucose Monitoring in At-Risk Newborns. https://ClinicalTrials.gov/show/NCT04386005.

47. Continuous Glucose Monitoring in Infants. https://ClinicalTrials.gov/show/NCT04458649.

48. Strict glycemic control in VLBW infants at high risk of glycemic disorders using a Continuous Glucose Monitoring System: randomized Controlled Clinical Trial. https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000037353.

6. Supplemental Material

Table 1

(24) Characteristics of included study

Methods	Randomize controlled trial, parallel, single center
Participants	Fifty newborns were arbitrarily allocated (1:1) (after 48 hours from birth) to receive computer-guided glucose infusion rate (GIR) with or without CGM (continuous glucose monitoring). Inclusion criteria where: I) Infants born ≤32 weeks of gestation, II) Birth weight ≤1500 g. From this study were excluded: I) Newborns with congenital malformations; II) Newborns with chromosomal abnormalities; III) Birth weight of <500g. All newborns wore a G4 Platinum CGM system, this device was worn for a maximum of 7 days., calibrations were performed twice daily.
Interventions	I) Unblinded group CGM, the GIR adjustments were driven by CGM and rate of glucose change. II)Blinded CGM group the GIR adjustments were driven using standard of care glucometer based on blood glucose determinations.

Outcomes	Primary: Percentage of time spent in euglycemic range (72-144mg/dl) Secondary: I) Percentage of time in mild hypoglycemia (47-71 mg/dl); II) Time spent in severe hypoglycemia (<47mg/dl); III) Percentage of time in mild hyperglycemia (145-180 mg/dl); IV) Percentage of time in severe hyperglycemia (>180mg/dl); V) Glucose variability
Notes	-----

Risk of Bias

	Risk	**Support**
Random sequence generation	**LOW**	Quote: “Patients were randomly assigned by using electronically generated block randomization of 5 blocks of 10 subjects per block (www. sealedenvelope.com) with an allocation ratio 1:1 to the randomization groups." Quote: “Opaque envelopes containing the allocation group were sealed and sequentially numbered according to an electronically generated randomization list.”
Allocation concealment	**LOW**	Quote: “Opaque envelopes containing the allocation group were sealed and sequentially numbered according to an electronically generated randomization list.”

Blinding of participants and personnel	**High**	Assigned intervention could not be blinded. Masking of the study intervention is very difficult.
Blinding of outcome assessment	**LOW**	Quote: “Data were electronically anonymized by using an individual alphanumeric code and analyzed by investigators not involved in patient enrollment or data collection.”
Incomplete outcome data	**LOW**	From the 50 participants that were initially randomised not all were included, six were excluded (four were transferred to a closer hospital, 2 required sensor replacement more than once and were discontinued as per protocol). This is a reasonable attrition and not expected to affect results. 88% of newborns completed the study;
Selective reporting	**LOW**	Protocol is available, reported on pre-defined outcomes.
Other bias	**LOW**	The study seems to have no other sources of bias

(30) **Table 2: Characteristics of included study**

Methods	Randomize controlled trial, parallel-group, multi-center
Participants	One hundred and eighty newborns were randomly assigned (1:1) (within 24 hours from birth) to receive glucose/ insulin infusion guided by CGM (continuous glucose monitoring) or by standard care (intermittent methods of glucose measure). Inclusion criteria where: I) Newborns ≤ 33 weeks gestation; II) Birth weight ≤1200g; III) <24h after birth; IV) Written consent from parent or guardian From this study were excluded: I) Newborns with congenital malformations; II) Newborns with congenital metabolic disorders. All infants had an Enlite glucose sensor (Medtronic, Northridge, CA, USA) inserted subcutaneously into the thigh. Calibration was done every 12h using blood sample utilizing Nova StatStrip meters (Nova Biomedical, Waltham, MA, USA) for measurements.
Interventions	I) For the newborns assigned to the CGM group, real time data was available to view by the clinical team, they were provided with a specifically designed guideline to better control blood glucose levels based on CGM readings. This guideline consisted of adjusting glucose infusion rates or insulin infusion rates. The guidelines were based on CGM data, but it was advised to check

	blood glucose values whenever there were rapid changes in CGM values. Or if CGM values dropped to less than 4 mmol/L. II)Infants assigned to the control group had blood glucose managed accordingly with standard methods. In this group, CGMS were used but data collected was masked to the clinical team.
Outcomes	Primary: Percentage of time spent in euglycemic (target) range (2,6-10 mmol/L). Secondary: as stated, "the proportion of time sensor glucose concentrations were in the target range of 4–8 mmol/L; overall mean sensor glucose concentration; sensor glucose concentration variability (assessed by within-patient standard deviation); proportion of time that sensor glucose concentrations were in the severe hyperglycaemic range (>15 mmol/L); incidence of hypoglycaemia (any recorded blood glucose concentration of 2·2–2·6 mmol/L or any continuous episode of sensor glucose concentration of <2·6 mmol/L for >1 h); severe hypoglycaemia (any recorded blood glucose ≤2·2 mmol/L); clinical outcomes: mortality before 36 weeks' corrected gestational age, retinopathy of prematurity (maximum grade across all examinations), bronchopulmonary dysplasia (need for supplemental oxygen or respiratory support at 36 weeks' corrected gestational age), infection (microbiologically confirmed or clinically suspected late onset invasive infection from trial entry until hospital discharge),

	necrotising enterocolitis (requiring surgical intervention including peritoneal drainage or causing death), patent ductus arteriosus (requiring medical or surgical treatment), intracerebral pathology before discharge, growth at the end of week 1 and at 36 weeks' corrected gestational age, nutritional intake in week 1 and use of insulin in weeks 1 and 2".	
Notes	------	
	Risk of Bias	
	Risk	**Support**
Random sequence generation	**LOW**	Quote: "Babies were randomly assigned (1:1) within 24 h of birth to receive either the intervention with real-time CGM or standard care until 7 days of age. Randomisation was done using a central web randomisation system, Trans European Network ALEA, using blocks of random size (four, six, eight), stratifying by recruiting centre and gestational age (<26 or ≥26 weeks)."
Allocation concealment	**Low**	Quote: "The programme will notify the local research team of treatment allocation who will then inform their clinical team regarding the practicalities of management"
Blinding of participants and personnel	**HIGH**	Quote: "Masking of the study intervention was not feasible."

Blinding of outcome assessment	**LOW**	Quote: "The real-time CGM device collected glucose data continuously but the values were masked to the clinical team (in an opaque bag with a tamper proof seal)"
Incomplete outcome data	**LOW**	From the 180 participants that were initially randomised not all were included, 25 newborns were excluded. This is a sensible attrition, and it is not likely to change results. 86% of newborns completed the study;
Selective reporting	**LOW**	Protocol is available, reported on pre-defined outcomes
Other bias	**LOW**	The study seems to have no other sources of bias

(23) Table 3

Characteristics of included study

Methods	**Randomized clinical trial, parallel, single center**
Participants	Forty-eight newborns, were randomly assigned, within 24 hours from birth and during their first 3 days of life to: I) Real time continuous glucose measure (CGM-group), total participants allocated to this group n=25; II) Intermittent capillary

	glucose testing (IGM-group), total participants allocated to this group n=23. Inclusion criteria where: I) Pre-term infants ≤32 weeks; II) Birth weight ≤1500g. From this study were excluded, as stated: "Serious congenital abnormalities, a skin condition that contraindicated continuous glucose monitoring, a transfer to another hospital during the first days of life or an absence of parental agreement".
Interventions	I) In CGM-group, blood glucose levels were measured using CGM, glucose values ≤60 mg/dl were notified by an alarm, they were then controlled by capillary blood testing. II) In IGM-group standard methods (intermittent capillary blood glucose testing), performed every 4 hours, were used to measure blood glucose levels. In the two groups, whenever glycemic values were in the range of 50 to 60 mg/dl, the influx of glucose supply was raised by 1 g/kg/day and the glycemic value was verified after 2 hours. Hypoglycemia events, defined as <50 mg/dl, were handled by an intravenous bolus of 10% dextrose (3 ml/kg) and an increase of glucose influx (+2 g/kg/day), and then tested 30 to 60 min later.
Outcomes	I) Number and duration of hypoglycemic (≤50 mg/dl) episodes per patient detected by CGMS
Notes	-----

Risk of Bias		
Bias	Risk	Support
Random sequence generation	**LOW**	Quote: "The random allocation sequence was automatically generated by the statistical software of the University of Tours, with 8 patients per block. Two series (one per birth weight category) of numbered and sealed envelopes were created, containing a note with the device to be used for each patient."
Allocation concealment	**Unclear**	Quote "Two series (one per birth weight category) of numbered and sealed envelopes were created, containing a note with the device to be used for each patient." Unclear whether envelops were opaque.
Blinding of participants and personnel	**HIGH**	Assigned intervention could not be blinded. Masking of the study intervention is very difficult.
Blinding of outcome assessment	**LOW**	Quote: "All the stored data (RT- and blind-CGMS) were then secondarily transferred to an online securized database and analyzed retrospectively with an access restricted to the principal investigator."
Incomplete outcome data	**LOW**	From the 47 participants that were initially randomised not all were included, 4 were excluded (2 in each group

		were discontinued). This is a sensible attrition and it is not likely to alter results. 91% of newborns completed the study;
Selective reporting	**LOW**	Outcomes pre-defined in protocol were reported on the final study.
Other bias	**LOW**	The study seems to have no other sources of bias

Table 4: Characteristics of excluded studies

Study	Reason for exclusion
(40)	A non-randomized feasibility study, that aims to evaluate the feasibility and reliability of a CGM system in a population of VLBW infants.
(35)	Randomized Controlled trail, that aims to evaluate the utility of CGM in improving the diagnosis and management of neonatal hypoglycemia in infants. Inclusion criteria: babies born more than 33 weeks and 6 days after the start of the pregnancy. Terminated (Insufficient eligible participants to meet recruitment goal).
(32)	Single-center feasibility study with a randomized parallel design, both groups had subcutaneous continuous glucose monitoring and the intervention group receiving closed-loop insulin delivery.

(41)	Randomized controlled trail, results published in another study **(24)**.
(42)	Randomized controlled trail, results published in another study **(23)**.
(43)	Prospective study, comparing data obtained by CGMS from the NIRTURE Trial with data obtained simultaneously using point of care glucose monitors.
(44)	Feasibility study nonrandomized.
(45)	Interventional, randomized, parallel assignment. Aims to study the utility of CGMS to monitor blood sugar in newborns. The investigators will evaluate the number of hypoglycemic events detected using CGM and compare it to standard methods. Inclusion criteria: Newborns >34 weeks born to mothers with gestational or pre-gestational diabetes. Exclusion criteria: **Infants <2000 g**
(31)	Single center, **pilot study**. Compared CGM with standard methods of blood glucose measurement.
(36)	REACT trial, results published in included study (30).

Table 5: Characteristics of ongoing studies

Study	Description
(37)	Ongoing Randomized clinical trial, that aims to assess the impacts of CGM on both short-term and long-term neurodevelopment. Not yet recruiting.
(46)	Ongoing clinical trial, not yet recruiting. Aims to evaluate the feasibility and precision of CGM in at-risk newborns.

(47)	Ongoing observational study, recruiting.
(48)	An ongoing randomized controlled trial, that aims to achieve a reduction on dysglycemic episodes varying glucose infusion rate.

Table 6: Results

	Number of studies	Number of participants	Statistical method	Effect size
All case mortality	----	----	----	----
Mortality before discharge	**2**	**230**	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.09, 1.50]
Mortality at 28 days	**1**	**50**	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
Mean time to resolve hypoglycemia	-----	----	----	----
Mean time to resolve hyperglycemia	----	----	----	----

Number of episodes of hyperglycemia per individual	**1**	**50**	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.84,0.04]
Number of episodes of hypoglycemia per individual	**2**	**98**	Mean Difference (IV, Fixed, 95% CI)	-1.39 [-4.59, 1.80]
Mean time spent in glycemic target range	**2**	**230**	Mean Difference (IV, Fixed, 95% CI)	10.00 [4.66, 15.34]
Intracerebral pathology	**2**	**230**	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.62, 1.49]
Skin lesions, skin infection, or adverse effects attributed to CGMS	**----**	**----**	**----**	----
Number of cases of ROP	**----**	**----**	**----**	----
Late onset of sepsis	**1**	**50**	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 3.97]

Percentage of weight lost during study	**2**	**230**	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.20, 0.28]
Bronchopulmonary dysplasia (need for respiratory support at 36 weeks' corrected gestational age)	**2**	**230**	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.14]

Figures

Fig. 7 Mortality before discharge

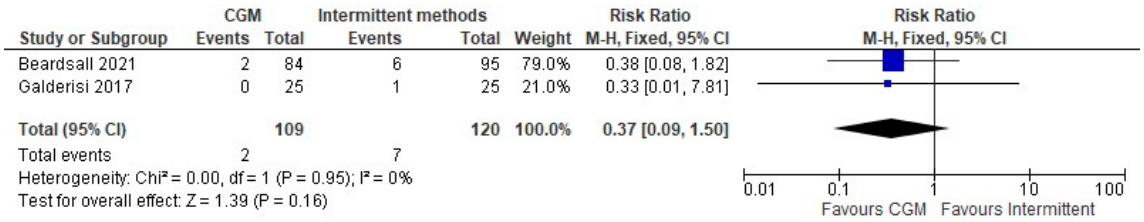


Fig. 8 Mortality at 28 days

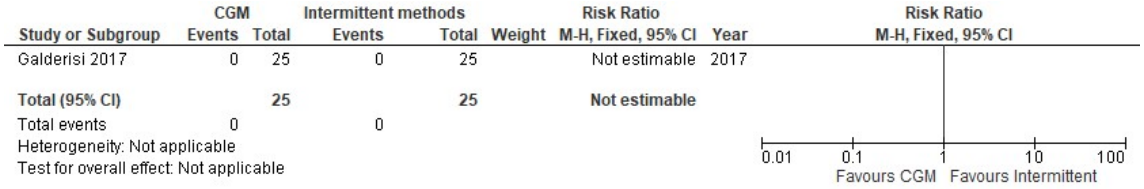


Fig. 9 Number of episodes of hyperglycemia per individual

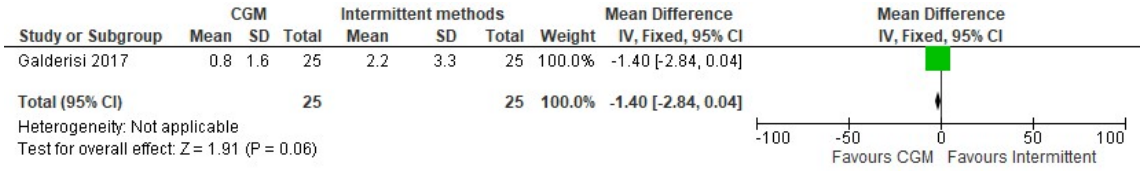


Fig. 10 Number of episodes of hypoglycemia per individual

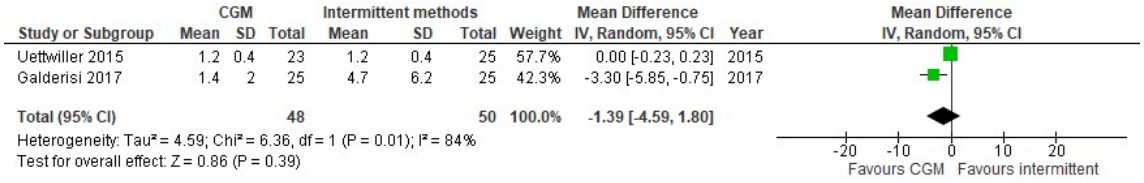


Fig. 11 Mean time spent in glycemic target range

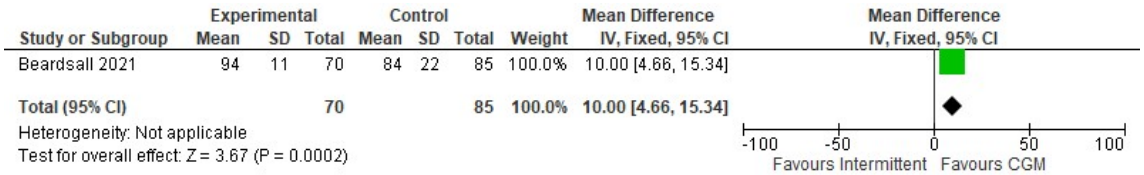


Fig. 12 Percentage of weight lost during study

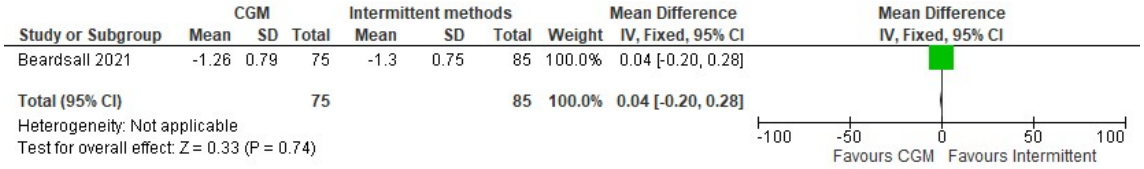


Fig. 13 Bronchopulmonary dysplasia

Fig. 14 Intracerebral pathology

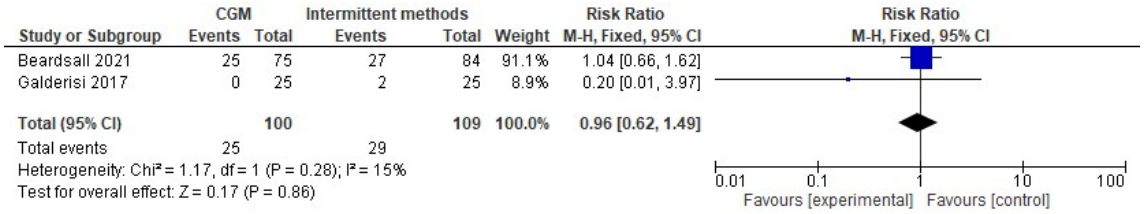
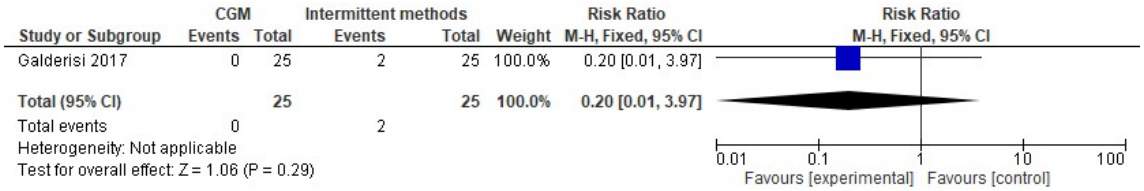


Fig. 15 Late onset of sepsis



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	Pag. 2, "Continuous Glucose Monitoring in Preterm infants- A systematic Review"
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Pag. 3, "abstract"
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	Pag. 9 "Why it is important to conduct this review"
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	Pag. 10 "Objectives"
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **– FACULTATIVO**	Não foi executado.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	Pag.11: "Inclusion criteria"
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **– MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases***	Pag 13: "Search methods"

		generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov. ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	Pag 13: "Electronic searches"
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	Pag. 15: "Study selection"
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	Pag 15: "Data collection and analysis"
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Pag. 15: "Data extraction"
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	Pag 16: "Assessment of risk of bias"
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Pag 16: "Measure of treatment effect".
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Pag 17: "Assessment of

PRISMA 2009 Checklist

			heterogeneity”
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Pag 18: “Subgroup analysis and investigation of heterogeneity”
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	Pag 19: “Search Results”
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	Tabela 1 a 3, “Supplemental Material”; “Characteristics of included studies”
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	Pag 23: “risk of bias in included studies” e tabela 1 a 3.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Pag. 24 a 31, “Effects of interventions”
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	Pag. 24 a 31, “Effects of interventions”
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Não foi executado.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	Pag 32: “Summary of evidence”
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	Pag 33: “Review limitations ”
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pag 34: “Future

		– MANDATÓRIO	considerations" e "Conclusion"
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Pag 34: "Declaration of competing interest"

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Journal of Pediatric Endocrinology and Metabolism
Information for Authors

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Acknowledgments: (If applicable).
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
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Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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- Manuscript is spell-checked and within the word limit for the type of article.
- References are in the correct format (Vancouver style) and cited sequentially in the text.
- References mentioned in the reference list are cited in the text and vice versa.
- Ethical approval is obtained and mentioned in the text.
- Numbers in the text, tables, or figures use decimal points, not commas.
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	Word count	Word count in abstract/structured (S), unstructured (U)	Number of keywords	Number of Tables & Figures	Number of references	Article
Research Article	3500	250, S*	3-6	8	50	Structured into Introduction, Materials (Subjects) and methods, Results, Discussion
Review Article	6000	200, U/S **	3-6	8	150	Structured
Mini Review	3500	200, U/S **	3-6	4	40	Structured
Opinion Paper	3500	250, U/S**	3-6	2	40	Structured
Point & Counterpoint	1500	200, U	3-5	2	15	Structured or unstructured
Short Communication	1500	200, S*	3-5	4	15	Abstract & unstructured text; Materials & methods are decribed in the legends to Figures and Tables
Case Report	1500	150, U/S***	3	2	10	Structured into Background, Case presentation, Learning points, What is new? (please give up to 3-5 bullet points)
Letter to the Editor & Reply	1200	n/a	3-5	2	10	Unstructured
Guidelines and Recommendations	3500	250, U	3-6	6	40	Structured
Editorial	1500	n/a	n/a	1	10	Structured or unstructured

*Background, Methods, Results, Conclusions; ** Background, Content, Summary and Outlook; *** Background, What is new? Case presentation, Conclusions.

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Systematic Reviews and Meta-Analyses of randomized controlled trials Please refer to the Preferred Reporting Items for Systematic Reviews and Meta- Analyses statement (**PRISMA**). Authors must include a

suitable PRISMA flow chart in their submission. The flow diagram depicts the flow of information through the different phases of a systematic review. A template of the PRISMA flow diagram is available **here** as a PDF and Word document.

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- **Articles in journals:** Alba P, Mitre N, Feldt M. More than one way to skin a thyroid. Managing pediatric hypothyroidism with weekly intramuscular levothyroxine. J Pediatr Endocrinol Metab 2016;29:745–8.
- **Articles in journals with 6 or more authors:** Klein K, Yang J, Aisenberg J, Wright N, Kaplowitz P, Lahlou N, et al. Efficacy and safety of triptorelin 6-month formulation in patients with central precocious puberty. J Pediatr Endocrinol Metab 2016;29:1241–8.
- **Articles ahead of print:** Analysis of growth hormone receptor gene expression in tall and short stature children. Pagani S, Radetti G, Meazza C, Bozzola M. J Pediatr Endocrinol Metab 2017 Mar 16. doi: 10.1515/jpem-2016-0355. [Epub ahead of print].
- **Articles in online only journals:** Labandeira CC, Kustatscher E, Wappler T. Floral assemblages and patterns of insect herbivory during the permian to triassic of Northeastern Italy. PloS One 2016 Nov 9;11:e0165205.
- **Editorial:** Arélin M, Beblo S. Newborn screening of metabolic disorders. [Editorial] . J Pediatr Endocrinol Metab 2016;29:1-3.
- **Letter to the Editor:** Weykamp C, Kuypers A, Bakkeren D, Franck P, Loon Dv, Gunnewiek JK, et al. Creatinine, Jaffe, and glucose: another inconvenient truth [Letter]. Clin Chem Lab Med 2015;53:e347-9.
- **Supplements:** Ploder M, Schroecksnadel K, Spittler A, Neurauter G, Roth E, Fuchs D. Moderate hyperhomocysteinema in trauma and sepsis indicates poor survival. Clin Chem Lab Med 2009;47:Suppl:S187.
- **Books and Monographs:** Kahn CR, Weir GC, editors. Joslin's diabetes mellitus, 13th ed. Philadelphia: Lea and Febiger, 1994:1068.
- **Chapters in Books:** Karnofsky DH, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, editor. Evaluation of chemotherapeutic agents. New York: Columbia University Press, 1949:191–205.
- **Website:** World Health Organization. WHO information for laboratory diagnosis of pandemic (H1N1) 2009 virus in humans update. Available at: http://www.who.int/csr/resources/publications/swineflu/WHO_Diagnostic_RecommendationsH1N1_20090521.pdf. Accessed: 6 Nov 2009.

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