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SUMMARY WITH CRITICAL APPRAISAL

Oral Glucose Gel for Neonatal Hypoglycemia: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines

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Abbreviations

AE	adverse event
CPS	Canadian Pediatric Society
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
hPOD	hypoglycemia Prevention with Oral Dextrose
IV	intravenous
NICU	neonatal intensive care unit
NHMRC	National Health and Medical Research Council
NRS	non-randomized studies
$NZD	New Zealand dollar
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Neonatal hypoglycemia is a common problem during the transition to extrauterine life.[1] Low blood glucose concentrations in the neonate are perhaps the most frequent biochemical abnormality encountered by healthcare providers caring for newborns.[2] As many as 15 out of every 100 babies, or half of higher risk babies, will have low blood glucose levels in the first few days after birth.[3] It is difficult to accurately describe the incidence of neonatal hypoglycemia as it varies due to the proportion of babies at risk in the sampled population, the screening guideline used, the threshold for defining hypoglycemia, and the method of analysis.[4]

The definition of neonatal hypoglycemia and the optimal strategy for diagnosis and management of affected newborns is a matter of debate.[2,4] Thresholds for intervention must have a wide safety margin due to the association of persistent or recurrent low glucose concentrations with increased risk of brain injury and cognitive and neurodevelopmental disabilities later in life.[4] Moreover, a single blood glucose value is not applicable to all clinical situations or all infants, as a 'normal' range of blood glucose is dependent upon infant size, gestation, and clinical condition.[5] Historically, a blood glucose concentration less than 2.6 millimoles per litre (mmol/L) has been identified as a threshold for intervention.[4,6] The Canadian Pediatric Society (CPS) recommends immediate intervention in a symptomatic baby with blood glucose concentration less than 2.6 mmol/L.[5] For asymptomatic at-risk babies, it is recommended that blood glucose be routinely checked until feeding is established and blood glucose is 2.6 mmol/L or more.[5] At-risk babies include those small (birth weight < 10th percentile) or large (birth weight > 90th percentile) for gestational age, infants born to a birthing parent with diabetes, and asymptomatic term or late preterm infants (≥ 35 weeks' gestation), although a number of additional gestational and fetal conditions may predispose newborn infants to neonatal hypoglycemia.[2,5,7]

For asymptomatic infants, management is focused on normalizing their blood glucose levels and preventing them from becoming symptomatic.[7] The first intervention is usually early and frequent oral feeding with breastfeeding strongly preferred, although infant formula supplementation may be used when breast milk is not available.[7] Intravenous (IV) dextrose is usually reserved for use when babies remain hypoglycemic after frequent oral feeding attempts and is the only intervention currently recommended by the CPS after unsuccessful feeding.[5] The use of IV dextrose usually requires admission to a neonatal intensive care unit (NICU) or specialty care nursery, which often necessitates physical separation of the birth parent and newborn and risks having an impact on breastfeeding

and bonding.[2] Other treatment options include antenatal expression of colostrum or skin-to-skin contact.

Oral glucose gel (also known as dextrose gel) is a non-invasive and inexpensive treatment option that can be administered on the postnatal ward to infants at risk of hypoglycemia.[3,8] Most often the concentrated aqueous gel (which may be locally compounded or commercially sourced) is massaged into the baby's inner cheek, after which feeding is encouraged. Following direct application to the oral mucosa, glucose rapidly enters the systemic circulation via the lingual and internal jugular veins, although a portion of the dose may also be swallowed and absorbed from the gastrointestinal tract.[3]

More information is needed to determine if oral glucose gel is clinically effective and safe when used for the prevention or treatment of transient neonatal hypoglycemia. There is uncertainty regarding whether or not the use of oral glucose gel can avoid separation of birthing parent and newborn, reduce admissions to the NICU or specialty nursery for administration of IV dextrose, or enhance breastfeeding uptake. It is also important to know if the use of oral glucose gel is cost-effective compared to standard care and if there are evidence-based clinical practice guidelines to inform the use of oral glucose gel as an intervention for neonatal hypoglycemia.

The purpose of this report is to synthesize and critically appraise the available evidence on the clinical effectiveness, cost-effectiveness, and guidelines for the use of oral glucose gel for neonatal hypoglycemia. The terms 'glucose' and 'dextrose' are used interchangeably in this report.

Research Questions

1. What is the clinical effectiveness of oral glucose gel for healthy term or late preterm neonates?
2. What is the cost-effectiveness of oral glucose gel for healthy term or late preterm neonates?
3. What are the guidelines informing the use of oral glucose gel for healthy term or late preterm neonates?

Key Findings

Limited evidence of high quality from one systematic review suggested that oral glucose gel administered in a hospital setting was clinically effective in preventing neonatal hypoglycemia in at-risk neonates. Evidence of moderate quality from two systematic reviews was inconclusive for oral glucose gel reducing the risk of separation of birthing parent and infant due to reporting of opposite effects. Limited evidence of low quality from four non-randomized studies was also inconclusive for oral glucose gel reducing admissions to neonatal intensive care or specialty care nurseries for treatment of hypoglycemia due to reporting of opposite effects. Limited evidence of moderate quality from two systematic reviews was inconclusive for oral glucose gel enhancing exclusive breastfeeding, as they reported opposite effects or lacked data. Evidence of moderate quality from one randomized controlled trial suggested that oral glucose gel improved quality of breastfeeding, although there is uncertainty regarding the assessment tool used. Low quality evidence on breastfeeding from four non-randomized studies is inconclusive as the studies reported opposite effects. Limited evidence of moderate quality from one systematic review and one non-randomized study suggested there was no difference in

adverse events between oral glucose gel and placebo. Due to the low event rates and paucity of safety outcomes reported in other studies, we concluded there is insufficient evidence in our report to evaluate the safety of oral glucose gel.

Limited evidence from one economic evaluation of moderate quality suggested that oral glucose gel is cost saving compared to standard care, despite wide variations in cesarean delivery rates, cost per dose of gel, cost per day spent in neonatal intensive care, and monitoring costs. Two-evidence based guidelines were identified; however, only one provided recommendations to inform the use of oral glucose gel.

The overall body of evidence considered in our report was heavily weighted by one randomized controlled trial from New Zealand.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main search to limit the retrieval by study type. A second broader search with only the neonates and hypoglycemia concepts was also included. Methodological filters were applied to limit retrieval of the second search to health technology assessments, systematic reviews, meta-analyses, and guidelines. For both searches, retrieval was limited to English language documents published between January 1, 2013 and June 4, 2018.

Rapid response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Healthy, term or late preterm neonates (birth to 48 hours of life) born in hospital, birthing centre, or home
Intervention	Oral glucose gel[a]
Comparator	Standard care (e.g., formula milk, breast milk, colostrum, skin-to-skin); no comparator
Outcomes	Clinical benefit or harm; cost; guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, and guidelines

[a] Also referred to as dextrose gel

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, or if they were published prior to 2013. Additionally, a randomized controlled trial (RCT) or non-randomized study (NRS) was not eligible for our review if it had been included in one of the included systematic reviews (SRs). Guidelines with unclear development methodology were also excluded.

Studies that reported on early preterm infants (less than 35 weeks' gestation) were not eligible for inclusion.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using the AMSTAR 2 tool,[9] RCTs and NRS were critically appraised using the Downs and Black Checklist,[10] the economic study was evaluated using the Drummond checklist,[11] and the evidence-based guidelines were assessed using the AGREE II instrument.[12] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively. Additional details on the strengths and limitations of each included SR, RCT, NRS, economic evaluation, or evidence-based guideline are provided in Appendix 3: Tables 6, 7, 8 and 9.

Summary of Evidence

Quantity of Research Available

A total of 349 citations were identified in the literature search. Following screening of titles and abstracts, 313 citations were excluded and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Of these 40 potentially relevant articles, 27 publications were excluded for various reasons, and 13 publications met the inclusion criteria and were included in this report. These comprised two SRs,[3,8] one RCT,[13] six NRS,[14-19] one economic evaluation,[20] and two evidence-based guidelines.[5,21,22] The included RCT[13] reported on outcomes for a subset of the original study population of a RCT (the Sugar Babies study)[6]) that is captured in one of the included SRs.[8] Two publications[5,21] were identified for one guideline because the treatment algorithm[5] referred to in the guideline was published separately. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The body of evidence includes two Cochrane SRs,[3,8] one RCT,[13] and six NRS[14-19] that addressed the clinical effectiveness of oral glucose gel for neonatal hypoglycemia. One economic evaluation[20] was identified that was a cost-analysis based on a RCT[6] included in one of the SRs,[8] and two evidence-based guidelines[5,21,22] provide recommendations to inform the use of oral glucose gel. Study characteristics are summarized below. Additional details regarding the characteristics of the included publications are available in Appendix 2: Tables 2, 3, 4 and 5.

Study Design

Systematic Reviews

In both SRs, [3,8] the standard methods of Cochrane and the Cochrane Neonatal Review Group were used to perform comprehensive literature searches in four or more electronic bibliographic databases. The date ranges covered by the searches were from database inception to January 2017[3] and to February 2016.[8] Both SRs included criteria for the inclusion of study types, participants, interventions, primary and secondary outcome measures, data collection and analysis, assessment of risk of bias, and assessment of the quality of evidence. One SR[3] included a single RCT from New Zealand published in 2016 (i.e., the Pre-hypoglycemia Prevention with Oral Dextrose [[hPOD] study)[23] whereas the other SR[8] included two RCTs (i.e., the Sugar Babies Study[6] published in 2013 from New Zealand an abstract by Troughton et al., from Northern Ireland published in 2000[24]). There was no overlap of studies in the SRs. Study eligibility in both SRs included RCTs and quasi-RCTs; however, one SR[3] also specified that cluster-randomized trials would be included, but not crossover trials. One of the SRs[8] planned to use meta-analyses to synthesize data from the included studies, but was able to do so for only one outcome. In both SRs, risk of bias was assessed using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions[11] and the quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[25] The number of patients included in the SR[3] with the single RCT was 416 while the number of patients included in the other SR[8] was 312. Further information about the characteristics of the included SRs is available in Appendix 2: Table 2.

Randomized Controlled Trial

The included RCT[13] reported on a subset of the original study population from the Sugar Babies Study[6] that is included in one of the SRs.[8] This study[6] was a prospective, double-blind, placebo-controlled RCT conducted at a single tertiary centre in New Zealand that assessed whether oral dextrose gel was more effective than placebo for reversal of neonatal hypoglycemia in 237 hypoglycemic babies. The study[13] that is included in this report provides prospectively-collected data on feeding that was not included in the original publication following treatment of 1 to 2 episodes of neonatal hypoglycemia in 211 babies.

Non-Randomized Studies

Two[16,18] of the included NRS were retrospective cohort studies conducted at single centers that compared pre/post implementation of a protocol using glucose gel for management of infants at risk of neonatal hypoglycemia. Sample sizes were 498[18] and 804.[16] Two NRS[17,19] were prospective chart audits conducted at single centers that evaluated pre/post implementation of a protocol using a glucose gel protocol for infants at risk of neonatal hypoglycemia. Sample sizes were 52[19] and 200.[17] One NRS[14] was a pilot study of 60 neonates at a single centre that compared the use of glucose gel with retrospective data from historical controls, whereas one NRS,[15] also a pilot study at a single centre, utilized a quasi-experimental design to compare use of dextrose gel with no treatment in 236 babies.

Further information about the characteristics of the included RCT and NRS is available in Appendix 2: Table 3.

Economic Evaluation

The one economic evaluation[20] included in this report was a cost-analysis of the use of dextrose gel compared to placebo as a primary treatment for neonatal hypoglycemia in the first 48 hours after birth. The time horizon was the duration of the infant's hospital stay and the perspective was that of the hospital (i.e., postnatal ward ± NICU) during the infant's initial hospital stay. A decision-tree model was constructed based on data from the Sugar Babies Study[6] that is included in one of the SRs[8] in this report. Cost inputs were derived from the New Zealand Ministry of Health's Weighted Inlier Equivalent Separations (2016). Key assumptions for the base case analysis were that the NICU was assumed to be Level II with an assumed average cost of $2,200 New Zealand dollars ($NZD) per day and that blood glucose concentrations would be measured using a blood gas analyzer with an assumed average cost per test. Multiple sensitivity analyses were undertaken by varying the cost of dextrose gel, rate of cesarean delivery, daily cost of NICU, and impact of blood glucose concentration monitoring. Additional details are available in Appendix 2: Table 4.

Guidelines

The two included evidence-based guidelines were developed by the Fetus and Newborn Committee of the CPS[5,21] and a multidisciplinary expert clinical practice guideline panel from the University of Auckland, New Zealand.[22] Evidence for both guidelines was derived from comprehensive literature searches of one or more electronic bibliographic databases. To assess the quality of the evidence, the CPS guideline[5,21] used the classification system of the Oxford Centre for Evidence-Based Medicine.[26] The University of Auckland guideline[22] used GRADE methods[25] and adapted National Health and Medical Research Council (NHMRC) methods to assess the quality of the evidence and the AGREE II[12] instrument to assess the methodological quality of evaluated guidelines. Neither guideline specifically stated that how recommendations were made (e.g., consensus, voting, or by some other method). Further information is available in Appendix 2: Table 5.

Year of Publication and Country of Origin

The two SRs, published in 2017[3] and 2016,[8] and the one included RCT[13] published in 2017, were all from New Zealand. The six NRS were published between 2016 and 2018, of which two were from Australia,[14,17] one was from the United Kingdom,[19] and three were from the United States.[15,16,18] The included economic evaluation[20] was published in 2018 and was from New Zealand. The two evidence-based guidelines were from Canada[5,21] and New Zealand.[22] The Canadian (CPS) guideline[5,21] was originally published in 2004 and re-affirmed in 2018, whereas the New Zealand guideline[22] was published in 2015.

Patient Population

Systematic Reviews

The patient populations in the two SRs differed slightly because one SR[3] evaluated use of oral glucose gel for prevention of neonatal hypoglycemia, whereas the other SR[8] evaluated oral glucose gel for treatment of neonatal hypoglycemia. Both SRs included studies conducted in hospitals providing maternity and neonatal services. One SR[3] included infants at risk of hypoglycemia defined as those born of a birthing parent with diabetes (gestational, type 1, and type 2 diabetes), small or large for gestational dates, and those born preterm (< 37 weeks) with other risk factors as determined by investigators, and who had had not yet received a diagnosis of, or treatment for, hypoglycemia. The other SR[8] included newborn infants from birth to discharge home who had hypoglycemia for any reason, but excluded

those who had received IV treatment for glucose maintenance at the time of hypoglycemia. Due to the small number of included RCTs in the SRs, the patient populations in each reflect those of the RCTs captured by the SRs. Detailed information regarding characteristics of the patient populations included in the SRs is available in Appendix 2: Table 2.

Randomized Controlled Trial

The patient population in the one included RCT[13] reflects the population enrolled in the Sugar Babies study[6] which included babies born at 35 weeks' gestation or older, were 48 hours or younger, and who were at risk of neonatal hypoglycemia (i.e., born of a birthing parent with diabetes [gestational, type 1, or type 2 diabetes], 35 or 36 weeks' gestation, small birth weight [< 10th percentile or < 2500 g], large birth weight [> 90th percentile or >4500 g], or other reasons such as poor feeding. Exclusion criteria were any prior treatment for neonatal hypoglycemia, serious congenital malformation, terminal disorders, or skin abnormalities that would prevent use of a continuous glucose monitor.[6] Of the 237 hypoglycemic babies originally randomized in the Sugar Babies study,[6] subsequent feeding data were available for 211 babies or 89% of the original study population.[13]

Non-Randomized Studies

All six NRS[14-19] were conducted at single centers which were hospitals providing maternity and neonatal services. All studies included babies ≥ 35 weeks' gestation at risk of neonatal hypoglycemia due to the risk factors previously identified (e.g., diabetic mothers, late pre-term gestation, small or large birth weight). One NRS[14] enrolled only babies with asymptomatic hypoglycemia born to diabetic mothers. Additional details regarding the population characteristics in each NRS are available in Appendix 2: Table 3.

No studies were identified in which included infants were born in a birthing centre or at home.

Economic Evaluation

The patient population upon which the base case analysis in the economic evaluation[20] was derived was taken from the Sugar Babies study,[6] which has previously been described in detail. The raw data from this study was used to model the proportions of infants who fell into each of the categories in the decision tree analysis as well as their length of stay on the postnatal ward and NICU, and monitoring and treatment specific to the management of hypoglycemia.[20] Infants who developed neonatal hypoglycemia were allocated into eight groups based on whether they were randomized to the intervention or control, whether they experienced a single or recurrent episode of hypoglycemia, and whether or not they were admitted to NICU.[20]

Guidelines

Both of the included evidence-based guidelines[5,21,22] are intended for healthcare professionals or caregivers who care for pregnant people and newborns who are at increased risk of neonatal hypoglycemia. The New Zealand guideline[22] also identifies policy makers in maternity and neonatal care among its target population.

Interventions and Comparators

The intervention in both SRs,[3,8] the RCT,[13] and five of the included NRS[14,16-19] was 40% dextrose (glucose) gel, either locally compounded or commercially sourced. The dose of

dextrose gel administered in almost all the studies was 200 milligrams per kilogram (mg/kg) or 0.5 millilitres per kilogram (mL/kg) and the method of administration usually involved first drying the baby's mouth with gauze and then massaging the dose into the buccal mucosa, after which the baby was encouraged to feed. In general, blood glucose concentration was measured 30 minutes after gel administration and if the baby remained hypoglycemic, or if hypoglycemia recurred at a later time, the intervention was repeated with a maximum of 3 to 6 doses administered over a 48 hour period. In the single RCT[23] that was included in one SR,[3] infants were randomized to one of four treatment groups: 40% dextrose gel at one of two doses(0.5 mL/kg = 200 mg/kg or 1 mL/kg=400 mg/kg), either once at one hour of age, or followed by three additional doses of dextrose (0.5 mL/kg before feeds in the first 12 hours).

In one NRS[15] the intervention was 77% dextrose gel sourced from a commercially-available product. As the economic evaluation[20] was based on the Sugar Babies study,[20] the intervention evaluated was 40% dextrose gel. The guideline from New Zealand[22] provides recommendations for use of 40% dextrose gel, whereas the CPS guideline[5,21] only provides recommendations for use of IV glucose.

The comparators specified in the SRs[3,8] were placebo, no treatment or standard care, or other therapies for prevention of neonatal hypoglycemia such as antenatal colostrum, early initiation of breastfeeding, supplementation with formula milk, or IV dextrose (which most often requires admission to the NICU). Based on the RCTs included in the SRs, the comparators evaluated were matched placebo gel in two studies [6,23] and feeding alone in one study.[24] The comparator in the one included RCT[13] was matched placebo gel.

In the six NRS, the comparators were historical controls in one study,[14] (i.e., breastfed infants subsequently treated with infant formula for treatment of hypoglycemia), retrospectively-identified infants treated according to a pre-glucose gel protocol that included supplementation with infant formula in three studies[17-19] and IV dextrose (10% dextrose in water) in one study[16] whereas in one NRS,[15] the comparator was no treatment (i.e., untreated at-risk infants born during the same time period at the same hospital). No studies were identified that included colostrum or skin-to-skin contact as comparators.

Outcomes

Systematic Reviews

Although both SRs[3,8] had identified a lengthy list of outcomes a priori, the small number of included RCTs resulted in outcomes only being available for risk of hypoglycemia (investigator-defined but considered to be blood glucose < 2.5 or 2.6 mmol/L in all included RCTs), type of treatment received for hypoglycemia, number of episodes of hypoglycemia per infant, separation of mother and infant for treatment of hypoglycemia, neonatal seizures, duration of initial hospital stay, and breastfeeding (at or after discharge and at six weeks or six months postpartum). One SR[3] reported on adverse events (AEs). One SR[8] reported outcomes at two years (corrected) age[27] for neurological and developmental disability, visual impairment, cerebral palsy, developmental delay/intellectual impairment, and executive dysfunction for infants who participated in the Sugar Babies study.[6] Development was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), executive function was assessed by various tests including the Behavior Rating Inventory of Executive Function (BRIEF-P) questionnaire completed by parents, visual acuity tests, audiology testing, neurological examination, and standard growth measurements, the details of which are reported elsewhere.[27]

Randomized Controlled Trial

Outcomes reported in the included RCT[13] were pre-feed alertness using a 4-point grading system where 1=awake and 4=too sleepy to feed, quality of breastfeeding using a breastfeeding assessment tool in routine use at the study site, duration of breastfeeding, and volume of infant formula taken by mouth or cup. A nurse or midwife who was blinded to the gel treatment recorded details about each feeding.

Non-Randomized Studies

A key outcome that was reported as either a primary or secondary outcome in each of the six NRS[14-19] was the admission of infants with hypoglycemia to the NICU. Other reported outcomes included blood glucose levels,[14,15,19] proportion of infants achieving, or time to, normoglycemia,[14,17] proportion of infants with hypoglycemia recurrence,[17] and breastfeeding.[16,18] Two NRS[16,18] also reported costs associated with a gel protocol relative to pre-implementation of the protocol .[18] One NRS[14] reported on AEs.

Economic Evaluation

The outcomes reported in the economic evaluation[20] were the average cost of treatment for hypoglycemia per infant which included postnatal ward costs, NICU costs, hypoglycemia screening and monitoring costs, and costs of therapy calculated in $NZD. Costs were presented as the encounter cost per infant (varying by single or recurrent episodes of hypoglycemia and whether or not the infant was admitted to NICU) and the average encounter cost per infant. The results of sensitivity analyses were also reported based on varying the cesarean delivery rate between 20% to 100%, the cost of dextrose gel between $NZD1.29 to $NZD86.00, NICU cost per day between $NZD1,100 to $NZD3,200 and excluding monitoring costs for NICU and all monitoring costs (which were assumed to be included in per diem costs).

Summary of Critical Appraisal

Detailed summaries regarding the strengths and limitations of the included SRs, RCT, NRS, economic evaluation, and evidence-based guidelines are provided in Appendix 3: Tables 6, 7, 8, and 9.

Systematic Reviews

Both SRs[3,8] were conducted according to standard methodology and reporting requirements for Cochrane reviews. An a priori design was described, comprehensive literature searches of 4 to 5 databases were conducted, types of studies, selection criteria, participants, interventions, and primary and secondary outcomes for the reviews were identified. Lists and characteristics of included studies were provided. Excluded studies were identified but comprised only one study in one SR[3] and none in the other SR.[8] One SR [3] included a single RCT (the Pre-hPOD study)[23] that was judged to have low risk of bias and the evidence was assessed as ranging from high to moderate quality using the GRADE method.[25] Caution was advised in interpreting some of the data due to low event rates (e.g., separation of birthing parent and infant, AEs). The majority (73%) of included infants in the RCT[23] were born to a birthing parent with diabetes which might affect the generalizability of the findings to other patient populations with different risk factors. The other SR[8] included two RCTs, for which one RCT (the Sugar Babies study)[6] was assessed to have low risk of bias and the other RCT,[24] which was only available in abstract form, to have insufficient detail to determine risk of bias, although some unexplained attrition was considered likely.

The quality of the evidence ranged from moderate to very low using the GRADE method.[25] The authors attempted a meta-analysis; however only one outcome measure could be pooled from the two RCTs (receipt of IV treatment); however, the estimates of effect were opposite and revealed no statistically significant differences.[8] In both SRs[3,8] data was not available for many of the pre-specified outcomes and only limited information on safety was reported.

Randomized Controlled Trial

The one RCT[13] included in this report reported on a subset of patients (89% of the study population) with data on breastfeeding from the Sugar Babies study[6] which was assessed to have low risk of bias and moderate quality of evidence. As this study comprises a subgroup or post-hoc analysis of the original study, it is unclear if was adequately powered to statistically compare outcomes between the treatment groups. The small sample size of some of the subgroups also renders the outcomes uncertain. Additional limitations are the validity of the breastfeeding assessment tool that was used to rate quality of each breast feeding as the tool was developed at the hospital that was the single center for the study and no information regarding its validation was provided.

Non-Randomized Studies

All six NRS[14-19] included in this report were single center, uncontrolled studies in which study participants and investigators were not blinded to treatment. Two studies[16,18] were retrospective analyses, two studies[17,19] were prospective chart audits; the remaining two pilot studies comprised one study[19] that utilized retrospective data from historical controls and another study,[15] that used a quasi-experimental design to compare dextrose gel with no treatment. Taken together, due to their non-randomized and unblinded designs, all the studies are limited by high risk of bias due to selection bias owing to lack of randomization and inadequate concealment of allocation, and performance and detection biases due to knowledge of the allocated intervention by participants and investigators. One study[15] used a different formulation of oral dextrose gel (77%) than was used in all other studies (40%) and reported outcomes for initial glucose concentrations that were opposite to those reported in the key RCTs[6,23] included in the SRs. There was a paucity of safety information from the NRS; one study[14] reported that no infants had an adverse reaction to the glucose gel. One NRS[14] was conducted in babies born to diabetic mothers therefore the results may not be generalizable to those with other risk factors.

Economic Evaluation

The key limitation in the included economic evaluation[20] was that all the effectiveness estimates were based on a single RCT(the Sugar Babies study).[6] The economic evaluation utilized a decision tree analysis approach to model overall costs which was clearly described and provided adequate detail about the model. Multiple sensitivity analyses were conducted and the choice of variables was justified. Costs were presented in aggregated form and not in disaggregated form, nor were costs discounted.

Guidelines

There was limited information available on the development of the CPS guideline[5,21] as the criteria for selecting the evidence and formulating the recommendations were not clearly described. In addition, the CPS guideline[5,21] did not provide any information on applicability (i.e., facilitators, barriers, or resource implications to its implementation or advice or tools on how the recommendations could be put into practice. The University of Auckland guidance[22] clearly described a rigorous development process for the guideline and its

applicability. Neither guideline[5,21,22] described seeking the views and preferences of the target population, an external review process, or a procedure for updating the guideline in the future.

Summary of Findings

The overall findings of this review are summarized below. Additional details are available in Appendix 4: Tables 10, 11, 12, and 13, in which the main study findings and author's conclusions are provided.

1. *What is the clinical effectiveness of oral glucose gel for healthy term or late preterm neonates?*

Hypoglycemia

One SR[3] that included a single RCT[23] that investigated four different dosing regimens of oral dextrose gel used for prevention of hypoglycemia in at-risk infants, found that based on high quality evidence, the gel (any dose) was associated with a statistically significant reduced risk of neonatal hypoglycemia compared with placebo in the first 48 hours after birth. On average, 8.3 infants would have had to receive prophylactic dextrose gel to prevent one additional case of neonatal hypoglycemia.[3] There was no statistically significant difference in the mean number of hypoglycemic episodes between the treatment groups. In the other SR[8] that investigated treatment of neonatal hypoglycemia with oral glucose gel, no data were available for the correction of hypoglycemia for each hypoglycemic event. In the key RCT[6] included in the SR, the primary outcome was treatment failure which was defined as blood glucose less than or equal to 2.6 mmol/L after two treatment attempts. The primary outcome was met as oral dextrose gel statistically significantly reduced the risk of treatment failure when compared with placebo.[6] The SR[8] did report that, based on evidence of very low quality, there was no statistically significant difference between dextrose gel and placebo or no treatment (feeding only) for the need for IV treatment for hypoglycemia.

Four NRS[14,15,17,18] reported on hypoglycemia outcomes. One study[14] reported that historical controls (asymptomatic hypoglycemic breastfed babies who received formula milk) achieved normoglycemia statistically significantly faster than infants treated with glucose gel; however, in all infants successfully treated with glucose gel, normoglycemia was achieved in 30 minutes. In another study,[15] the first blood glucose concentration taken 30 minutes after administration of prophylactic dextrose gel to infants at risk of hypoglycemia was not significantly different from controls (untreated at-risk infants), whether measured by bivariate or multivariate analyses. This study used a 77% glucose gel which the researchers speculated may have caused a hyperinsulinemic response, or alternatively, exogenous dextrose had a only a minimal effect on glucose homeostasis.[15] In one NRS[17] there was no statistically significant difference in the proportion of neonates achieving normoglycemia when post-implementation of a dextrose gel protocol (dextrose gel plus feed supplementation) was compared with pre-implementation of the protocol (feed supplementation alone). Of note; hypoglycemia recurrence was statistically significantly higher in the post-implementation group.[17] Another NRS[18] reported a significantly higher proportion of asymptomatic hypoglycemic infants had increased blood glucose levels after use of dextrose gel with feeding as compared with feeding alone.

Duration of hospital stay

One SR[3] found no statistically significant difference in the duration (mean days) of hospital stay per infant between oral dextrose gel and placebo. Similarly, one NRS[17] reported no significant difference in the length of hospital stay when post-implementation of a glucose gel protocol was compared with pre-implementation of the protocol.

Admissions to NICU

There were six NRS[14-19] that reported results for admission to NICU or a special care nursery as a study outcome. Of these, two studies[14,15] found no statistically significant differences between infants who received glucose gel compared with historical controls,[14] or controls who received no treatment.[15] In contrast, three NRS[16-18] reported that statistically significant lower proportions of infants required transfer to the NICU following implementation of a glucose gel protocol when compared with pre-implementation. Another NRS[19] reported a reduction in total admissions to NICU following implementation of a protocol for use of oral dextrose gel as a first-line treatment for neonatal hypoglycemia compared to pre-implementation; however, no statistical comparison was conducted.

Separation of birthing parent and infant for treatment of hypoglycemia

One SR[3] found no statistically significant difference between oral dextrose gel (any dose) and placebo in the separation of birthing parent and infant for treatment of hypoglycemia based on moderate quality evidence from one RCT.[23] Caution is warranted in interpretation of these results due to the small event rates. The other included SR[8] found that infants treated with dextrose gel were statistically significantly less likely to be separated from their birthing parent for treatment of hypoglycemia based on moderate quality evidence from one RCT.[6]

Breastfeeding

One SR[3] found no statistically significant difference between oral dextrose gel (any dose) and placebo in the rates of exclusive breastfeeding at discharge or breastfeeding at six months based on moderate quality evidence from one RCT.[23] The other included SR[8] found that infants treated with dextrose gel were more likely to be exclusively breastfed after discharge based on moderate quality evidence from one RCT.[6] No data were reported in this SR for breast feeding at six months of age, which was a pre-specified outcome. The one included RCT[13] reported that there were no statistically significant differences in pre-feed alertness scores, duration of breastfeeding, or volume of formula milk taken between babies treated with dextrose gel or placebo. Breastfed babies; however, were found to have statistically significantly better quality breastfeeding scores after dextrose gel compared with placebo, as measured using an in-house breastfeeding assessment tool.[13] It was concluded that treatment of hypoglycemic babies with dextrose gel does not depress subsequent feeding and may improve breastfeeding quality.[13]

Four NRS[15,16,18] included outcomes pertaining to breastfeeding. One NRS[15] found no statistically significant difference in the proportion of infants who were exclusively breastfed compared to untreated controls. In contrast, two NRS[16,18] found a statistically significant higher proportion of infants were exclusively breastfed after implementation of a glucose gel protocol compared with pre-implementation of the protocol. One NRS[19] reported a higher proportion of babies were still breastfeeding at three months following implementation of a glucose gel protocol compared with pre-implementation of the protocol; however, no statistical comparison was made.

Adverse events

One SR[3] reported that there were no statistically significant differences between oral dextrose gel and placebo in the number of adverse events (including choking or vomiting at time of administration) based on moderate quality evidence from one RCT.[23] Caution is warranted in interpretation of these results due to the small event rates. In the other included SR,[8] based on one RCT[6] the investigators reported no adverse outcomes. One NRS[14] reported that no infants had an AE to glucose gel in the study.

Long-term neurodevelopmental and disability outcomes

One SR[3] did not report any data for long-term neurodevelopmental and disability outcomes. The other SR[8] included a 2-year follow-up[27] of one of the included RCTs.[27] The SR reported that there was no statistically significant difference between dextrose gel and placebo based on evidence of very low quality for any major neurosensory disability after two years. Similarly, there were no differences between treatment groups for overall developmental disability, visual impairment or severity, cerebral palsy, developmental delay/intellectual impairment measured by the composite scores of the Bayley IIIscale, or executive function as assessed by the BRIEF-P composite score.[8]

Birthing parent with diabetes

An important risk factor for the development of neonatal hypoglycemia is if a birthing parent has diabetes (i.e., gestational, type 1, or type 2 diabetes).[1] Therefore, we sought to identify the proportion of infants in each included study who were born to a birthing parent with diabetes. For the two included SRs, the proportion of infants was 73%[3] and 39%.[8] In the one included RCT,[13] based on the Sugar Babies study,[6] the proportion was 39%. Across the six NRS,[14-19] the proportion of infants born to a birthing parent with diabetes ranged from 10% to 100%. We are unable to report outcomes grouped by the diabetes status of the birthing parent. The possible exception is the one NRS[14] that enrolled only infants born to a birthing parent with diabetes. In this study infants who received oral glucose gel took longer to achieve normoglycemia compared to historical controls who received infant formula.[14] Nonetheless, all infants treated successfully with oral glucose gel reached normoglycemia within 30 min and had numerically (but not statistically significantly) reduced admissions to a specialty care nursery.[14] These results should be considered in the context of the study design which was a small retrospective pilot study (N=60).

2. *What is the cost-effectiveness of oral glucose gel for healthy term or late preterm neonates?*

The cost of treating neonatal hypoglycemia using 40% dextrose gel in the base case analysis of the economic evaluation[20] included in our report had an overall cost of $NZD6,863.81 compared to a cost of $NZD8,178.25 for standard care (placebo). Therefore, the use of oral glucose gel was associated with a savings of $NZD 1,314.44 per infant treated. Sensitivity analyses demonstrated that treatment of an infant with neonatal hypogycemia with dextrose gel remained cost savings despite wide variations in cesarean delivery rates (20% to 100%), cost per dose of dextrose gel ($NZD1.29 to $NZD86.00), and cost per day of a stay in NICU ($NZD1,100 to $NZD3,200). The effect of varying monitoring costs by excluding blood glucose monitoring performed in the NICU or all monitoring costs, also resulted in dextrose gel being the less costly option. The key driver of costs between the two treatment arms was attributed to NICU admission for hypoglycemia.

Two NRS[16,18] reported cost savings subsequent to implementation of an oral dextrose gel protocol for neonatal hypoglycemia. Savings were based on total hospital charges for

infants admitted to NICU[16] and the cost of care (physician and hospital billing charges) for asymptomatic infants with hypoglycemia treated in a newborn nursery with feeds ± dextrose gel compared to the NICU with IV dextrose.[18]

Additional details on the findings from these studies are located in Appendix 4: Tables 11 and 12.

3. *What are guidelines informing the use of oral glucose gel for healthy term or late preterm neonates?*

Two evidence-based guidelines from Canada[5,21] and New Zealand[22] were identified. Only one of the evidence-based guidelines[22] provides recommendations for the use of 40% oral dextrose gel (200 mg/kg or 0.5 mL/kg) to treat babies 35 weeks' gestation or more and less than or equal to 48 hours after birth diagnosed with neonatal hypoglycemia. For babies with severe hypoglycemia (< 1.2 mmol/L), oral dextrose gel can be used as an interim measure while arranging for urgent medical review and treatment.[22] The recommendations are associated with a NHMRC strength of recommendation B (i.e., the body of evidence can be trusted to guide practice in most situations) and a Conditional Grade of recommendation (i.e., the benefits probably outweigh the benefits).

The CPS guideline[5,21] did not provide recommendations for the use of oral glucose gel, but rather recommends enteral supplementation for asymptomatic infants with blood glucose levels of 1.8 mmol/L to 2.5 mmol/L to augment caloric intake (Grade of recommendation: D; level 5, opinion). Furthermore, in symptomatic infants or asymptomatic infants who have failed to respond to enteral supplementation, are recommended to be treated with IV dextrose solution (Grade of recommendation: C; level 4, studies or extrapolations from level 2 or 3 studies).[5,21]

The detailed recommendations from the guidelines are located in Appendix 4: Table 13.

Limitations

There are various limitations associated with the evidence in our report for the use of oral glucose gel for neonatal hypoglycemia. A key limitation is that the preponderance of evidence in support of the use of oral glucose gel for the treatment of neonatal hypoglycemia is derived from a single RCT (the Sugar Babies study)[6] from New Zealand. This study comprised the key RCT included in one SR,[8] was the original study for the one included RCT,[13] was the source of all effectiveness inputs in the economic evaluation,[20] and was the primary evidence considered in the development of one evidence-based guideline.[22] Similarly, the main evidence for use of oral glucose gel for prophylaxis of neonatal hypoglycemia is also derived from a single study (the Pre-hPOD study),[23] which is also from New Zealand. Although these studies were assessed as having low risk of bias and having moderate to high quality of evidence, it is not known if the results are generalizable to Canadian clinical practice as there may be geographic differences in the manner in which neonatal care is provided between countries. Unfortunately, no Canadian clinical or cost-effectiveness studies were identified in our literature search.

Although the population of interest for this report was initially identified as healthy, term neonates, no studies could be identified in which oral glucose gel was used in infants at 37 weeks' or more gestation. As a result, the scope was expanded to include healthy, late preterm neonates, defined as 35 weeks' or more gestation, as they comprise a relevant patient population for Canadian practice. It should be noted that the CPS guideline[5] recommends routine care and feeding on demand for infants without risk factors for

neonatal hypoglycemia as long as the infant remains well. Risk factors for neonatal hypoglycemia identified in the CPS guideline[5] are small or large for gestational age, infants of a birthing parent with diabetes, and preterm infants, which largely comprise the population considered in this report.

The CPS guideline[5] was dated 2004; however, it was stated in the guideline that it had been re-affirmed on February 28, 2018. No information was provided to explain what process was followed for re-affirmation; however, it was noted that the two RCTs from New Zealand (published in 2013[6] and 2016[23]) that comprise the majority of evidence for use of oral glucose gel in our report were not referenced in the guideline. Furthermore, the only intervention recommended by the CPS guideline[5] for unwell babies with blood glucose less than or equal to 2.6 mmol/L or in at-risk babies following unsuccessful feeding is IV dextrose.

Information on the impact of oral glucose gel on breastfeeding was inconclusive. For example, one SR[3] found no difference whereas the other SR[8] reported a difference in rates of exclusive breastfeeding after discharge. Across all studies that reported breastfeeding outcomes, it did not appear that factors that could have influenced uptake of breastfeeding were controlled for (e.g., breastfeeding promotion, interaction with healthcare professionals or lactation experts, use of artificial nipples, availability of infant formula or donor breast milk, and follow-up support).

Lastly, there was very limited evidence available to assess the safety of oral glucose gel. One SR[3] reported that there were no differences between oral dextrose gel and placebo in the number of AEs, but cautioned that the results were based on very low event rates. There was one NRS[14] that reported that no infants had an AE to glucose gel. It is unclear if the lack of safety outcomes in the included studies could be due to the perception that orally administered glucose is assumed to be safe. The formulations of oral glucose gel used in the studies comprised both locally prepared and commercially sourced products. As such, the formulations could contain artificial flavorings, colorings, and food preservatives in addition to glucose. The studies included in our report did not provide this level of detail nor was it within the scope of this report to evaluate formulation characteristics. It was concluded that there was insufficient evidence identified in our report to evaluate the safety of oral glucose gel.

Conclusions and Implications for Decision or Policy Making

The current report summarizes the results of two SRs,[3,8] one RCT[13], six NRS,[14-19] one economic evaluation,[20] and two evidence-based guidelines.[5,21,22]

Limited evidence of high quality from one SR[3] that included a single RCT[23] suggests that oral glucose gel (any dose) is clinically effective in preventing neonatal hypoglycemia compared to placebo in at-risk babies (small or large birth weight, born to a birthing parent with diabetes, and late preterm 35 weeks' or more gestation). The other SR[8] that included two RCTs[6,24] did not report any data for outcomes pertaining to correction of hypoglycemic events. The primary outcome in the key included RCT[6] in the SR was treatment failure (i.e., blood glucose less than 2.6 mmol/L after two treatment attempts) which was statistically significantly reduced with oral dextrose gel compared with placebo. Limited evidence of low quality pertaining to hypoglycemia from four NRS is inconclusive as opposite treatment effects were reported in the studies.

Evidence for oral glucose gel reducing the risk of separation of birthing parent and infant is inconclusive. One SR[3] reported no difference in separation with use of oral glucose gel compared to placebo based on evidence of moderate quality and small event rates. In contrast, the other SR[8] reported that, based on evidence of moderate quality, oral dextrose gel reduced the incidence of separation of birthing parent and infant for treatment of hypoglycemia. It is possible that the discrepancy is due to differences in the patient populations as one SR[3] focused on prevention of hypoglycemia in at-risk infants whereas the other SR[8] focused on treatment of infants with hypoglycemia, thus infants may have been more likely to be admitted to the NICU in the latter population. Limited evidence of low quality from six NRS[14-19] pertaining to admissions to NICU or to a specialty care nursery is inconclusive as the studies reported opposite treatment effects or did not make statistical comparisons. One SR[3] suggests there is no difference in the duration of the initial hospital stay per infant between those who received oral dextrose gel or placebo.

Limited evidence of moderate quality from one SR[3] suggests that there is no difference in the proportion of infants who were exclusively breastfed at discharge between those who received oral dextrose gel compared to placebo. Similarly, no treatment differences were reported for breastfeeding at six weeks' postpartum based on evidence of moderate quality.[3] In contrast, the other SR[8] reported that dextrose gel increased the likelihood of exclusive breastfeeding at two weeks of age based on evidence of moderate quality; however, no data were available for exclusive breast feeding at six months of age which was another outcome identified in the SR. In the one included RCT,[13] there were no differences in pre-feed alertness scores, breastfeeding duration, and volume of formula taken, between infants who received oral dextrose gel for treatment of hypoglycemia compared to placebo; however, oral dextrose gel was associated with improved quality of breastfeeding, although there is uncertainty regarding the validity of the assessment tool used in the study. Limited evidence of low quality from four NRS[15,16,18] with regard to the association of oral dextrose gel with enhanced breastfeeding is inconclusive as opposite treatment effects were reported in the studies.

Limited evidence of moderate quality from one SR[3] and one NRS[14] suggest that there is no difference in AEs between oral dextrose gel and placebo; however, due to the low event rates in these studies and paucity of safety outcomes reported in other studies, we concluded that there is insufficient evidence to evaluate safety of oral glucose gel.

One SR[8] reported that no evidence suggests there is a difference between dextrose gel and placebo in major neurologic disability, developmental disability, cerebral palsy, developmental delay, or executive function at two years of age or older; however, caution must be exercised in interpreting the results due to wide confidence intervals, small sample sizes, and low event rates.[8]

One economic evaluation[20] of moderate quality suggests that oral dextrose gel is cost saving compared to standard care and is supported by sensitivity analyses that included wide variations in cesarean delivery rates, cost per dose of dextrose gel, cost per day spent in NICU, and monitoring costs. A key limitation of the evaluation was that all effectiveness estimates were based on a single RCT[6] from New Zealand and it is not known if the findings are applicable to Canadian practice settings.

Two-evidence based guidelines[5,21,22] were identified; however, only one guideline[22] provided recommendations for the use of oral glucose gel that were based primarily on the results of a single RCT[6] from New Zealand.

Further research is required to validate and confirm the clinical and cost-effectiveness of oral glucose gel in healthy, term (37 weeks or more gestation) neonates as well as in a Canadian or North American setting. It is unknown how geographic differences may have affected treatment outcomes. The preponderance of evidence for use of oral glucose gel for the prevention or treatment of neonatal hypoglycemia is derived from RCTs [6,23] that were conducted in New Zealand. One of the RCTs[6] comprised the main evidence considered in one SR,[8] was the original study for the included RCT,[13] was the source of all effectiveness inputs in the economic evaluation,[20] and was the primary evidence considered in the development of one evidence-based guideline,[22] thus heavily weighting the overall body of evidence upon the results of this study.

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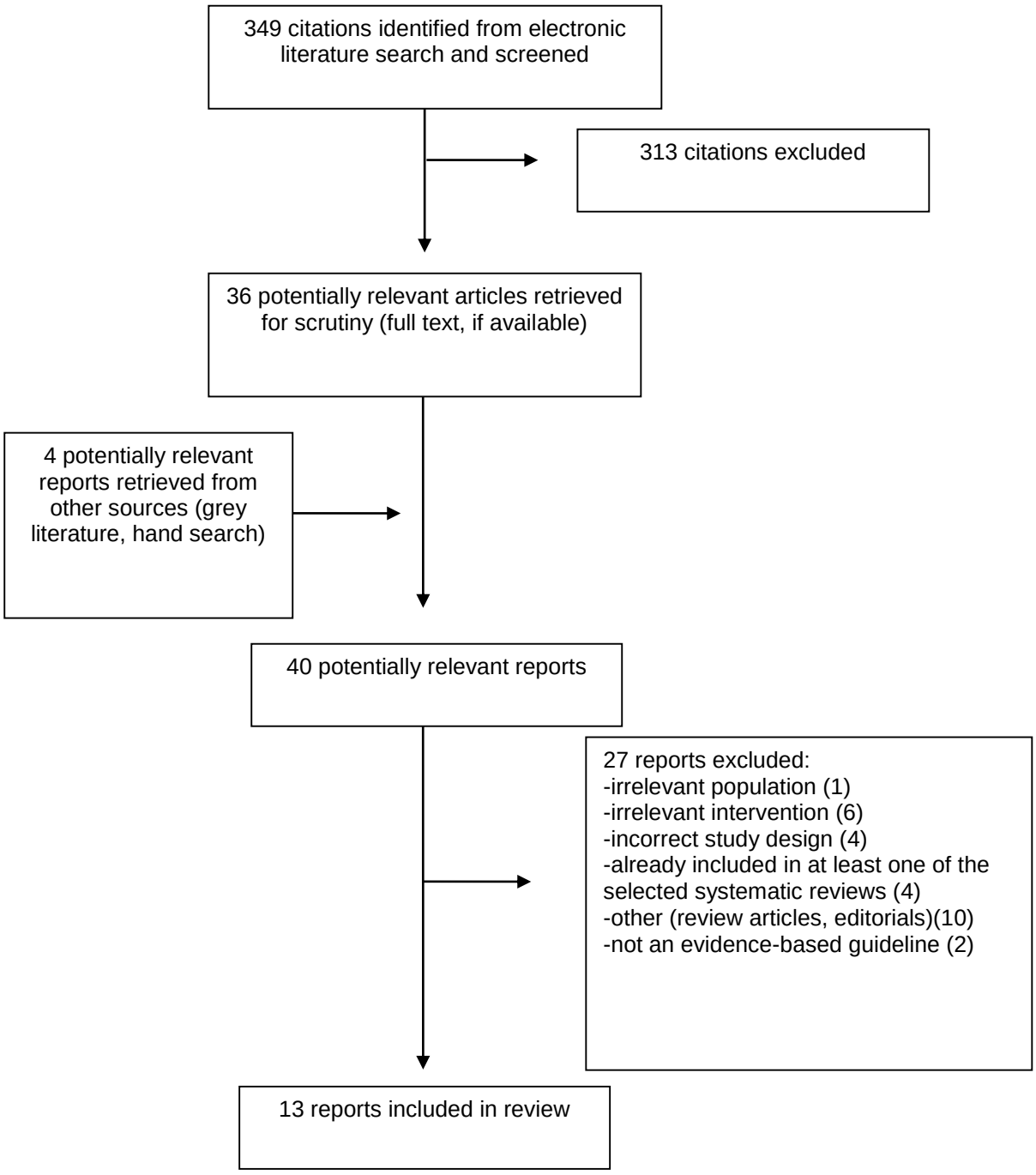
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Hegarty, 2017[3] New Zealand	A Cochrane systematic review of RCTs and quasi-RCTs (including cluster-randomized trials, but not crossover trials) published from the inception of the searched databases (i.e., Cochrane Central Register of Controlled Trials, MEDLINE, Embase, and CINAHL) to January 2017. Clinical trial databases, conference proceedings, and reference lists of retrieved articles were also searched. 1 RCT (the Pre-hPOD study; Hegarty, 2016[23]) from New Zealand was included.	416 newborn infants at risk of neonatal hypoglycemia, but without an apparent indication for admission to NICU. The study population in the Pre-hPOD study[23] included infants of mothers with diabetes, late preterm [35 or 36 weeks' gestation], small (birth weight < 10th percentile or < 2.5 kg), large (birth weight > 90th percentile or > 4.5 kg), and of ≥ 35 weeks' gestation and ≥ 2.2 kg birth weight infants.	Intervention: Dextrose gel (of any concentration and at any dose or number of doses, given orally) Comparator: Placebo, no treatment/standard care, or other therapies for prevention of neonatal hypoglycemia such as antenatal expression of colostrum, early initiation of breastfeeding, supplementation or substitution of breast-feeding with formula milk Interventions were to be commenced within the first 24 h following birth	Outcomes: -Hypoglycemia (investigator-defined) -Major neurological disability at ≥ 2 years of age -Hypoglycemia (blood glucose < 2.6 mmol/L) -Receipt of treatment for hypoglycemia -AEs -Separation from mother for treatment of hypoglycemia -Breast feeding -Duration of hospital stay -Neurological sequelae Follow-up: -Hypoglycemia outcomes were measured in the first 48 h after birth; other outcomes (e.g., breastfeeding) at 6 weeks; long-term follow-up planned at ≥ 2 years of age
Weston, 2016[8] New Zealand	A Cochrane systematic review and meta-analysis of RCTs and quasi-RCTs published from the inception of the searched databases (i.e., Cochrane Central Register of Controlled Trials, MEDLINE, Embase, CINAHL, and Web of Science) to February 2016. Clinical trial databases and hand searches of, conference proceedings and specific scientific	312 newborn infants who were hypoglycemic for any reason. The study population in the Sugar Babies study[6] study included infants of mothers with diabetes, late preterm [35 or 36 weeks' gestation], small (birth weight < 10th percentile or < 2.5 kg), large (birth weight > 90th percentile or > 4.5 kg) less than 48 postnatal hours old and	Intervention: Dextrose gel (at any dose given orally) Comparator: Placebo, no treatment or other therapies (including IV bolus)	Outcomes: -Correction of hypoglycemia (investigator-defined) for each hypoglycemia event -Major neurological disability at ≥ 2 years of age -Receipt of IV treatment or other medications for hypoglycemia -Blood glucose level -Hypoglycemia -AEs -Separation from

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	meetings were conducted. 2 RCTs (the Sugar Babies study; Harris, 2013,[6] Harris,2016[27]) from New Zealand and Troughton, 2000[24] from Northern Ireland were included.	at risk for hypoglycemia. The study population in the Troughton 2000[24] study were hypoglycemic infants ≥ 36 weeks gestation with blood glucose < 2.5 mmol/L admitted to the NICU. .		mother for treatment of hypoglycemia -Breast feeding -Duration of hospital stay -Neurological sequelae <u>Follow-up</u>: -Hypoglycemia outcomes were measured in the first 48 h after birth; other outcomes (e.g., breastfeeding) at 6 weeks. Results from the long-term follow-up of the Sugar Babies study (Harris, 2016[27]) at ≥ 2 years of age were included in the systematic review.

AE = adverse event; NICU = neonatal intensive care unit; hPOD = hypoglycemia prevention with oral dextrose; IV = intravenous; mmol/L = millimoles per litre; RCT = randomized controlled trial

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Randomized Controlled Trial				
Weston, 2017[13] New Zealand Note: This publication reports on a subset of the original study population from the Sugar Babies study (Harris, 2013[6]) which is included in the systematic review by Weston, 2016.[8] This publication describes prospectively-collected data on feeding following treatment of 1 or 2 episodes of neonatal hypoglycemia that are not included in the Weston, 2016[8] systematic review.	Prospective, double-blind, placebo-controlled RCT conducted at a single tertiary referral maternity hospital	Inclusion criteria: Infants born at ≥ 35 weeks' gestation, ≤ 48 h old at risk of neonatal hypoglycemia. Risk factors included mother with diabetes (gestational, T1D, T2D), preterm (35 or 36 weeks' gestation, small birth weight (< 10th percentile or < 2500 g) or large birth weight (> 90th percentile or > 4500 g), or poor feeding. Exclusion criteria: Any previous treatment for neonatal hypoglycemia, serious congenital malformation, terminal disorders, or skin abnormalities preventing use of a continuous glucose monitor.	Intervention: 40% dextrose gel in a 3 mL oral syringe (n=118) Dose: 200 mg/kg (0.5 mL/kg) massaged into the buccal mucosa after which babies were fed according to maternal choice Comparator: matched placebo (2% carboxy-methyl cellulose gel) (n=119)	Outcomes reported in this analysis are: -Pre-feed alertness -Quality of breast feeding -Duration of breast feeding -Volume of formula taken (Treatment of 1 or 2 episodes of neonatal hypoglycemia defined as any blood glucose level < 2.6 mM measured on a blood gas analyzer)
Non-Randomized Clinical Trials				
Barber, 2018[14] Australia	Pilot study comparing the intervention with retrospective data from matched historical controls at a single centre	Inclusion criteria: Infants born to mothers with diabetes from ≥ 36 weeks' gestation with asymptomatic hypoglycemia Exclusion criteria: NR	Intervention: 40% glucose gel in a 2 mL oral syringe (n=36) Dose: 0.5 mL/kg administered sublingually and/or massaged into the buccal mucosa Comparator: historical controls (breastfed infants subsequently treated with formula for the treatment of hypoglycemia) (n=24)	Outcomes reported: -Blood glucose levels -Time to normoglycemia -Special care nursery admission -AEs

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
Coors, 2018[15] United States	Pilot quasi-experimental study comparing the intervention with no treatment at a single centre	Inclusion criteria: At-risk infants (born to mothers with diabetes who were asymptomatic, late pre-term [35 to 36 weeks of gestation] with birth weight < 2500 g or > 4500 g) at risk for hypoglycemia Exclusion criteria: Symptomatic infants, did not meet gestational age or body weight criteria and no risk factors, chromosomal or congenital abnormalities, hyperinsulinemic disorders, received hypoglycemia treatment after 72 h, transferred to NICU before first feeding, received IV fluids or undocumented feeding times.	Intervention: 77% dextrose gel (n=72) Dose: 0.5 mL/kg rubbed into the buccal mucosa Comparator: No treatment (i.e., untreated at-risk infants born during the same time period) (n=164)	Primary: -Blood glucose concentration 30 minutes after the first milk feeding (controls) or dextrose gel administration (prophylactic subjects) Secondary: -Rate of NICU admission for IV dextrose
Makker, 2018[16] United States	Retrospective study comparing pre/post implementation of a revised protocol using the intervention for management of infants at risk for neonatal hypoglycemia at a single centre	Inclusion criteria: Infants ≥ 35 weeks' gestation and ≥ 2000 g birthweight at increased risk of hypoglycemia due to mothers with diabetes, late preterm (35 to 36 weeks gestation) or small or large birthweight. Exclusion criteria: Transfer to the NICU for an indication other than hypoglycemia, suspicion of a genetic disorder, failure to adhere to the glucose management protocol	Intervention: Gel protocol (40% glucose gel as adjunctive therapy for infants at risk of hypoglycemia) (n=383) Dose: 200 mg/kg or 0.5 mL/kg into the buccal mucosa immediately before feeding at every intervention point that called for an early or additional feeding Comparator: Pre-gel protocol (infants at risk of hypoglycemia were treated with 2 mL/kg bolus IV D10W depending upon blood	Primary: -Rate of transfer of infants to the NICU for treatment of hypoglycemia with a continuous infusion of D10W Secondary: -Rate of exclusive breastfeeding -Total NICU charges in the at-risk study population

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
			glucose level) concentration (n=421)	
Ter, 2017[17] Australia	Prospective audit of pre/post implementation of a protocol using the intervention in the management of neonatal hypoglycemia at a single centre	Inclusion criteria: Infants ≥ 36 weeks gestation at risk and treated for hypoglycemia Exclusion criteria: < 36 weeks' gestation and/or admitted to NICU for reasons other than hypoglycemia	Intervention: Gel protocol (40% dextrose gel in addition to feed supplementation) (n=100) Dose: 200 mg/kg or 0.5 mL/kg through buccal administration Comparator: Pre-gel protocol (feed supplementation alone) (n=100)	Primary: -Admission to NICU for hypoglycemia Secondary: -Proportion of neonates who achieved normoglycemia (defined as blood glucose ≥ 2.6 mmol/L) with no clinical signs after 1 or 2 treatment attempts -Proportion of neonates with hypoglycemia recurrence after normoglycemia and 1 or 2 treatment attempts
Rawat, 2016[18] United States	Retrospective chart review of pre/post implementation of a protocol using the intervention in the management of asymptomatic hypoglycemia at a single centre	Inclusion criteria: Asymptomatic infants ≥ 35 weeks' gestational age, < 48 h old, small or large for gestational age, mother with diabetes, cord pH < 7.10, cord base excess <-10 mEq/L, as well maternal treatment with beta-blockers, oral hypoglycemic agents, indomethacin, or nifedipine Exclusion criteria: Symptomatic hypoglycemia and congenital malformations	Intervention: Gel protocol (40% dextrose gel in 3 mL oral syringes in addition to feed supplementation) (n=250) Dose: 200 mg/kg or 0.5 mL/kg applied to buccal mucosa; maximum of 3 doses in the first 48 h Comparator: Feed supplemental only (n=248)	Primary: -Transfer to the NICU for IV dextrose Secondary: -Exclusive breastfeeding rates at discharge -Cost savings associated with the gel protocol
Stewart, 2016[19] United Kingdom	Prospective audit of pre/post implementation of a protocol using the intervention in the management of neonatal hypoglycemia	Inclusion criteria: Infants at risk of transient hypoglycemia including mother with diabetes, < 2.5 kg or > 4.5 kg birthweight, < 37 weeks gestation	Intervention: Gel protocol (40% dextrose gel) (n=24) Dose: 0.5 mL/kg or 1 fingertip per kg applied between lips and gums	Outcomes reported: -Admissions to NICU -Temperature < 36° C on admission -Mean blood glucose level on admission

Table 3: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes
	at a single centre	Exclusion criteria: NR	followed by feeding Comparator: Pre-gel protocol (supplementation with infant formula) (n=28	-Treatment with IV dextrose -Mean length of stay in NICU -No of days stay in NICU or high dependency unit or special care unit for neonatal hypoglycemia Follow-up: -Compared the one month period before the intervention was implemented versus the one month period after implementation

AE = adverse events; D10W = dextrose 10% in water intravenous solution; IV = intravenous; mg/kg = milligram per kilogram; mL/kg = millilitre per kilogram; NR = not reported; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus

Table 4: Characteristics of Included Economic Evaluation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Glasgow, 2018[20] New Zealand	Type: Cost analysis Time Horizon: Duration of the infant's postnatal hospital stay Perspective: Hospital (postnatal ward ± NICU) during the infant's initial hospital stay	To evaluate the costs of using dextrose gel as a primary treatment for neonatal hypoglycemia in the first 48 h after birth compared with standard care	Infants at risk of neonatal hypoglycemia (including infants of mothers with diabetes) enrolled in the Sugar Babies study (Harris, 2013[6])	Intervention: Dextrose gel 40% Comparator: Placebo	Decision tree model	Data from the Sugar Babies study[6] was used to model the categories in the decision tree, length of stay on postnatal ward and NICU, monitoring and treatment. Costs (i.e., postnatal ward, NICU, hypoglycemia screening and monitoring, and costs of therapy) were calculated using the New Zealand Ministry of Health's Weighted Inlier Equivalent Separations, 2016.	For the base case analysis, NICU was assumed to be Level II and average cost was NZD$2200 per day. Admission of < 1 day was rounded to 1 whole day. For infants admitted to NICU, it was assumed blood glucose concentrations would be measured using a blood gas analyzer with average cost per test of NZD$33.36. Costs were collected and recorded in NZD$ with base year of 2016-2017.

NICU = neonatal intensive care unit; NZD$ = New Zealand dollars; RCT = randomized controlled trial

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
2004 Canadian Pediatric Society Screening Guidelines for Newborns at Risk for Low Blood Glucose[21] and Algorithm for the Screening and Immediate Management of Babies at Risk for Neonatal Hypoglycemia, Year[5] (Reaffirmed 2018)						
This guideline and algorithm is intended for any healthcare professionals or caregivers in Canada who treat newborns.	Both screening and management of neonatal hypoglycemia are addressed in this guideline. Management of asymptomatic hypoglycemia includes increased breastfeeding frequency, supplementation with breast milk or breast milk substitute, increased carbohydrate intake (e.g., dextrose water), or IV glucose therapy.	Outcomes were not considered a priori, but were reported as part of the process of evaluating the evidence. Outcomes identified within these guidelines include blood glucose levels, screening modalities and timing, asymptomatic and symptomatic hypoglycemia, interventions, and education or counseling of caregivers.	A MEDLINE database search was performed for studies up to March 2004 as well as the Cochrane Library for reviews and articles relating to glucose and feeding. The guidelines were re-affirmed in February 2018.	The classification system of the Oxford Centre for Evidence -Based Medicine was used to grade the evidence.[26] Level of evidence ranged from 1a (systematic reviews of RCTs) to 5 (expert opinion). The resulting recommendations were graded as Grade A (consistent Level 1 studies) to Grade D (Level 5 evidence or troublingly inconsistent or inconclusive studies of any level).	Recommendations were developed and graded by the Fetus and Newborn Committee of the Canadian Pediatric Society. No information on the methodology used to produce or assign a strength to a recommendation was provided.	No information on guideline validation was provided.
2015 Oral Dextrose Gel to Treat Neonatal Hypoglycemia: Clinical Practice Guidelines, University of Auckland[22]						
This guideline is intended for health professionals who care for pregnant women where the baby is at increased risk of neonatal hypoglycemia (e.g., material diabetes, growth	The use of oral dextrose gel in babies diagnosed with neonatal hypoglycemia. This guideline does not cover screening criteria, diagnosis of neonatal hypoglycemia, or the use of	Primary outcomes were treatment of hypoglycemia (investigator defined) and any neurological impairment at ≥ 2 years of age including any visual impairment,	Systematic literature search of MEDLINE, EMBASE, Central, CINAHL, Web of Science, and Scopus databases from inception to October 2014 was undertaken. In	Quality of included studies was assessed using GRADE methods and adapted NHMRC methods. The methodological quality of the guidelines was assessed using AGREE II.[12]	A multidisciplinary expert clinical practice guideline panel developed the guideline using procedures recommended by the NHMRC 1998 and the former New Zealand Guidelines Group 2012.	No information on guideline validation was provided

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
restriction, macrosomia, and preterm birth), or newborns with neonatal hypoglycemia, pregnant women and their partners, and policy makers in maternity and neonatal care.	oral dextrose gel given to prevent the development of hypoglycemia.	cerebral palsy, motor impairment, hearing impairment, or developmental delay. Secondary outcomes included blood glucose, levels, hypoglycemia-related outcomes, healthcare resource utilization, separation of mother and baby, breast feeding, formula, brain imaging, etc.	addition, the proceedings of relevant scientific meetings were also searched.			

IV = intravenous; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation NHMRC = National Health and Medical Research Council

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews using the AMSTAR 2 Checklist[9]

Strengths	Limitations
Hegarty, 2017[3]	
-An apriori design was described -A comprehensive literature search using criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group was performed of 4 databases (Cochrane Central Register of Controlled Trials [CENTRAL], MEDLINE, Embase, and CINAHL. In addition, clinical trial databases, conference proceedings, and reference lists of retrieved articles were also searched. -Literature searches were conducted from database inception to January 2017 -An explanation for the selection of study design was provided -A list of the included studies was provided (i.e., only 1 RCT was included) -Characteristics of the included study were provided -A list of excluded studies was provided -Study selection was done by 2 reviewers and data extraction was independently done by 2 reviewers using a previously developed data extraction form -The methodological quality and risk of bias of the included study was assessed using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions -The overall risk of bias was judged to be low -The quality of the evidence was assessed independently by 2 reviewers using the GRADE approach as outlined in the GRADE Handbook -The evidence was determined to range from high quality to moderate quality -All randomized infants were analyzed with no withdrawals (no attrition bias) -Conflict of interest declaration was included -Source of funding for the systematic review was disclosed	-Evidence is based on one RCT conducted in two hospitals in New Zealand -Results are reported for all doses of oral dextrose gel combined -The majority of included infants (~73%) were born to diabetic mothers which may affect generalizability of the trial results to other infant populations -No trials were identified that compared oral dextrose gel with no intervention or other therapies for prevention of neonatal hypoglycemia (e.g., breastfeeding, supplementation with infant formula) -Blinding of outcome assessment (detection bias) in the included study was unclear -Minimal or no data was available for many of the pre-specified outcomes of the review (e.g., long-term neurodevelopmental and disability outcomes as well as many other secondary outcomes) -Event rates were low for other prespecified outcomes (e.g., AEs, separation of mother and baby)
Weston, 2016 [8]	
-An apriori design was described -A comprehensive literature search was performed of 5 databases (Cochrane Central Register of Controlled Trials [CENTRAL], MEDLINE, Embase, CINAHL and Web of Science. In addition, searches of international clinical trial networks and handsearches of proceedings of specific scientific meetings were conducted. -Literature searches were conducted from database inception to February 2016 -An explanation for the selection of study design was provided -A list of the included studies was provided (i.e., only 2 RCTs were included) -Characteristics of the included studies were provided -No studies were excluded -Study selection was done by 2 reviewers and data extraction was independently done by 2 reviewers using a previously	- Evidence is based on two RCTs that each were conducted at a single centre -The intervention (dextrose gel) could be locally prepared or provided commercially) -Results are reported for all doses of oral dextrose gel combined -One of the included RCTs (Troughton, 2000[24]) was available only in abstract form with limited data -The study designs of the 2 RCTs differed somewhat as the study by Harris, 2013[6] compared oral dextrose gel with placebo, each followed by a milk feed of maternal choice, whereas the study by Troughton, 2000[24] compared oral dextrose gel plus a feed compared to a feed alone -The Toughton 2000[24] abstract had insufficient detail to assess any of the components of risk of bias; however, unexplained attrition appeared to be likely therefore the authors concluded the risk of bias was high

Table 6: Strengths and Limitations of Systematic Reviews using the AMSTAR 2 Checklist[9]

Strengths	Limitations
developed and piloted data extraction form -The methodological quality and risk of bias of the included study was assessed using the criteria in the Cochrane Handbook for Systematic Reviews of Interventions -The overall risk of bias was judged to be low for the Sugar Babies study (Harris 2013[6] and the Harris 2016[27] 2-year follow-up cohort) -The quality of the evidence was assessed independently by 2 reviewers using the GRADE approach as outlined in the GRADE Handbook -The evidence was determined to range from moderate to very low quality -Statistical heterogeneity was assessed and considered when interpreting study results -Conflict of interest declaration was included -Source of funding for the systematic review was disclosed	-For the only outcome measure for which data from the two RCTs could be pooled (i.e., receipt of IV treatment), estimates of effect were opposite and were not statistically significantly different -Data was not available for many of the pre-specified outcomes of the review

GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; RCT = randomized controlled trial

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[10]

Strengths	Limitations
Randomized Controlled Trial	
Weston, 2017[13]	
-Objectives of the study were clearly described -The intervention, comparator, and main outcomes of the study were clearly described -Screening criteria for study eligibility were described in the original publication of the Sugar Babies study(Harris, 2013[6]) -Study patients in the intervention and comparator groups were recruited from the same population, using the same inclusion criteria, over the same period -Study patients were randomized to treatment -Assessors (i.e., nurse or midwife) were blinded to treatment allocation and recorded details about each feeding -Patient characteristics were clearly described in the original publication (Harris, 2013[6]) -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -The study setting was appropriate (i.e., tertiary care maternity hospital)	-Single centre RCT -As the analysis comprises a subgroup or post-hoc analysis, it is unclear if the study was adequately powered to statistically compare outcomes between the two treatment arms -The small sample size of some of the subgroups renders the outcomes uncertain -Patient flow was not described - The quality of each breastfeeding was recorded using a breastfeeding assessment tool developed and used at the tertiary hospital that was the single centre for the study; no information was provided regarding its validation -No AEs or other safety outcomes were reported
Non-Randomized Trials	
Barber, 2018[14]	
-Objectives of the study were clearly described -The intervention and main outcomes were clearly described -Screening criteria for study eligibility were described -Study patients in the intervention and comparator groups were recruited from the same study site using the same inclusion criteria, albeit at different time periods -Patient characteristics were clearly described and it was stated that there was a good match between groups with the exception of the type of diabetes (e.g., gestational, type 1 or type 2 diabetes) in mothers with diabetes -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the main study outcomes -Actual probability values were reported -Valid and reliable main outcome measures were used -Analyses were by ITT -It was stated that no infants had an adverse reaction to the glucose gel -The study setting was appropriate	-Single centre non-randomized uncontrolled study -Pilot study with small sample sizes -Only infants admitted to a ward with an onsite blood gas analyzer were included, thus comprising a convenience sample of infants admitted to the postnatal ward -Included only infants born mothers with diabetes, therefore, generalizability of results to infants with other risk factors for hypoglycemia is limited -Study participants and investigators were not blinded to treatment -Retrospective data from medical records were used for the comparison group
Coors, 2018[15]	
-Objectives of the study were clearly described	-Single centre non-randomized uncontrolled study

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[10]

Strengths	Limitations
-The intervention and main outcomes were clearly described -Screening criteria for study eligibility were described -Study patients in the intervention and comparator groups were recruited from the same study site using the same inclusion criteria during the same time period -Patient characteristics were clearly described -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the main study outcomes -Actual probability values were reported -Valid and reliable main outcome measures were used -Analyses were by ITT -The study setting was appropriate	-Infants were enrolled into the study only when investigators were available resulting in disproportionate treatment groups (i.e., n=72 in the intervention group and n=164 in the control group) and imbalances in baseline demographic characteristics (e.g., birthweight, gestational age, age at first blood glucose sample) -A different formulation of dextrose gel with higher carbohydrate concentration (77%) was used than in other studies (40%) which may have caused a hyperinsulinemic response -The study ended due to researcher unavailability -No AEs or safety outcomes were reported -Study participants and investigators were not blinded to treatment
Makker, 2018[16]	
-Objectives of the study were clearly described -The intervention and main outcomes were clearly described -Screening criteria for study eligibility were described -Study patients in the intervention and comparator groups were recruited from the same study site using the same inclusion criteria, albeit at different time periods one year apart -Patient characteristics were clearly described and it was stated that demographic characteristics were similar in the two one year periods -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the main study outcomes -Actual probability values were reported -Valid and reliable main outcome measures were used -Analyses were by ITT -The study setting was appropriate	-Single centre non-randomized uncontrolled study -Study participants were sequentially enrolled -Study participants and investigators were not blinded to treatment -Retrospective data from medical records one year prior to implementation of the intervention were used for the comparison group -No AEs or safety outcomes were reported
Ter, 2017[17]	
-Objectives of the study were clearly described -The intervention and main outcomes were clearly described -Screening criteria for study eligibility were described -Study patients in the intervention and comparator groups were recruited from the same study site using the same inclusion criteria, albeit at different time periods (i.e., pre/post implementation of the intervention) -Patient characteristics were clearly described and it was stated that the two groups were comparable with no significant differences in risk factors for hypoglycemia -Main findings were clearly described -Appropriate statistical tests were used to assess the main study outcomes -Actual probability values were reported -Valid and reliable main outcome measures were used -Analyses were by ITT	-Single centre non-randomized uncontrolled study -Study participants were sequentially enrolled (convenience sample) -Measures of random variability were not reported (only P-values) -Study participants and investigators were not blinded to treatment -Retrospective data from medical records were used for the comparison group (i.e., therefore dependent on the accuracy of documentation by clinical staff; however, whenever possible the information was confirmed by consulting other sources) -No AEs or safety outcomes were reported

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[10]

Strengths	Limitations
-The study setting was appropriate	
Rawat, 2016[18]	
-Objectives of the study were clearly described -The intervention and main outcomes were clearly described -Screening criteria for study eligibility were described -Study patients in the intervention and comparator groups were recruited from the same study site using the same inclusion criteria, albeit at different time periods (approximately 6 months apart) -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the main study outcomes -Actual probability values were reported -Valid and reliable main outcome measures were used -Analyses were by ITT -The study setting was appropriate	-Single centre non-randomized uncontrolled study -Only limited information on patient characteristics was provided -Unclear how costs and the economic impact of using the intervention were derived -Study participants and investigators were not blinded to treatment -Retrospective data collected during the pre-intervention period was done using the electronic medical record whereas after implementation of the intervention, data was prospectively entered in by study personnel -Economic assessment did not include the costs associated with breastfeeding -No follow-up data to determine breastfeeding rates after discharge -No AEs or safety outcomes were reported
Stewart, 2016[19]	
-Objectives of the study were clearly described -The intervention and main outcomes were clearly described -Screening criteria for study eligibility were described -Study patients in the intervention and comparator groups were recruited from the same study site using the same inclusion criteria, albeit at different time periods (one month apart) -Patient characteristics were clearly described and -Main findings were clearly described -Valid and reliable main outcome measures were used -Analyses were by ITT -The study setting was appropriate	-Single centre non-randomized uncontrolled study -Small sample sizes (i.e., total admissions to NICU for primary transitional hypoglycemia were 41 and 11 patients, in the pre- and post-implementation groups, respectively) -No statistical comparisons of main study outcomes -Study participants and investigators were not blinded to treatment -Retrospective data from medical records were used for the comparison group -No AEs or safety outcomes were reported

AE = adverse event; ITT = intention-to-treat; NICU = neonatal intensive care unit; RCT = randomized controlled trial

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[11]

Strengths	Limitations
Glasgow, 2018[20]	
-Research question and objective of the cost-analysis were clearly stated and justified -The perspective (hospital postnatal ward ± NICU) was clearly stated -The time horizon (length of infant's initial hospital stay) was clearly stated -The source of the effectiveness data (the Sugar Babies study; Harris 2013[6]) was clearly stated and details provided -The use of a decision-tree to model overall costs was clearly described and details about the model were provided. -Currency and prices were stated to be in NZD$ -Sensitivity analyses were conducted and choice of variables was justified -The answer to the study question was provided and conclusions based on the data reported were clearly stated	-Effectiveness estimates were based on a single study (the Sugar Babies study; Harris 2013[6]) -Costs relating to the mother's antenatal care or due to any complications experienced by, or additional costs incurred specifically by the mother were excluded -Quantities of the resources used were not reported separately from their unit costs -Costs were presented only in aggregated form (i.e., overall encounter cost or average cost of treatment) and not in disaggregated form -Costs were not discounted -Currency (NZD$) was not adjusted for inflation

NICU = neonatal intensive care unit; NZD$ = New Zealand dollar

Table 9: Strengths and Limitations of Guidelines using AGREE II[12]

Item	Guideline	
	Canadian Pediatric Society, 2004 [5,21]	University of Auckland, 2015 [22]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	X	X
6. The target users of the guideline are clearly defined.	✓	✓
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	✓	✓
8. The criteria for selecting the evidence are clearly described.	X	✓
9. The strengths and limitations of the body of evidence are clearly described.	✓	✓
10. The methods for formulating the recommendations are clearly described.	X	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	✓
12. There is an explicit link between the recommendations and the supporting evidence.	X	✓
13. The guideline has been externally reviewed by experts prior to its publication.	X	X
14. A procedure for updating the guideline is provided.	X	X
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	✓	✓
16. The different options for management of the condition or health issue are clearly presented.	✓	✓
17. Key recommendations are easily identifiable.	✓	✓

Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	X	✓
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X	✓
20. The potential resource implications of applying the recommendations have been considered.	X	✓
21. The guideline presents monitoring and/or auditing criteria.	✓	✓
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	✓	✓
23. Competing interests of guideline development group members have been recorded and addressed.	X	X

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Hegarty, 2017[3]	
Study population (N=416): infants of mothers with diabetes (n=301; 73%), preterm (n=27; 6%), small (n=49; 12%), large (n=38; 9%) and more than one risk factor (n=10; 2%). Overall, 277 infants were randomized 2:1 to 40% oral dextrose gel or placebo gel (hydroxymethylcellulose) and to one of the following regimens: 0.5 mL/kg once (66 dextrose; 34 placebo), 1 mL/kg (73 dextrose; 36 placebo), 0.5 mL/kg for four doses (68 dextrose; 35 placebo), and 1 mL/kg once followed by 0.5 mL/kg for three additional doses (70 dextrose; 33 placebo) Reported outcomes (dextrose gel versus placebo): -Neonatal hypoglycemia (n=415) risk ratio= 0.76 (95% CI: 0.62; 0.94); risk difference=-0.13 (95% CI: -0.23; -0.03); NNT, on average 8.3 infants would have to receive prophylactic oral dextrose gel to prevent one additional case of neonatal hypoglycemia -Receipt of oral dextrose gel treatment for hypoglycemia (n=415); risk ratio=0.79 (95% CI: 0.56; 1.12) -Other medication for treatment for hypoglycemia (n=415); risk ratio=0 (95% CI: 0, 0) -Number of episodes of hypoglycemia (n=186); mean difference=-0.18 (95% CI: -0.55; 0.19) -AEs (e.g., choking or vomiting at time of administration) (n=413); risk ratio=1.09 (95% CI: 0.55; 2.17) -Separation of mother and infant (NICU admission for hypoglycemia) (n=415); risk ratio=0.46 (95% CI: 0.21; 1.01) -Neonatal seizures (n=415); risk ratio=1.5 (95% CI: 0.06; 36.58) -Duration of initial hospital stay (days) (n=411); mean difference=-0.19 (95% CI: -0.66; 0.28) -Exclusive breastfeeding at discharge (n=415); risk ratio=1.00 (95% CI: 0.86; 1.15) Breastfeeding at 6 weeks postpartum (n=386); risk ratio=1.06 (95% CI: 0.88; 1.29)	The authors concluded that: *"Oral dextrose gel reduced the risk of neonatal hypoglycemia in at-risk infants in a single trial. Results showed no statistically significant differences in the number of adverse events or in the risk of separation of infant from mother for the treatment of hypoglycemia between babies who received oral dextrose gel and those given placebo. Caution is suggested in interpreting data for the latter two outcomes owing to low event rates. Available evidence is limited to a cohort of at-risk infants, most of whom were infants of diabetic mothers and were treated on the postnatal ward. Minimal data available for many of the prespecified outcomes of this review showed no long-term neurodevelopmental and disability outcomes. Additional evidence is needed to assess the efficacy and safety of dextrose gel for prevention of neonatal hypoglycemia."*[3] (page 2)
Weston, 2016[8]	
Study population (N=312) Detailed demographic data was only available from the Sugar Babies study (Harris, 2013[6] (n=237): infants of mothers with diabetes (n=92; 39%), preterm (n=90; 38%), small (n=62; 26%), and large (n=22; 9%) birthweight. Overall, 237 infants were randomized 1:1 to 40% oral dextrose gel or placebo gel (2% carboxymethyl cellulose) and to the regimen: 200 mg/kg (0.5 mL/kg). Blood glucose was measured 30 minutes later and if the baby remained hypoglycemic or had recurrent hypoglycemia, treatment was repeated up to a maximum of 6 doses over 48 h. Reported outcomes (dextrose gel versus placebo): -No results for correction of hypoglycemia (investigator-defined) for each event of hypoglycemia (i.e., the primary outcome)	The authors concluded that: *"Treatment of infants with neonatal hypoglycemia with 40% dextrose gel reduces the incidence of mother-infant separation for treatment and increases the likelihood of full breastfeeding after discharge compared with placebo gel. No evidence suggests occurrence of adverse effects during the neonatal period or at two years' corrected age. Oral dextrose gel should be considered first-line treatment for infants with neonatal hypoglycemia."*[8] page 2

Table 10: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion

-Major neurosensory disability (2-year follow-up) (n=184) risk ratio=6.27 (95% CI: 0.77; 51.03)
-IV treatment for hypoglycemia (n=312) risk ratio=0.81 (95% CI: 0.29; 2.25)* This was the only outcome for which meta-analysis could be conducted and the 2 RCTs provided estimates in opposite direction, but neither study provided findings that showed independent statistical significance. Heterogeneity was high (I^2 = 72%)
-Increased blood glucose 30 to 90 minutes after treatment (n=75) mean difference=0.40 (95% CI: -0.14; 0.94)
-Separation of mother and infant (for treatment of hypoglycemia) (n=237) risk ratio=0.54 (95% CI: 0.31; 0.93)
-Neonatal seizures (n=237) risk ratio=0.0 (95% CI: 0; 0)
-Exclusive breastfeeding after discharge (n=237) risk ratio=1.10 (95% CI: 1.01; 1.18)
-Developmental disability at age ≥ 2 years (n=184) risk ratio=1.11 (95% CI: 0.75; 1.63)
-Visual impairment and severity at age ≥ 2 years (n=183) risk ratio=1.17 (95% CI: 0.72; 1.89)
-Cerebral palsy and severity at age ≥ 2 years (n=183) risk ratio=5.16 (0.25; 106.12)
-Developmental delay/intellectual impairment and severity at ≥ 2 years (n=183) risk ratio=1.07 (95% CI: 0.71; 1.61)
-Developmental impairments - Bayley III scores at 2-year follow-up (all mean difference):
  -Cognitive (n=183) -1.0 (95% CI: -3.92; 1.92)
  -Language (n=182) 0.0 (95% CI: -3.93; 3.93)
  -Motor (n=183) 0.0 (95% CI: -2.76; 2.76)
  -Social, emotional (n=178) 1.0 (95% CI: -3.56; 5.56)
  -General adaptive (n=180) 2.0 (95% CI: -1.95; 5.95)
-Executive function at 2-year follow-up (all mean difference):
  -Executive function composite score (n=179) 0.90 (95% CI: -0.29; 2.09)
  -BRIEF-P Index- Global Executive Composite (n=182) 2.0 (95%CI: -1.20; 5.20)
-AEs were not estimable	

AE = adverse event; Bayley III = Bayley Scale of Infant and Toddler Development, 3rd Edition; BRIEF-P = Behaviour Rating Inventory of Executive Funtion - Preschool Version; CI = confidence interval; IV = intravenous; NICU =neonatal intensive care unit; NNT = number needed to treat

Table 11: Summary of Findings of Included Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Trial	
Weston, 2017[13]	
Baseline demographics: 39% of infants were born to mothers with diabetes (from Sugar Babies study; Harris 2013[6]) Results of feeding after treatment (dextrose gel or placebo): <u>All episodes (dextrose gel versus placebo), n (%) or median (range)</u>: -Alert before feeding (n=102); 44/63 (70%) versus 39/61 (64%); OR=1.30 (95% CI: 0.62; 2.77); *P*=0.49 -Good breast feeding (n=129); 61/78 (78%) versus 45/82 (55%); OR=3.54 (95% CI: 1.30; 9.67); *P*=0.01 -Duration of breast feeding (n=51); 20 min (3 to 90) versus 25 min (2 to 80); *P*=0.62 -Formula milk taken (n=24); 4.6 mL/kg (2.2 to 11.3) versus 6.4 mL/kg (2.0 to 8.9); *P*=0.30 <u>Episodes treated with 2 doses (dextrose gel versus placebo), n (%) or median (range)</u>: -Alert before feeding (n=26); 7/15 (47%) versus 6/12 (50%); OR=0.88 (95% CI: 0.19; 4.00); *P*=86 -Good breast feeding (n=26); 11/14 (79%) versus 8/12 (66%); OR=1.83 (95% CI: 0.32; 10.57); *P*=0.50 -Duration of breast feeding (n=10); 20 min (3 to 25) versus 25 min (5 to 70); *P*=0.40 -Formula milk taken (n=5); 6.5 mL/kg (3.9 to 11.3) versus 8.7 mL/kg (NR); *P*=NR No safety outcomes were reported	The authors concluded that: *"Treating hypoglycemic babies with dextrose gel 200 mg/kg does not suppress feeding and may improve breastfeeding quality."* (page F539)
Non-Randomized Trials	
Barber, 2018[14]	
Baseline demographics: 100% of infants were born to mothers with diabetes <u>Mean blood glucose levels (dextrose gel versus historical controls)</u>: -Baseline: 2.3 ± 0.2 mmol/L (both groups) -15 min after first treatment: 2.6 mmol/L versus 2.8 mmol/L; *P*=0.07 -30 min after second treatment: 2.7 mmol/L versus 3.2 mmol/L; *P*=0.003 -64% of infants in the glucose gel group compared to 96% of historical controls were administered a second treatment (no statistical comparison was made) -All infants treated with glucose gel reached normoglycemia within 30 min	The authors concluded that: *"Our results support previous research in other countries, indicating that sublingual/buccal glucose gel is a promising treatment in infants diagnosed with asymptomatic hypoglycaemia. The glucose gel treatment provided rapid and controlled improvements in blood glucose levels. The formula group had a larger increase in blood glucose levels with greater variance in response. There were no adverse reactions to glucose gel, and we did not detect significant differences in special care nursery admissions between the two groups, although we were underpowered for this outcome. Our results must be interpreted with caution, given our low subject numbers. While some individual Australian hospitals have developed protocols utilizing glucose gel treatment,many do not. Further research into glucose gel treatment is required to justify development."* (page 7)

Table 11: Summary of Findings of Included Clinical Studies

Main Study Findings	Authors' Conclusion
-81% of infants in the glucose gel group compared to 96% of historical controls did not require admission to the special care nursery; *P*=0.08 -Reported that no infants had an AE to the glucose gel	
Coors, 2018[15]	
Baseline demographics: 53% of infants were born to mothers with diabetes First glucose concentration (dextrose gel versus control): -52.1 ± 17.1 mg/dLversus 50.5 ± 15.3 mg/dL; *P*=0.69 NICU admission for IV dextrose (dextrose gel versus control), n/N (%): -7/72 (9.7%) versus 24/164 (14.6%); *P*=0.40 Exclusive breastfeeding (dextrose gel versus control), n/N (%) -45/72 (63%) versus 111/164 (68%): *P*=0.57 In a multivariate analysis, the first glucose concentration was not different (*P* =0.18) for infants in the prophylaxis group compared with the control group after controlling for risk factors and the age at first glucose measurement. No safety outcomes were reported	The authors concluded that: *"Prophylactic dextrose gel did not reduce transient neonatal hypoglycemia or NICU admissions for hypoglycemia. The carbohydrate concentration of Insta-Glucose (77%) may have caused a hyperinsulinemic response, or alternatively, exogenous enteral dextrose influences glucose homeostasis minimally during the first few hours when counter-regulatory mechanisms are especially active."* (page 1)
Makker, 2018[16]	
Baseline demographics: 28% of infants were born to mothers with diabetes Proportion of study population requiring transfer to NICU, n (%): - 34 (8.1%) (pre-gel protocol) versus 14 (3.7%) (gel protocol); OR=0.43 (95% CI: 0.22; 0.83); *P*=0.01 Rate of exclusive breastfeeding, n (%): -27 (6%) (pre-gel protocol) versus 73 (19%) (gel protocol); *P*<0.001 -no statistical difference in NICU admissions in exclusively breastfed babies and non-exclusively breastfed babies either for either the pre-gel or gel protocol -no statistically significant difference in length of stay in NICU or in nursery stay for babies eventually admitted to NICU or not admitted to NICU -no statistically significant difference in the proportion of infants receiving an IV bolus of D10W; however, more infants receiving a bolus of IV D10W during the pre-gel protocol (68%) compared to the gel protocol (38%) were admitted to the NICU; *P*<0.001 -Total hospital charges for infants admitted to NICU was USD$801,276 (pre-gel protocol) compared to USD$387,688 (gel	The authors concluded that: *"Our study supports the adjunctive use of glucose gel to reduce NICU admissions and total hospitalization expense."* (page 1)

Table 11: Summary of Findings of Included Clinical Studies

Main Study Findings	Authors' Conclusion
protocol) No safety outcomes were reported	
Ter, 2017[17]	
Baseline demographics: 30% of infants were born to mothers with diabetes (both diet-controlled and insulin-dependent diabetes) NICU admissions, n (%): -29 (29%) (pre-gel protocol) versus 14 (14%) (gel protocol); *P*=0.01 Normoglycemia after 1 or 2 treatment attempts in postnatal wards, n (%): -71 (71%) (pre-gel protocol) versus 75 (75%) (gel protocol); *P*=0.52 Length of hospital stay, days, mean (SD): -4.4 (2.9) (pre-gel protocol) versus 4.1 (4.5) (gel protocol); *P*=0.55 Recurrence of hypoglycemia, n/N (%) -22/71 (31%) (pre-gel protocol) versus 37/75 (49%) (gel protocol); *P*=0.02 No safety outcomes were reported	The authors concluded that: *"In conclusion, 200 mg/kg of 40% dextrose gel is effective in the management of neonatal hypoglycaemia in the postnatal ward setting, reducing NICU admission and mother–infant separation."* (page 410)
Rawat, 2016[18]	
Baseline demographics: 28% of infants in the dextrose gel + feeds group and 30% of infants in the feeds alone group were born to mothers with diabetes Proportion of infants with increased blood glucose level, n/N (%): -184/250 (74%) with dextrose gel + feeds versus 144/248 (58%) with feeds alone; *P*<0.01 Transfer of infants from the newborn nursery to NICU for IV dextrose: -25/1000 live births with dextrose gel + feeds versus 35/1000 live births with feeds alone; *P*<0.01 Absolute risk reduction for IV dextrose therapy after introduction of dextrose gel was 15.54% (95% CI: 7.32; 23.76) and NNT was 7 (95% CI: 4.2; 13.7) Exclusive breastfeeding, n (%): -28% with dextrose gel + feeds versus 19% with feeds alone; *P*=0.03 Implementation of the protocol incorporating dextrose gel was reported to result in an overall savings of USD$642,951 over the	The authors concluded that: *"Use of dextrose gel with feeds reduced the need for IV fluids, avoided separation from the mother and promoted breastfeeding. Neonates who failed dextrose gel therapy were more likely to be large for gestational age, delivered by cesarean section, and had lower baseline blood glucose levels."* (page 1)

Table 11: Summary of Findings of Included Clinical Studies

Main Study Findings	Authors' Conclusion
six month period or USD$2593 per patient with asymptomatic hypoglycemia No safety outcomes were reported	
Stewart, 2016[19]	
Baseline demographics (infants admitted to NICU, n/N (%): -3/11 (27%) of infants in the post-implementation (dextrose gel + feeds) group and 4/41 (10%) of infants in the pre-gel implementation (feeds only) group were born to mothers with diabetes Total admissions to NICU for primary transitional neonatal hypoglycemia, n/N (%): -41/380 (10.8%) pre-implementation versus 11/339 (3.2%) post-implementation Temperature < 36.0º C on admission, n (%): -4 (10%) pre-implementation versus 0 (0) post-implementation Mean length of stay in NICU (days): -5.8 pre-implementation versus 3.8 post-implementation Total special care unit days for primary transitional hypoglycemia (days): -228 pre-implementation versus 42 post-implementation Breastfed babies who were still breastfeeding at 3 months, n (%): -8 (29%) pre-implementation versus 15 (63%) post-implementation No statistical comparisons were made No safety outcomes were reported	The authors concluded that: *"This initiative demonstrates that evidence-based guidelines with multidisciplinary team input can improve standards of care."* (page F344)

AE = adverse event; CI = confidence interval; IV = intravenous; NICU = neonatal intensive care unit; NNT = number needed to treat; NR = not reported; OR = odds ratio; SD = standard deviation; USD$ = United States dollars;

Table 12: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
Glasgow, 2018[20]	
Base case analysis: -The average cost for management of an infant with neonatal hypoglycemia was NZD$6863.81 (dextrose gel) and NZD$8178.25 (placebo); a difference, or savings, of NZD$1314.44 per infant treated Sensitivity analyses demonstrated that dextrose gel remained cost savings with wide variations in cesarean delivery rates, cost of dextrose gel, NICU stay, and costs of monitoring (all differences are mean [SD]): -When the cesarean delivery rate was reduced to 20%, the difference between dextrose gel and placebo increased to NZD$1587.67 (NZD$538.25) and when the cesarean delivery rate increased to 100%, the difference decreased to NZD$476.62 (NZ$445.07) -When the cost of dextrose gel was reduced to NZD$1.29, the difference between treatments was NZD$1352.76 (NZD$539.90) and when the cost was increased to NZD$86.00, the difference was NZD$1204.44 (NZD$539.06) -When the NICU cost per day decreased to NZ$110, the difference was NZD$665.96 (NZ$344.41) and when the NICU cost per day increased to $3200, the difference was NZD$1931.50 (NZ$725.40) -When monitoring costs were excluded for NICU, the difference was NZD$1269.74 (NZD$529.99) -When all monitoring costs were excluded (assumed to be included in per diem costs), the difference was NZD$1269.02 (NZD$530.90) The key driver in overall costs between the two treatment arms was the admission of an infant to NICU for management of neonatal hypoglycemia.	The authors concluded that: *"Use of buccal dextrose gel reduces hospital costs for management of neonatal hypoglycemia. Because it is also noninvasive, well tolerated, safe, and associated with improved breastfeeding, buccal dextrose gel should be routinely used for initial treatment of neonatal hypoglycemia."* (page 1)

NICU = neonatal intensive care unit; NZD$ = New Zealand dollar; SD = standard deviation

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
2004 Canadian Pediatric Society Screening Guidelines for Newborns at Risk for Low Blood Glucose[21] and Algorithm for the Screening and Immediate Management of Babies at Risk for Neonatal Hypoglycemia, Year[5] (Reaffirmed 2018)	
"Enteral supplementation may be used in asymptomatic infants with blood glucose levels of 1.8 mmol/L to 2.5 mmol/L to augment caloric intake, rechecking levels in 60 min to identify persistent hypoglycemia." (p. 8)	Grade of Recommendation: D (Level 5, Opinion)
"It is recommended that symptomatic, hypoglycemic infants (and asymptomatic infants who have failed to respond to enteral supplementation) be treated with IV dextrose solution. Consider investigation, consultation and pharmacologic intervention if target blood glucose levels are not achieved by IV dextrose." (p. 8)	Grade of Recommendation: C (Level 4 studies or extrapolations from Level 2 or 3 studies)
2015 Oral Dextrose Gel to Treat Neonatal Hypoglycemia: Clinical Practice Guidelines, University of Auckland[22]	
"In babies diagnosed with neonatal hypoglycemia, treat with 40% oral dextrose gel: • *When babies are ≥ 35 weeks' gestational age and younger than 48 h after birth* • *Use a dose of 200 mg/kg (0.5 mL/kg), up to two doses given 30 minutes apart per episode of hypoglycemia and a maximum of six doses of oral dextrose gel in 48 h* • *For babies with severe hypoglycemia (<1.2 mmol/L) use oral dextrose gel as an interim measure while arranging for urgent medical review and treatment* • *Pediatric medical advice should be sought if a baby has severe hypogylcemia (<1.2 mmol/L) following two doses of oral dextrose gel one hour after first detection of hypoglycemia, or requires six doses of oral dextrose gel to treat neonatal hypoglycemia in 48 h"* (page 2) • Note: additional practice points are summarized in the guideline.	NHMRC Strength of Recommendation: B (i.e., the body of evidence can be trusted to guide practice in most situations) Grade of Recommendation: Conditional (i.e., the benefits probably outweigh harms)

IV = intravenous; NHMRC = National Health and Medical Research Council