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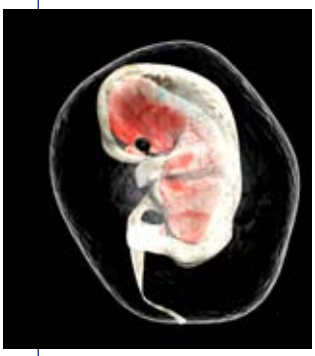
RESEARCH


CHRISTIAN DARKIN/SPL

THIS WEEK'S RESEARCH QUESTIONS

One embryo or two?

Concerns about the risks of having twins or triplets have led to a gradual reduction in the number of embryos transferred during in vitro fertilisation (IVF). D J McLernon and colleagues have now filled an important gap in the evidence base for this practice, answering additional questions on the effect of single versus double embryo transfer in different subgroups of women and on secondary outcomes such as miscarriage, preterm delivery, and low birth weight (p 34).

Their meta-analysis of individual patient data from randomised trials found that elective single transfer is safer than double and, although live birth rates are lower after single transfer in a fresh IVF cycle, this difference is overcome by replacement of an additional frozen single embryo. As using a frozen embryo avoids the need for surgery to harvest an egg, the authors argue in the full online version of the paper that "many would consider that this is a relatively small price to pay compared with the long term consequences of [multiple and] preterm birth" (*BMJ* 2010;341:c6945).

Transmission of HIV via breast feeding


MAURO FERMARIELLO/SPL

The risk of mother to child transmission of HIV is estimated to be as high as 25-35%. Transmission can occur in the uterus, during delivery, and during breast feeding, although not much is known about the rates of infection via breast feeding.

According to Jean Humphrey and colleagues, who conducted a study of more than 4000 Zimbabwean infants and mothers who ever tested HIV positive during the 24 month study period, the risk of breastfeeding associated transmission can be as high as one in four (p 37). The proportion of infants who were infected at age 2 was higher in women who seroconverted during the postnatal period than in those who appeared to have to seroconverted before breast feeding.

The authors also found that among women who seroconverted postnatally, roughly two thirds of cases of breastfeeding associated transmission occurred during the first three months after infection, when antibody levels would be too low to be detected by diagnostic tests designed to detect HIV antibodies, such as ELISA.

Managing intrauterine growth restriction at term


JOSEPH NETTIS/SPL

Intrauterine growth restriction at term is associated with increased perinatal morbidity and mortality. Obstetricians often induce labour in such cases to prevent negative outcomes and stillbirth, although this procedure is also has its risks.

K E Boers and colleagues conducted an equivalence trial in the Netherlands to establish whether induction is associated with worse neonatal outcomes than expectant monitoring, the other common approach to managing intrauterine growth restriction (p 35). Pregnant women who had a singleton pregnancy beyond 36 weeks' gestation with suspected intrauterine growth restriction were randomly allocated to induction or expectant monitoring. The difference in the incidence of the primary outcome—a composite measure of adverse neonatal outcome—between the induction and expectant monitoring groups was not statistically significant.

"This is an important study, and will probably inform clinical care for the foreseeable future," write editorialists Louise Kenny and Lesley McCowan (p 2). They suggest that the lack of difference in adverse outcomes supports the use of either strategy, depending on the wishes of the woman, although they advise that induction of labour may be more appropriate to prevent stillbirth.

Deaths in early life in England: what explains the gap between rich and poor?

The brilliant gapminder.org website, founded by Swedish professor of international health Hans Rosling, has an array of animated graphics about poverty and mortality, including this one on neonatal deaths worldwide: http://tiny.cc/xnbbk. Unsurprisingly, the UK hardly figures on gapminder.org's global charts. But even in the UK trends in neonatal mortality raise important questions.

Lucy Smith and colleagues' retrospective cohort study analysed time trends in perinatal mortality in England to understand why poorer babies are at increasingly greater risk than richer ones, despite a government target to reduce the deprivation gap in infant mortality in England by 10% between 2003 and 2010 (p 38). While all cause neonatal mortality fell between 1997-9 and 2006-7, excess deaths associated with deprivation increased from 1997-9 to 2003-5 and then decreased in 2006-7. Nearly 80% of the deprivation gap was explained by differences in deaths related to either immaturity or congenital anomalies.

In the full online version of the paper the authors say that research on the link between deprivation and prematurity should be a major priority.

Clinical effectiveness of elective single versus double embryo transfer: meta-analysis of individual patient data from randomised trials

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EDITORIAL by Templeton

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STUDY QUESTION What is the effectiveness of cleavage stage elective single embryo transfer compared with double embryo transfer after in vitro fertilisation?

SUMMARY ANSWER Compared with double embryo transfer, elective single transfer increased the chance of delivering a term singleton live birth and reduces the risk of multiple births and low birth weight. Although live birth rates are lower after single transfer in a fresh IVF cycle, this difference is overcome by replacement of an additional frozen single embryo.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Double embryo transfer results in a high twin rate, which is associated with increased perinatal morbidity. Elective single embryo transfer reduces the risk of unfavourable perinatal outcomes, and an additional frozen cycle results in live birth rates similar to double embryo transfer.

Selection criteria for studies

We searched Medline, Embase, Cochrane Central Register of Controlled Trials, meta-Register of Controlled Trials, conference proceedings, and contacted researchers in the field. Randomised controlled trials comparing clinical effectiveness of cleavage stage elective single versus double embryo transfer in women undergoing IVF were included.

Primary outcomes

The main outcomes of interest were live birth, multiple live birth, preterm delivery (≤37 weeks), term singleton delivery (>37 weeks), and delivery of at least one low birthweight baby (<2500 g).

Main results and role of chance

Eight trials were included (three were unpublished). Data on individual patients were received for all 1367 women randomised to elective single embryo transfer (n=683) and double embryo transfer (n=684). The live birth rate after a fresh IVF cycle was lower in the elective single group than the double group (adjusted odds ratio 0.50, 95% confidence interval 0.39 to 0.63), as was the multiple birth rate (0.04, 0.01 to 0.12). The odds of a cumulative live birth in the elective single group after transfer of an additional frozen embryo were not significantly different from those in the double group. The adjusted odds of delivering at least one low birthweight baby after elective single embryo transfer were a third of those after double embryo transfer (0.36, 0.15 to 0.87). The adjusted odds ratio for elective single versus double embryo transfer was 4.93 (2.98 to 8.18) for term singleton delivery and 0.33 (0.20 to 0.55) for preterm delivery.

Bias, confounding, and other reasons for caution

Information regarding the quality of the three unpublished studies was obtained from trial protocols and from the trialists. These trials had limited sample size (n=93 in total) compared with the published trials, and two of the three were stopped because of poor recruitment. Their inclusion is important, however, as they alleviate systematic bias. Variation in entry criteria and clinical protocols among the trials mean that we cannot exclude an element of clinical heterogeneity. Most trials focused on women with "good prognosis" and so our findings might not be generalisable beyond this group.

Study funding/potential competing interests

This review was funded by the Wellcome Trust.

EFFECT OF ELECTIVE SINGLE EMBRYO TRANSFER (ESET) AND DOUBLE EMBRYO TRANSFER (DET) ON LIVE BIRTH AND PERINATAL OUTCOMES AFTER IVF

Outcomes	Proportion (%) of eSET	Proportion (%) of DET	Adjusted odds ratio (95% CI)
Fresh cycle			
Live birth*	181/683 (27)	285/683 (42)	0.50 (0.39 to 0.63)
Multiple live birth†	3/181 (2)	84/285 (29)	0.04 (0.01 to 0.12)
Delivery of at least one low birthweight baby (<2500 g)†	14/181 (8)	69/284 (24)	0.36 (0.15 to 0.87)
Term singleton delivery†	158/181 (87)	169/284 (60)	4.93 (2.98 to 8.18)
Preterm delivery (24-37 weeks)†	23/181 (13)	85/284 (30)	0.33 (0.20 to 0.55)
Fresh and frozen SET			
Cumulative live birth‡	132/350 (38)	149/353 (42)	0.85 (0.62 to 1.15)
Cumulative multiple live birth§	1/132 (1)	47/149 (32)	0.02 (0.002 to 0.12)

Denominators: *women (one lost to follow-up and excluded from DET group); †live births; ‡women (from two trials that included additional frozen SET); §live births (from two trials with additional frozen SET).

Induction versus expectant monitoring for intrauterine growth restriction at term: randomised equivalence trial (DIGITAT)

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STUDY QUESTION For intrauterine growth restriction at term, is there any difference in adverse neonatal outcomes with induction of labour compared with expectant monitoring?

SUMMARY ANSWER Fetal, and maternal, outcomes after induction of labour at term are equivalent to those after expectant management with monitoring.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Induction in intrauterine growth restriction might increase neonatal respiratory problems and operative delivery rates, so expectant management is commonly recommended. Our results suggest that women who are keen on non-intervention can safely choose expectant management with intensive maternal and fetal monitoring; however, induction is also a reasonable strategy to prevent neonatal morbidity and stillbirth.

Design

The Disproportionate Intrauterine Growth Intervention Trial At Term (DIGITAT) is a multicentre randomised equivalence trial run by the Dutch Obstetric Consortium. Pregnant women were randomly allocated to either induction within 48 hours of randomisation or expectant monitoring with daily fetal movement counts and twice weekly heart rate tracings, ultrasound examination, maternal blood pressure measurement, assessment of proteinuria, laboratory tests of liver and kidney function, and full blood count. Allocation was computer generated in a 1:1 ratio with stratification for centre and parity.

Participants and setting

Pregnant women between 36+0 and 41+0 weeks' gestation who had a singleton fetus in cephalic presentation, suspected intrauterine growth restriction, and who were under specialised obstetric care were recruited. Suspected intrauterine growth restriction was defined as fetal abdominal circumference below the 10th percentile, estimated fetal weight below the 10th percentile, or flattening of the growth curve in the third trimester.

Primary outcome

The primary outcome was a composite measure of adverse neonatal outcome, defined as death before hospital discharge, five minute Apgar score of less than 7, umbilical artery pH of less than 7.05, or admission to neonatal intensive care.

Main results and the role of chance

A total of 321 pregnant women were allocated to induction and 329 to expectant monitoring. Infants in the induction group were delivered 10 days earlier (mean difference −9.9 days, 95% CI −11.3 to −8.6) and weighed 130 g less (mean difference −130 g, 95% CI −188 g to −71 g) than babies in the expectant monitoring group. A total of 17 (5.3%) infants in the induction group experienced the composite adverse neonatal outcome, compared with 20 (6.1%) in the expectant monitoring group (difference −0.8%, 95% CI −4.3% to 3.2%). Caesarean sections were performed on 45 (14.0%) mothers in the induction group and 45 (13.7%) in the expectant monitoring group (difference 0.3%, 95% CI −5.0% to 5.6%).

Harms

We encountered no maternal or perinatal deaths.

Bias, confounding, and other reasons for caution

Many thousands of participants would be required to measure the effects of induction on perinatal death.

The relatively favourable neonatal outcomes in both study groups could reflect the fact that participants received cautious attention and clinicians were more alert to possible complications.

Generalisability to other populations

Participants were younger, less educated, and smoked more than women who declined, which might affect the generalisability of the results. The study results should be extrapolated with caution to settings where close monitoring cannot be offered.

Study funding and potential competing interests

This study was funded by ZonMw, the Netherlands Organisation for Health Research and Development health care efficiency programme (grant number 945-04-558). The authors declare no conflicts of interest.

Trial registration number

International Standard Randomised Controlled Trial number ISRCTN10363217.

NEONATAL OUTCOMES FOR INDUCTION OF LABOUR COMPARED WITH EXPECTANT MONITORING IN INTRAUTERINE GROWTH ESTRICTION AT TERM

	Induction of labour group (n=321)	Expectant monitoring group (n=329)	Difference in percentage (95% CI)
Composite adverse neonatal outcome	17 (5.3)	20 (6.1)	−0.8 (−4.3 to 2.8)
Fetal and neonatal deaths	0	0	—
Apgar score after five minutes <7	7 (2.2)	2 (0.6)	1.6 (−0.2 to 3.4)
Arterial pH <7.05†	4 (1.4)	10 (3.5)	−2.1 (−4.6 to 0.5)
Admission to intensive care	9 (2.8)	13 (4.0)	−1.2 (−4.0 to 1.6)
Admission to Intermediate care	155 (48.4)	118 (36.3)	12.1 (4.6 to 19.7)*

Table shows number (%). *P<0.05. †n=279 for induction, n=288 for expectant monitoring.

Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial

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STUDY QUESTION Does dietary supplementation with B vitamins or omega 3 fatty acids prevent further cardiovascular events in patients with a history of ischaemic heart disease or stroke?

SUMMARY ANSWER No, daily ingestion of either or both supplements did not show any benefits on risk of major cardiovascular events.

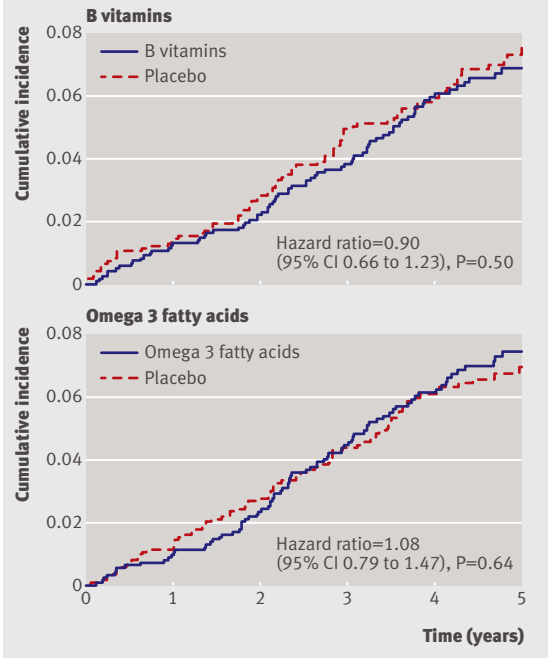
WHAT IS KNOWN AND WHAT THIS PAPER ADDS Observational studies have reported inverse associations of cardiovascular disease with dietary intake or plasma levels of B vitamins and omega 3 fatty acids, but results of randomised trials have been contradictory. This trial found no significant effects of supplementation with B vitamins or with omega 3 fatty acids on risk of major cardiovascular events in patients with established coronary or cerebrovascular disease.

Design

The SU.FOL.OM3 trial was a multicentre, double blind, randomised, placebo controlled trial of the effects of daily dietary supplementation with B vitamins or omega 3 fatty acids, or both, on risk of cardiovascular disease. With a 2×2 factorial design, the trial compared a supplement containing 5-methyltetrahydrofolate (560 µg), vitamin B-6 (3 mg), and vitamin B-12 (20 µg) against placebo, and a supplement of omega 3 fatty acids (600 mg of eicosapentaenoic and docosahexaenoic acids at a ratio of 2:1) against placebo. Median duration of supplementation was 4.7 years.

Randomisation was by block sequence stratified by age (45–54, 55–64, or 65–80 years), sex, prior disease at enrolment (myocardial infarction, acute coronary syndrome without myocardial infarction, or ischaemic stroke), and recruitment centre.

DIETARY SUPPLEMENTATION AND INCIDENCE OF FIRST MAJOR CARDIOVASCULAR EVENT



Participants and setting

Physicians in 257 centres throughout France recruited 2501 participants (1987 men and 514 women) aged 45–80 years with a history of myocardial infarction, unstable angina, or ischaemic stroke. These were randomised to one of the four treatment groups.

Primary outcome

The primary outcome was a major vascular event—non-fatal myocardial infarction, ischaemic stroke, or death from cardiovascular disease—measured biannually by questionnaire and annually by visit to an assessment centre. All events were adjudicated by two independent committees of cardiologists or neurologists who were blinded to treatment allocation.

Main results and the role of chance

Allocation to B vitamins lowered plasma homocysteine concentrations by 19% compared with placebo, but had no significant effect on the incidence of major vascular events (75/1242 (6.0%) of patients *v* 82/1259 (6.5%), hazard ratio 0.90 (95% CI 0.66 to 1.23), P=0.50). Allocation to omega 3 fatty acids increased plasma concentrations of these fatty acids by 37% compared with placebo, but also had no significant effect on major vascular events (81/1253 (6.5%) *v* 76/1248 (6.1%), hazard ratio 1.08 (0.79 to 1.47), P=0.64).

Harms

Side effects (chiefly gastrointestinal disturbances, nausea, and cutaneous reactions) accounted for 2.1% of participants stopping treatment (2.6% of those taking fatty acids, 2.0% taking B vitamins, and 1.6% taking placebo).

Bias, confounding, and other reasons for caution

The duration of supplementation and follow-up and the doses used for dietary supplementation could have been insufficient to observe significant effects. Also the interval between the initial cardiovascular event and the start of supplementation may have been too great: in trials that found a protective effect of omega 3 fatty acids the interval was shorter and the beneficial effect appeared early.

Study funding/potential competing interests

The trial was supported by the French Ministry of Research, Ministry of Health, Sodexo, Candia, Unilever, Danone, Roche Laboratory, Merck EPROVA GS, and Pierre Fabre Laboratory.

Trial registration number

Current Controlled Trials ISRCTN41926726.

Mother to child transmission of HIV among Zimbabwean women who seroconverted postnatally: prospective cohort study

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STUDY QUESTION Are breastfeeding women who seroconvert to HIV during the postnatal period at high risk of transmitting the virus to their infants?

SUMMARY ANSWER The risk of breastfeeding associated transmission is very high during the first three to six months after maternal infection and is mirrored by a high but transient peak in breast milk HIV load.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS This study confirms with a far greater sample size than previously studied that mother to child transmission rates are high among women who seroconvert to HIV postnatally.

Participants and setting

Mother-infant pairs in urban Zimbabwe who were enrolled within 96 hours of delivery into the Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO) trial (1997-2001).

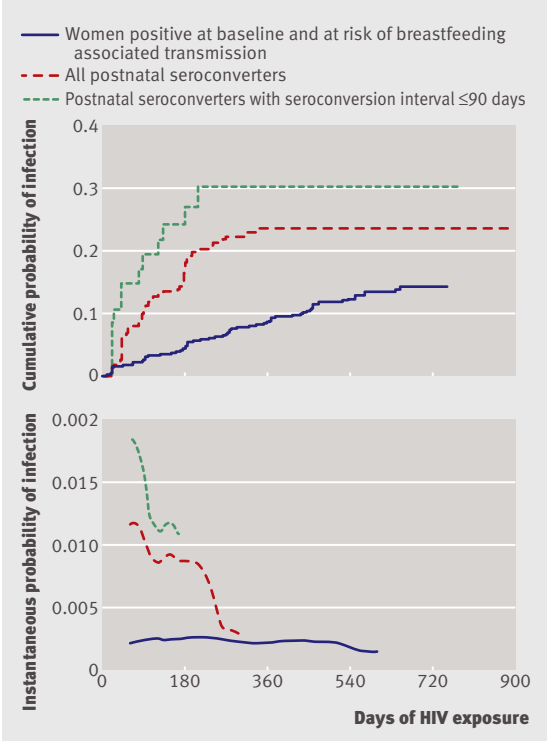
Design, size, and duration

Four groups of mothers who ever tested positive for HIV and their infants were included in this analysis: 4495 mothers who tested HIV positive at baseline with enzyme linked immunosorbent assay (ELISA); 2870 baseline positive mothers (a subgroup of the 4495 women) whose infant tested HIV negative with polymerase chain reaction (PCR) at six weeks and were therefore at risk of breastfeeding associated transmission; 334 mothers who seroconverted to HIV postnatally while breast feeding their infants; and 17 mothers who tested HIV negative by ELISA but HIV positive by PCR at baseline.

Main results and the role of chance

Among mothers who tested HIV positive at baseline and whose infant tested HIV negative at six weeks, breastfeeding associated transmission was responsible for an average of 8.96 infant infections per 100 child years of breast feeding (95% CI 7.92 to 10.14) and varied little over the breastfeeding period. Conversely, for mothers who seroconverted postnatally, breastfeeding associated transmission averaged 34.56 infant infections per 100 child years (95% CI 26.60 to 44.91) during the first nine months after maternal infection, declined to 9.50 (95% CI 3.07 to 29.47) during the next three months, and was zero thereafter. Median plasma HIV concentration in the seroconverting mothers declined from 5.0 $\log_{10}$ copies/mL at the last negative ELISA to 4.1 $\log_{10}$ copies/mL at 9-12 months after infection, whereas breast milk HIV load was 4.3 $\log_{10}$ copies/mL 0-30 days after infection but rapidly declined to 2.0 $\log_{10}$ copies/mL and <1.5 $\log_{10}$ copies/mL by 31-90 days and more than 90 days, respectively. Among the 17 women who were seroconverting during delivery, 75% of their infants were HIV infected or had died by 9 months of age. An estimated 18.6% to 20.4% of all breastfeeding associated transmission observed in the ZVITAMBO trial occurred among mothers who seroconverted postnatally.

CUMULATIVE AND INSTANTANEOUS PROBABILITY OF BREASTFEEDING ASSOCIATED TRANSMISSION OF HIV



Bias, confounding, and other reasons for caution

ZVITAMBO was conducted before antiretroviral therapy or prophylactic regimens were available. Our estimate that 20% of all breastfeeding associated HIV transmissions occur among women who seroconverted postnatally is likely to be an underestimate where these regimens are being implemented because these interventions will substantially reduce mother to child transmission among HIV positive women identified antenatally but will reach few women who seroconvert postnatally.

Generalisability to other populations

These findings are generalisable to other breastfeeding populations in Africa.

Study funding/potential competing interests

The ZVITAMBO Project was supported by several international grants (see bmj.com). The authors declare no competing interests.

Nature of socioeconomic inequalities in neonatal mortality: population based study

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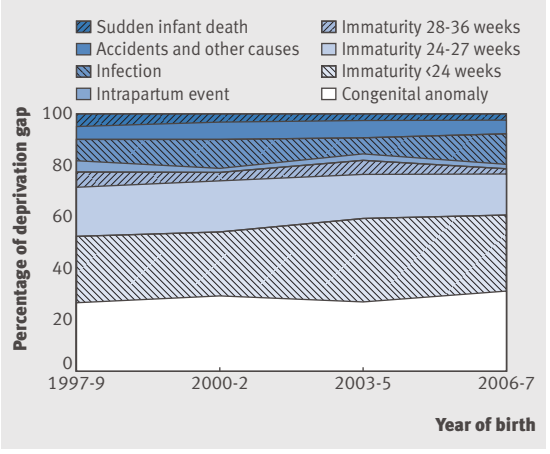
STUDY QUESTION How do specific causes of neonatal death contribute to socioeconomic inequalities in neonatal mortality?

SUMMARY ANSWER Preterm birth and congenital anomalies accounted for almost 80% of the deprivation gap in neonatal mortality.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS A government target was introduced to reduce the deprivation gap in infant mortality in England by 10% by 2010, yet the gap has widened. Nearly 80% of the deprivation gap in neonatal mortality in England results from differences in deaths related to either immaturity or congenital anomalies, and future strategy needs to concentrate on reducing deaths from these causes.

PERCENTAGE OF DEPRIVATION GAP IN ALL CAUSE MORTALITY EXPLAINED BY EACH CAUSE OF DEATH OVER TIME



Participants and setting

We included all neonatal deaths of singleton infants born between 1 January 1997 and 31 December 2007 in England.

Design, size, and duration

This was a retrospective cohort study. We combined data on cause specific neonatal death with national birth data by year of birth and socioeconomic level based on the UK index of multiple deprivation 2004 score at super output area level. We calculated the cause specific neonatal mortality rate per 10 000 births by deprivation tenth and year of birth and estimated the relative deprivation gap by comparing the rate in the most deprived tenth with that in the least deprived tenth. We assessed the contribution of each cause of death to the overall relative deprivation gap.

Main results and the role of chance

In the 11 year period studied, 18 524 neonatal deaths of singleton infants occurred. Neonatal mortality fell between 1997-9 and 2006-7 (from 31.4 to 25.1 per 10 000 live births). The relative deprivation gap increased from 2.08 in 1997-9 to 2.68 in 2003-5, before decreasing to 2.35 in 2006-7. The most common causes of death were immaturity and congenital anomalies. Mortality rates for all causes fell over time except mortality due to immaturity at <24 weeks' gestation, which showed the widest relative deprivation gap (2.98 in 1997-9, 4.14 in 2003-5, and 3.16 in 2006-7). For congenital anomalies, immaturity, and accidents and other specific causes, the relative deprivation gap widened between 1997-9 and 2003-5, before a slight fall in 2006-7. For intrapartum events and sudden infant deaths (only 13.5% of deaths), the relative deprivation gap narrowed slightly. Deaths due to immaturity and congenital anomalies explain most of the deprivation gap in all cause neonatal mortality, increasing from 77% in 1997-9 to a peak of 82% in 2003-5 and then falling to 79% in 2006-7. The remaining causes account for only 20% of the deprivation gap. The percentage of the gap explained by sudden infant deaths fell over time from 5% in 1997-9 to 2.5% in 2006-7.

Bias, confounding, and other reasons for caution

We had no access to individual measures of deprivation and risk behaviour, which might show inequalities in neonatal mortality not seen with area deprivation measures. Despite this, provided the results are treated with caution and trends are not extrapolated beyond the time period under study, our methods are relatively straightforward and provide a way for health service planners to monitor up to date trends in mortality. Lack of national information on post-neonatal deaths prevented an analysis of infant mortality for the whole period, but sensitivity analyses of infant mortality in 1997-2003 showed extremely similar patterns to those for neonatal mortality.

Generalisability to other populations

The cause specific analyses we used here could provide much greater insight into socioeconomic inequalities in neonatal mortality on a global level and allow all countries to more fully understand their early childhood mortality rates and prioritise appropriate interventions. Our results may be generalisable to countries with similar mortality profiles.

Study funding/potential competing interests

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