Admissions for hypoglycaemia after 35 weeks of gestation: perinatal predictors of cost of stay

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Abstract

**Background:** Hypoglycaemia accounts for approximately one tenth of term admissions to neonatal units, can cause long-term neurodevelopmental impairment and is associated with significant burden to the affected infants, families and the health system.

**Objective:** To define the prevalence, length and cost of admissions for hypoglycaemia in infants born at greater than 35 weeks gestation and to identify antenatal and perinatal predictors of those outcomes.

**Material and Methods:** This was a retrospective audit of infants admitted for hypoglycaemia between 1/1/2012 and 31/12/2015, in a level three neonatal intensive care unit at King’s College Hospital NHS Foundation Trust, London. The main outcome measures were the prevalence, length and cost of admissions for hypoglycaemia and antenatal and postnatal predictors of the length and cost of stay.

**Results:** There were 474 admissions for hypoglycaemia (17.8% of total admissions). Their median (IQR) blood glucose on admission was 2.1 (1.7-2.4) mmol/L, gestation at delivery 38.1 (36.7-39.3) weeks, birthweight percentile 31.4 (5.4–68.9), their length of stay was 3.0 (2.0-5.0). Admissions equated to a total of 2107 hospital days. The total cost of stay was 1,316,591 GBP. The antenatal factors associated with admission for hypoglycaemia were maternal hypertension (19.8%), maternal diabetes (24.5%), FGR (25.9%) and pathological intrapartum cardiotocograph (23.4%). In 13.7% of cases there was no associated pregnancy complication. Multivariate logistic regression analysis demonstrated lower gestational age, z-score birthweight squared, exclusive breastfeeding and maternal prescribed nifedipine were independently associated with the length and cost of stay.

**Conclusions:** Hypoglycaemia accounted for approximately one fifth of admissions after 35 weeks gestation. Lower gestational age and admission blood glucose, low and high z-score birthweight, maternal nifedipine and exclusive breastfeeding are associated with longer duration of stay.
**Short title:** Neonatal admissions for hypoglycaemia >35 weeks

**Key words:** Hypoglycaemia, neonatal admissions, cost of stay, length of stay, fetal growth restriction.
The aims of this study were to determine the prevalence of admissions for hypoglycaemia in late preterm and term infants to a tertiary neonatal unit, to report the length and cost of those admissions and identify independent antenatal and perinatal predictors of the length and cost of stay.

**Materials and Methods**

**Study design**

A retrospective audit of admissions between 1/1/2012 and 31/12/2015 of infants born after 35 weeks of gestational age with hypoglycaemia to the neonatal unit at King’s College Hospital NHS Foundation Trust (KCH), London was performed. Infants with a birth weight of <1.8 kg or a gestational age <34 completed weeks were routinely admitted to the neonatal unit, irrespective of blood sugar homeostasis and were excluded from this study. The study was registered as an audit with the Clinical Governance Department of KCH.

On admission to the neonatal unit, the infant’s symptoms, temperature and blood glucose levels were recorded. Subsequently, the following information was collected from the maternal and neonatal medical notes: maternal antenatal diabetes (yes/no), maternal antenatal hypertension (yes/no), maternal antenatal treatment with labetalol (yes/no), maternal antenatal treatment with nifedipine (yes/no), maternal antenatal treatment with methyldopa (yes/no), other significant maternal medical conditions (autoimmune disease, asthma, renal and cardiac disease) (yes/no), FGR (yes/no), maternal pyrexia >38°C (yes/no), pathological cardiotocograph (CTG) (yes/no), delivery by caesarean section (yes/no), antibiotic administration in labour (yes/no), Apgar score at 5 minutes <7 (yes/no),[16] male sex (yes/no), singleton pregnancy (yes/no), gestational age at delivery and birthweight, age of admission (hours), exclusive breastfeeding (yes/no).

Screening for gestational diabetes (GDM) was according to local protocols.

**Definitions of maternal, antenatal and labour outcomes**

Maternal hypertension was defined as a systolic or diastolic blood pressure
\[ \geq 140\text{mmHg and } \geq 90\text{mmHg, respectively, on two occasions four hours apart.}[17] \]

Treatment of maternal hypertension was based on the recommendations of the National Institute for Health and Care Excellence,[18] modified by locally derived prediction models for the maternal response to beta-blockers.[19] Women with previous GDM or BMI >40kg/m\(^2\) underwent a 75g oral glucose tolerance test (OGTT) at 16-20 weeks and repeated at 28 weeks if the first OGTT was normal. All other pregnant women (regardless of other risk factors) had a random venous plasma glucose sample taken at 26 to 28 weeks of gestation and if the level was \(\geq 6.7\text{mmol/l} \) an OGTT was undertaken. The diagnosis of maternal gestational diabetes was made if an OGTT with a fasting glucose \(>5\text{mmol/l}\) and/or 2 hour \(\geq 7.8\text{mmol/l}\). Fetal growth restriction was defined as a newborn with a birth weight below the third percentile or with birth weight above the third percentile but with abnormal Doppler waveforms and/or oligohydramnios.[20] A CTG trace was defined as pathological according to national guidelines.[21] The birthweight z-score and percentile was calculated based on locally derived birthweight reference ranges.[22] In order to assess the effect of FGR and fetal macrosomia on the length and/or cost of stay, we included in the regression models the linear and quadratic term of birthweight z-score.

**Definition of hypoglycaemia and measuring devices**

A blood glucose level below 2.6 mmol/L was used to define neonatal hypoglycaemia.[23] The blood glucose measurement in the postnatal ward and in the neonatal unit was undertaken by whole blood analysis using hand held glucometers (Ascensia Contour blood glucose meter, Bayer Healthcare LLC, PA, USA) which underwent a two-point calibration on a daily basis.

**Management of hypoglycaemia**

The management of infants at risk of hypoglycaemia in the postnatal ward and after admission to the neonatal unit was in accordance with national guidelines.[11] Infants required high dependency care if the intravenous dextrose concentration required to maintain blood glucose levels exceeded 12.5% and a percutaneously
The maternal/antenatal, labour, neonatal and admission data of the admitted infants are presented in Table 1. One hundred and sixteen mothers had diabetes (24.5%), 94 had hypertension (19.8%), 69 had pyrexia >38°C in labour (14.6%), 123 of the infants had FGR (25.9%) and 111 (23.4%) had a pathological CTG prior to delivery (Table 1, Figure 1). There was an overlap of pathologies in 18.8% of cases, whilst in 13.7% there was no associated pregnancy complication.

The cumulative length of stay of the admitted infants was 2,107 days, of which 960 days were in the high dependency care (HDU). Fifty-six percent of the admitted infants were discharged by day three of stay, 85% were discharged by day 7 of stay and 90% were discharged by day 10 of stay (Figure 2). The cumulative cost of stay of the admitted infants was 1,316,591 GBP (329,148 GBP per year), of which 842,880 GBP related to high dependency costs.

**Univariate regression analysis**

The length and cost of stay were significantly associated with: history of maternal diabetes, maternal use of Nifedipine, FGR, maternal administration of antibiotics in labour, pathological CTG, gestational age at delivery, square of the birth weight z-score, age on admission, admission blood sugar and exclusive breastfeeding (Table 2).

There was no association between length or cost of stay and: neonatal symptoms, admission temperature, delivery by caesarean section, maternal pyrexia in labour >38°C, Apgar score at 5 minutes<7, gender, singleton birth, maternal hypertension or other medical conditions, maternal treatment with labetalol or methyldopa (data not presented).

**Multivariate regression analysis**

Multivariate regression analysis demonstrated that greater length of admission ($R^2 = 0.13$, $p<0.0001$) and cost of admission ($R^2 = 0.14$, $p<0.0001$) were independently associated with lower gestational age and blood glucose level on admission, exclusive breastfeeding, maternal use of nifedipine, pathological intrapartum CTG,
and small and large birthweight (table 3).

Age of admission, maternal administration of antibiotics in labour, maternal diabetes and FGR were not independent predictors of length or cost of stay (data not presented).

**Discussion**

We have demonstrated that hypoglycaemia after 35 weeks accounts for nearly one fifth of neonatal admissions, costing approximately 1.3 million GBP over a four year period in one tertiary NICU. Lower gestational age and admission blood glucose, low and high z-score birthweight, maternal nifedipine and exclusive breastfeeding were associated with longer duration of stay.

To our knowledge this is the first study to examine the association of maternal disease and intrapartum events with the morbidity related to neonatal hypoglycaemia as assessed by the length and cost of admission.

The prevalence of admissions for hypoglycaemia in our unit, however, was higher than previously reported. In a recent national report, the prevalence of admissions for hypoglycaemia was 10% for term admissions,[2] whilst in our study this was 23.3%. In our population, 86% of those with a prolonged admission had pre-existing maternal medical disease (hypertension or diabetes), maternal antihypertensive treatment, FGR or intrapartum complications (maternal antibiotics in labour, pathological CTG). It is, therefore, possible that the reported 10% national rate is not uniform across all units, but varies according to the prevalence of maternal risk factors in local populations.

Our study highlights that the severity of neonatal hypoglycaemia may be the result of the interplay of antenatal, intrapartum and postnatal risk factors. The maternal disease determines the milieu of fetal development and to an extent is responsible for the ability of the fetus to adapt to the stress of labour and early postnatal life. Impaired maternal glucose homeostasis during pregnancy, leads to fetal hyperglycaemia and transient hyperinsulinism.[9] A growth restricted infant will have
impaired gluconeogenesis and low glycogen stores.[25] In our study, maternal diabetes and FGR were not independent predictors of length and cost of stay. This is possibly because their effect was masked by the quadratic effect of the birthweight z-score, which showed increased length and cost of stay in low and high birthweight z-scores.

Maternal hypertension can predispose to neonatal hypoglycaemia via multiple mechanisms. Hypertension in pregnancy is strongly associated both with glucose intolerance[26, 27] and placental insufficiency leading to fetal growth restriction.[27] Furthermore, beta-blockers (antihypertensive therapy) have been associated with interruption of glycogenolysis in the neonate due to transplacental transfer.[28] Interestingly, in our cohort, maternal use of nifedipine rather than labetalol was associated with prolonged stay and increased cost. The evidence for labetalol as a cause for neonatal hypoglycaemia, however, is conflicted. Some epidemiological studies have reported an association after controlling a small number of confounders [10] whilst others argue that it is the fetal growth restriction, secondary to the placental insufficiency, which causes the need for treatment and is responsible for the neonatal hypoglycaemia.[15] Our results showing that nifedipine was associated with longer stay and higher cost likely reflects our practice in the choice of antihypertensive agents in pregnancy. We have previously developed a prediction model for the response to labetalol treatment in pregnancy by using maternal demographic and central haemodynamic data.[29] Women with low cardiac output-high resistance are more likely to respond to a vasodilator, such as nifedipine. Such pregnancies, are associated with established or impending fetal growth restriction as the vasoconstriction is a compensatory mechanism for the reduced intravascular space.[30, 31] It is therefore, likely that in our multivariate model Nifedipine is a proxy for fetal growth restriction.

The increased risk of hypoglycaemia in late preterm infants is the result of immature hepatic glycogenolysis and gluconeogenesis and limited enteral intake due to gastrointestinal immaturity and poor suck–swallow coordination.[32] In agreement with the above, our study identified low gestational age as an independent predictor
of admission for hypoglycaemia in infants more than 35 weeks of gestation. In our study, exclusive breastfeeding was also identified as an independent predictor of admission for neonatal hypoglycaemia. Early breastfeeding support increases the likelihood of successful breastfeeding and milk production. For both public health and economic benefit, i.e. promotion of successful breastfeeding and avoidance of neonatal admissions, it could be argued that focusing of intensive early support for breastfeeding in this high risk group should be prioritised.[33]

We acknowledge as a limitation that this was a retrospective study that focused on the characteristics of the admitted infants and did not explore that management in the postnatal ward. Nevertheless, our study group represents the most severe end of the spectrum of hypoglycaemia with regard to morbidity and cost.

In conclusion, hypoglycaemia after 35 weeks of gestation accounted for nearly a fifth of neonatal admissions in our population. Lower gestational age and admission blood glucose, low and high z-score birthweight, maternal nifedipine and exclusive breastfeeding are associated with longer duration and higher cost of stay.
References


Characteristics in Live Births and Stillbirths. Fetal Diagn Ther. 2012 Jul 26


Legend to figures

**Figure 1:** Venn diagram demonstrating the overlapping of maternal diabetes, hypertension, fetal growth restriction and pathological intrapartum cardiotocograph in our cohort.

**Figure 2:** Histogram of days of stay in our cohort. The vertical dashed lines demonstrate the percentage of infants discharged by day 3 and 10 of admission.
Table 1: Antenatal, labour and neonatal characteristics of the admitted infants (N=474)
Data presented as Mean (standard deviation) and median (interquartile range) for normally and not normally distributed data, respectively.

<table>
<thead>
<tr>
<th></th>
<th>Maternal diabetes</th>
<th>Fetal growth restriction</th>
<th>Maternal hypertension</th>
<th>Treatment with labetalol</th>
<th>Treatment with nifedipine</th>
<th>Treatment with methyldopa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antenatal, n (%)</strong></td>
<td>116 (24.5)</td>
<td>123 (25.9)</td>
<td>94 (19.8)</td>
<td>59 (12.4)</td>
<td>29 (6.1)</td>
<td>14 (2.9)</td>
</tr>
<tr>
<td><strong>Labour, n (%)</strong></td>
<td>Maternal pyrexia &gt; 38 °C</td>
<td>127 (26.8)</td>
<td>Pathological cardiotocograph</td>
<td>111 (23.4)</td>
<td>Apgar at 5 minutes &lt; 7</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delivery by CS</td>
<td></td>
<td></td>
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<tr>
<td><strong>Neonatal</strong></td>
<td>Female gender, n (%)</td>
<td>226 (47.7)</td>
<td>Singleton birth, n (%)</td>
<td>392 (82.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gestational age (weeks)</td>
<td>38.1 (36.7-39.3)</td>
<td>Birthweight centile</td>
<td>31.4 (5.4–68.9)</td>
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<tr>
<td></td>
<td>Birthweight z score</td>
<td>-0.52 (1.69)</td>
<td>Birthweight &lt; 3rd centile, n (%)</td>
<td>99 (20.9)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Birthweight &lt; 10th centile, n (%)</td>
<td>158 (33.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Birthweight &gt; 90th centile, n (%)</td>
<td>68 (14.3)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Birthweight &gt; 97th centile, n (%)</td>
<td>44 (9.3)</td>
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<tr>
<td><strong>Admission</strong></td>
<td>Age on admission (hours)</td>
<td>9.0 (6.0-15.0)</td>
<td>Blood sugar (mmol/L)</td>
<td>2.1 (1.7-2.4)</td>
<td>Temperature (°C)</td>
<td>36.6 (0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exclusive bottle feeding, n (%)</td>
<td>54 (11.4)</td>
<td>Symptomatic on admission, n (%)</td>
<td>122 (25.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total days of stay</td>
<td>3.0 (2.0-5.0)</td>
<td>Days of stay in High Dependency Unit</td>
<td>1.0 (0.0-2.0)</td>
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<td></td>
<td></td>
<td></td>
<td>Days of stay in Special Care baby unit</td>
<td>3.0 (2.0-3.0)</td>
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### Table 2: Significant univariate predictors of length and cost of stay

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Length of stay (days)</th>
<th>Cost of stay (GBP)</th>
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<tbody>
<tr>
<td></td>
<td>R-square</td>
<td>p-value</td>
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<tr>
<td>Admission blood sugar (mmol/L)</td>
<td>0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age on admission (hours)</td>
<td>0.03</td>
<td>&lt;0.0001</td>
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<tr>
<td>Birthweight z-score square</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Gest. age at delivery (weeks)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Pathological CTG</td>
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<td>0.01</td>
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<tr>
<td>Antibiotics in labour</td>
<td>0.04</td>
<td>&lt;0.0001</td>
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<tr>
<td>Maternal diabetes</td>
<td>0.007</td>
<td>0.03</td>
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<tr>
<td>Maternal use of Nifedipine</td>
<td>0.02</td>
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<td>Fetal growth restriction</td>
<td>0.01</td>
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### Table 3: Multivariate regression analysis for log-length and log-cost of stay

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<th>Length of stay (log-days)</th>
<th>Cost of stay (log-GBP)</th>
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<tr>
<td></td>
<td>Coefficient beta</td>
<td>Confidence intervals</td>
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<tr>
<td>Gestational age</td>
<td>-0.024</td>
<td>-0.042 to -0.006</td>
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<td>Blood Glucose</td>
<td>-0.121</td>
<td>-0.175 to -0.068</td>
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<tr>
<td>Exclusive breastfeeding</td>
<td>0.097</td>
<td>0.004 to 0.191</td>
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<tr>
<td>Nifedipine</td>
<td>0.181</td>
<td>0.050 to 0.007</td>
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<tr>
<td></td>
<td>0.312</td>
<td>0.007</td>
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<td>--------------------------</td>
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<tr>
<td>Pathological CTG</td>
<td>0.097</td>
<td>0.168</td>
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<table>
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<td>Birth weight</td>
<td>0.016</td>
<td>-0.036</td>
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<td>Birth weight square</td>
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