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The association between birthweight and perinatal mortality risk in gestational diabetes pregnancies: A retrospective cohort study

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Manuscript

The association between birthweight and perinatal mortality risk in gestational diabetes pregnancies: A retrospective cohort study.

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Abstract

Background

In the general obstetric population the lowest perinatal mortality risk for babies occurs between the 75th and 90th growth percentiles, and as birthweights decrease below this level perinatal risk increases. No study has yet explored risk versus birthweight percentile for Gestational Diabetes pregnancies so the primary aim of this study is to evaluate this relationship.

Methods

Using data from a large perinatal data collection in the Australian State of Queensland, babies born between 2010 and 2023 from 92,621 singleton gestational diabetes pregnancies between 24 and 42 weeks gestation were stratified into six birthweight percentile categories for which stillbirth and neonatal mortality rates were compared and odds ratios for mortality calculated using multivariable logistic regression and

adjusting for multiple potential confounders. The reference category was the 75th to 90th percentile group.

Mortality rates were also compared after adjusting for death to delivery intervals of two and five days and for the presence or absence of congenital abnormalities.

Results

The lowest mortality risk occurred for babies in the 75-90th birthweight percentile group, and mortality risk increased as birthweights decreased below this level. With reference to the 75-90th percentile, Odds Ratios for mortality by group were :- 25-<75%, 2.01(95%CI 1.32-3.17); 10-<25%, 2.71(95%CI1.64-4.54); <10%, 7.77(95%CI 4.99-12.5); 90-<97%, 1.37(95%CI 0.76-2.47); and >=97%, 2.55(95%CI 1.42-4.54).

After adjustments for death-to-delivery intervals of two and five days and for the presence or absence of congenital abnormalities larger babies remained at lower risk than babies below the 25th percentile.

Conclusion

In the absence of evidence from prior studies of significant treatment benefit for babies, the observed association of increasing mortality with decreasing birthweight for the majority of babies of treated gestational diabetes pregnancies should spark debate about the current practice of medically, and particularly pharmacologically, restricting the growth of these babies.

Background

It is generally recognized that a baby being under the 10th growth percentile antenatally, or Small for its Gestational Age (SGA), is at increased risk for stillbirth, but most perinatal deaths actually occur in babies who are apparently appropriately grown and in the 'normal range'[1,2]. Although 'normal' in size some of these babies may for various reasons have been prevented from reaching their optimum growth potential[3], and could be considered 'normal weight but growth restricted'[4].

In the general obstetric population the lowest mortality risk is for babies with a birthweight (BW) between the 75-95th growth percentiles[1,2,4-9], possibly reflective of good intrauterine nutrition[2], but as birthweights decrease below this level mortality risk increases[5], almost doubling below the 15-25th centiles[1,2,4-7,9]. Risk also increases for the few babies above the 97th percentile[1,2,4,8].

Whether similar relationships exist between intrauterine growth and mortality for babies of gestational diabetes pregnancies (GDM babies) has not been studied and the primary aim of this study is to see whether there is an association and if so to evaluate its nature. Our hypothesis is that a similar pattern will be seen in the babies of GDM pregnancies as in other pregnancies.

This issue may be important because one of the main aims of gestational diabetes (GDM) management is to decrease the antenatal growth of babies, so any relationships between growth and mortality could have implications for practice.

The interval between the times of a baby's demise and delivery may affect weight/gestation associations, as may the inclusion or exclusion of babies with

congenital abnormalities, so a secondary aim of the study will be to examine any effects of these considerations on the outcome data.

Methods

De-identified individual patient data from the Queensland Perinatal Data Collection (PDC) was obtained from the Statistical Reporting and Co-ordination unit of the Statistical Services Branch of the Queensland Department of Health (now renamed Data Services Branch).

The study data includes singleton births between 24 and 42 completed weeks gestation in the Australian State of Queensland to antenatal patients with a diagnosis of Gestational Diabetes, between and including the years 2010 and 2023. Multiple pregnancies and women with pre-existing Diabetes are excluded.

Data from all Queensland births are routinely entered into the PDC data base by the attending midwives or doctors, and the collection is quality assured on a regular basis.

Birthweight percentiles adjusted for the baby's sex and gestational age were calculated using the latest available Australian population data[10]. Births outside the 24-42 week window were excluded as daily birthweight standards were not available for these gestations.

Birthweight percentiles were divided into six categories – (1) <10%, (2)10-<25%, (3) 25-<75%, (4) 75-<90%, (5) 90-<97%, (6) 97% and over.

The 75-<90th percentile category, being the percentile group with the lowest perinatal mortality in previous studies, was used as the reference category.

The main outcome is perinatal mortality (PNM), a combination of stillbirth (SB) and neonatal death (ND = death in the first 28 days of life).

Data obtained from the PDC included maternal age, indigenous status, parity, smoking status, body mass index (BMI), number of antenatal visits, assisted conception, pre-existing hypertension, pregnancy associated hypertension or pre-eclampsia.

Foetal/baby details included sex, gestational age, birthweight, livebirth, stillbirth, and neonatal death.

The number of mother/baby pairs is 92,621.

A baby in whom the sex could not be determined and a baby with no recorded birthweight were excluded from the analysis.

There was no missing data for babies' sex, birthweight, gestational age, stillbirth or neonatal death.

Missing data numbers for other variables included BMI (839), smoking status (212), number of antenatal visits (43), indigenous status (6) and parity (1).

Missing data was imputed using Multiple Imputation by Chained Equations, with five imputations and twenty iterations, and including all variables in the data set. The imputed group selected was that with mean BMI closest to the mean BMI in the unimputed data.

The data from the PDC capped maternal age data at <16 and >45 yrs. We allocated to these women ages 16 or 45.

Similarly, BMI data was capped at < 18 and > 40 kg/m^2. and we allocated to these women BMIs of 18 or 40.

The incidence of stillbirth, neonatal death and perinatal mortality was calculated for each birthweight percentile category and tabled as numbers per thousand.

Different models were tested using multivariable logistic regression to calculate odds ratios and 95% confidence intervals for the comparison of risks of perinatal mortality and stillbirth in the different birthweight centile groups after adjusting for confounders.

Confounders or effect modifiers were selected based on availability from the PDC dataset, use in other similar studies, published risk factors for stillbirth in Queensland, and clinical experience.

All potential confounders were included initially, and backward selection/omission used to construct a model, with decisions to leave variables in/out based on residual deviances, Likelihood Ratio Testing and clinical experience. Interaction terms were included/excluded in a similar manner.

The time interval between a baby's demise and delivery is in most cases unknown. Weight for gestational age at delivery will be different from weight for gestational age at the earlier time of death, which may lead to an overestimation of stillbirth risk in small babies and an underestimation in large babies[7]. The size of this effect is unknown and most stillbirth studies do not account for it, although some, for example Gardosi et al[3], have estimated 48 hours and made an appropriate adjustment. A consensus of expert opinion in our health service as to the likely size of this interval in our hospitals was

130 ‘within a few days’, and ‘no longer than four or five days’, so we have included an
131 assessment of the effect of two and five day intervals on our outcomes.

132 We included babies with congenital abnormalities in the analysis for a number of
133 reasons. Most abnormalities have no bearing on the risk of death, and decisions to
134 include/exclude different conditions would introduce selection bias. Importantly, the
135 two main studies forming the evidence base for the current paradigm of GDM diagnosis
136 and treatment as it relates to foetal wellbeing both included babies with congenital
137 abnormalities[11,12], so not to include these babies would disconnect our findings from
138 the evidence base. Nevertheless, in addition to the main analysis we compared the
139 associations of birthweight percentile and perinatal mortality if babies with congenital
140 abnormalities had been excluded. ‘Congenital abnormalities’ as a category were not
141 sub-divided but were considered as a group as provided in the perinatal data by the
142 data custodians.

143 Statistical analysis was done using R Studio Version 2026.01.1+403, 2026 Posit
144 Software, PBC.

145 **Results**

146 A total of 92,621mother/baby pairs with a diagnosis of gestational diabetes were
147 included in the study.

148 Figure 1 relates birthweight percentile to mortality and shows the lowest mortality risk
149 occurred between the 75th and 90th percentiles. Mortality risk increased as birthweights
150 decreased below or increased above this level.

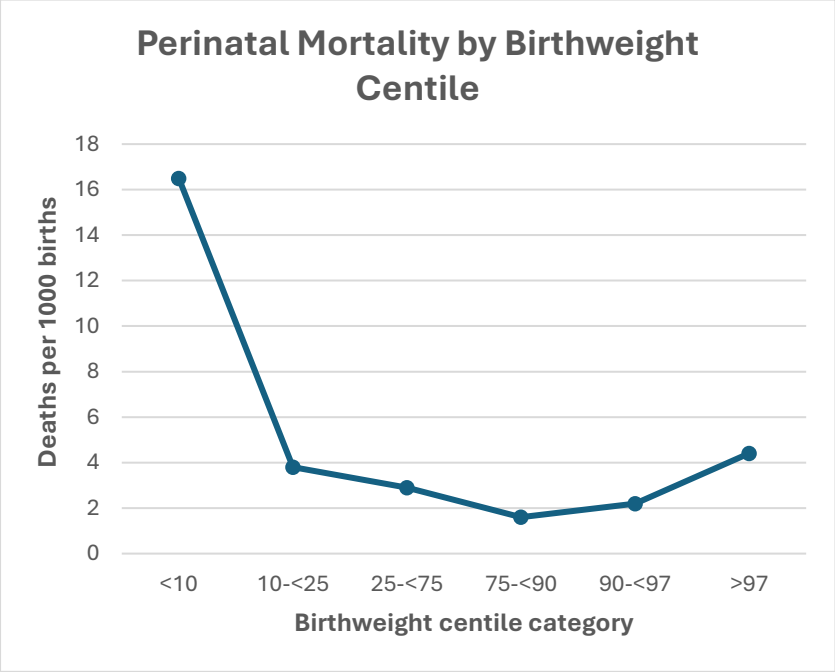


Figure 1 Perinatal mortality by birthweight centile,

Gestational Diabetes, Queensland, 2010-2023

Table 1 compares numbers per thousand and the odds of mortality at different birthweight percentiles.

The highest risk at 16.5/1000 occurred for babies with birthweights below the 10th percentile, followed by babies above the 97th percentile with a risk of 4.3/1000. Babies

between the 10th and 25th percentiles had stillbirth and perinatal mortality risks of 2.1/1000 and 3.8/1000 respectively.

The lowest stillbirth and perinatal mortality risks at 0.8/1000 and 1.6/1000 occurred for babies between the 75th and 90th percentiles and the stillbirth risk remained low up to the 97th centile.

Table 2 compares relative risks after adjustments for death to delivery intervals of zero, two and five days.

Table 3 shows risk comparisons for babies with and without congenital abnormalities, and with adjustments for different death to delivery intervals.

Overall, with death to delivery intervals of two or five days, and with the inclusion or exclusion of babies with congenital abnormalities, the babies with larger birthweights continued to have better outcomes than small babies.

Discussion

In this cohort the lowest mortality risk for GDM babies occurred at birthweights between the 75th and 90th growth percentiles, and as a baby's growth decreased below this level mortality risk increased, as it did above the 97th percentile.

Babies in the 10-25th percentile group, who would generally be considered normally grown, had a mortality risk twice that of those between the 75th and 90th percentiles (Table 1), and the lowest risk for stillbirth appeared to extend beyond the 90th up to the 97th percentile, a phenomenon seen in other studies [1,2,8].

These results suggest that although sometimes labelled ‘overgrown’, even ‘foetopathic’, most large GDM babies are in fact healthy.

The apparent mortality benefit of improved growth seen here is consistent with studies where up to 80% of stillbirths are below the median weight for gestational age, and where risks increase for birthweights below the 50th percentile, and particularly below the 20-30th percentiles[2,7,8,9].

A lower mortality risk with increasing birthweight may also not be unexpected in view of studies finding improved placental blood flow, reduced foetal hypoxia and less intrapartum distress as babies approach the 80-90th weight percentiles[4,13], increased perinatal asphyxia in babies who are thin compared to those who are not[14,15], reduced stillbirth risk seen with programmes to increase foetal size by maternal nutritional supplementation[16,17], and decreased risk of adult diabetes, cardiovascular disease and stroke in larger babies[2].

Although the relative risks change with adjustments for different death to delivery intervals larger babies remained at lower risk of mortality compared with babies less than the 25th percentile (Table 2), and the relation between birthweight and neonatal death, which unlike stillbirth is unaffected by the death to delivery interval, followed a similar pattern to perinatal mortality overall.

The exclusion of babies with congenital abnormalities also changed the relative risks but again an overall relationship between size and mortality persisted (Table 3).

A goal of GDM management is to decrease the growth of large babies, but because it is impossible to predict in mid pregnancy which will be the few very large babies who may

theoretically benefit from size reduction, babies of all sizes experience treatment related growth restraint[18].

This is achieved by means of what is in effect a medically prescribed weight reduction diet with mothers as intermediaries, intensified with diabetes medications in half of cases in Queensland[18], and most of the weight lost, unlike in adult diets, is lean mass rather than fat[19].

Considering the demonstrated association between decreasing size and increasing mortality the question arises whether medically decreasing a baby's size could inadvertently increase mortality risk.

A treatment related increase in mortality, if it did exist, may be acceptable if balanced by significant treatment benefits for babies, but although GDM treatment decreases intrauterine growth, the evidence to date has not shown improvements in foetal, neonatal or childhood outcomes as a result[20-24].

Whether or not there are benefits, there are potential disadvantages with GDM treatment aside from any possible effects of growth reduction. Pharmacological treatment may increase the number of babies small for gestational age[25,26], and a labelling effect of medication prescription may lead to an increase in labour induction and early-term births[18]. In addition, the American Diabetes Association recommends against the first line use of the diabetes drug Metformin, commonly used in this cohort, which may circulate in babies at levels higher than in their mothers and about which there are long term safety concerns[27].

It has been said that if choosing between actions where the potential loss may be great while the potential gain may be small, it is best to avoid the risk of great loss[28]. A perinatal death is a terrible loss, and although the differences in absolute risk may be small, and the association between reducing birthweight and increasing mortality cannot be shown to be causal, this consideration would seem to suggest the need for a review of the current practice of medical, and particularly pharmacological restraint of the intrauterine growth of babies in gestational diabetes pregnancies.

This being a large cohort from a diverse obstetric population there is no reason to think the results would not be generalisable to other populations, although similar studies in other groups of GDM patients would be important.

Weaknesses of this study include our inability to account for different babies being born to the same mother, which challenges the assumption of independent observations, although we note that in a similar study corrections for clustering did not significantly affect the overall findings[8]. We could not account for potential effects of any changes in GDM diagnosis or treatment practice which may have occurred during the time period of the study.

Conclusion

This study has shown that for the majority of babies of mothers diagnosed as gestational diabetes there is a correlation between decreasing growth and increasing mortality. As an aim of gestational diabetes management is to decrease the growth of babies, often with pharmacological intensification, and as there have been no

evidence-based benefits apparent from this growth reduction, the demonstrated association should in our opinion prompt a review of current practice.

List of Abbreviations

SGA – Small for gestational age

BW – Birthweight

GDM – Gestational diabetes

PDC – Perinatal Data Collection

PNM – Perinatal mortality

SB – Stillbirth

ND – Neonatal death

BMI – Body mass index

Declarations

Ethics approval was granted by the Darling Downs Hospital and Health Services Human Research and Ethics Committee, Approval Ref. LNR/2024/QTDD/108352.

A waiver of consent was granted from the Darling Downs Health Human Research and Ethics Committee and in authorising this project Section 150 of the Hospital and Health Boards Act 2011 (Qld) was considered and an exemption from the requirement to obtain Public Health Act approval was granted for access to this non-identifiable data from the Statistical Services Branch.

All authors consent to publication in BMC Pregnancy and Childbirth.

No author has any competing interests.

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The data used in this study is available by application to the Data Services Branch of the Queensland Department of Health (DLQ@health.qld.gov.au) and following approval of the application by the Data Custodians.

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Outcome	**Stillbirth** (n) n/1000	**Neonatal Death** (n) n/1000	**Perinatal Mortality** (n) n/1000	**Perinatal Mortality** aOR* (95% CI) p-value
Birthweight Centile (n)				
<10 (6,916)	(82) 11.9	(32) 4.6	(114) 16.5	7.77 (4.99-12.50) <.001
10-<25 (11,088)	(23) 2.1	(19) 1.7	(42) 3.8	2.71 (1.64-4.54) <.001
25-<75 (42,883)	(80) 1.9	(43) 1.0	(123) 2.9	2.01 (1.32-3.17) .002
75-<90 (16,592)	(14) 0.8	(12) 0.7	(26) 1.6	Ref
90-<97 (9,710)	(10) 1.0	(11) 1.1	(21) 2.1	1.37 (0.76-2.47) .29
97 or more (5,432)	(18) 3.2	(6) 1.1	(24) 4.3	2.55 (1.42-4.54) .002

*aOR: adjusted for maternal age, indigenous status, parity, smoking status, number of antenatal visits, assisted reproduction, BMI, essential hypertension, hypertensive disorder of pregnancy.

Table 1: Perinatal outcome by birthweight centile, Gestational Diabetes, Queensland, 2010-2023

Foetal demise to delivery interval (days)	**Zero**	**Two**	**Five**
Stillbirth	aOR* (95%CI) p-value	aOR* (95%CI) p-value	aOR* (95%CI) p-value
Birthweight centile			
<10%	9.15 (5.18-17.28) <.001	5.34 (3.22-9.19) <.001	2.44 (1.53-3.96) <.001
10-<25%	2.54 (1.3-5.15) .007	1.45 (0.77-2.73) 0.24	1.15 (0.67-1.96) 0.62
25-<75%	2.36 (1.37-4.39) .004	1.54 (0.96-2.59) 0.09	0.87 (0.57-1.35) 0.53
75-<90%	Ref	Ref	Ref
90-<97%	1.20 (0.51-2.72) 0.66	0.90 (0.41-1.86) 0.78	0.86 (0.46-1.57) 0.64
97% or more	3.53 (1.72-7.37) .001	2.7 (1.43-5.10) .002	1.96 (1.11-3.43) .02
Perinatal Mortality			
Birthweight centile			
<10%	7.77 (4.99-12.5) <.001	5.6 (3.69-8.67) <.001	3.33 (2.25-5.0) <.001
10-<25%	2.71 (1.64-4.54) <.001	1.93 (1.19-3.14) .008	1.61 (1.04-2.48) 0.03
25-<75%	2.01 (1.32-3.17) .002	1.55 (1.06-2.35) 0.03	1.06 (0.75-1.54) 0.74
75-<90%	Ref	Ref	Ref
90-<97%	1.37 (0.76-2.47) 0.29	1.14 (0.65-1.98) 0.63	1.06 (0.64-1.72) 0.81
97% or more	2.55 (1.42-4.94) .002	2.20 (1.28-3.75) .004	1.79 (1.08-2.93) 0.02

*aOR: adjusted for maternal age, indigenous status, parity, smoking status, number of antenatal visits, assisted reproduction, BMI, essential hypertension, hypertensive disorder of pregnancy.

Table 2: Perinatal outcome by birthweight centile with adjustments for foetal demise-to-delivery intervals of two and five days, Gestational Diabetes, Queensland, 2010-2023.

					All babies including those with congenital abnormalities		
Foetal Demise to Delivery Interval (days)	zero	zero	two	five	zero	two	five
	Neonatal Death n/1000	**Stillbirth** n/1000			**Perinatal Mortality** n/1000		
Birthweight centile							
<10%	4.6	11.9	11.0	8.6	16.5	15.5	13.2
10-<25%	1.7	2.1	1.8	2.3	3.8	3.5	4.1
25-<75%	1.0	1.9	1.8	1.6	2.9	2.8	2.6
75-<90%	0.7	0.8	1.3	2.0	1.6	2.0	2.7
90-<97%	1.1	1.0	1.1	1.6	2.2	2.3	2.8
97% or more	1.1	3.2	3.9	4.2	4.4	5.0	5.3
					Only babies without congenital abnormalities		
	Neonatal Death n/1000	**Stillbirth** n/1000			**Perinatal Mortality** n/1000		
<10%	1.6	8.7	8.1	6.3	10.4	9.7	7.9
10-<25%	0.4	1.1	1.2	1.6	1.5	2.0	2.0
25-<75%	0.7	1.5	1.4	1.3	2.2	1.9	1.9
75-<90%	0.3	0.6	1.0	1.4	0.8	1.7	1.7
90-<97%	0.6	0.3	0.4	0.9	0.9	1.4	1.4
97% or more	0.6	2.6	2.8	3.0	3.2	3.6	3.6

Table 3: Perinatal outcome by birthweight centile and Foetal demise-to-delivery interval, All babies and Babies without congenital abnormalities, Gestational Diabetes, Queensland, 2010-2013.