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Neonatal hypoglycemia in diabetic mothers: A systematic review.

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Abstract

Hypoglycemia occurs in approximately 8-30% of neonates born to mothers with diabetes. The full extent of the individual and contextual risk factors of hypoglycemia remains unclear and no systematic review of the available studies exists to date. We identified published studies using PubMed and EBSCO host search engines. A modified STROBE statement was used to assess studies' strengths, weaknesses, and generalizability. A total of 16 articles were eligible for full text review. The clinical risk factors in these studies were broadly classified into two: infant-related and mother-related risk factors. The identified infant-related risk factors were SGA, macrosomia, prematurity, lower cord blood glucose, ponderal index and male sex. On the other hand, mother-related risk factors includes maternal hyperglycemia, ethnic origin, diabetes diagnosed prior to 28 weeks of gestation, pre-pregnancy BMI of ≥ 25 kg/m^2, blood glucose, maternal diabetes type and maternal HbA1c. Irrespective of diabetes type, infants born to diabetic mothers appear to have a higher risk of developing hypoglycemia compare to those born to normal mothers. The overall evidence suggested that these studies mainly focus on the clinical characteristics of infants and mothers. Future research should focus on the identification of risk factors at the individual and contextual levels that can independently predict neonatal hypoglycemia. Appropriate emphasis should also be given to better define neonatal hypoglycemia.

Keywords: Neonatal hypoglycemia, Diabetic mothers, Birth complications, Risk factors.

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Background

Neonatal hypoglycemia is a common metabolic abnormality in newborns due to inability to maintain glucose homeostasis [1,2]. Glucose is an essential primary substrate for the brain and its consumption by the brain is high and as a result, neurons and glial cells are susceptible to hypoglycemia [3,4]. Therefore, glucose homeostasis is crucial for the overall physical development of newborns [5]. Throughout gestation, maternal glucose provides all the glucose for the fetus via facilitated diffusion across the placenta according to a maternal-to-fetal glucose concentration gradient [5]. Hypoglycemia was defined by studies as early as 1937 as "mild" (2.2–3.3 mmol/l), "moderate" (1.1–2.2 mmol/l), and "severe" (<1.1 mmol/l) [6]. A specific blood glucose concentration to define neonatal hypoglycemia for infants is a subject of controversy [7-10]. However, it is generally accepted that neonatal hypoglycemia is defined by a plasma glucose level of less than 30 mg/dl or 1.65 mmol/l in the first 24 h of life [11]. To date, hypoglycemia remains one of the major metabolic abnormalities of the newborn [12-14].

The most common symptoms of neonatal hypoglycemia are shakiness, tachycardia, lethargy, and temperature irregularities [15,16]. In the presence of these symptoms, neonatal hypoglycemia is defined as capillary plasma glucose of less than 46 mg/dl (2.6 mmol/l) [15]. Prolonged neonatal hypoglycemia may also cause neuroglycopenic signs such as seizure, coma, cyanotic episodes, apnea, bradycardia or respiratory distress and hypothermia [4,17].

Several clinical conditions could be associated with neonatal stress that could affect glucose homeostasis of the newborn infant including infection, asphyxia, congenital heart disease, decreased substrate availability as a result of birth defects, prematurity and fetal growth restriction, islet cell hyperplasia, erythroblastosis fetalis, and Beckwith-Wiedemann Syndrome [4,18-22]. In addition, endocrine abnormalities such as pan-hypopituitarism, hypothyroidism, adrenal insufficiency, increased glucose utilization, sepsis and perinatal asphyxia could also be associated with neonatal hypoglycemia [17,18]. Although in most of these neonates, hypoglycemia is transient and asymptomatic, unrecognized hypoglycemia may lead to neonatal seizures, coma, and neurologic injury [15,23-26].

The risk of developing hypoglycemia among infants

born from diabetic mothers is even higher [27-34]. Hypoglycemia occurs in approximately 8-30% of neonates born to mothers with diabetes, with an estimated incidence rate of approximately 27% among infants born to women with diabetes compared to 3% among apparently healthy full-term infants born to non-diabetic women [35-38]. Although the predisposing risk factors for the development of neonatal hypoglycemia in diabetic pregnancies are thought to be mainly related to poor maternal glycemic control, neonatal weight at birth, and gestational age at delivery, the full extent of the individual and contextual risk factors remains unclear. In addition, to date, no systematic reviews of the available studies exist [39,40].

Our objective is to conduct a systematic review of the literature on the risk factors for hypoglycemia in infants of diabetic mothers. Accordingly, all relevant empirical studies on neonatal hypoglycemia in diabetic mothers were reviewed and appraised for methodological quality. The results were summarized in a way that informs both clinical practice and future research.

Method

Search Strategy

We identified published studies using PubMed and EBSCOhost search engines. The search was carried out by using the population, intervention, control, and outcome (PICO) strategy. The following concepts and related key words searched in their respective PICO category and they were finally combined together: (1) neonatal terms (‘neonate, ‘neonates’, ‘neonatal’, ‘newborn’, ‘newborns’ and ‘infant’), (2) diabetes and pregnancies terms (‘pregnancy in diabetics’, ‘diabetic mothers’, ‘diabetic pregnancy’, ‘pregnancy in diabetes’) and outcome terms (‘hypoglycemia’, ‘hypoglycaemia’, ‘hypoglycemic’ and ‘neonatal hypoglycemia’). We included all empirical studies published in the English language between January 1, 2000 and March 31, 2016. Additional studies were identified from reference lists of identified articles. The following inclusion and exclusion criteria were used to identify relevant articles:

Inclusion Criteria

(1) Observational studies, (2) neonatal hypoglycemia is used as the primary outcome of interest, (3) neonates born from type 1 (defined as blood glucose ≥ 11.1 mmol/l), type 2 (defined as fasting blood glucose ≥ 7.0 mmol/l or ≥ 11.1 mmol/l during OGTT) or gestational diabetic mothers (defined as having at least two plasma glucose measurements during the diagnostic test of the following OGTT glucose threshold values: 5.3 mmol/l fasting, 10.0 mmol/l at 1 h, 8.7 mmol/l at 2 h and 7.8 mmol/l at 3 h), (4) has appropriate comparison group, (5) neonatal hypoglycemia diagnosed within 3 days of life, and outcome defined in the ranges of 20 to 50 mg/dl or 1.1-2.8 mmol/l.

Exclusion Criteria

(1) Animal studies, (2) review articles, (3) articles published in non-English language, (4) articles published prior to 2000, and (5) poorly defined comparison group.

Data Abstraction and Overall Assessment of Studies

The abstracts of all potential publications were reviewed initially by the first (B.A.) and the second (O.O.) authors to identify eligible publications for further review. Full text screening was made by the two authors through detailed review of the complete text of each article using the inclusion/exclusion criteria as a guideline. The two authors then independently reviewed publications that were identified for inclusion. Relevant study attributes were extracted from the selected publications using standardized forms developed for the systematic review project by the authors. A third author (M.A) mediated to resolve any disagreements between the authors.

The STROBE (Strengthening the Reports of Observational Studies in Epidemiology) Statement (checklist of items that should be included in reports of observational studies) was used to assess studies’ strengths, weaknesses, and generalizability. An explanation and elaboration article that discusses each checklist item and gives methodological background and published examples of transparent reporting were used in conjunction with the STROBE checklist [41]. As most of the studies in this topic are observational, we used the STROBE checklist as a guide to systematically evaluate the studies that were included in this review. The STROBE checklist has 21 items with 15 items relevant to all three study designs (i.e., cohort, case-control, and cross-sectional studies) and 4 are specific for each. However, items 1-3 (background and objectives), 6b (for matched studies), 11 (quantitative variables) and 22 (funding information) were removed as they were not applicable to the included studies. Therefore, a modified 15-item STROBE checklist was used to critically appraise study quality for this systematic review.

Results

Study Selection

A total of 1233 titles were identified on PubMed and EBSCOhost in the initial literature search, 1202 of which were excluded by the first screening based on the title or abstract, leaving 31 articles for full-text review (Figure 1). Thirteen of these studies met the inclusion criteria and an additional 3 articles were included from references listed these articles, resulting in 16 eligible studies, most of which were based on observational studies (Table 1) [27,35,41]. The main reasons for excluding studies after full review were (i) hypoglycemia was not listed as primary outcome, (ii) comparison group were not defined and, (iii) hypoglycemia was not defined within the specified range of 1.7-2.8 mmol/l.

We identified four prospective cohorts, one nested case-control and ten retrospective cohort studies that examined the various clinical risk factors for hypoglycemia in diabetic mothers. Mother’s diabetes types included Gestational Diabetes Mellitus (GDM), Type-1 Diabetes Mellitus (T1D) and type-2 diabetes mellitus (T2D). Other

Table 1. *Description of included neonatal hypoglycemia studies*

Author(s) (Year)	Design, *N*	Location	Patients Clinical Characteristics	Mother's Diabetes Type	Definition of Hypoglycemia, mmol/l/mg/dl	Glucose Measurement Method (infant, mother)	Outcome Measured (hour after birth)	Risk Factors Assessed
Agrawal et al. (2000) [22]	Prospective cohort, 38	Australia	38 term infants of well-controlled diabetic, ≥ 37 wk gestation, 5 pre-existing diabetes, 35 GDM, 16 managed on insulin, 17 on diet	GDM	<2/36	Hexokinase; QIDTM	0.5, 1, 2	UBCG, RDS, BW
Majeed et al. (2011) [44]	Prospective Cohort, 150	Malaysia	139 GDM (76.7% diet control, 23.3% insulin), 11 pre-existing	GDM	≤ 2.6/47	NS, BioRad D-10	3	HbA1c
Bollepalli et al. (2010) [56]	Retrospective Cohort, 229	U.S.	302 singleton, asymmetric LGA (63), symmetric LGA (67), asymmetric non-LGA (30), symmetric non-LGA (142)	T1D	<1.1/20	NS; Ames Dextrometer	NS	HB; AC, RD, PC
Ferrara et al. (2007) [55]	Nested Case–Control, 2444	U.S.	1560 infants with neonatal complications, 884 control infants	GDM	<2.2/40	NS; Hexokinase	NS	MS, HB
Garcia-Patterson et al. (2012) [57]	Retrospective Cohort, 2092	Spain	2029 NH infants and 63 non-NH infants; 2029 pregnancies of women with GDM	GDM	<2.22	Cornblath criteria; NS	48	GA, CBG, HbA1c, IT, BMI, WDP, MP, NG
Das et al. (2009) [58]	Retrospective cohort, 305	U.S.	305 singleton neonates with a birth weight of ≥ 4000 g	GDM	<2.8/50	NS	NS	RDS; BI; CH, HS,
Metzger et al. (2014) [35]	Retrospective cohort, 576	Israel	576 term infants, 37–42 week gestation, non-complicated vaginal delivery	GDM-A1, GDM-A2, IDDM	(>2.6/47), Mild (2.2/40-2.5/45), Moderate (1.7/31-2.1/38), Severe (<1.7/31)	Glucometer Elite XL; NS	1, 2, 4, 6, 8	AGA, SGA, LGA, CD, MA, MH, MSAF
Mitrovic et al. (2014) [59]	Retrospective cohort, 156	Serbia	94 mothers with GDM, 48 T1D, 14 T2D; 106 controls	GDM; T1D	NS	NS	NS	AS; BW, GA,CD, PE
Persson et al. (2012) [43]	Prospective cohort study, 3517	Sweden	3517 singletons, 32–43 week gestation	T1D	<2.6/47	NS	6	AS; BT, ARD; HB
Ramos et al. (2012) [15]	Retrospective Cohort, 385	U.S.	Singleton pregnancies diagnosed with GDM b/n 12 and 34 week (191), T2D (51)	GDM; T2D	<2.5/45	Sure Step Flexx Glucose Meter; NS	0.5	PI; GA, CD, MA, MOGCT; CD

Flores-le Roux et al. (2012) [27]	Prospective Cohort,190	Spain	190 infants, 39.3 week mean gestational age; 3349 mean birth weight	GDM	Normal (>2.5/45), Mild (2.2/40-2.4/43), Moderate (1.6/29-2.1/38), Severe (<1.6/29)	Chromogen Reagent Strips; NS	1, 2, 4, 8, 12, 18, 24	PBMI; IG; GA; IL; CD; BW; LGA; AC; UCPH
Ryan et al. (2012) [60]	Retrospective cohort, 274	Canada	55 T1D, 55 T2D, 164 GDM	GDM, T1D, T2D	<2/26	Capillary Blood Glucose; NS	Hourly	MBG
Sarkar et al. (2003) [42]	Prospective cohort, 160	U.S.	Infants born at ≥ 36 wk to women with GDM (class Al) over a period of 16 months; Infants born at ≥ 36 wk to nondiabetic women	GDM-A1	<2.2/40	glucose oxidase; NS	0.5-1, 3	BW, GA, AC, MC, HbA1c
Taylor et al. (2002) [61]	Retrospective Cohort, 107	UK	12.9 years of average duration of Type-1 Diabetes; 44 primigravidas	T1D	<2.5/45	Yellow Springs	NS	MC
Tundidor et al. (2012) [62]	Retrospective Cohort, 2299	Spain	Singleton pregnancies of women with GDM; <22 week gestation	GDM	<2.6/47	NS	NS	PB, AS, LGA, SGA, OT, JD, CM, RDS, PT, HC, PM
VanHaltren et al. (2013)	Retrospective Cohort, 326	Australia	39 week average Gestation; 3300 g. average birth weight; 15% LGA infants	GDM, T1D, T2D	<2.6/47	Automated bench top blood gas; NS	0, 4	MI, TDM, HbA1c, BGL, GA, PM, BW

UCBG: Umbilical Cord Blood Glucose; RDS: Respiratory Distress Syndrome; BW: Birth Weight; NS: Not Stated; HbA1c: Glycated Hemoglobin; HB: Hyperbilirubinemia; AC: Acidosis; PC: Polycythemia; MS: Macrosomia; GA: Gestational Age; IT: Insulin Treatment; BMI: Body Max Index; WDP: Weight During Pregnancy; MP: Multiple Pregnancy; NG: Newborn Gender, BI: Birth Injury; CH: Cephalhaematoma, HS: Hospital Stay; CD: Cephalhaematoma; CD: Cesarean Delivery; MA: Maternal Age; MH: Maternal Hypertension; MSAF: Meconium-Stained Amniotic Fluid; AS: Apgar Score; PE: Pre-Eclampsia; BT: Birth Trauma; ARD: Acute Respiratory Disorders; PI: Ponderal Index; MOGCT: Maternal Oral Glucose Challenge Test; PBMI: Pregestational BMI: IG: Insulin in Gestation; IL: Insulin in Labor; UCPH: Umbilical Cord Venous pH; MBG: Maternal Blood Glucose; MC: Microsomia; PT: Polycythemia; HC: Hypocalcaemia; PM: Perinatal Mortality; CM: Congenital Malformation; OT: Obstetric Trauma; JD: Jaundice; PB: Preterm Birth; MI: Maternal Insulin; TDM: Type of Gestational Diabetes; PM: Prematurity

details on included studies are summarized in Table 1. A total of 13,248 infants were identified in the 16 included studies. The key findings are described in the following section (Table 2).

Critical Appraisal

The two authors agreed initially on 228 out of 250 (95%) items on the modified STROBE checklist. All disagreements were resolved by discussion among the two reviewers. Overall, the quality scores of the included studies ranged from 26.66% to 86.66%, with a median of 46.66%. Included studies were classified as high quality if the individual quality scores were ≥ 80%; studies were classified as moderate quality for quality scores between 80% and 59% and studies with quality scores below 60% was classified as low quality. Accordingly, a total of five high quality, two moderate quality and nine low quality studies were identified [11,16,20,22,28-39]. The individual item, assessment responses, and quality scores can be found in Table 3.

Clinical Significance and Risk Factors of Neonatal Hypoglycemia

Four prospective cohort studies examined various

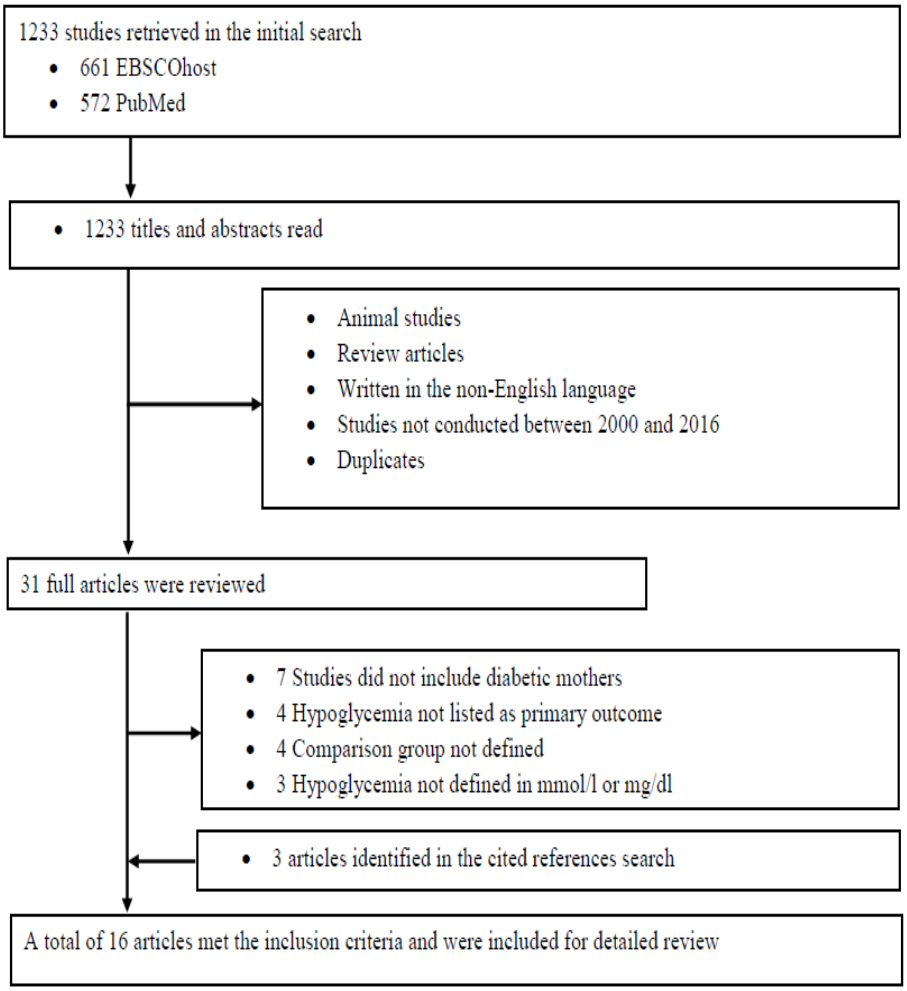

Figure 1: *Selection process for including studies in the systematic review*

risk factors of hypoglycemia in neonates of women with different diabetes type [22,27,42,43]. Roux et al. [27] prospectively examined glucose levels in infants of women with GDM and the influence of maternal, gestational and peripartum factors on the development of hypoglycemia. They found that hypoglycemic infants were more frequently Large for Gestational Age (LGA) (29.3% vs. 11.3%), had lower umbilical cord pH (7.28 vs. 7.31), and their mothers had more frequently been hyperglycemic during labor (18.8% vs. 8.5%). The study obtained data from infants born in a hospital to mothers with GDM over a period of 30 months. After adjusting for confounding factors, umbilical cord venous pH [odds ratio (OR): 0.04, 95% Confidence Interval (CI): 0.261–0.99)] and Pakistani origin patients (OR: 2.94; 95% CI: 1.14 7.55) were significantly and independently associated with hypoglycemia. Similarly, Agrawal et al. [22] found that infants of mothers diagnosed with GDM or preexisting diabetes prior to 28 weeks gestation were at a higher risk of developing hypoglycemia compared to those with maternal diabetes diagnosed at 28 weeks gestation (OR: 7.2, 95% CI: 1.3-40.7). However, there was no difference in the cord blood glucose levels between infants with or without hypoglycemia.

Sarkar et al. [42] on the other hand, examined the risk of developing hypoglycemia in infants born to women with diet-controlled GDM (GDM-A1), insulin-requiring (GDM-A2) and Insulin-Dependent Diabetes (IDDM) at ≥ 36 weeks of gestation compared to infants born to healthy controls using data obtained over a period of 16 months. They found that there is no significant difference in the incidence of hypoglycemia in infants born to GDM-A1 (4.3%) compared to infants born to healthy controls (4.4%). They concluded that infants born to GDM Class A1 women at ≥ 36 weeks of gestation are not at increased risk of developing hypoglycemia. Cordero and Landon also found a 3% incidence of transient hypoglycemia in healthy full-term infants born to non-diabetic women [37,38].

Using national data from the Swedish Medical Birth Registry, Persson et al. [43] investigated whether disproportionate body composition is a risk factor for perinatal complications, including hypoglycemia, in LGA infants born to mothers with T1D. Their findings showed that there was no significant difference in the risk for hypoglycemia between proportionate LGA (OR: 1.42, 95% CI: 1.01-2.0) and disproportionate LGA infants (OR: 1.42, 95% CI: 0.97-2.08) compared to Appropriate for Gestational Age (AGA). Disproportionate LGA was defined as Ponderal Index (PI)>90th centile and proportionate <90th centile LGA according to gestational age and sex (Table 2) [44-63] . Similar results were

Table 2. *Results of included studies of hypoglycemic neonates born from diabetic mothers*

Authors (s). (Years)	Main Results
Agrawal et al. (2000) [22]	Hypoglycemia in 18 (47%) infants developed during the first 2 h of life. There was no difference in the cord blood glucose levels between infants with or without hypoglycemia. Infants of mothers with diabetes diagnosed prior to 28 weeks gestation were at a higher risk of developing hypoglycemia (OR 7.2, 95% CI: 1.3–40.7). Hypoglycemic infants were of significantly higher birth weight (3681) compared to normal infants (3160).
Majeed et al. (2011) [44]	There were 16 neonates who were hypoglycemic at delivery. The area under the Receiver Operator Characteristics (ROC) curve for predicting neonatal hypoglycemia was 0.997 with a 95% CI of 0.992 to 1. The optimal threshold value for HbA1c in predicting NH was 6.8%.
Bollepalli et al. (2010) [56]	Asymmetric LGA infants had 3.5 (95% CI: 1.4, 8.7), 2.2 (95% CI: 1.2, 4.2) and 3.2 (95% CI: 1.7, 5.9) fold greater odds of hypoglycemia, hyperbilirubinemia and composite morbidity, respectively, compared with symmetric non-LGA infants.
Ferrara et al. (2007) [55]	A total of 486 with infants with hypoglycemia, 488 with macrosomia, and with hyperbilirubinaemia were identified. Women with GDM by ADA criteria had an increased risk of having an infant with hypoglycemia (OR: 2.61, 95% CI: 0.99–6.92), macrosomia (3.40, 95% CI: 1.55–7.43) or hyperbilirubinaemia (2.22, 95% CI: 0.98–5.04) compared to healthy control infants.
Garcia-Patterson et al. (2012) [57]	The rate of hypoglycaemia in neonates was 3% (63). Maternal pre-pregnancy BMI of $\geq$ 25 kg/m^2 was an independent predictor of hypoglycaemia irrespective of potential intermediate variables being included in the model (OR: 2.11, 95% CI: 1.10–4.03) or without (OR: 2.66, 95% CI: 1.44–4.92).
Das et al. (2009) [58]	The incidence of hypoglycemia among IDMs was 56.1% compared to non-IDMs 28.6%. There was significantly more hypoglycemia among the group weighing >4500 g compared to the group weighing 4000–4499 g. Compared to IDMs, non-IDMs were born later (40 vs. 38 week), were more likely to be delivered vaginally (70% vs. 34%) and had a higher incidence of birth injury than IDMs (8% vs. 2.4%).
Metzger et al. (2014) [35]	Among the neonates in the study group 29 (36.7%) had at least one hypoglycemia value of <47 mg/dl and 8 (10.1%) had a value of <40 mg/dl in the first 8 h of life. After controlling confounding factors such as birth weight, delivery number, and grasp evaluation only lower cord blood glucose significantly predicted hypoglycemia for each decrease of 10 mg/dl (OR 2.11, 95% CI: 1.1–4.03).
Mitroviu et al. (2014) [59]	The incidence of neonatal hypoglycemia was 52% in mothers with Type 1 diabetes, and 16.5% in mothers with Type 2 diabetes or GDM. The incidence neonatal morbidities such as hypoglycemia, pathological jaundice, and other neonatal pathologies at birth, was statistically significantly higher and Apgar scores after 1 min and after 5 min were statistically significantly lower in the mothers with diabetes (type 1 and 2) compared to the healthy women.
Persson et al. (2012) [43]	Neonatal morbidities were significantly more frequent in LGA compared to AGA infants. The proportions of preterm births and girls were significantly higher in LGA infants (44% preterm and 52% girls) compared with AGA infants (30% preterm and 47% girls) born to women with Type 1 diabetes. The risks of hypoglycemia were comparable between P-LGA and D-LGA infants. No significant difference in risk was found between AGA and P-LGA and D-LAG.
Ramos et al. (2010) [15]	The incidence of hypoglycaemia was 18% (44/242). The incidence was significantly higher in those requiring pharmacotherapy (25% vs. 3%). The frequency of hypoglycaemia between the glyburide and insulin-treated pregnancies did not differ significantly (23% vs. 27%). The frequency of hypoglycaemia was statistically associated with birth weight, macrosomia and ponderal index. Ponderal index was the strongest predictor of hypoglycaemia (OR: 5.59, 95% CI: 1.34–23.25).
Flores-le Roux et al. (2012) [27]	A total of 23 (12.1%) mild, 20 (10.5%) moderate and 5 (2.6%) severe hypoglycemia were observed. Hypoglycemic infants were more frequently LGA (29.3% vs. 11.3%) had lower umbilical cord pH (7.28 vs. 7.31) and their mothers had more frequently been hyperglycemic during labor (18.8% vs. 8.5%). Pakistani origin (OR: 2.94; 95% CI: 1.14 7.55) and umbilical cord venous pH (OR: 0.04, 95% CI: 0.261–0.99) were significantly and independently associated with hypoglycemia in multivariate analysis.
Ryan et al. (2012) [60]	The NH rate was 7.3% (4.9% in GDM mothers and 10.9% of mothers with pre-existing diabetes). The insulin-glucose infusion was used in 47% of women with T1D, T2D, and GDM requiring $\geq$ 0.5 units/kg/day of insulin during pregnancy and in 8% of women with GDM treated by diet or <0.5 units/kg/day of insulin. The overall rate of maternal hypoglycaemia was low (6.6% with blood glucose $\leq$ 3.5 mmol/L and 1.5% $\leq$ 3.0 mmol/L) pre-delivery; 13.9% of women had a blood glucose level $\geq$ 7.0 mmol/L. Standardized management for diabetic women in labour using an intravenous insulin-glucose protocol was effective in achieving stable maternal blood glucose levels with low rates of neonatal hypoglycaemia.

Sarkar et al. (2003) [42]	The incidence of hypoglycemia was 4.3% in the GMD-A1 group compared to the control, 4.4%. Neonatal morbidity in infants born to GDM-A1 women is similar to that seen in infants of non-diabetic women. Unlike infants of insulin-dependent diabetic and insulin requiring GDM women, infants born to GDM-A1 women at 36 weeks of gestation or more were not at increased risk of developing hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia, hyperbilirubinemia, birth trauma or birth asphyxia. Infants born at 36 weeks or more gestation to class A1 GDM women can be managed like any other normal full-term infant born to a non-diabetic woman.
Taylor et al. (2002) [61]	Hypoglycemia correlates with maternal hyperglycemia in labor, not with HbA1c during pregnancy. Blood glucose was less than 2.5 mmol/l in 50 neonates and was less than 2.0 mmol/l in 18 neonates. Maternal blood glucose control in pregnancy had no bearing on the incidence of NH, but maternal blood glucose during labor influenced neonatal blood glucose if over 8 mmol/l.
Tundidor et al. (2012) [62]	Male sex was an independent predictor of neonatal hypoglycemia (OR 2.13) and CS (OR 1.48). As to neonatal hypoglycaemia, intravenous glucose was required in 16.7% of infants (7.4% in female vs. 24.2% in male fetuses; NS). The increased risk of neonatal hypoglycemia in male fetuses of mothers with GDM is also the most relevant result in terms of clinical practice, advising an increased awareness of neonatal hypoglycemia in these new-borns.
VanHaltren et al. (2013)	Hypoglycaemic episodes occurred in 109 (33.4%) infants. Macrosomia was present in 15% of the infants. Maternal diabetes Type, HbA1c, prematurity, macrosomia and temperature instability were identified as risk factors for neonatal hypoglycaemic.

obtained by Leperque et al. [64] while Ballard et al. [65] and Bollepalli et al. [56] contrasted the result. In a nested case-control study, Ferrara et al. [29] found that women with GDM defined by American Diabetes Association (ADA) criteria had an increased risk of having an infant with hypoglycemia (OR: 2.61, 95% CI: 0.99–6.92), although not statistically significant. The study used a group practice database that included 16 hospitals and provides medical services to approximately 3.0 million people. Their findings supported the ADA 2000 recommendations (GDM, 2000) to adopt lower plasma glucose thresholds proposed by Carpenter and Coustan for the diagnosis of GDM [42].

We also identified ten retrospective cohort studies and one nested case-control study that examined the risk of developing hypoglycemia in infants born to mothers with different diabetic conditions [15,35,56-63]. Most of these observational studies were conducted using medical institution based databases.

Garcia-Patterson et al. [57] examined the relationship between maternal pre-pregnancy BMI and hypoglycemia among infants born to women with GDM with a gestational age higher than 22 weeks using databases from a tertiary care center. Maternal pre-pregnancy BMI ≥ 25 kg/m^2 was determined as an independent predictor of hypoglycemia irrespective of potential intermediate variables being included in the model (OR: 2.11, 95% CI: 1.10–4.03) or without (OR: 2.66, 95% CI: 1.44–4.92). The rate of hypoglycemia in neonates was 3% (63). On the other hand, Metzger et al. [35] examined the impact of duration of delivery room breastfeeding on blood glucose levels (BGL) during the first hours of life among term neonates born to mothers with GDM and to examine its relationship with hypoglycemia using a medical center database. Among the neonates in the study group, 29 (36.7%) had at least one hypoglycemia value of <47 mg/dl and 8 (10.1%) had a value of <40 mg/dl in the first 8 h of life. After controlling confounding factors such as birth weight, delivery number and grasp evaluation only lower cord blood glucose significantly predicted hypoglycemia for each decrease of 10 mg/dl (OR 2.11, 95% CI: 1.1–4.03). The mean glucose at the first hour of life was 56.2 mg/dl (range 28–105 mg/dl). A trend towards a higher incidence of normoglycaemia (>40 mg/dl) was recorded for the longer duration of delivery room breastfeeding subgroup (OR: 1.923 95% CI: 0.984-3.76) [66]. However, the duration of delivery room breastfeeding did not influence the rate of hypoglycemia. In contrast to this findings, Chertok et al. [67] found that breastfed infants had a significantly higher mean BGL (3.20 mmol/l) compared to those who were formula fed (2.68 mmol/l). One reason for the different results could arise from the definition of hypoglycemia. In Garcia-Patterson et al. [57] hypoglycemia was defined as "normal" ($\geq$ 2.6 mmol/l), "mild hypoglycemia" (2.2–2.5 mmol/l), "moderate hypoglycemia" (1.7–2.1 mmol/l) and "severe hypoglycemia" (1.7 mmol/l). While Chertok et al. [67] defined hypoglycemia as BGL<1.93 mmol/l and borderline hypoglycemia was 1.93–2.48 mmol/l. In addition to differences in measurement, the difference in adjusting factors may have contributed to the apparent contrast in the results.

Ramos et al. [15] assessed factors associated with hypoglycemia in a cohort of pregnancies with T2D and GDM. The incidence of hypoglycemia in this study was 18% (44/242). The frequency of hypoglycemia between the glyburide and insulin-treated pregnancies did not differ significantly (23% vs. 27%). Maternal age $\geq$ 35 years (OR: 2.78, 95% CI: 1.13–6.85) and Ponderal Index (OR: 5.59 95% CI: 1.34–23.25), a measure of fetal adiposity, significantly predicted hypoglycemia. Similarly, Majeed et al. [44] investigated if maternal glycated hemoglobin (HbA1c) was a good predictor of hypoglycemia. As hypothesized HbA1c in late pregnancy, between 36 and 38 weeks of gestation, significantly predicted hypoglycemia in the newborn, giving an area under the ROC curve of 0.99 with a 95% CI of 0.992 to 1. A ROC curve determined the optimal cut-off point for maternal HbA1c level in predicting hypoglycemia, was 51 mmol/l (6.8%).

Table 3. *Description of methodological quality assessment*

Items	Agrawal et al. (2000) [22]	Majeed et al. (2011) [44]	Bollepalli et al. (2010) [56]	Ferrara et al. (2007) [55]	Garcia-Patterson et al. (2012) [57]	Das et al. (2009) [58]	Metzger et al. (2014) [35]	Mitrovic et al. (2014) [59]	Persson et al. (2012) [43]	Ramos et al. (2010) [15]
1. Study design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Setting	Yes	Yes	Yes	Yes	No	No	No	No	No	No
3. Participants	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
4. Variables	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes
5. Measurement	Yes	No	No	Yes	Yes	No	Yes	No	No	No
6. Bias	No	No	No	No	No	No	No	No	Yes	No
7. Study size	No	No	No	No	No	No	No	No	Yes	No
8. Statistical methods	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
9. Discriptive data	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Outcome data	No	No	No	Yes	No	Yes	No	No	No	No
11. Main results	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Key Result	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	No
13. Limitations	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
14. Interpretation	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes
15. Generalizability	Yes	No	No	Yes	No	No	No	No	Yes	No
Percentages of Yes (%)	*12/15=80.00*	*10/15=66.66*	*9/15=60.00*	*13/15=86.66*	*7/15=46.66*	*6/15=40.00*	*6/16=40.00*	*4/15=26.66*	*12/15=80.00*	*7/15=46.66*

Flores-le Roux et al. (2012) [27]	Ryan et al. (2012) [60]	Sarkar et al. (2003) [42]	Taylor et al. (2002) [61]	Tundidor et al. (2012) [62]	VanHaltren et al. (2013)
Yes	Yes	Yes	Yes	Yes	Yes
Yes	No	Yes	No	No	No
Yes	No	Yes	Yes	Yes	Yes
Yes	Yes	Yes	No	No	No
Yes	No	No	No	No	No
Yes	No	No	No	No	No
No	No	Yes	No	Yes	No
Yes	Yes	Yes	No	Yes	Yes
Yes	Yes	Yes	Yes	Yes	Yes
No	No	No	No	Yes	No
Yes	Yes	Yes	Yes	Yes	No
Yes	No	Yes	No	No	No
Yes	No	Yes	No	No	Yes
Yes	No	Yes	No	No	Yes
Yes	No	Yes	No	No	No
13/15=86.66	*5/15=33.33*	*12/15=80.00*	*4/15=26.66*	*7/15=46.66*	*6/15=40.00*

However, various studies gave mixed results regarding the association between maternal HbA1c and hypoglycemia. Using logistic regression Kline and Edwards also found that a third trimester HbA1c of >6.5% (47.54 mmol/l) had a stronger association with neonatal hypoglycemia requiring intervention when compared to maternal delivery BGLs (OR: 3.89, 95% CI: 1.42-10.68). However, Taylor et al. [62] found that hypoglycemia correlates with maternal hyperglycemia in labor, not with HbA1c during pregnancy. They found that maternal blood glucose during labor influenced neonatal blood glucose if over 8 mmol/l.

Discussion

Neonatal hypoglycemia is the most common metabolic abnormality in newborn infants due to the inability to maintain glucose homeostasis [1,12]. To date, the full extent of various risk factors of hypoglycemia in infants of diabetic mothers are not known. Our findings are the result of a systematic search for all relevant studies on hypoglycemia in diabetic mothers and critical appraisal of methodologies and study quality assessment.

We found few prospective studies that carefully examined the clinical and demographic risk factors of hypoglycemia among neonates. However, the majority of studies identified in our literature review were observational of retrospective design that used existing institutional databases. As a result, after assessing studies' strengths, weaknesses and generalizability using the STROBE Statement, the overall quality of evidence was low [68]. The clinical risk factors in these studies can be broadly classified into two: infant-related and mother-related clinical risk factors. The infant-related significant risk factors identified in these study were SGA, LGA, macrosomia, prematurity, lower cord blood glucose, Ponderal Index and male sex [15,35,43,56,58,63]. On the other hand, mother-related significant risk factor of hypoglycemia includes maternal hyperglycemia, ethnic origin, diabetes diagnosed prior to 28 weeks of gestation, pre-pregnancy BMI $\geq$ 25 kg/m^2, hyperglycemia, blood glucose, maternal diabetes type and material HbA1c [22,27,44,57,61,63]. Although several other risk factors were considered in these studies, the statistically significant risk factors are important for understanding the clinical management of the study population and future studies using multilevel design of risk assessment. Irrespective of diabetes type, it appears that infants of diabetic mothers have a higher risk of hypoglycemia compared to those born to normal mothers [42,55].

Overall, the results of the individual studies assessed various risk factors. However, a consistent pattern of risks of hypoglycemia among infants of diabetic mothers was not identified which may be the result of several factors. First, as the definition of clinical significance of hypoglycemia remains one of the contentious issues in contemporary neonatology, individual studies included in this review used different definitions of hypoglycemia ranging from <1.1 mmol/l to <2.8 mmol/l. The variation in the definition of hypoglycemia has an important implication on the predictive power of individual studies. The standard of care in most neonatology units involves close surveillance if the plasma glucose concentration is less than 2.2 mmol/l [69-77]. Second, mothers included in this review were diagnosed with diabetes. However, there was variation in the type of diabetes. The review included mothers with T1D, T2D, GDM, which are commonly recognized [49,50]. Sarkar et al. [42] pointed out that the incidence of hypoglycemia and the associated risk factors may vary based on the specific type of diabetes. Third, about 65% of studies identified in the review were observational studies that used existing data collected as part of standard of care (i.e., not for research purpose). In this regard, collecting prospective data or using national registry data may have provided more consistent predictors of hypoglycemia. Fourth, individual studies used different measurements of blood glucose. Although, more than 76% of studies specified their blood glucose measurement methods, variations in these methods, measurement time, and place (laboratory vs. bedside) may have affected the accuracy of blood glucose measurement. Similarly, a recent systematic review identified 18 studies that examined neonatal hypoglycemia and its relationship to neurodevelopmental outcomes found a higher rate of heterogeneity among studies [78]. In our study, we also found major clinical heterogeneity in patient characteristics, measurement of hypoglycemia, design, and quality. As a result, statistical pooling of result to conduct a meta-analysis was not carried out.

Overall, the majority of the studies in our review were observational in design, which makes an inference of causality difficult, especially when different protocols were followed to measure, handle and analyze blood sampling. Less than a third of the studies used a prospective design to minimize errors associated with measuring exposure. Key limitations include the possibility of publication bias. As our review found both positive and negative results, publication bias may not be a great concern for the current review. The fact that our systematic review included studies only written in English may be another limitation. However, previous studies have shown that language restrictions in systematic reviews have minimal effect on the results [79,80]. The fact that 47 percent of studies did not report a laboratory measurement for confirmation of neonatal hypoglycemia and the lack of generally acceptable definition of neonatal hypoglycemia may have affected the proper dictation of the outcome. However, as all studies followed a written clinical protocol in the management of hypoglycemia, the bias associated with laboratory confirmation is not differential.

Conclusion and Recommendations for Future Research

In summary, there is evidence supporting the clinical importance of giving attention to infants of diabetic mothers. Irrespective of the type of diabetes, infants of diabetic mothers have a higher risk of developing hypoglycemia compared to those born to mothers without diabetes. However, the studies included in this review mainly focused on the clinical characteristics of the infants and mothers. Future research should also

focus on identifying other factors that may increase the risk of neonatal hypoglycemia such as neighborhood and institutional characteristics including, genetics, socioeconomic status, and disparities in health care delivery. This can be accomplished by taking the following three steps:

1. Defining neonatal hypoglycemia using the multiple clinical cut-of-points to identify the most salient risk factors.
2. Using large population based national registry database that is developed to facilitate the conduct of analyses pertaining to neonatal complications will help to obtain adequate comparison groups. Most of the studies included in this review used hospital based data that is generated as part of standard of care.
3. Stratifying the mother's diabetes type to identify the significance of T1D, T2D and GDM on the risk of developing neonatal hypoglycemia.
4. Using multilevel statistical models to incorporate the individual and contextual characteristics of infants and mothers.

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