PAPERS AND SHORT REPORTS

Maternal fatness and viability of preterm infants

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Abstract

To investigate the effect of maternal fatness on the mortality of infants born preterm up to the corrected age of 18 months 795 mother-infant pairs were studied. Maternal fatness was defined by Quetelet's index (weight/(height^2)) and all infants weighed less than 1850 g at birth. In 771 mother-infant pairs maternal age, complications of pregnancy, mode of delivery, parity, social class, and the baby's sex and gestation were analysed by a logistic regression model for associations with infant mortality (but deaths from severe congenital abnormalities and those occurring during the first 48 hours after birth were excluded). In a subgroup of 284 mother-infant pairs all infant deaths except those from severe congenital abnormalities were analysed in association with the infant's birth weight and gestation and the mother's height and weight; this second analysis included another 24 infants who had died within 48 hours after birth. In the first analysis mortality overall was 7% (55/771), rising from 4% (71/173) in thin mothers (Quetelet's index <20) to 15% (6/40) in mothers with grades II and III obesity (Quetelet's index >30). After adjusting for major demographic and antenatal factors, including serious complications of pregnancy, maternal fatness was second in importance only to length of gestation in predicting death of infants born preterm. In the second analysis mortality overall was 15% (44/284), rising from 9% (5/53) in thin mothers to 47% (8/17) in mothers with grades II and III obesity. In both analyses the relative risk of death by 18 months post-term was nearly four times greater in infants born to obese mothers than in those born to thin mothers. In addition, maternal fatness was associated with reduced birth weight, whereas it is associated with macrosomia in term infants.

These data differ fundamentally from those reported in full term babies of obese mothers. It is speculated that the altered metabolic milieu in obesity may reduce the ability of the fetus to adapt to extrauterine life if it is born preterm.

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Introduction

Several studies have examined the outcome of babies born to obese mothers. Most showed that obese mothers delivered infants with higher mean birth weights[1-7] and several that perinatal mortality did not increase with maternal obesity, even though obese mothers are at high risk of developing complications during pregnancy, including hypertension, pre-eclampsia, and diabetes, and of having interventive deliveries.[1 6-10] It has been suggested, however, that any deleterious effects of these complications on the fetus are offset by the reduced incidence of both preterm delivery and intrauterine growth retardation found with maternal obesity.[2 11]

Previous studies on maternal obesity focused on normal populations of infants born in maternity units, and few data exist on the effects of maternal fatness on the high risk group of infants born preterm. Furthermore, although attention has been paid to the relation between maternal obesity and neonatal death, little information exists on maternal obesity and postneonatal mortality. We investigated the effect of maternal fatness (estimated from Quetelet's index,[12] or body mass index: weight/(height^2)) on mortality to 18 months of age (corrected for prematurity), birth weight, and important demographic and antenatal factors in 795 preterm infants.

Subjects and methods

In the first study 771 preterm infants of mean gestation 31 (SE 0·1) weeks who were participating in a larger study of feeding in five centres were

included.[13] All infants weighed less than 1850 g at birth; only those with major congenital abnormalities were excluded. The clinical course of mother and infant was monitored and information obtained at follow up until 18 months post-term. The mother's weight (to the nearest 100 g) was always measured in the first trimester of pregnancy. Maternal height was measured to the nearest millimetre by us with a Stadiometer. Quetelet's index was calculated as weight (kg)/(height (m)^2).[12 14] For part of the analysis mothers were divided into four categories according to the value of the index: up to 20 (thin), 20-25 (normal), 25-30 (grade I obesity), and over 30 (grades II and III obesity). This classification is based on that of Garrow and Webster.[14]

Factors analysed, in addition to Quetelet's index and the death of the baby, included maternal age; hypertensive disease (a blood pressure of 140/90 mm Hg and above before the onset of pregnancy); pre-eclampsia (hypertension related to pregnancy without oedema or proteinuria was also included in this group for the analysis); diabetes (high fasting blood glucose concentration or abnormal results on testing of glucose tolerance, or both); vaginal bleeding in pregnancy; anaemia (haemoglobin concentration 110 g/l or less); mode of delivery; parity; social class; and the sex, birth weight, and gestation of the infant. Gestational age was assessed from maternal dates unless these differed by more than two weeks from the clinical estimate (based on the early scan and neonatal examination), when the clinical estimate was used.

Subjects were entered into the feeding study in five centres within 48 hours after birth, as described[13]; thus death of the infant, the main outcome in this present study, had often occurred before entry into the study. Therefore in a second study we examined complete data from one of the five centres on birth weight, gestation, mother's weight and height, and whether the infant died for all infants born in the centre. The 284 infants included an additional 24 who had died within 48 hours after birth.

Statistical analyses included χ^2 tests to compare proportions and linear and logistic regression to test for trends. Logistic regression was used for binary dependent variables such as mortality, and linear regression for the continuous dependent variables. Although the data in the tables have been broken down by category of maternal fatness (as defined above), we treated Quetelet's index as a continuous rather than categorical variable in the statistical analyses.

TABLE I—*Relation between demographic and clinical factors and maternal fatness*

	Maternal fatness (Quetelet's index)				
	Thin (<20)	Normal (20-25)	Grade I obesity (25-30)	Grades II and III obesity (>30)	Significance (p value)*
No (%) of women	173 (22)	442 (57)	116 (15)	40 (5)	
Mean (SE) age (years)	26 (0·4)	27 (0·3)	27 (0·5)	28 (0·8)	<0·05
No (%) of primiparas	58 (100)	57 (252)	57 (66)	53 (21)	NS
No (%) with complications of pregnancy:					
Pre-eclampsia	24 (14)	106 (24)	32 (28)	15 (38)	<0·005
Hypertension	4 (2·3)	25 (5·7)	15 (13)	7 (18)	<0·0001
Diabetes	1 (0·6)	4 (0·9)	3 (2·6)	3 (7·5)	<0·005
Anaemia	13 (8)	17 (4)	2 (2)	2 (5)	NS
Vaginal bleeding	52 (30)	146 (33)	48 (41)	8 (20)	NS
No (%) who had caesarean section	75 (43)	228 (52)	74 (64)	23 (58)	<0·02
			Infant data		
Mean (SE) birth weight (g)	1429 (21)	1394 (15)	1359 (29)	1312 (56)	<0·005
Mean (SE) gestation (weeks)	31 (0·2)	31 (0·1)	31 (0·3)	31 (0·5)	NS

*From linear regression analysis with Quetelet's index as continuous dependent variable rather than as categorised here.

TABLE II—*Mortality in babies born preterm up to 18 months corrected age according to maternal fatness (deaths from congenital abnormalities and those occurring within 48 hours after birth are excluded). Values are proportions (percentages) of infants*

	Maternal fatness (Quetelet's index)			
	Thin (<20)	Normal (20-25)	Grade I obesity (25-30)	Grades II and III obesity (>30)
Infant mortality	7/173 (4)	31/442 (7)	11/116 (9)	6/40 (15)

Results

FIRST STUDY (FIVE CENTRES)

Table I shows that 15% (116/771) of mothers had grade I obesity and 5% (40/771) grade II or III obesity. With increasing maternal fatness infant birth weight decreased ($p<0·005$) and the incidence of hypertension ($p<0·0001$), pre-eclampsia ($p<0·005$), and gestational or insulin dependent diabetes ($p<0·005$) increased. Maternal fatness was also associated with a higher maternal age ($p<0·05$) and a greater rate of caesarean section ($p<0·02$), but no effect of fatness was detected on gestation, anaemia, bleeding in pregnancy, or maternal parity.

All these factors were included, together with social class, in a linear regression model with Quetelet's index as the dependent variable. Fatness was related to hypertension ($p<0·0001$), pre-eclampsia ($p<0·0001$), diabetes ($p<0·001$), lower social class ($p<0·01$), and lower birth weight ($p<0·01$), but the higher rate of caesarean section in obese mothers (seen in table I) was not observed after adjusting for these mothers' increased incidence of hypertension and pre-eclampsia.

Table II shows raw data on mortality of babies to 18 months corrected age: 4% of babies born to thin mothers died and this proportion rose to 15% in mothers with grades II and III obesity ($p<0·01$). The mortality overall was 7%. Thirty four babies died before discharge from the neonatal unit (median age of death 13 days; upper and lower quartiles 5 and 39 days) and 21 died subsequently at 117 (67 and 368) days. The increase in mortality with maternal fatness was similar in babies dying before and after discharge from the neonatal unit (with the χ^2 test for trend $p<0·05$ for both).

A logistic regression model was constructed relating death (dependent variable) to the infant's gestation, birth weight, and sex and to the mother's age, parity, social class, and whether her pregnancy was complicated by hypertensive disease, pre-eclampsia, vaginal bleeding, or anaemia. The only factors significantly related to death of the child were gestation ($p<0·01$), birth weight ($p<0·02$), and maternal fatness ($p<0·02$). The relative risk of death before 18 months post-term after adjusting for birth weight and gestation was 3·7 times greater for the child of a mother with grade II or III obesity than for the child of a thin mother (confidence interval for relative risk 1·3 to 10·9).

Although this study concerns the relation of maternal rather than neonatal factors to infant mortality, we explored the possibility that maternal obesity resulted in the birth of an infant in poor condition and hence at risk. We found no relation, however, between maternal fatness and a low Apgar score at five minutes (less than 5), an arterial pH less than 7·2 in the first hour, and whether the baby was intubated within 30 minutes after birth or required mechanical ventilation for over 24 hours.

SECOND STUDY (ONE CENTRE)

This study, which included all neonatal deaths apart from those from major congenital abnormalities, consisted of 284 babies, 44 of whom died (15%) by 18 months corrected age. Table III shows that mortality rose from 9% for babies born to thin mothers to 47% for those born to mothers with grade II or III obesity ($p<0·005$). The incidence of grade II or III obesity was 4% (9/240) in mothers whose babies survived and 18% (8/44) in mothers whose babies died ($p<0·001$).

In a logistic regression model the death of an infant (dependent variable) was related to birth weight, gestation, and maternal fatness; significance was reached only for gestation ($p<0·001$) and maternal fatness ($p<0·05$). After adjustment for gestation the relation between fatness and death was linear, as found in the first study, and not curvilinear as suggested by the raw data in

table III. This model was used to calculate the risk of the baby's dying in each category of maternal fatness at 33, 30, and 27 weeks' gestation (table IV). As found in the first study the relative risk of the baby's dying at each gestation was 3·7 times greater for babies born to mothers with grade II or III obesity than for those born to thin mothers.

TABLE III—*Mortality in babies born preterm up to 18 months corrected age according to maternal fatness (deaths from congenital abnormalities are excluded). Values are proportions (percentages) of infants*

	Maternal fatness (Quetelet's index)			
	Thin (<20)	Normal (20-25)	Grade I obesity (25-30)	Grades II and III obesity (>30)
Infant mortality	5/53 (9)	23/172 (13)	8/42 (19)	8/17 (47)

TABLE IV—*Estimated relative risk of death before 18 months post-term according to gestational age and maternal fatness (deaths from major congenital abnormalities are excluded). Ratios are numbers dying to numbers surviving*

	Maternal fatness (Quetelet's index)			
	Thin (<20)	Normal (20-25)	Grade I obesity (25-30)	Grades II and III obesity (>30)
Weeks of gestation:				
33	1:74	1:47	1:30	1:20
30	1:16	1:10	1:6·7	1·4·3
27	1:3·7	1:2·3	1:1·5	1:1

Discussion

In this study of nearly 800 premature infants and their mothers maternal fatness emerged as one of the most important factors associated with the survival of an infant born preterm. In the first study based on five centres infants whose mothers had grade II or III obesity were nearly four times more likely to die in the period up to 18 months post-term than those born to thin mothers. As this study excluded deaths of infants within 48 hours after birth we investigated data from one centre on all infants without major congenital anomalies and observed an identical relative risk of death in babies of fat and thin mothers.

We used Quetelet's index (weight/(height^2)) to assess maternal fatness. This formula has been validated against other methods for estimating body fat in vivo and shown to be a reliable index.[14] For clarity we presented data in four categories of maternal fatness based on those suggested by Garrow and Webster.[14] In our statistical analyses, however, Quetelet's index was treated as a continuous variable to avoid an arbitrary cut off point in defining obesity. As in many studies, we always recorded maternal weights in the first trimester, which may not always reflect weight before pregnancy. Our statistics on infant mortality must therefore be interpreted according to the mother's weight in early pregnancy.

In a logistic regression model relating death of the baby to gestation, birth weight, serious complications during pregnancy (including hypertension, pre-eclampsia, diabetes, bleeding, and anaemia), mode of delivery and maternal age, parity, social class, and fatness we found, remarkably, that the only consistent association other than gestation was maternal fatness. In addition, an interesting possibility raised by our data and requiring further exploration is that mortality is lower in the child born preterm to a thin mother than in one born to a mother of "normal" weight.

Our data differ from those reported for infants born full term to obese mothers. In most studies on infants born at term mortality was not raised with maternal obesity[1 6-10]; when an increase in perinatal mortality rates was observed it was related to complications of pregnancy and not to maternal obesity itself.[15] We found that obese mothers of premature babies as in other studies showed a considerable increase in the incidence of hypertension, toxaemia, and diabetes during pregnancy, although the high infant mortality was independent of these complications. Infants born at term to obese mothers tend to be large for gestation and are more often obviously macrosomic[1-7 11]; conversely, premature infants showed decreasing birth weight for gestation with increasing maternal fatness. The large infants born at term to obese mothers are probably not underweight earlier in gestation and we therefore speculate that obese mothers who deliver preterm are a special group whose fetuses might, for instance, be more prone to placental insufficiency.

The reason why maternal fatness was so strongly associated with reduced viability in infants born preterm cannot be deduced from this study. The babies did not require more resuscitation at delivery. The high mortality in babies of obese mothers is unlikely to relate to their special family or social circumstances because infant mortality was independent of social class, and the increase in infant mortality with maternal fatness was the same in infants dying early while still in hospital and in those dying much later after discharge home. A trend towards increased duration of ventilatory support in babies of fatter mothers was found (not reported here), but the analysis was confounded because ventilation was curtailed if the infant died.

As a birth weight of less than 1850 g was a criterion for entering the study a selection bias towards smaller infants at longer gestations existed. This did not, however, account for our findings, which we confirmed in infants below 32 weeks' gestation who all fulfilled the entry criterion. Our study was not large enough to analyse the results by cause of death. When death from congenital malformations was excluded most deaths in babies born of both fat and thin mothers were a direct consequence of prematurity: early deaths usually related to severe hyaline membrane disease, intraventricular haemorrhage, pneumothorax, infection, and necrotising enterocolitis and later deaths to chronic lung disease and sudden infant death syndrome. On preliminary analysis no obvious pattern of death emerged in infants of fat mothers, but a larger sample is needed.

Obese mothers are known to have metabolic abnormalities, notably, gestational and insulin dependent diabetes,[2] which we also found. Metabolic abnormalities in the mother might programme the fetus in such a way that it is less able to adapt to extrauterine life if born preterm, but this hypothesis needs further investigation. In view of the strength of the association between maternal fatness and the subsequent viability of preterm infants, we suggest that studies are now required to investigate whether this association is causal; such work might throw light on why individual infants vary so much in their prognosis after premature birth.

We thank the staff of the special care baby units in Cambridge, Ipswich, King's Lynn, Norwich, and Sheffield for their help and cooperation; Dr Gillian Gandy, Penny Lucas, Lynn DiCarlo, Susan Cork, Elaine Duncanson, Jane Jones, and Anthea Mansfield for help with collection of the data; and Farley Health Products Ltd for financial support.

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(Accepted 12 February 1988)