Mortality patterns among very preterm babies: a comparative analysis of two European regions in France and England

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Objective: To explore the differences in outcome of very preterm pregnancies between two geographically defined populations in Europe with similar socioeconomic characteristics and healthcare provision but different organisational arrangements for perinatal care.

Design: Prospective cohort study.

Setting: Nord Pas-de-Calais (NPC), France, and Trent, UK.

Participants: All pregnancy outcomes 22⁺⁰ to 32⁺⁶ weeks' gestational age for resident mothers.

Outcome measures: Mortality patterns (antepartum death, intrapartum death, labour ward death and neonatal unit death) among very preterm babies were analysed by region. Multinomial logistic regression was used to model regional differences for a variety of pregnancy outcomes and to adjust for regional differences in the organisation of perinatal care.

Results: Delivery of very preterm infants was significantly higher in Trent compared with NPC (1.9% v 1.5% of all births, respectively ($p < 0.001$)). Stillbirth rate was significantly higher in NPC than in Trent (23.0%, 95% CI 20.0% to 26.5% v 14.4%, 95% CI 12.3% to 16.6%, respectively ($p < 0.001$)) and survival to discharge was higher in Trent than in NPC (74.6%, 95% CI 71.9% to 77.1% v 66.7%, 95% CI 63.3% to 69.9%, respectively ($p < 0.001$)). Probability of intrapartum and labour ward death in NPC was more than five times higher than Trent (relative risk 5.3, 95% CI 2.2 to 13.1 ($p < 0.001$)).

Conclusion: The high rate of very preterm deliveries and the larger proportion of these infants recorded as live born in Trent appear to be the cause of the excess neonatal mortality seen in the routine statistics. Information about very preterm babies (not usually included in routine statistics) is vital to avoid inappropriate interpretation of international perinatal and infant data. This study highlights the importance of including deaths before transfer to neonatal care and emphasises the need to include the outcome of all pregnancies in a population in any comparative analysis.

Despite the recognition that direct comparison of international figures for perinatal and infant mortality is fraught with difficulty, such data still attract media headlines and are widely taken at "face value" by the public and political parties. Many publications have highlighted the limitations,^{1–4} including differences in definitions, registration and delivery policies, of which the latter may reflect differences in ethical attitude. Of course, there are almost inevitably real variations in mortality that require investigation and explanation at a regional or national level. However, identifying genuine differences, free of these confounding variables, has proved difficult.

As perinatal and infant mortality rates have reduced in developed countries and neonatal intensive care has developed, the impact of very preterm deliveries on such rates has increased. Although preterm births <33 weeks' gestation constitute less than 2.0% of all births, they account for at least one-third of perinatal deaths. The impact of organisation of obstetric and neonatal care for these preterm births has been studied by many observers in a range of countries, but the results have been inconsistent. It is possible that some of the inconsistencies noted by these studies have been the result of the difficulty in establishing genuine like-for-like comparisons in which all births can be considered and disease severity adjustments appropriately made.^{5–9}

The aim of the present study was, therefore, to explore the differences in outcome of very preterm pregnancies between two geographically defined populations in Europe (Nord Pas-de-Calais (NPC) in northern France and the former Trent Health Region in central England) for which detailed information

was available about the outcome of all births <33 weeks' gestation. These populations are known to have similar socioeconomic characteristics and access to healthcare, but differ considerably in terms of their organisational arrangements for perinatal care.

METHODS

Ethical approval was obtained in both regions included in the study. The study population included all preterm infants between 22⁺⁰ and 32⁺⁶ weeks of gestation, born to mothers resident in the Trent region (UK) and NPC (France) during the year 1997, regions of similar size and demographic characteristics. Terminations of pregnancy for congenital anomalies were excluded because it is known that "late" terminations of this type are more common in France.¹⁰ Although this practice clearly influences perinatal mortality rates,¹¹ we wished to focus on the care of the normally formed baby born preterm. Therefore, we also excluded live born infants with lethal congenital anomalies.

In NPC, data were collected via the EPIPAGE study¹² which incorporated every delivery (still and live births) in nine areas of France that occurred between 22 and 32 weeks of gestation in 1997. We validated the completeness of data by comparing obstetric birth records in labour wards with neonatal questionnaires in 10 randomly selected maternity units. There were no missing cases. Midwives and paediatricians recorded perinatal characteristics on standardised questionnaires. Data

Abbreviations: CESDI, Confidential Enquiry into Stillbirths and Deaths in Infancy; NPC, Nord Pas-de-Calais; TNS, Trent Neonatal Survey

Table 1 Regional classification of maternity units by level of care

Region and level of care	No. of maternity units	Unit size (births)	Description
Nord Pas-de-Calais	48		
Level I	31	500–2800	Maternity unit with no on-site neonatal unit
Level II	12	1200–2600	Maternity unit with on-site neonatal unit that cares for very preterm babies who do not need prolonged ventilation
Level III	5	2000–3000	Maternity unit with on-site neonatal unit that accepts outside referrals and has a neonatologist on-site 24 h/day
Trent	20		
Level I	6	200–1750	Midwifery led unit/maternity unit with no on-site neonatal intensive care unit
Level II	10	2000–4300	Maternity unit with on-site neonatal unit that cares for inborn population of very preterm babies but does not accept outside referrals
Level III	4	3000–5600	Maternity unit with on-site neonatal unit that accepts outside referrals and has a neonatologist on-site 24 h/day

for the Trent region were collected by the Trent Neonatal Survey (TNS)¹³ and the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI).¹⁴ All of the perinatal services in Trent contribute to the TNS, and units in adjacent regions also permit data collection on Trent infants. The database holds information relating to all infants of ≤ 32 weeks' gestation born to a Trent resident mother and admitted to a neonatal unit since that time. Data for the TNS are collected by five part-time research nurses who regularly visit all of the neonatal units and complete a standardised dataset for each baby. Information is obtained from the clinical records, discussions with staff and, where appropriate, personal observation. Data regarding immature infants who died outside a neonatal unit were obtained from CESDI.¹⁴ This longstanding validated study accurately reports, from a variety of sources, data about all infants delivering after 20 weeks' gestation, either born dead or who die in the first year of life.¹⁵ Thus, from these two sources (TNS and CESDI) we extracted data equivalent to that available from NPC in France. We validated these data using neonatal unit admission and labour ward books and mortality data from the Office of National Statistics. A common dataset was created that included similarly defined variables for the two regions.

Each region classifies its maternity units into three levels of care. For this analysis, we used each region's pre-existing classification (table 1). In 1997 in NPC, 54 815 births were delivered in 48 maternity units, of which 31 had no on-site neonatal unit. Among the 17 remaining maternity units five were tertiary centres. Twelve maternity units had an on-site neonatal unit that only carried out a few hours of assisted ventilation. In Trent 59 394 births occurred in 20 maternity units, of which six had no on-site neonatal intensive care unit (three were midwifery-led units where there were no deliveries of very preterm infants). Of the 14 Trent units with on-site neonatal care available, all had round-the-clock medical cover. Four of these 14 units provided a genuine tertiary service with regular referrals from other hospitals. All of the remaining hospitals aimed to provide intensive care for a proportion of the babies in the locality they served, although the size of this proportion varied markedly with some providing mainly short-term support before transfer.

We analysed the mortality patterns among very preterm babies by region, using a four-part classification based on the timing of the death: antepartum death, intrapartum death, death on labour ward and death on neonatal units. χ^2 tests were used to compare the distribution of the timing of death and the proportion of babies alive at discharge by region. We

excluded births ≤ 25 weeks' gestation from the analyses by level of care, because of possible unit-specific and region-specific variability in attitudes about the limit of viability. Multinomial logistic regression was used to model the impact of level of care and region on mortality for all babies alive at onset of labour, adjusting for gestational age and birth weight. Intrapartum deaths or deaths on the labour ward and deaths in the neonatal intensive care unit were compared with survivors at discharge from neonatal intensive care. Birth weight was expressed as a difference from the mean within each gestational age by region to adjust for the higher average birth weight of babies in Trent.

RESULTS

Table 2 shows routine demographic and perinatal data for the NPC and Trent regions and study data on the population of very preterm births. The two populations were similar in terms of size and stillbirth and perinatal mortality rates. However, following adjustment of the Trent data from the UK stillbirth definition of 24 weeks' gestational age to the 28-week definition used in France in 1997, the stillbirth rate in Trent was significantly lower than in NPC (3.7/1000 total births compared with 5.1/1000 total births, respectively ($p < 0.001$)). The neonatal mortality rate was not significantly different between the two regions. There was an excess of mothers aged under 20 years in Trent.

The rate of delivery of babies 22–32 weeks' gestation was more than a quarter higher in Trent than NPC (1.9%, 95% CI 1.7% to 2.1% and 1.5%, 95% CI 1.4% to 1.6%, respectively ($p < 0.001$)) a significant difference (table 2). The mortality trends observed at the population level were also seen for very preterm infants. The very preterm stillbirth rate was significantly higher in NPC than in Trent (23.0%, 95% CI 20.0% to 26.5% and 14.4%, 95% CI 12.3% to 16.6%, respectively ($p < 0.001$)), whereas the rate of hospital death for very preterm babies was similar in both regions (10.2%, 95% CI 8.3% to 12.8% and 11.1%, 95% CI 9.3% to 13.1%, respectively). Overall, out of all very preterm births, the proportion surviving to discharge from hospital was significantly higher in the Trent region (74.6%, 95% CI 71.9% to 77.1% compared with 66.7%, 95% CI 63.3% to 69.9% in NPC ($p < 0.001$)). Few deaths occurred after the neonatal period: only six in Trent and seven in NPC.

To explore in more depth the timing of mortality in very preterm babies, the two populations were divided into three gestational age groups (table 3). Across all gestational ages

Table 2 Demographic, births and perinatal mortality data for all births and very preterm births in Nord Pas-de-Calais (NPC) and Trent regions, 1997

	NPC	Trent
Data on all births in 1997 (routine statistics)		
Population (million)	3.97	4.60
Population density (n/km ²)	262.5	321.5
Number of obstetric units	50	20
Number of neonatal units	16	17
Live births	54 815	59 394
Births to mothers <20 years (%)	3.7	8.7
Births to mothers 40+ years (%)	2.0	1.6
Births outside marriage (%)	41.1	39.9
Total period fertility rate	1.87	1.68
Perinatal mortality in 1997 (routine statistics) (rate (95% CI))		
Published stillbirth rate*	5.1 (4.5 to 5.8)	5.0 (4.5 to 5.6)
Stillbirth rate standardised to French definition		3.7 (3.2 to 4.3) ↓
Published perinatal mortality rate*	7.7 (7.0 to 8.5)	7.9 (7.2 to 8.6)
Perinatal mortality rate standardised to French definition		6.7 (6.0 to 7.5)
Neonatal mortality rate†	3.2 (2.7 to 3.8)	4.0 (3.5 to 4.6)
Very preterm babies in 1997 (study data)		
All births 22–32 weeks' gestation (n)	929	1224
Terminations of pregnancy and lethal anomalies (n)	109	75
Births 22–32 weeks gestation excluding terminations (n and % of all births)	820	1149
Stillbirths (n and % very preterm infants)	189	165
Death in hospital (n and % very preterm infants)	84	127
Babies surviving to discharge (n and % very preterm infants)	547	857

Sources of routine data: Office of National Statistics for Trent and National Institute for Statistics and Economic Studies (INSEE) for NPC.

*Rate per 1000 total births; †Rate per 1000 live births.

↓ Significantly lower than NPC; ↑ Significantly higher than NPC

Table 3 Mortality by gestational age in two regions: Trent and Nord Pas-de-Calais (NPC), 1997

	NPC	Trent	Significance
	n (%)	n (%)	
<26 weeks' gestational age			
Death before labour	65 (47.1)	50 (28.9)	p1<0.001
Intrapartum death	20 (14.5)	24 (13.9)	p2=NS
Death in labour ward	24 (17.4)	22 (12.7)	
Death in neonatal unit	10 (7.2)	50 (28.9)	
Alive at discharge	19 (13.8)	27 (15.6)	
Total	138 (100.0)	173 (100.0)	
26–28 weeks of GA			
Death before labour	41 (20.7)	41 (15.2)	p1=NS
Intrapartum death	5 (2.5)	5 (1.9)	p2=0.014
Death in labour ward	7 (3.5)	5 (1.9)	
Death in neonatal unit	32 (16.2)	35 (13.0)	
Alive at discharge	113 (57.1)	184 (68.0)	
Total	198 (100.0)	270 (100.0)	
28–32 weeks of GA			
Death before labour	54 (11.2)	45 (6.4)	p1<0.001
Intrapartum death	4 (0.8)	0 (0.0)	p2=0.002
Death in labour ward	6 (1.2)	0 (0.0)	
Death in neonatal unit	5 (1.0)	15 (2.1)	
Alive at discharge	415 (85.8)	646 (91.5)	
Total	484 (100.0)	706 (100.0)	

p1, overall difference between the two distributions; p2, difference in the proportion alive at discharge.

Table 4 Mortality by level of care for very preterm births of 26–32 weeks' gestational age for Nord Pas-de-Calais (NPC) and Trent regions, 1997

	NPC*	Trent†	Significance
	N (%)	N (%)	
Level I			
Death before labour	36 (16.7)	8 (18.6)	p1=NS
Intrapartum/labour ward death	5 (2.3)	1 (2.3)	p2=NS
Death in neonatal unit	6 (2.8)	2 (4.7)	
Alive at discharge	169 (78.2)	32 (74.4)	
Total	216 (100.0)	43 (100.0)	
Level II			
Death before labour	17 (15.2)	45 (8.5)	p1=0.003
Intrapartum/labour ward death	5 (4.5)	6 (1.2)	p2=0.001
Death in neonatal unit	9 (8.0)	26 (4.9)	
Alive at discharge	81 (72.3)	451 (85.4)	
Total	112 (100.0)	528 (100.0)	
Level III			
Death before labour	42 (11.9)	31 (7.9)	p1=0.005
Intrapartum/labour ward death	12 (3.4)	2 (0.5)	p2=0.005
Death in neonatal unit	22 (6.2)	21 (5.3)	
Alive at discharge	277 (78.5)	340 (86.3)	
Total	353 (100.0)	394 (100.0)	

p1, overall difference between the two distributions; p2, difference in the proportion alive at discharge.

*Missing data for level of care, Nord Pas-de-Calais, n=1.

†Missing data for level of care, Trent, n=11 (home deliveries or out of region).

Figure 1 Proportion of total births and preterm births (26–32 weeks' gestation): Trent and Nord Pas-de-Calais (NPC), 1997.

babies were more likely to die before labour in NPC. Interestingly the rate of survival to discharge in babies <26 weeks' gestation was similar in the two regions but in Trent a far higher proportion of these deaths occurred on neonatal units. A greater proportion of the whole cohort of very preterm infants born were admitted to a neonatal unit in Trent (NPC 594/820; 72.4%, 95% CI 69.2% to 75.5% v Trent 957/1149; 83.3%, 95% CI 81.0% to 85.4%) suggesting a possible difference in the recording of live births. Survival to discharge in the cohort of all births, including stillbirths, was significantly better in Trent for babies 26–28 weeks' gestation and for babies 28–32 weeks' gestation ($p = 0.002$).

Table 4 explores the effect of level of care of the hospital of delivery on the observed mortality patterns in the two regions. Due to the possible policy differences noted in table 3 infants <26 weeks' gestation were excluded from this analysis. Figure 1 shows the differences in patterns of care provision between the two regions. In Trent very few births ($n = 4936$ (8.3%)) and fewer very preterm deliveries ($n = 43$ (4.5%)), 26–32 weeks' gestation) occurred in level I units without on-site neonatal intensive care provision. This compares with over half the births (58.7%) and approximately a third of very preterm deliveries (31.6%) in level I units in the NPC. Level II units deliver the majority of births and very preterm births in Trent (58.2% and 54.9%, respectively) whereas less than a fifth of births and very preterm births occur in such units in NPC (17.6% and 16.5%, respectively). The pattern of death in level II and level III units

was similar to that observed in relation to the data in table 3. Rates of survival to discharge were higher in level II and level III units in Trent than in equivalent units in NPC.

Table 5 shows the impact of the level and region of care presented as the relative risk ratio for type of death compared with survivors, adjusted for birth weight and gestational age. Antepartum deaths are excluded from this analysis. The relative risk of intrapartum stillbirth and labour ward death compared with being discharged alive in level II units was 2.5 times the corresponding risk in level III units for babies of >25 weeks' gestational age. Although there was an over fivefold significant relative risk of intrapartum and labour ward deaths than being discharged alive in very preterm infants in NPC compared with the corresponding risk in Trent (relative risk ratio 5.3, 95% CI 2.2 to 13.1) the probability of dying after transfer to a neonatal unit was not significantly different between the two regions.

DISCUSSION

International comparisons of perinatal and neonatal mortality rates indicate that the figures for UK are consistently high.¹⁶ Definitional differences may account for a proportion of the excess perinatal mortality rates but this is not the case for neonatal mortality in which all gestational ages are included. Our study indicates that the apparent excess neonatal mortality found in Trent compared with NPC is due to two factors: (a) the rate of delivery among <33 weeks' infants is over a quarter higher in Trent; (b) a considerably higher proportion of these babies recorded as being born alive and offered intensive care. The excess number of deaths, after being born alive, in infants <26 weeks' gestation is, alone, sufficient to explain the difference in the neonatal mortality rates calculated from "routine data". One opposing, though only partial, explanation could be that a greater proportion of very preterm infants in NPC are recorded as stillbirths, possibly due to the large proportion of these infants born in level I units.

The greatest differences in mortality between the regions were observed for those deaths occurring before transfer to a neonatal unit, namely, antepartum, intrapartum and labour ward deaths. Such variations have been found to be inconsistent within countries and thus may reflect national legislation and also differences in ethics-related decision making.¹⁷ In many countries such babies may not be included in routine statistics. They are often excluded from databases on very preterm infants when these are based on intensive care admissions. These results underline the importance of including deaths before transfer to a neonatal intensive care unit in any comparative analysis of mortality—that is, analyses must

Table 5 Intrapartum or labour ward deaths and deaths on neonatal units of ≤ 26 weeks' gestational age, compared with neonatal unit survivors in Nord Pas-de-Calais (NPC) and Trent regions

	Intrapartum/labour ward deaths	Death in neonatal units
	Relative risk ratio (95% CI)	Relative risk ratio (95% CI)
Born in level III unit	1.0	1.0
Born in level I unit	2.0 (0.7 to 5.9)	1.4 (0.6 to 3.3)
Born in level II unit	2.5 (1.0 to 6.3)*	1.8 (1.0 to 3.0)*
	$p = 0.045$	$p = 0.039$
Born in Trent	1.0	1.0
Born in NPC	5.3 (2.2 to 13.1)*	1.5 (0.9 to 2.6)
	$p < 0.001$	

Adjusted for gestational age and birthweight.

*Significantly higher than baseline comparison group.

What is already known on this topic

- Direct comparisons of international perinatal and infant mortality statistics are often misleading.

What this study adds

- To carry out appropriate international comparisons concerning mortality, information about the total cohort of preterm infants is required.
- The higher rates of preterm deliveries and the registration of a larger proportion of such infants as live born in the UK compared with NPC account for the excess neonatal mortality seen in the UK.

include the outcome of all pregnancies in a population. For example, survival rates among infants <26 weeks' gestation who were transferred for neonatal intensive care were higher in NPC than in Trent (19/29, 65.5% v 27/77, 35.1%, respectively ($p=0.005$)) although the overall survival remained similar (19/138, 13.8% v 27/173, 15.6%, respectively).

The place of birth affected both the timing of death and overall survival. Antepartum death rates were higher in level I units in both localities, reflecting that once such demise is detected, in-utero transfer of mothers to higher-level units with neonatal intensive care facilities is no longer required, unless indicated by maternal morbidity. These higher rates could also reflect less obstetric intervention for compromised fetuses in these settings. Antepartum, labour ward and neonatal deaths were higher in level II units than in level III units in NPC. In contrast, the differences in outcome between level II and III units were less marked in Trent. It is difficult to draw too many conclusions about an effect from "type of unit" as definitions were not consistent in the two settings. For example one or two of the level II units in Trent had more deliveries each year than the level III units in NPC. Level II units in Trent routinely offer neonatal intensive care to their inborn population and care for a higher volume of very preterm babies every year than level II units in NPC. Given that about a third of all very preterm babies are indicated deliveries,¹⁸ some of the observed difference will also, correctly, reflect local policies about the most appropriate setting to deliver a compromised baby. Such an effect may explain why, in both settings, level II units had higher overall mortality adjusted for gestational age and birth weight in babies alive at the onset of labour.

After adjusting for level of care at birth, gestational age and birth weight, mortality was higher in NPC, with a fivefold risk ratio in the intrapartum and labour ward death group. It is possible that this is the result of "poor care" by the perinatal services in NPC, however, we have no evidence of such an effect. We do have evidence that the French healthcare system is generally better resourced than that of the UK with health spending per head of population in the latter only 70–80% of that in France at the time of the study. Therefore it seems possible that the French perinatal services are less aggressive in providing intensive care to very preterm infants. However, it is impossible to tell if this results from differences in medical policies, based on the existing evidence regarding the outcome of very preterm infants, or whether it is a reflection of differences in attitude to very preterm infants between the two societies—that is, French parents are less likely to support aggressive obstetric or neonatal intervention when very preterm delivery seems inevitable.

As well as explaining apparent differences in the routine data for perinatal and neonatal mortality our results have major implications for planning and policy. In two populations with similar numbers of births, the region of Trent had 329 more very preterm births and 363 more neonatal intensive care admissions than NPC. The demand for neonatal intensive care cots is usually calculated with respect to the total number of births, and clearly it would be inappropriate to use the same formula for both these settings. Teenage pregnancies may contribute to the rate of very preterm infants in Trent and adjustment for maternal age may, therefore, need to be made when calculating the number of neonatal intensive care cots required. However, the underlying reason for the rate of teenage pregnancy in Trent needs further investigation.

This study, like most others looking at mortality among newborns, did not include information on risk factors for preterm birth. It would seem that developed countries should begin to focus less on the crude figures for neonatal and perinatal mortality and more on understanding the underlying

health events and treatment policies that have the strongest influence on these figures. Trying to understand why prematurity rates differ so markedly between apparently similar countries would seem to be a good place to start.

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AUTHOR CONTRIBUTIONS

ESD, JZ, DJF and PT designed this comparative study. JZ, BM and ESD carried out the statistical analysis. ESD wrote the first draft of the paper and all authors commented and provided input for the final version. ESD is the guarantor for the paper.

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