Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

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Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

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Abstract

Objective: To investigate temporal trends in multiple birth rates and associated neonatal mortality by socioeconomic deprivation and maternal age in England.

Design: Population cohort study

Setting: England

Participants: All live births and stillbirths (01/01/1997-31/12/2008).

Main outcome measures: Multiple maternity rate, stillbirth and neonatal death rate by year of birth, decile of socioeconomic deprivation and maternal age.

Results: The overall rate of multiple maternities increased over time (+0.64% p.a. 95% CI (0.47% to 0.81%)) with an increase in twin maternities (+0.85% p.a. 95% CI (0.67% to 1.0%)) but a large decrease in triplet and higher order maternities (-8.32% p.a. 95%CI (-9.39% to -7.25%)). Multiple maternities were significantly lower in the most deprived areas, and this was most evident in the older age groups. Women over 40 years of age from the least deprived areas had a 50% increased rate of multiple births compared to similar aged women from the most deprived areas (Rate ratio 0.66 95% CI (0.61 to 0.73)). Multiple births remain at substantially higher risk of neonatal mortality (RR 6.30 (6.07 to 6.53)). However, for stillbirths, while twins remain at higher risk, this has decreased over time (1997-2000: RR 2.89 (2.69 to 3.10); 2005-2008: RR 2.22 (2.06 to 2.40)). Socioeconomic inequalities existed in mortality for both singletons and multiple births.

Conclusions: This period has seen increasing rates of twin pregnancies and decreasing rates of higher order births which have coincided with changes in recommendations regarding assisted reproductive techniques. Socioeconomic differences in multiple births may reflect differential access to these treatments. Improved monitoring of multiple pregnancies and an increased proportion of di-chorionic twins are likely to have led to the reductions in stillbirths over this time.

Strengths and limitations

- This study uses national routinely collected data which have the advantage of being readily available and having national coverage. Our statistical analyses allowed the exploration of time trends and interactions between risk factors, information which is not available from standard published tables on multiple births in the UK.
- These national data lack detail on the chorionicity of the multiple births, gestation or ART which prevented further exploration of the impact of these factors on multiple birth incidence and mortality. Data collection on these factors commenced in 2013 in the UK allowing a more detailed understanding of this in the future.
- While we could not link births from the same maternity, our sensitivity analyses comparing the overall estimated number of multiple maternities with published data showed that this method estimated the overall number to within 1% of the actual rates and so any impact on the findings presented here is likely to be small.

What this paper adds

What is already known on this topic

Babies from multiple maternities are at significantly increased risk of mortality compared with singletons.

The number of multiple births in England has risen with the increased use of assisted conception services.

There is no consensus on whether these trends in multiple births are seen for all socioeconomic groups.

What this adds

While triplet and higher order maternity rates are falling, the rate of twin maternities continues to increase, particularly among older mothers.

Rates of multiple birth are much lower among older women from the most deprived areas suggesting differential access to assisted reproductive techniques (ART).

Unlike singleton births, the stillbirth rate for twins has fallen which may be due to improved care or changes in the ratio of mono-chorionic and di-chorionic twins due to increased use of ART.

Despite improvements in mortality, multiple births remain at substantially higher risk of poor outcomes compared to singleton births.

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Introduction

Recent decades have seen a major increase in multiple births rates globally[1]. In England and Wales, twin maternities increased from 0.9% of deliveries in the early 1980's to 1.4% in the late 1990's[2 3], and this is similar to patterns described outside the UK[4 5]. Most noticeably, there were dramatic changes in England for triplet and higher order maternities with major increases from around 0.01% of deliveries in the 1980s peaking at 0.05% in the late 1990's. More recent evidence indicates a reversal of this trend with rates of triplet pregnancies declining until 2001[6] to 0.04%.

These rapid temporal increases in multiple births are of key concern. Multiple births have a large impact on health care costs because of the increased health risk compared to singletons. Despite improvements in perinatal outcomes in recent decades, twin and triplet pregnancies are associated with increased risks of obstetric and neonatal complications including preterm birth[7], intrauterine growth restriction[8], twin-twin transfusion syndrome[9] and congenital abnormalities[10]. Consequently while multiple births account for only a small percentage of births, (3% in England and the US), these infants are at greatly increased risk of adverse outcomes, with 16% of neonatal deaths in England being multiple births[2 11].

The increase seen in the rate of multiple birth are generally attributed to the introduction and rises in access to assisted reproductive technologies (ART) and increasing maternal age. However, there is little research assessing whether the widespread increase in the use of ART has led to changes in the rate of multiple births across all socioeconomic groups due to differential access to treatment. Research in the late 1990's[12] highlighted higher rates of multiple births to higher social class families where the father had a higher social class but these analyses excluded those born to single or unemployed parents thus potentially underestimating any socioeconomic inequalities. While standard tables on multiple births and associated mortality are available nationally (www.ons.gov.uk) they do not offer the ability to explore the inter-relationships between factors such as maternal age, and socioeconomic deprivation over time.

Here we combine national data to update temporal trends and explore the effects of socioeconomic deprivation and maternal age on twin and higher order multiple maternity rates in England and associated stillbirth and neonatal mortality.

Methods

Data were obtained on all live births to mothers resident in England between 1 January 1997 and 31 December 2008 by multiplicity of birth, year of birth, maternal age, birth weight, sex, Primary Care Trust and deprivation decile (using the area-level Index of Multiple Deprivation 2004[13] from the UK Office for National Statistics (ONS; www.statistics.gov.uk). Information on stillbirths and neonatal deaths (death before 28 days of life) for the same period were obtained from the Centre for Maternal Child Enquiries (CMACE; www.cmace.org.uk), which collected neonatal mortality data as part of its national perinatal mortality surveillance work funded by the National Patient Safety Agency. Data included cause of death, gestational age, and super output area of mother's residence (geographical populations of approximately 1500 residents).

Estimating the number of maternities

The birth data we obtained from ONS did not allow multiple births from a single maternity to be linked together. Therefore, the number of multiple maternities (multiple pregnancies resulting in at least one registered live birth or stillbirth) had to be estimated. The number of twin maternities was estimated by calculating the total number of live and still births recorded as being from twin maternities by PCT, mother's age group (5 year bands), year of birth and deprivation decile, resulting in 99660 categories overall. The number of twin births in each category was then divided by two to give the number of twin maternities (rounded up to the nearest whole number to include maternities where one fetus in the pregnancy ended in an unrecorded fetal loss). Similarly for the data on triplets and higher order multiple births the number of maternities was taken as 1/3 of the births from higher order multiple pregnancies (again rounded up to the nearest whole number). Our estimated total number of multiple maternities differed by only 1% from the published total number of multiple maternities in England for 1997-2001[6] (ONS) indicating any underestimation of multiple maternities was negligible.

We measured socioeconomic deprivation by using an area level measure of deprivation, the index of multiple deprivation for 2004[13] at the super output area level. This measure of multiple deprivation is made up of seven domain indices at the super output area level, which relate to income, employment, health and disability, education, skills and training,

barriers to housing and services, and living environment and crime. Super output areas are the smallest areas for which these deprivation data are available; although some degree of heterogeneity will exist within them, the small size of the areas (only 1500 residents) limits this. We ranked all super output areas in England by deprivation score and divided them into 10 groups with approximately equal populations of births: 1 (least deprived) to 10 (most deprived). If neonatal mortality was the same for all deprivation groups, a similar proportion of neonatal deaths would be expected in each tenth.

Statistical analysis

The number of *maternities* by multiplicity of birth (singleton, twin, triplet and higher order) and the rate of multiple maternities were calculated by maternal age (5 year bands), deprivation decile and year of birth. Poisson regression models were then used to assess trends in the rate of multiple maternities by maternal age and deprivation decile over time. Interactions were fitted to assess time trends and maternal age differences in the rate of multiple births by socioeconomic deprivation.

The number of *births* was then used to calculate stillbirth and neonatal mortality rates by multiplicity of birth, deprivation decile, year of birth and maternal age. Poisson regression models including interactions were used to explore trends over time by socioeconomic deprivation and maternal age. Analyses were undertaken using STATA v12.

Results

There were 7278707 live births and 32475 stillbirths over the 12 year period of which 210446 births were twins (29 per 1000) and 6795 from a triplet or higher order pregnancy (1 per 1000). This corresponded to 7202637 estimated maternities, of which 106310 were twin maternities (15 per 1000) and 2386 triplet or higher order maternities (3 per *10000*).

Trends in the incidence of multiple maternities

The rate of multiple maternities, i.e. the proportion of all maternities resulting in a multiple birth increased over the 12 year time period by 0.64% per year (95% CI (0.47% to 0.81%) from 14.7 per 1000 maternities in 1997 to 15.6 per 1000 in 2008 (Table 1). These trends

differed between twins and higher order multiple births (Table 1). Univariable analyses showed that the rate of twin maternities increased over time by 0.85% per year (95% CI (0.67% to 1.00%)), while in contrast, there was a consistent year on year reduction of 8.32% per year (95% CI (-7.25% to -9.39%)) in the proportion of triplet and higher order maternities with rates halving over the 12 year period.

The increase in multiple maternities over time was strongly associated with changing patterns of maternal age. There was a steady overall increase in the proportion of all maternities among women aged over 35 years, rising from 13.7% in 1997 to 20.1% in 2008. Since the rate of multiple maternity increased with increasing maternal age (Figure 1) this led to an increase in multiple maternities. Furthermore the data also indicated that for women aged 40 years and over the rate of multiple maternities increased over the period of the study, while for all other age groups there was little change over time. Based on the Poisson multivariable model exploring year of birth and maternal age, women aged 40 years and over were 2.95 times more likely to deliver twins than women under 20 years in 1997 and this increased to 3.57 times more likely in 2007 (1997: RR 2.95; 95% CI (2.69 to 3.22); and in 2008: RR 3.57; 95% CI (3.30 to 3.86)) (P<0.0001). For triplets and higher order births women aged 40 years and over were more than 10 times more likely to deliver triplets or higher order multiples than women under 20 (RR 10.12; 95% CI (7.04 to 14.56)) but numbers were too small to assess trends over time.

Exploring rates by socioeconomic deprivation showed that the rates of multiple maternities decreased with increasing deprivation from 18.0 per 1000 in the least deprived decile to 12.1 in the most deprived decile (Table 2). Poisson univariable regression models showed a 33% lower rate of multiple pregnancies in the most deprived decile compared to the least deprived (RR 0.67; 95% CI (0.66 to 0.69)). The pattern when based on just twin maternities was similar (RR 0.68; 95% CI (0.66 to 0.69)) but a wider gap was seen for triplet and higher order maternities (RR 0.42; 95% CI (0.37 to 0.48)). Multivariable analyses showed that the deprivation gap for all multiple births did not significantly change over time (P=0.97) but did vary with maternal age (Table 3; P<0.0001). There was no evidence of a difference in multiple maternity rates in women under 20 years of age (RR comparing most and least deprived deciles: 1.03; 95% CI (0.92 to 1.17)), but there was a widening gap with increasing age (over 40 years RR 0.66; 95% CI (0.61 to 0.73)) (Figure 2a and 2b). Looking at these

patterns by type of multiple birth, showed no evidence of a change in the deprivation effect over time for twins. However there was a significant reduction in the deprivation gap for triplet and higher order pregnancies from a 63% reduced risk of triplets for women from the most deprived decile compared to the least deprived in 1997-2000 compared to a 44% reduced risk in 2005-2008.

Trends in stillbirth and neonatal death among multiple births

Rates of stillbirth were over twice as high in twin births as in singletons (RR 2.49; 95% CI (2.39 to 2.60)) and 4 times higher in triplets and higher order births (RR 4.40; 95% CI (3.70 to 5.24)). The number of triplet and higher order births were too small for more detailed analysis and so models were fitted for singletons and twin births only. While stillbirth rates among singletons showed no evidence of change over time (Table 4), there was a dramatic reduction in stillbirth rates among twins. Consequently while in 1997-2000, twins were at 2.89 (95% CI (2.69 to 3.10)) times the risk of stillbirth compared to singletons, this had reduced to 2.22 (95% CI (2.06 to 2.40)) by 2005-2008. Babies born to mothers from the most deprived decile showed higher rates of stillbirth for both singletons (RR 2.03; 95% CI (1.96 to 2.10) and twins (RR 1.57; 95% CI (1.38 to 1.79)) compared to babies born to mothers from the least deprived decile but there was no evidence of a deprivation gap for triplets and higher order births (0.72; 95% CI (0.40 to 1.28)). While this relative deprivation gap for stillbirth appears narrower for twins than singletons, (1.57 compared to 2.03), the absolute deprivation gap in stillbirth is much wider for twins due to the higher mortality; For twin births there were 44.0 additional stillbirths per 10000 births in the most deprived decile compared with the least deprived decile, while for singletons this gap was 27.9 additional stillbirths per 10000 births. There was no evidence of a differential improvement over time in the rate of stillbirths among multiple births between deprivation deciles.

Neonatal mortality was considerably higher for twins (RR 6.30; 95% CI (6.07 to 6.53)) and triplets (RR 15.47; 95% CI (13.73 to 17.43) compared with singletons. Mortality increased with increasing deprivation for both singletons (most deprived decile versus least deprived decile RR 2.33; 95% CI (2.22 to 2.44)) and twin births (RR 1.85; 95% CI (1.67 to 2.06)) but not for triplets (RR 1.24; 95% CI (0.85 to 1.81)). Neonatal mortality rates improved over time for all births (Table 4), with a greater percentage improvement for neonatal mortality among

singletons but a greater absolute improvement among twins, since the rates were much higher.

Discussion

Main findings

We have shown a continued trend of increasing multiple pregnancies in England, both in terms of rates and absolute numbers of deliveries. The findings highlight that this is due to an increase in the rate of twin maternities over the last 12 years. In contrast the rate of triplets and higher order maternities has halved. Substantial differences were seen by socioeconomic deprivation with a lower rate of multiple births among women from the most deprived areas and this was most evident among women over 35 years of age. Stillbirth rates have fallen considerably among twin births unlike the static picture seen for singletons. The recent improvements also observed in neonatal mortality have benefited both singleton and twin births, but wide socioeconomic inequalities exist in mortality for all births.

Possible explanations for findings and comparisons with other work

The observed reduction in the rate of triplet and higher order births continues the pattern observed by Simmons et al[6] up until 2001, and coincides with changes in the regulatory framework in England governing ART. Although the chances of a successful implantation when undergoing fertility treatments such as in-vitro fertilisation or gamete intra-fallopian transfer treatment is significantly improved by increasing the number of embryos or eggs transferred, multiple births, particularly triplets and higher order pregnancies, are at significantly greater risk of poor outcome compared to singletons. Therefore in 2001 the Human Fertilisation and Embryology Authority (http://www.hfea.gov.uk/) introduced regulations to limit the transfer of a maximum of two embryos per cycle, except in exceptional circumstances. With sporadic compliance, this policy was tightened further in 2004, so that a maximum of two embryos could be transferred to women under the age of 40 with no exceptions, and a maximum of three transferable to women aged 40 and over. Further evidence suggests that in women under 37 years elective single embryo transfer is

recommended[14] to improve outcomes. Our findings of a reduction in the rate of triplet and higher order maternities coincide with these changes in regulation.

Our data suggest that women from deprived areas, particularly those over 35 years, were less likely to have a multiple birth than women from less deprived areas. While our data cannot determine the reasons for this, one possible explanation is differential access to cycles of assisted reproductive techniques. Carson et al[15] using data from the UK Millennium cohort showed that the income of families of infants conceived through ART was substantially higher than for families of infants resulting from planned or unplanned natural conceptions. A UK survey of Primary Care Trusts has indicated that in the vast majority of Trusts, there is provision for only one cycle of treatment paid for by the NHS (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_101073 2009). Consequently further cycles of treatment need to be paid for by the couple and with charges of between £4000 and £8000 per cycle, this is likely to exclude low income couples. NICE guidelines have recently been updated from those written in 2004 and now recommend up to three cycles of IVF for women under 40 years and 1 cycle for women aged 40-42 years[16] being paid for by the NHS. For those areas under the new commissioning architecture that follow these guidelines, inequalities in access may be reduced with a consequent increase in multiple maternities in the most deprived women. No national data exist to explore access to assisted conception by deprivation and research is needed to assess this issue. Similar socioeconomic inequalities in multiple birth rates are likely to be seen in developed countries with similar provision of ART but the deprivation gap is likely to be even greater in those countries where ART is only available privately.

We have observed considerable reductions in stillbirth rates over time for multiple births unlike singletons, where rates have remained static for the last decade. This may relate to the introduction of recommendations for changes in antenatal care, including improved early diagnosis and in-utero management of twin-twin transfusion syndrome in mono-chorionic twins. However Glinianaia et al[17] in a smaller UK regional study found no change in stillbirth rates over time for either mono-chorionic or di-chorionic twins but mono-chorionic twins have a considerably higher risk of stillbirth than di-chorionic twins predominantly due to twin-twin transfusion syndrome. The apparent improvement in stillbirth rates we have observed may also be partially explained by a change to the proportion of mono-chorionic

versus di-chorionic twins over time. Around 16% of assisted conception multiple pregnancies result in mono-chorionic twins[18] and so a rise in the proportion of multiple births arising from ART would lead to a substantial rise in the proportion of di-chorionic twin births. If this is the explanation it should then be possible to observe an overall reduction in the rate of stillbirth for twins but no improvement in the chorionic specific rates of stillbirth. Since there are no national data on chorionicity we cannot determine to what extent the changes in stillbirth rates are related to changes in the proportion of mono-chorionic twins or to actual improvements in care. However stillbirth rates for twin births improved across all deprivation groups and so it is likely that multiple factors contributed to the observed change in stillbirth rates.

Compared to singletons, there was a smaller deprivation gap in the rate of stillbirth and neonatal death for twins and no significant deprivation gap for triplets and higher order births. However the absolute deprivation gap was wider. Research on explanations for the deprivation gap in neonatal mortality among singleton births has shown it is predominantly explained by increased rates of prematurity and its associated complications[19]. Multiple births are at much higher risk of prematurity with the rate of preterm birth (<37 weeks gestation) being ten times higher among multiple births and with half of all multiple births being born at these gestations[11]. Intrauterine growth restriction is also associated with deprivation[20] and increased complications of prematurity. However it is suggested that both small size and premature delivery in the case of multiple births may be more related to physiological adaptation to the more limited intra-uterine environment[21] in contrast to the proposed mechanisms in singleton births where maternal or fetal pathology is often implicated. Without further research it is not possible to estimate the extent to which prematurity is responsible for the deprivation gap in neonatal deaths among multiple births.

Strengths and limitations

This study uses national routinely collected data to evaluate trends in multiple birth rates. These data have the advantage of being readily available and having national coverage. They lack detail on the chorionicity of the multiple births and so differences in trends could not be investigated between mono-chorionic and di-chorionic twins. While the focus of increased twinning has been associated with di-chorionic twins relating to assisted

conception techniques, data is now indicating that these techniques also lead to increases in mono-chorionic twins and outcomes in these twins are particularly poor[17]. We also did not have information on the use of ART. Whilst information on chorionicity and the use of ART is not currently available nationally, data collection on these factors will commence from January 2013 as part of the MBRRACE-UK programme. This will provide a national picture of chorionicity and ART among stillbirths and infant deaths in the future.

The data we obtained did not link births from the same maternity. Consequently we had to estimate the number of multiple maternities which is prone to error as a result of a lack of data on late fetal losses. Similarly early selective fetocide for congenital anomalies may lead to misclassification of some multiple pregnancies as singleton births. However our sensitivity analyses comparing the overall estimated number of multiple maternities with published data showed that this method estimated the overall number to within 1% of the actual rates and so any impact on the findings presented here is likely to be small. National data were also unavailable on gestational age for this time period which prevented exploration or adjustment of mortality for prematurity. Furthermore while national published data are available, they do not offer the ability to explore interactions between risk factors.

Implications and future research needs

The continuing rise in multiple birth rates and overall increases in births over the last 12 years has had a large impact on the absolute numbers of twin and triplets delivered in England. While there has been a reduction in the rate of triplet and higher order births, which are the most at risk of neonatal death, there are now around 1300 more multiple births a year in England compared to 1997. Since over half of all multiple births are born prematurely[11], increasing healthcare provision and NHS costs for neonatal and longer term care arising from this group of babies will ensue.

Current national data prevent detailed exploration of socioeconomic inequalities in access to ART in England. However, recently established procedures for national data collection of this information will enable monitoring of such trends in the future. This will also permit an assessment of whether recent changes in the guidelines for provision of assisted conception

techniques in the UK, increasing the permitted number of cycles open to women under 39 years, have led to improved access to ART services across all socioeconomic groups.

Table 1: Number (and rate per 1000 maternities) of singleton and multiple maternities, England 1997-2008

	All maternities	Singleton maternities	Multiple maternities					
			All multiples		Twins		Triplets and above	
	N	N	N	Rate/1000	N	Rate/1000	N	Rate/1000
1997	602383	593558	8825	14.7 (14.3 to 15.0)	8526	14.2 (13.9 to 14.5)	299	0.50 (0.44 to 0.56)
1998	596232	587530	8702	14.6 (14.3 to 14.9)	8399	14.1 (13.8 to 14.4)	303	0.51 (0.45 to 0.57)
1999	583714	575172	8542	14.6 (14.3 to 14.9)	8286	14.2 (13.9 to 14.5)	256	0.44 (0.39 to 0.50)
2000	567157	558765	8392	14.8 (14.5 to 15.1)	8136	14.3 (14.0 to 14.7)	256	0.45 (0.40 to 0.51)
2001	558109	549757	8352	15.0 (14.6 to 15.3)	8140	14.6 (14.3 to 14.9)	212	0.38 (0.33 to 0.43)
2002	560122	551598	8524	15.2 (14.9 to 15.5)	8357	14.9 (14.6 to 15.2)	167	0.30 (0.26 to 0.35)
2003	584180	575394	8786	15.0 (14.7 to 15.4)	8649	14.8 (14.5 to 15.1)	137	0.23 (0.20 to 0.28)
2004	601147	591971	9176	15.3 (15.0 to 15.6)	9020	15.0 (14.7 to 15.3)	156	0.26 (0.22 to 0.30)
2005	606808	597618	9190	15.1 (14.8 to 15.5)	9043	14.9 (14.6 to 15.2)	147	0.24 (0.21 to 0.28)
2006	628974	619205	9769	15.5 (15.2 to 15.8)	9620	15.3 (15.0 to 15.6)	149	0.24 (0.20 to 0.28)
2007	648385	638315	10070	15.5 (15.2 to 15.8)	9935	15.3 (15.0 to 15.6)	135	0.21 (0.18 to 0.25)
2008	665426	655058	10368	15.6 (15.3 to 15.9)	10199	15.3 (15.0 to 15.6)	169	0.25 (0.22 to 0.30)

Table 2: Number of singleton and multiple maternities and rate per 1000 maternities by deprivation decile, England 1997-2008

Deprivation Decile (1= least deprived)	All maternities	Singleton maternities	Multiple maternities					
			All multiples		Twins		Triplets and above	
			N	Rate /1000	N	Rate /1000	N	Rate /1000
1	720135	707142	12993	18.0 (17.7 to 18.4)	12681	17.6 (17.3 to 17.9)	312	0.43 (0.39 to 0.48)
2	718363	705833	12530	17.4 (17.1 to 17.8)	12175	16.9 (16.6 to 17.3)	355	0.49 (0.45 to 0.55)
3	720421	708292	12129	16.8 (16.5 to 17.1)	11826	16.4 (16.1 to 16.7)	303	0.42 (0.38 to 0.47)
4	721281	709734	11547	16.0 (15.7 to 16.3)	11270	15.6 (15.3 to 15.9)	277	0.38 (0.34 to 0.43)
5	722794	711547	11247	15.6 (15.3 to 15.9)	11015	15.2 (15.0 to 15.5)	232	0.32 (0.28 to 0.37)
6	721632	710992	10640	14.7 (14.5 to 15.0)	10407	14.4 (14.1 to 14.7)	233	0.32 (0.28 to 0.37)
7	720952	710806	10146	14.1 (13.8 to 14.3)	9964	13.8 (13.6 to 14.1)	182	0.25 (0.22 to 0.29)
8	718171	708591	9580	13.3 (13.1 to 13.6)	9383	13.1 (12.8 to 13.3)	197	0.27 (0.24 to 0.32)
9	716909	707727	9182	12.8 (12.5 to 13.1)	9031	12.6 (12.3 to 12.9)	151	0.21 (0.18 to 0.25)
10	721979	713277	8702	12.1 (11.8 to 12.3)	8558	11.9 (11.6 to 12.1)	144	0.20 (0.17 to 0.23)

Table 3: Rate ratio (95%CI) of multiple maternities for most deprived versus least deprived decile by maternal age adjusted for year of birth

	Deprivation gap: Most deprived tenth versus least deprived	
Maternal age	Rate ratio	95%CI
Under 20	1.04	(0.92 to 1.17)
20-24	0.97	(0.92 to 1.03)
25-29	0.94	(0.90 to 0.97)
30-34	0.88	(0.85 to 0.91)
35-39	0.81	(0.78 to 0.85)
40 and over	0.66	(0.61 to 0.73)

Table 4 Stillbirth and neonatal mortality numbers and rate per 10000 births by multiplicity, year of birth and deprivation decile

Year of birth	Deprivation decile	Number of births		Number of deaths				Rate per 10000 births			
		All births		Stillbirths		Neonatal death		Stillbirths		Neonatal death	
		Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1997-2000	1 Least deprived	239999	8120	709	73	442	96	28.5	89.9	17.8	118.2
								26.5 to 30.7	71.5 to 113.1	16.2 to 19.5	96.8 to 144.4
	2	235870	7641	790	74	540	119	32.4	96.8	22.1	155.7
								30.2 to 34.7	77.1 to 121.6	20.3 to 24.1	130.1 186.4
	3	236165	7344	794	83	550	106	32.5	113.0	22.5	144.3
								30.4 to 34.9	91.1 to 140.1	20.7 to 24.5	119.3 to 174.6
	4	234004	7234	869	102	620	116	36.0	141.0	25.7	160.4
								33.7 to 38.4	116.1 to 171.2	23.7 to 27.8	133.7 to 192.4
	5	232935	6806	906	83	617	146	37.7	122.0	25.7	214.5
								35.4 to 40.3	98.3 to 151.2	23.8 to 27.8	182.4 to 252.3
	6	229589	6424	1028	76	652	132	43.5	118.3	27.6	205.5
								40.9 to 46.2	94.5 to 148.1	25.6 to 29.8	173.3 to 243.7
	7	226312	6053	1066	87	738	130	45.8	143.7	31.7	214.8
								43.2 to 48.7	116.5 to 177.3	29.5 to 34.1	180.9 to 255.1
	8	224985	5661	1146	81	770	143	49.6	143.1	33.4	252.6
								46.8 to 52.6	115.1 to 177.9	31.1 to 35.8	214.4 to 297.6
	9	224902	5530	1240	76	863	111	53.8	137.4	37.4	200.7
								50.9 to 56.8	109.8 to 172.1	35.0 to 40.0	166.7 to 241.8
	10 Most deprived	230264	5202	1321	77	1006	123	56.1	148.0	42.7	236.5
								53.1 to 59.2	118.4 to 185.1	40.1 to 45.4	198.1 to 282.2
2001-2004	1 Least deprived	229489	8105	709	84	360	105	29.8	103.6	15.1	129.6
								27.7 to 32.1	83.7 to 128.4	13.7 to 16.8	107.0 to 156.9
	2	228585	7919	702	71	411	105	29.6	89.7	17.4	132.6
								27.5 to 31.9	71.1 to 113.1	15.8 to 19.1	109.5 to 160.5
	3	228075	7612	777	69	421	92	32.9	90.6	17.8	120.9
								30.7 to 35.3	71.6 to 114.8	16.2 to 19.6	98.5 to 148.3
	4	226919	7121	811	56	539	103	34.6	78.6	23.0	144.6
								32.3 to 37.1	60.5 to 102.2	21.1 to 25.0	119.2 to 175.5
	5	226069	7054	934	69	500	110	40.0	97.8	21.4	155.9
								37.6 to 42.7	77.3 to 123.8	19.6 to 23.4	129.4 t o188.0
	6	225121	6480	952	67	602	103	41.1	103.4	26.0	159.0
								38.5 to 43.8	81.4 to 131.4	24.0 to 28.1	131.0 to 192.8
	7	224729	6377	1129	84	664	111	48.8	131.7	28.7	174.1
								46.1 to 51.8	106.4 to 163.1	26.6 to 31.0	144.5 to 209.7
	8	225297	5805	1249	67	769	121	54.0	115.4	33.3	208.4
								51.1 to 57.1	90.8 to 146.6	31.0 to 35.7	174.4 to 249.1
	9	226995	5613	1295	70	839	126	55.6	124.7	36.0	224.5
								52.7 to 58.8	98.7 to 157.6	33.7 to 38.6	188.5 to 267.3
	10 Most deprived	227441	5413	1389	76	892	122	59.6	140.4	38.3	225.4
								56.6 to 62.8	112.1 to 175.8	35.9 to 40.9	188.7 to 269.1

2005-2008	1 Least deprived	237654	8947	672	64	345	89	27.2	71.5	14.0	99.5
								25.2 to 29.4	56.0 to 91.4	12.6 to 15.5	80.8 to 122.4
	2	241378	8574	719	66	383	116	28.7	77.0	15.3	135.3
								26.7 to 30.9	60.5 to 98.0	13.9 to 16.9	112.8 to 162.3
	3	244052	8522	751	67	483	125	29.7	78.6	19.1	146.7
								27.7 to 31.9	61.9 to 99.9	17.5 to 20.9	123.1 to 174.8
	4	248811	7979	921	64	481	101	35.8	80.2	18.7	126.6
								33.6 to 38.2	62.8 to 102.5	17.1 to 20.5	104.2 to 153.8
	5	252543	7925	1004	62	536	110	38.5	78.2	20.6	138.8
								36.2 to 41.0	61.0 to 100.3	18.9 to 22.4	104.1 to 198.2
	6	256282	7681	1051	80	611	128	39.8	104.2	23.1	166.7
								37.5 to 42.3	83.7 to 129.7	21.4 to 25.0	143.1 to 203.4
	7	259765	7268	1175	78	691	124	44.0	107.3	25.9	170.6
								41.5 to 46.6	86.0 to 134.0	24.0 to 27.9	134.2 to 193.7
	8	258309	7072	1300	72	735	114	49.0	101.8	27.7	161.1
								46.4 to 51.7	80.8 to 128.3	25.7 to 29.8	134.2 to 193.7
	9	255830	6688	1324	74	819	127	50.4	110.6	31.2	189.9
								47.8 to 53.2	88.1 to 139.0	29.1 to 33.4	159.6 to 226.0
	10 Most deprived	255572	6276	1388	75	886	130	53.0	119.5	33.8	207.1
								50.3 to 55.8	95.3 to 149.9	31.7 to 36.1	174.4 to 246.0

Contributors: LS, DF, and ED conceived the study idea and designed the study. LS analysed and interpreted the data with help from BM. DF, ED, SJJ and EB contributed to interpretation of the data. LS wrote a first draft of the manuscript, and all co-authors critically revised the manuscript. The guarantor is LS.

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Ethical approval: None needed

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Data sharing: No additional data available from the corresponding author but they are available from the Office for National Statistics

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Figure 1: Rate of multiple maternities per 1000 births by year of birth and mother's age

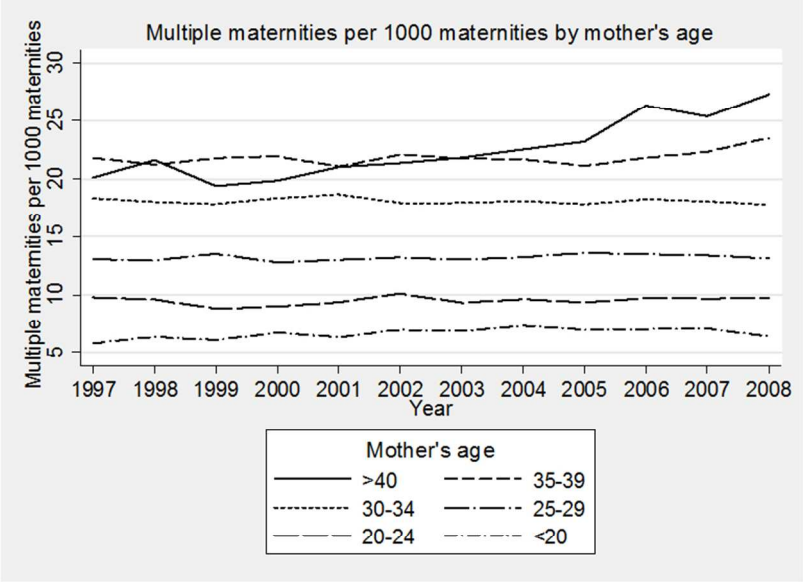

Figure 1: Rate of multiple maternities per 1000 births by year of birth and mother's age
254x190mm (96 x 96 DPI)

Figure 2a and 2b: Rate of multiple maternities per 1000 maternities over time by maternal age for women from the least deprived and most deprived deciles of deprivation

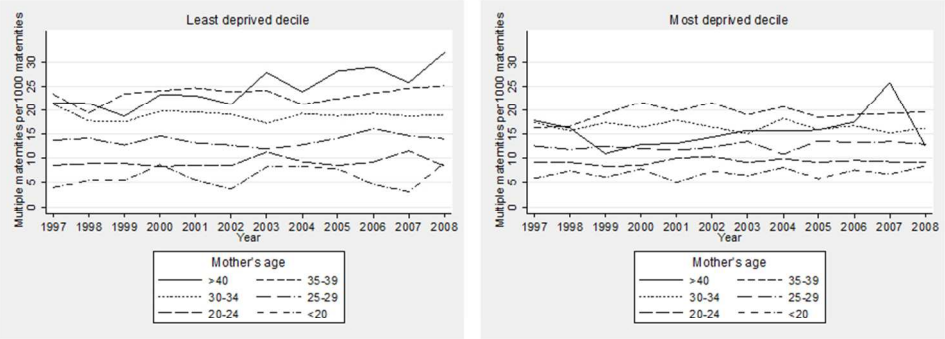

Figure 2a and 2b: Rate of multiple maternities per 1000 maternities over time by maternal age for women from the least deprived and most deprived deciles of deprivation
254x190mm (96 x 96 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1,P3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P6
Objectives	3	State specific objectives, including any prespecified hypotheses	P6
Methods			
Study design	4	Present key elements of study design early in the paper	P7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*P7*
Bias	9	Describe any efforts to address potential sources of bias	P7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P8
		(*b*) Describe any methods used to examine subgroups and interactions	P8
		(*c*) Explain how missing data were addressed	P7,P8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	P7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P8,P9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P8,P9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	P8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	P8-P10

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	P7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

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Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

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Contributors: LS, DF, and ED conceived the study idea and designed the study. LS analysed and interpreted the data with help from BM. DF, ED, SJJ and EB contributed to interpretation of the data. LS wrote a first draft of the manuscript, and all co-authors critically revised the manuscript. The guarantor is LS.

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Ethical approval: None needed

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Data sharing: No additional data available from the corresponding author but they are available from the Office for National Statistics

Abstract

Objective: To investigate temporal trends in multiple birth rates and associated stillbirth and neonatal mortality by socioeconomic deprivation and maternal age in England.

Design: Population cohort study

Setting: England

Participants: All live births and stillbirths (01/01/1997-31/12/2008).

Main outcome measures: Multiple maternity rate, stillbirth and neonatal death rate by year of birth, decile of socioeconomic deprivation and maternal age.

Results: The overall rate of multiple maternities increased over time (+0.64% p.a. 95% CI (0.47% to 0.81%)) with an increase in twin maternities (+0.85% p.a. 95% CI (0.67% to 1.0%)) but a large decrease in triplet and higher order maternities (-8.32% p.a. 95%CI (-9.39% to -7.25%)). Multiple maternities were significantly lower in the most deprived areas, and this was most evident in the older age groups. Women over 40 years of age from the most deprived areas had a 34% lower rate of multiple births compared to similar aged women from the most deprived areas (Rate ratio 0.66 95% CI (0.61 to 0.73)). Multiple births remain at substantially higher risk of neonatal mortality (RR 6.30 (6.07 to 6.53)). However, for stillbirths, while twins remain at higher risk, this has decreased over time (1997-2000: RR 2.89 (2.69 to 3.10); 2005-2008: RR 2.22 (2.06 to 2.40)). Socioeconomic inequalities existed in mortality for both singletons and multiple births.

Conclusions: This period has seen increasing rates of twin pregnancies and decreasing rates of higher order births which have coincided with changes in recommendations regarding assisted reproductive techniques. Socioeconomic differences in multiple births may reflect differential access to these treatments. Improved monitoring of multiple pregnancies is likely to have led to the reductions in stillbirths over this time.

Strengths and limitations

- This study uses national routinely collected data which have the advantage of being readily available and having national coverage. Our statistical analyses allowed the exploration of time trends and interactions between risk factors, information which is not available from standard published tables on multiple births in the UK.
- These national data lack detail on the chorionicity of the multiple births, gestation or ART which prevented further exploration of the impact of these factors on multiple birth incidence and mortality. Data collection on these factors commenced in 2013 in the UK allowing a more detailed understanding of this in the future.
- While we could not link births from the same maternity, our sensitivity analyses comparing the overall estimated number of multiple maternities with published data showed that this method estimated the overall number to within 1% of the actual rates and so any impact on the findings presented here is likely to be small.

What this paper adds

What is already known on this topic

Babies from multiple maternities are at significantly increased risk of mortality compared with singletons.

The number of multiple births in England has risen with the increased use of assisted conception services.

There is no consensus on whether these trends in multiple births are seen for all socioeconomic groups.

What this adds

While triplet and higher order maternity rates are falling, the rate of twin maternities continues to increase, particularly among older mothers.

Rates of multiple birth are much lower among older women from the most deprived areas suggesting differential access to assisted reproductive techniques (ART).

Unlike singleton births, the stillbirth rate for twins has fallen which may be due to improved care or changes in the ratio of mono-chorionic and di-chorionic twins due to increased use of ART.

Despite improvements in mortality, multiple births remain at substantially higher risk of poor outcomes compared to singleton births.

Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

Introduction

Recent decades have seen a major increase in multiple births rates globally[1]. In England and Wales, twin maternities increased from 0.9% of deliveries in the early 1980's to 1.4% in the late 1990's[2 3], and this is similar to patterns described outside the UK[4 5]. Most noticeably, there were dramatic changes in England for triplet and higher order maternities with major increases from around 0.01% of deliveries in the 1980s peaking at 0.05% in the late 1990's. More recent evidence indicates a reversal of this trend with rates of triplet pregnancies declining until 2001[6] to 0.04%.

These rapid temporal increases in multiple births are of key concern. Multiple births have a large impact on health care costs because of the increased health risk compared to singletons. Despite improvements in perinatal outcomes in recent decades, twin and triplet pregnancies are associated with increased risks of obstetric and neonatal complications including preterm birth[7], intrauterine growth restriction[8], twin-twin transfusion syndrome[9] and congenital abnormalities[10]. Consequently while multiple births account for only a small percentage of births, (3% in England and the US), these infants are at greatly increased risk of adverse outcomes, with 16% of neonatal deaths in England being multiple births[2 11].

The increase seen in the rate of multiple birth are generally attributed to the introduction and rises in access to assisted reproductive technologies (ART) and increasing maternal age. However, there is little research assessing whether the widespread increase in the use of ART has led to changes in the rate of multiple births across all socioeconomic groups due to differential access to treatment. Research in the late 1990's[12] highlighted higher rates of multiple births to higher social class families where the father had a higher social class but these analyses excluded those born to single or unemployed parents thus potentially underestimating any socioeconomic inequalities. While standard tables on multiple births and associated mortality are available nationally (www.ons.gov.uk) they do not offer the ability to explore the inter-relationships between factors such as maternal age, and socioeconomic deprivation over time.

Here we combine national data to update temporal trends and explore the effects of socioeconomic deprivation and maternal age on twin and higher order multiple maternity rates in England and associated stillbirth and neonatal mortality.

Methods

Data were obtained on all live births to mothers resident in England between 1 January 1997 and 31 December 2008 by multiplicity of birth, year of birth, maternal age, birth weight, sex, Primary Care Trust and deprivation decile (using the area-level Index of Multiple Deprivation 2004[13] from the UK Office for National Statistics (ONS; www.statistics.gov.uk). Information on stillbirths and neonatal deaths (death of a live-born baby within the first 28 days of life) for the same period were obtained from the Centre for Maternal Child Enquiries (CMACE; www.cmace.org.uk), which collected neonatal mortality data as part of its national perinatal mortality surveillance work funded by the National Patient Safety Agency. Data included cause of death, gestational age, and super output area of mother's residence (geographical populations of approximately 1500 residents).

Estimating the number of maternities

The birth data we obtained from ONS did not allow multiple births from a single maternity to be linked together. Therefore, the number of multiple maternities (multiple pregnancies resulting in at least one registered live birth or stillbirth) had to be estimated. The number of twin maternities was estimated by calculating the total number of live and still births recorded as being from twin maternities by PCT, mother's age group (5 year bands), year of birth and deprivation decile, resulting in 99660 categories overall. The number of twin births in each category was then divided by two to give the number of twin maternities (rounded up to the nearest whole number to include maternities where one fetus in the pregnancy ended in an unrecorded fetal loss). Similarly for the data on triplets and higher order multiple births the number of maternities was taken as 1/3 of the births from higher order multiple pregnancies (again rounded up to the nearest whole number). Our estimated total number of multiple maternities differed by only 1% from the published total number of multiple maternities in England for 1997-2001[6] (ONS) indicating any underestimation of multiple maternities was negligible.

We measured socioeconomic deprivation by using an area level measure of deprivation, the index of multiple deprivation for 2004[13] at the super output area level. This measure of multiple deprivation is made up of seven domain indices at the super output area level, which relate to income, employment, health and disability, education, skills and training,

barriers to housing and services, and living environment and crime. Super output areas are the smallest areas for which these deprivation data are available and are based on census geography with around 1500 residents in each; although some degree of heterogeneity will exist within them, the small size of the areas limits this. We ranked all super output areas in England by deprivation score and divided them into 10 groups with approximately equal populations of births: 1 (least deprived) to 10 (most deprived). If neonatal mortality was the same for all deprivation groups, a similar proportion of neonatal deaths would be expected in each tenth.

Statistical analysis

The number of *maternities* by multiplicity of birth (singleton, twin, triplet and higher order) and the rate of multiple maternities were calculated by maternal age (5 year bands), deprivation decile and year of birth. Poisson regression models were then used to assess trends in the rate of multiple maternities by maternal age and deprivation decile over time. Interactions were fitted to assess time trends and maternal age differences in the rate of multiple births by socioeconomic deprivation.

The number of *births* was then used to calculate stillbirth and neonatal mortality rates by multiplicity of birth, deprivation decile, year of birth and maternal age. Poisson regression models including interactions were used to explore trends over time by socioeconomic deprivation and maternal age. Analyses were undertaken using STATA v12.

Results

There were 7278707 live births and 32475 stillbirths over the 12 year period of which 210446 births were twins (29 per 1000) and 6795 from a triplet or higher order pregnancy (1 per 1000). This corresponded to 7202637 estimated maternities, of which 106310 were twin maternities (15 per 1000) and 2386 triplet or higher order maternities (3 per *10000*).

Trends in the incidence of multiple maternities

The rate of multiple maternities, i.e. the proportion of all maternities resulting in a multiple birth increased over the 12 year time period by 0.64% per year (95% CI (0.47% to 0.81%)

from 14.7 per 1000 maternities in 1997 to 15.6 per 1000 in 2008 (Table 1). These trends differed between twins and higher order multiple births (Table 1). Univariable analyses showed that the rate of twin maternities increased over time by 0.85% per year (95% CI (0.67% to 1.00%)), while in contrast, there was a consistent year on year reduction of 8.32% per year (95% CI (-7.25% to -9.39%)) in the proportion of triplet and higher order maternities with rates halving over the 12 year period.

The increase in multiple maternities over time was strongly associated with changing patterns of maternal age (Table 2) . There was a steady overall increase in the proportion of all maternities among women aged over 35 years, rising from 13.7% in 1997 to 20.1% in 2008. Since the rate of multiple maternity increased with increasing maternal age (Figure 1) this led to an increase in multiple maternities. Furthermore the data also indicated that for women aged 40 years and over the rate of multiple maternities increased over the period of the study, while for all other age groups there was little change over time. Based on the Poisson multivariable model exploring year of birth and maternal age, women aged 40 years and over were 2.95 times more likely to deliver twins than women under 20 years in 1997 and this increased to 3.57 times more likely in 2007 (1997: RR 2.95; 95% CI (2.69 to 3.22); and in 2008: RR 3.57; 95% CI (3.30 to 3.86)) (P<0.0001). For triplets and higher order births women aged 40 years and over were more than 10 times more likely to deliver triplets or higher order multiples than women under 20 (RR 10.12; 95% CI (7.04 to 14.56)) but numbers were too small to assess trends over time.

Exploring rates by socioeconomic deprivation showed that the rates of multiple maternities decreased with increasing deprivation from 18.0 per 1000 in the least deprived decile to 12.1 in the most deprived decile (Table 3). Poisson univariable regression models showed a 33% lower rate of multiple pregnancies in the most deprived decile compared to the least deprived (RR 0.67; 95% CI (0.65 to 0.69)). The pattern when based on just twin maternities was similar (RR 0.68; 95% CI (0.65 to 0.69)) but a wider gap was seen for triplet and higher order maternities (RR 0.46; 95% CI (0.38 to 0.56)). Multivariable analyses showed that the deprivation gap for all multiple births did not significantly change over time (P=0.97) but did vary with maternal age (Table 4; P<0.0001). There was no evidence of a difference in multiple maternity rates in women under 20 years of age (RR comparing most and least deprived deciles: 1.03; 95% CI (0.92 to 1.17)), but there was a widening gap with increasing

age (over 40 years RR 0.66; 95% CI (0.61 to 0.73)) (Figure 2a and 2b). Looking at these patterns by type of multiple birth, showed no evidence of a change in the deprivation effect over time for twins. However there was a significant reduction in the deprivation gap for triplet and higher order pregnancies from a 63% reduced risk of triplets for women from the most deprived decile compared to the least deprived in 1997-2000 compared to a 44% reduced risk in 2005-2008.

Trends in stillbirth and neonatal death among multiple births

Table 4 and 5 show the crude rates for stillbirth and neonatal death by multiplicity for year of birth and deprivation, while table 6 shows the rates from the multivariable model including both time period and deprivation decile. Rates of stillbirth were over twice as high in twin births as in singletons (RR 2.49; 95% CI (2.39 to 2.60)) and 4 times higher in triplets and higher order births (RR 4.40; 95% CI (3.70 to 5.24)). The number of triplet and higher order births were too small for more detailed analysis and so models were fitted for singletons and twin births only. While stillbirth rates among singletons showed no evidence of change over time (Table 4), there was a dramatic reduction in stillbirth rates among twins. Consequently while in 1997-2000, twins were at 2.89 (95% CI (2.69 to 3.10)) times the risk of stillbirth compared to singletons, this had reduced to 2.22 (95% CI (2.06 to 2.40)) by 2005-2008. Babies born to mothers from the most deprived decile showed higher rates of stillbirth for both singletons (RR 1.94; 95% CI (1.84 to 2.05) and twins (RR 1.54; 95% CI (1.28 to 1.85)) compared to babies born to mothers from the least deprived decile but there was no evidence of a deprivation gap for triplets and higher order births (0.88; 95% CI (0.39 to 2.00)). While the relative deprivation gap for stillbirth appears narrower for twins than singletons, (1.54 compared to 1.94), the absolute deprivation gap in stillbirth is much wider for twins due to the higher mortality; For twin births there were 47.0 additional stillbirths per 10000 births in the most deprived decile compared with the least deprived decile, while for singletons this gap was 27.9 additional stillbirths per 10000 births. There was no evidence of a differential improvement over time in the rate of stillbirths among multiple births between deprivation deciles. Neonatal mortality was considerably higher for twins (RR 6.30; 95% CI (6.07 to 6.53)) and triplets (RR 15.47; 95% CI (13.73 to 17.43) compared with singletons. Mortality increased with increasing deprivation for both singletons (most deprived decile versus least deprived decile RR 2.41; 95% CI (2.25 to 2.58)) and twin births

(RR 1.93; 95% CI (1.66 to 2.26)) but not for triplets (RR 0.89; 95% CI (0.51 to 1.56)). Neonatal mortality rates improved over time for all births (Table 4 and 6), with a greater percentage improvement for neonatal mortality among singletons but a greater absolute improvement among twins, since the rates were much higher.

Discussion

Main findings

We have shown a continued trend of increasing multiple pregnancies in England, both in terms of rates and absolute numbers of deliveries. The findings highlight that this is due to an increase in the rate of twin maternities over the last 12 years. In contrast the rate of triplets and higher order maternities has halved. Substantial differences were seen by socioeconomic deprivation with a lower rate of multiple births among women from the most deprived areas and this was most evident among women over 35 years of age. Stillbirth rates have fallen considerably among twin births unlike the static picture seen for singletons. The recent improvements also observed in neonatal mortality have benefited both singleton and twin births, but wide socioeconomic inequalities exist in mortality for all births.

Possible explanations for findings and comparisons with other work

The observed reduction in the rate of triplet and higher order births continues the pattern observed by Simmons et al[6] up until 2001, and coincides with changes in the regulatory framework in England governing ART. Although the chances of a successful implantation when undergoing fertility treatments such as in-vitro fertilisation or gamete intra-fallopian transfer treatment is significantly improved by increasing the number of embryos or eggs transferred, multiple births, particularly triplets and higher order pregnancies, are at significantly greater risk of poor outcome compared to singletons. Therefore in 2001 the Human Fertilisation and Embryology Authority (http://www.hfea.gov.uk/) introduced regulations to limit the transfer of a maximum of two embryos per cycle, except in exceptional circumstances. With sporadic compliance, this policy was tightened further in 2004, so that a maximum of two embryos could be transferred to women under the age of

40 with no exceptions, and a maximum of three transferable to women aged 40 and over. Further evidence suggests that in women under 37 years elective single embryo transfer is recommended[14] to improve outcomes. Currently UK fertility units must have a maximum multiple birth rate of 10% (http://www.hfea.gov.uk/). Our findings of a reduction in the rate of triplet and higher order maternities coincide with these changes in regulation. A possible additional factor influencing the rate of triplets could be the increased frequency of fetal reduction in multi-fetal pregnancies in the first trimester. In the UK death of an unborn fetus would not be registered if delivered before 24 weeks of gestation. For those deliveries where a fetal reduction occurred before 24 weeks gestation and the fetus was known to have died the death should not be registered as a stillbirth but there may be some variation in interpretation of the legislation.

Our data suggest that women from deprived areas, particularly those over 35 years, were less likely to have a multiple birth than women from less deprived areas. While our data cannot determine the reasons for this, one possible explanation is differential access to cycles of assisted reproductive techniques. Carson et al[15] using data from the UK Millennium cohort showed that the income of families of infants conceived through ART was substantially higher than for families of infants resulting from planned or unplanned natural conceptions. A UK survey of Primary Care Trusts has indicated that in the vast majority of Trusts, there is provision for only one cycle of treatment paid for by the NHS (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_101073 2009). Consequently further cycles of treatment need to be paid for by the couple and with charges of between £4000 and £8000 per cycle, this is likely to exclude low income couples. NICE guidelines have recently been updated from those written in 2004 and now recommend up to three cycles of IVF for women under 40 years and 1 cycle for women aged 40-42 years[16] being paid for by the NHS. For those areas under the new commissioning architecture that follow these guidelines, inequalities in access may be reduced with a consequent increase in multiple maternities in the most deprived women. No national data exist to explore access to assisted conception by deprivation and research is needed to assess this issue. Similar socioeconomic inequalities in multiple birth rates are likely to be seen in developed countries with similar provision of ART but the deprivation gap is likely to be even greater in those countries where ART is only available privately.

We have observed considerable reductions in stillbirth rates over time for multiple births unlike singletons, where rates have remained static for the last decade. This may relate to the introduction of recommendations for changes in antenatal care, including improved early diagnosis and in-utero management of twin-twin transfusion syndrome in mono-chorionic twins. However Glinianaia et al[17] in a smaller UK regional study found no change in stillbirth rates over time for either mono-chorionic or di-chorionic twins but mono-chorionic twins have a considerably higher risk of stillbirth than di-chorionic twins predominantly due to twin-twin transfusion syndrome. The apparent improvement in stillbirth rates we have observed may also be partially explained by a change to the proportion of mono-chorionic versus di-chorionic twins over time. Around 16% of assisted conception multiple pregnancies result in mono-chorionic twins[18] and so a rise in the proportion of multiple births arising from ART would lead to a substantial rise in the proportion of di-chorionic twin births. If this is the explanation it should then be possible to observe an overall reduction in the rate of stillbirth for twins but no improvement in the chorionic specific rates of stillbirth. Since there are no national data on chorionicity we cannot determine to what extent the changes in stillbirth rates are related to changes in the proportion of mono-chorionic twins or to actual improvements in care. However stillbirth rates for twin births improved across all deprivation groups and so it is likely that multiple factors contributed to the observed change in stillbirth rates.

Compared to singletons, there was a smaller deprivation gap in the rate of stillbirth and neonatal death for twins and no significant deprivation gap for triplets and higher order births. However the absolute deprivation gap was wider. Research on explanations for the deprivation gap in neonatal mortality among singleton births has shown it is predominantly explained by increased rates of prematurity and its associated complications[19]. Multiple births are at much higher risk of prematurity with the rate of preterm birth (<37 weeks gestation) being ten times higher among multiple births and with half of all multiple births being born at these gestations[11]. Intrauterine growth restriction is also associated with deprivation[20] and increased complications of prematurity. However it is suggested that both small size and premature delivery in the case of multiple births may be more related to physiological adaptation to the more limited intra-uterine environment[21] in contrast to the proposed mechanisms in singleton births where maternal or fetal pathology is often

implicated. Without further research it is not possible to estimate the extent to which prematurity is responsible for the deprivation gap in neonatal deaths among multiple births.

Strengths and limitations

This study uses national routinely collected data to evaluate trends in multiple birth rates. These data have the advantage of being readily available and having national coverage. They lack detail on the chorionicity of the multiple births and so differences in trends could not be investigated between mono-chorionic and di-chorionic twins. While the focus of increased twinning has been associated with di-chorionic twins relating to assisted conception techniques, data is now indicating that these techniques also lead to increases in mono-chorionic twins and outcomes in these twins are particularly poor[17]. We also did not have information on the use of ART. Whilst information on chorionicity and the use of ART is not currently available nationally, data collection on these factors will commence from January 2013 as part of the MBRRACE-UK programme. This will provide a national picture of chorionicity and ART among stillbirths and infant deaths in the future.

The data we obtained did not link births from the same maternity. Consequently we had to estimate the number of multiple maternities which is prone to error as a result of a lack of data on late fetal losses. Similarly early selective fetocide for congenital anomalies may lead to misclassification of some multiple pregnancies as singleton births. However our sensitivity analyses comparing the overall estimated number of multiple maternities with published data showed that this method estimated the overall number to within 1% of the actual rates and so any impact on the findings presented here is likely to be small. Unfortunately, in the analysis of stillbirths and neonatal deaths we could not take account of the correlated nature of the outcomes of multiple births from the same pregnancy. The confidence intervals presented here are consequently likely to have been narrower had this adjustment been possible, but this is unlikely to have impacted upon our conclusions. National data were also unavailable on gestational age for this time period which prevented exploration or adjustment of mortality for prematurity. Furthermore while national published data are available, they do not offer the ability to explore interactions between risk factors.

Implications and future research needs

The continuing rise in multiple birth rates and overall increases in births over the last 12 years has had a large impact on the absolute numbers of twin and triplets delivered in England. While there has been a reduction in the rate of triplet and higher order births, which are the most at risk of neonatal death, there are now around 1300 more multiple births a year in England compared to 1997. Since over half of all multiple births are born prematurely[11], increasing healthcare provision and NHS costs for neonatal and longer term care arising from this group of babies will ensue. These high risks for multiple births support the policies in place to reduce the rate of multiple births in the UK and the need to consider reviewing the practice of allowing multiple egg or embryo transfer in older women.

Current national data prevent detailed exploration of socioeconomic inequalities in access to ART in England. However, recently established procedures for national data collection of this information will enable monitoring of such trends in the future. This will also permit an assessment of whether recent changes in the guidelines for provision of assisted conception techniques in the UK, increasing the permitted number of cycles open to women under 39 years, have led to improved access to ART services across all socioeconomic groups.

Table 1 Number of singleton and multiple maternities and rate per 1000 maternities by year of birth and rate ratio compared to 1997, England 1997-2008

	All maternities	Singleton maternities	Multiple maternities								
			All multiples			Twins			Triplets and above		
	N	N	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio
1997	602383	593558	8825	14.7 14.3 to 15.0	1 -	8526	14.2 13.9 to 14.5	1 -	299	0.50 0.44 to 0.56	1 -
1998	596232	587530	8702	14.6 14.3 to 14.9	1.00 0.97 to 1.03	8399	14.1 13.8 to 14.4	1.00 0.97 to 1.03	303	0.51 0.45 to 0.57	1.02 0.87 to 1.20
1999	583714	575172	8542	14.6 14.3 to 14.9	1.00 0.97 to 1.03	8286	14.2 13.9 to 14.5	1.00 0.97 to 1.03	256	0.44 0.39 to 0.50	0.88 0.75 to 1.04
2000	567157	558765	8392	14.8 14.5 to 15.1	1.01 0.98 to 1.04	8136	14.3 14.0 to 14.7	1.01 0.98 to 1.04	256	0.45 0.40 to 0.51	0.91 0.77 to 1.07
2001	558109	549757	8352	15.0 14.6 to 15.3	1.02 0.99 to 1.05	8140	14.6 14.3 to 14.9	1.03 1.00 to 1.06	212	0.38 0.33 to 0.43	0.77 0.64 to 0.91
2002	560122	551598	8524	15.2 14.9 to 15.5	1.04 1.01 to 1.07	8357	14.9 14.6 to 15.2	1.05 1.02 to 1.09	167	0.30 0.26 to 0.35	0.60 0.50 to 0.73
2003	584180	575394	8786	15.0 14.7 to 15.4	1.03 1.00 to 1.06	8649	14.8 14.5 to 15.1	1.05 1.02 to 1.08	137	0.23 0.20 to 0.28	0.47 0.39 to 0.58
2004	601147	591971	9176	15.3 15.0 to 15.6	1.04 1.01 to 1.07	9020	15.0 14.7 to 15.3	1.06 1.03 to 1.09	156	0.26 0.22 to 0.30	0.52 0.43 to 0.63
2005	606808	597618	9190	15.1 14.8 to 15.5	1.03 1.00 to 1.06	9043	14.9 14.6 to 15.2	1.05 1.02 to 1.08	147	0.24 0.21 to 0.28	0.49 0.40 to 0.59
2006	628974	619205	9769	15.5 15.2 to 15.8	1.06 1.03 to 1.09	9620	15.3 15.0 to 15.6	1.08 1.05 to 1.11	149	0.24 0.20 to 0.28	0.48 0.39 to 0.58
2007	648385	638315	10070	15.5 15.2 to 15.8	1.06 1.03 to 1.09	9935	15.3 15.0 to 15.6	1.08 1.05 to 1.11	135	0.21 0.18 to 0.25	0.42 0.34 to 0.51
2008	665426	655058	10368	15.6 15.3 to 15.9	1.06 1.03 to 1.09	10199	15.3 15.0 to 15.6	1.08 1.05 to 1.11	169	0.25 0.22 to 0.30	0.51 0.42 to 0.62

Table 2: Number of singleton and multiple maternities and rate per 1000 maternities by maternal age and rate ratio compared to the youngest age group, England 1997-2008

	All maternities	Singleton maternities	Multiple maternities								
			All multiples			Twins			Triplets and above		
	N	N	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio
Under 20	507245	503878	3367	6.6 6.4 to 6.9	1 -	3331	6.6 6.3 to 6.8	1 -	36	0.07 0.05 to 0.10	1 -
20-24	1333053	1320339	12714	9.5 9.3 to 9.7	1.44 1.38 to 1.49	12559	9.4 9.3 to 9.6	1.43 1.38 to 1.49	155	0.12 0.10 to 0.14	1.64 1.14 to 2.35
25-29	1964391	1938450	25941	13.2 13.0 to 13.4	1.99 1.92 to 2.06	25462	13.0 12.8 to 13.1	1.97 1.90 to 2.05	479	0.24 0.22 to 0.27	3.44 2.45 to 4.82
30-34	2108007	2069823	38184	18.1 17.9 to 18.3	2.73 2.63 to 2.83	37223	17.7 17.5 to 17.8	2.69 2.60 to 2.79	961	0.46 0.43 to 0.49	6.42 4.60 to 8.96
35-39	1075723	1052170	23553	21.9 21.6 to 22.2	3.30 3.18 to 3.42	22952	21.3 21.1 to 21.6	3.25 3.13 to 3.37	601	0.56 0.52 to 0.61	7.87 5.62 to 11.02
40 and over	214218	209281	4937	23.0 22.4 to 23.7	3.47 3.32 to 3.63	4783	22.3 21.7 to 23.0	3.40 3.25 to 3.55	154	0.72 0.61 to 0.84	10.1 7.05 to 14.56

Table 3: Number of singleton and multiple maternities and rate per 1000 maternities by deprivation decile and rate ratio compared to the least deprived decile, England 1997-2008

Deprivation Decile (1= least deprived)	All maternities	Singleton maternities	Multiple maternities								
			All multiples			Twins			Triplets and above		
			N	Rate /1000	Rate ratio	N	Rate /1000	Rate ratio	N	Rate /1000	Rate ratio
1	720135	707142	12993	18.0	1	12681	17.6	1	312	0.43	1
				17.7 to 18.4	-		17.3 to 17.9	-		0.39 to 0.48	-
2	718363	705833	12530	17.4	0.97	12175	16.9	0.96	355	0.49	1.14
				17.1 to 17.8	0.94 to 0.99		16.6 to 17.3	0.94 to 0.99		0.45 to 0.55	0.98 to 1.33
3	720421	708292	12129	16.8	0.93	11826	16.4	0.93	303	0.42	0.97
				16.5 to 17.1	0.91 to 0.96		16.1 to 16.7	0.91 to 0.96		0.38 to 0.47	0.83 to 1.14
4	721281	709734	11547	16.0	0.89	11270	15.6	0.89	277	0.38	0.89
				15.7 to 16.3	0.87 to 0.91		15.3 to 15.9	0.87 to 0.91		0.34 to 0.43	0.75 to 1.04
5	722794	711547	11247	15.6	0.86	11015	15.2	0.87	232	0.32	0.74
				15.3 to 15.9	0.84 to 0.88		15.0 to 15.5	0.84 to 0.89		0.28 to 0.37	0.63 to 0.88
6	721632	710992	10640	14.7	0.82	10407	14.4	0.82	233	0.32	0.75
				14.5 to 15.0	0.80 to 0.84		14.1 to 14.7	0.80 to 0.84		0.28 to 0.37	0.63 to 0.88
7	720952	710806	10146	14.1	0.78	9964	13.8	0.78	182	0.25	0.58
				13.8 to 14.3	0.76 to 0.80		13.6 to 14.1	0.76 to 0.81		0.22 to 0.29	0.49 to 0.70
8	718171	708591	9580	13.3	0.74	9383	13.1	0.74	197	0.27	0.63
				13.1 to 13.6	0.72 to 0.76		12.8 to 13.3	0.72 to 0.76		0.24 to 0.32	0.53 to 0.76
9	716909	707727	9182	12.8	0.71	9031	12.6	0.72	151	0.21	0.49
				12.5 to 13.1	0.69 to 0.73		12.3 to 12.9	0.70 to 0.73		0.18 to 0.25	0.40 to 0.59
10	721979	713277	8702	12.1	0.67	8558	11.9	0.67	144	0.20	0.46
				11.8 to 12.3	0.65 to 0.69		11.6 to 12.1	0.65 to 0.69		0.17 to 0.23	0.38 to 0.56

Table 4 : Stillbirth and neonatal mortality: numbers and rate per 10000 births by multiplicity and year of birth, England 1997-2008

Year of birth	Live births		Stillbirths		Neonatal death		Rate per 10000 births			
							Stillbirths		Neonatal death	
	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1997-2000	2305156	65203	9869	812	6798	1222	42.6	123.0	29.5	187.4
							41.8 to 43.5	114.8 to 131.8	28.8 to 30.2	177.2 to 198.2
2001-2004	2258773	66786	9947	713	5997	1098	43.8	105.6	26.6	164.4
							43.0 to 44.7	98.2 to 113.7	25.9 to 27.2	155.0 to 174.4
2005-2008	2499891	76230	10305	702	5970	1164	41.1	91.2	23.9	152.7
							40.3 to 41.9	847. to 98.3	23.3 to 24.5	144.2 to 161.7

Table 5 : Stillbirth and neonatal mortality: numbers and rate per 10000 births by multiplicity and deprivation decile, England 1997-2008

Decile of deprivation	Live births		Stillbirths		Neonatal death		Rate per 10000 births: Stillbirths		Rate per 10000 births: Neonatal death	
	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1	705052	24951	2090	221	1147	290	29.6	87.8	16.3	116.2
							28.3 to 20.9	77.0 to 100.2	15.4 to 17.2	103.6 to 130.4
2	703622	23923	2211	211	1334	340	31.3	87.4	19.0	142.1
							30.0 to 32.7	76.4 to 100.1	18.0 to 20.0	127.8 to 158.1
3	705970	23259	2322	219	1454	323	32.8	93.3	20.6	138.9
							31.5 to 34.1	81.7 to 106.5	19.6 to 21.7	124.5 to 154.9
4	707133	22112	2601	222	1640	320	36.6	99.4	23.2	144.7
							35.3 to 38.1	85.9 to 112.3	22.1 to 24.3	129.7 to 161.5
5	708703	21571	2844	214	1653	366	40.0	98.2	23.3	169.7
							38.5 to 41.5	85.9 to 112.3	22.2 to 24.5	153.2 to 188.0
6	707961	20362	3031	223	1865	363	42.6	108.3	26.3	178.3
							41.1 to 44.2	95.0 to 12.35	25.2 to 27.6	160.8 to 197.6
7	707436	19449	3370	249	2093	365	47.4	126.4	29.6	178.7
							45.8 to 49.0	111.6 to 143.1	28.3 to 30.9	169.4 to 207.9
8	704896	18318	3695	220	2274	378	52.1	118.7	32.3	206.4
							50.5 to 53.9	104.0 to 135.4	31.0 to 33.6	186.6 to 228.2
9	703868	17611	3859	220	2521	364	54.5	123.4	35.8	206.7
							52.8 to 56.3	108.1 to 140.8	34.4 to 37.2	186.5 to 229.1
10	709179	16663	4098	228	2784	375	57.5	135.0	39.3	225.1
							55.7 to 59.2	118.6 to 153.7	37.8 to 40.7	203.4 to 249.0

Table 6: Stillbirth and neonatal mortality: numbers and rate per 10000 births by multiplicity, year of birth and deprivation decile

Year of birth	Deprivation decile	Live births		Stillbirths		Neonatal death		Rate per 10000 births			
								Stillbirths		Neonatal death	
		Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1997-2000	1 Least deprived	239290	8047	709	73	442	96	29.5	89.9	18.5	119.3
								27.4 to 31.8	71.5 to 113.1	16.8 to 20.3	97.7 to 145.7
	2	235080	7567	790	74	540	119	33.5	96.8	23.0	157.3
								31.2 to 35.9	77.1 to 121.6	21.1 to 25.0	131.4 to 188.2
	3	235371	7261	794	83	550	106	33.6	113.0	23.4	146.0
								31.4 to 36.0	91.1 to 140.1	21.5 to 25.4	120.7 to 176.6
	4	233135	7132	869	102	620	116	37.1	141.0	26.6	162.6
								34.7 to 39.7	116.1 to 171.2	24.6 to 28.8	135.6 to 195.1
	5	232029	6723	906	83	617	146	38.9	122.0	26.6	217.2
								36.4 to 41.5	98.3 to 151.2	24.6 to 28.8	184.6 to 255.4
	6	228561	6348	1028	76	652	132	44.8	118.3	28.5	207.9
								42.1 to 47.6	94.5 to 148.1	26.4 to 30.8	175.3 to 246.6
	7	225246	5966	1066	87	738	130	47.1	143.7	32.8	217.9
								44.4 to 50.0	116.5 to 177.3	30.5 to 35.2	183.5 to 258.8
	8	223839	5580	1146	81	770	143	50.9	143.1	34.4	256.3
								48.1 to 54.0	115.1 to 177.9	32.1 to 36.9	217.5 to 301.9
	9	223662	5454	1240	76	863	111	55.1	137.4	38.6	203.5
								52.2 to 58.3	109.8 to 172.1	36.1 to 41.2	169.0 to 245.1
	10 Most deprived	228943	5125	1321	77	1006	123	57.4	148.0	43.9	240.0
								54.4 to 60.5	118.4 to 185.1	41.3 to 46.7	201.1 to 286.4
2001-2004	1 Least deprived	228780	8021	709	84	360	105	30.9	103.6	15.7	130.9
								28.7 to 33.3	83.7 to 128.4	14.2 to 17.4	108.1 to 158.5
	2	227883	7848	702	71	411	105	30.7	89.7	18.0	133.7
								28.5 to 33.1	71.1 to 113.1	16.4 to 19.9	110.5 to 162.0
	3	227298	7543	777	69	421	92	34.1	90.6	18.5	122.0
								31.8 to 36.5	71.6 to 114.8	16.8 to 20.4	99.4 to 149.6
	4	226108	7065	811	56	539	103	35.7	78.6	23.8	145.8
								33.4 to 38.3	60.5 to 102.2	21.9 to 25.9	120.2 to 176.8
	5	225135	6985	934	69	500	110	41.3	97.8	22.2	157.5
								38.7 to 44.1	77.3 to 123.8	20.3 to 24.2	130.6 to 189.8
	6	224169	6413	952	67	602	103	42.3	103.4	26.9	160.6
								39.7 to 45.1	81.4 to 131.4	24.8 to 29.1	132.4 to 194.8
	7	223600	6293	1129	84	664	111	50.2	131.7	29.7	176.4
								47.4 to 53.3	106.4 to 163.1	27.5 to 32.0	146.4 to 212.5
	8	224048	5738	1249	67	769	121	55.4	115.4	34.3	210.9
								52.4 to 58.6	90.8 to 146.6	32.0 to 36.8	176.5 to 252.0
	9	225700	5543	1295	70	839	126	57.1	124.7	37.2	227.3
								54.0 to 60.2	98.7 to 157.6	34.7 to 39.8	190.9 to 270.7
	10 Most deprived	226052	5337	1389	76	892	122	61.1	140.4	39.5	228.6
								57.9 to 64.4	112.1 to 175.8	37.0 to 42.1	191.4 to 273.0

2005-2008	1 Least deprived	236982	8883	672	64	345	89	28.3	71.5	14.6	100.2
								26.2 to 30.5	56.0 to 91.4	13.1 to 16.2	81.4 to 123.3
	2	240659	8508	719	66	383	116	29.8	77.0	15.9	136.3
								27.7 to 32.0	60.5 to 98.0	14.4 to 17.6	113.6 to 163.6
	3	243301	8455	751	67	483	125	30.8	78.6	19.9	147.8
								28.6 to 33.1	61.9 to 99.9	18.2 to 21.7	124.1 to 176.2
	4	247890	7915	921	64	481	101	37.0	80.2	19.4	127.6
								34.7 to 39.5	62.8 to 102.5	17.7 to 21.2	105.0 to 155.1
	5	251539	7863	1004	62	536	110	39.8	78.2	21.3	139.9
								37.4 to 42.3	61.0 to 100.3	19.6 to 23.2	116.1 to 168.6
	6	255231	7601	1051	80	611	128	41.0	104.2	23.9	168.4
								38.6 to 43.6	83.7 to 129.7	22.1 to 25.9	141.6 to 200.3
	7	258590	7190	1175	78	691	124	45.2	107.3	26.7	172.5
								42.7 to 47.9	86.0 to 134.0	24.8 to 28.8	144.6 to 205.7
	8	257009	7000	1300	72	735	114	50.3	101.8	28.6	162.9
								47.7 to 53.1	80.8 to 128.3	26.6 to 30.7	135.5 to 195.7
	9	254506	6614	1324	74	819	127	51.8	110.6	32.2	192.0
								49.0 to 54.6	88.1 to 139.0	30.1 to 34.5	161.4 to 228.5
	10 Most deprived	254184	6201	1388	75	886	130	54.3	119.5	34.9	209.6
								51.5 to 57.2	95.3 to 149.9	32.6 to 37.2	176.5 to 249.0

Data sharing

No data available from the authors but may be obtained from ONS.

Contributorship

LS, DF, and ED conceived the study idea and designed the study. LS analysed and interpreted the data with help from BM. DF, ED, SJJ and EB contributed to interpretation of the data. LS wrote a first draft of the manuscript, and all co-authors critically revised the manuscript. The guarantor is LS.

Competing interests

All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years , no other relationships or activities that could appear to have influenced the submitted work.

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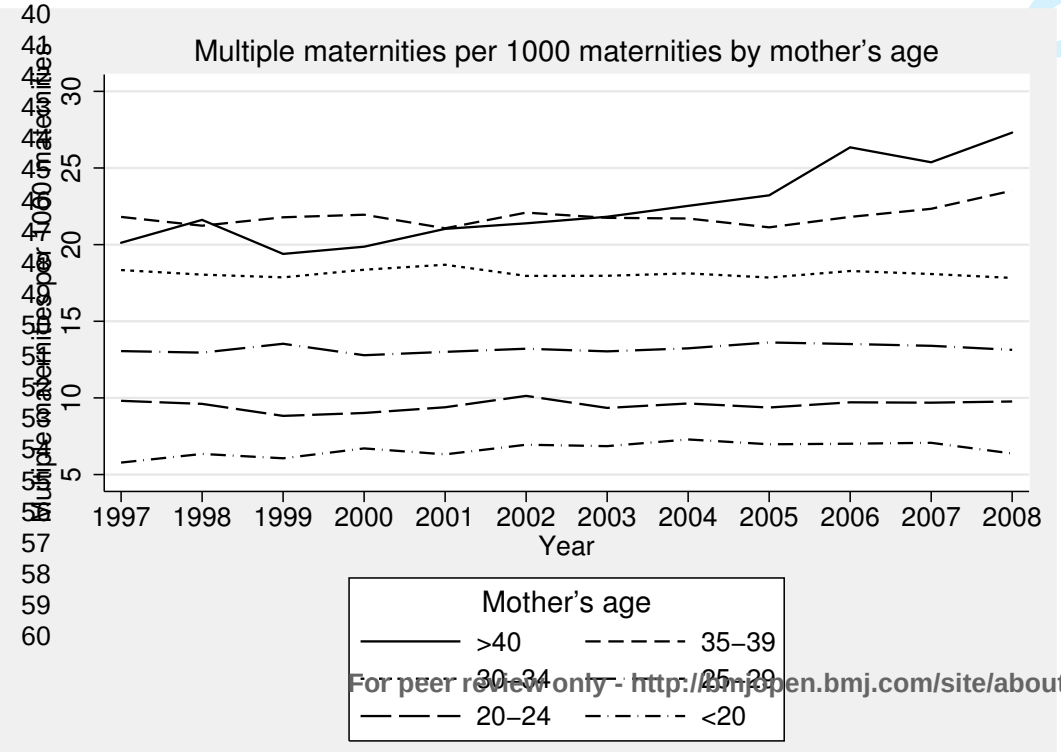
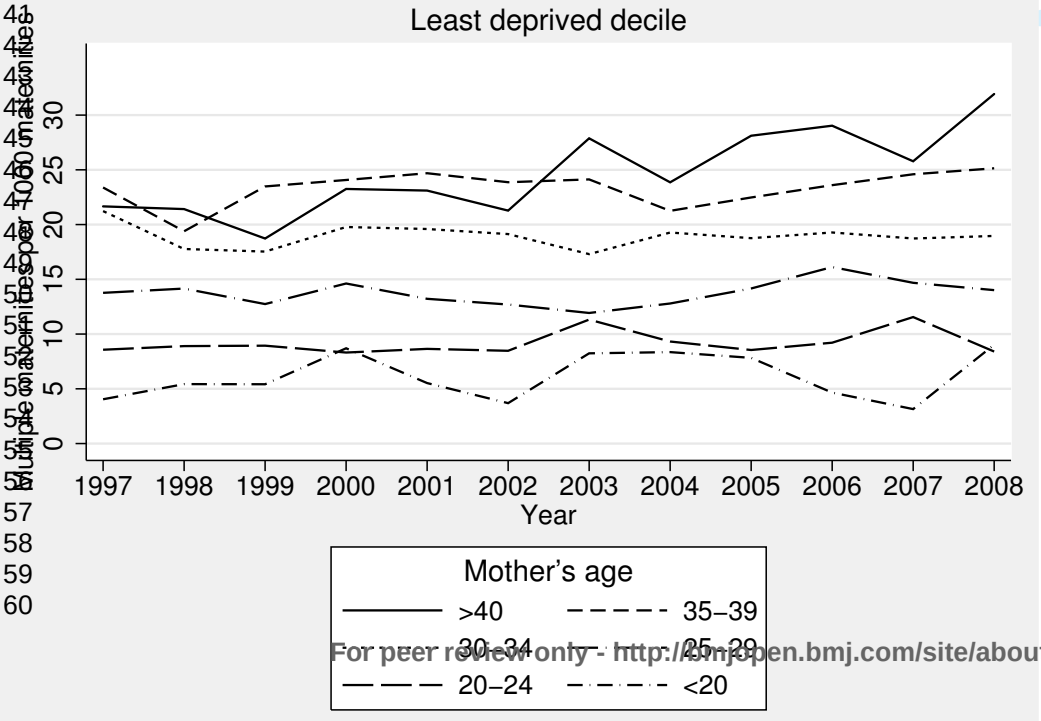
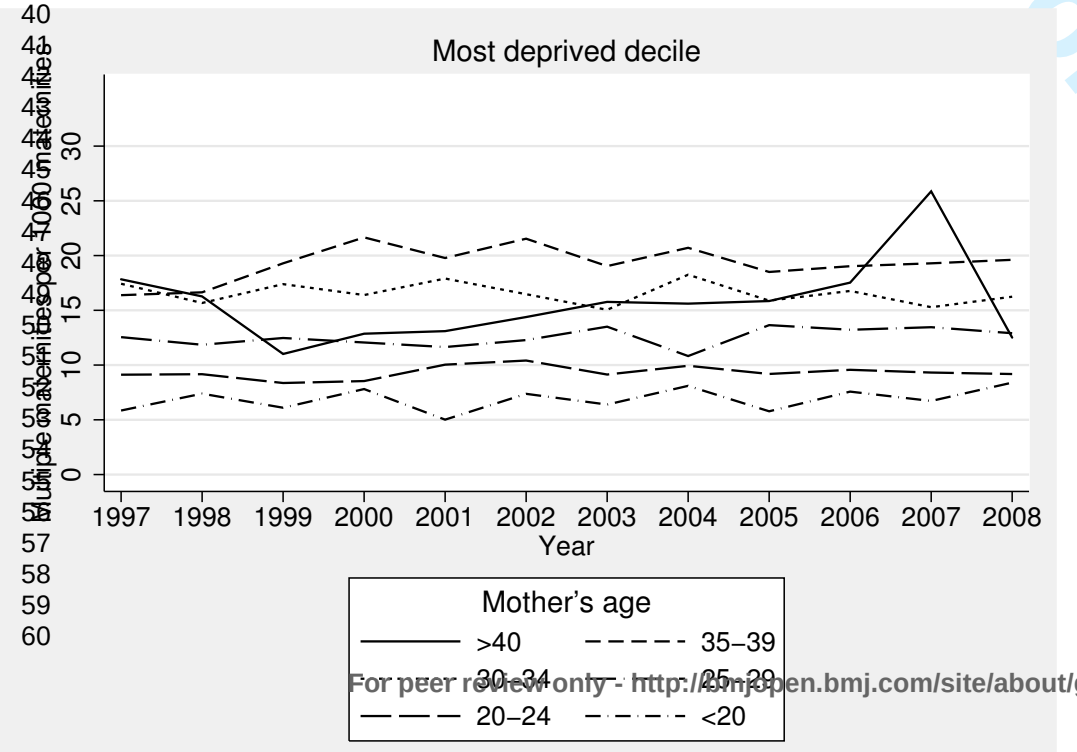
Figure 1: Rate of multiple maternities per 1000 maternities by year of birth and mother's age.

Figure 2a and 2b: Rate of multiple maternities per 100 maternities over time by mother's age from the least and most deprived deciles of deprivation.







Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years , no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None needed

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Data sharing: No additional data available from the corresponding author but they are available from the Office for National Statistics

Abstract

Objective: To investigate temporal trends in multiple birth rates and associated stillbirth and neonatal mortality by socioeconomic deprivation and maternal age in England.

Design: Population cohort study

Setting: England

Participants: All live births and stillbirths (01/01/1997-31/12/2008).

Main outcome measures: Multiple maternity rate, stillbirth and neonatal death rate by year of birth, decile of socioeconomic deprivation and maternal age.

Results: The overall rate of multiple maternities increased over time (+0.64% p.a. 95% CI (0.47% to 0.81%)) with an increase in twin maternities (+0.85% p.a. 95% CI (0.67% to 1.0%)) but a large decrease in triplet and higher order maternities (-8.32% p.a. 95%CI (-9.39% to -7.25%)). Multiple maternities were significantly lower in the most deprived areas, and this was most evident in the older age groups. Women over 40 years of age from the most~~least~~ deprived areas had a ~~50~~34% lower~~increased~~ rate of multiple births compared to similar aged women from the most deprived areas (Rate ratio 0.66 95% CI (0.61 to 0.73)). Multiple births remain at substantially higher risk of neonatal mortality (RR 6.30 (6.07 to 6.53)). However, for stillbirths, while twins remain at higher risk, this has decreased over time (1997-2000: RR 2.89 (2.69 to 3.10); 2005-2008: RR 2.22 (2.06 to 2.40)). Socioeconomic inequalities existed in mortality for both singletons and multiple births.

Conclusions: This period has seen increasing rates of twin pregnancies and decreasing rates of higher order births which have coincided with changes in recommendations regarding assisted reproductive techniques. Socioeconomic differences in multiple births may reflect differential access to these treatments. Improved monitoring of multiple pregnancies ~~and an increased proportion of di-chorionic twins are~~is likely to have led to the reductions in stillbirths over this time.

Strengths and limitations

- This study uses national routinely collected data which have the advantage of being readily available and having national coverage. Our statistical analyses allowed the exploration of time trends and interactions between risk factors, information which is not available from standard published tables on multiple births in the UK.
- These national data lack detail on the chorionicity of the multiple births, gestation or ART which prevented further exploration of the impact of these factors on multiple birth incidence and mortality. Data collection on these factors commenced in 2013 in the UK allowing a more detailed understanding of this in the future.
- While we could not link births from the same maternity, our sensitivity analyses comparing the overall estimated number of multiple maternities with published data showed that this method estimated the overall number to within 1% of the actual rates and so any impact on the findings presented here is likely to be small.

What this paper adds

What is already known on this topic

Babies from multiple maternities are at significantly increased risk of mortality compared with singletons.

The number of multiple births in England has risen with the increased use of assisted conception services.

There is no consensus on whether these trends in multiple births are seen for all socioeconomic groups.

What this adds

While triplet and higher order maternity rates are falling, the rate of twin maternities continues to increase, particularly among older mothers.

Rates of multiple birth are much lower among older women from the most deprived areas suggesting differential access to assisted reproductive techniques (ART).

Unlike singleton births, the stillbirth rate for twins has fallen which may be due to improved care or changes in the ratio of mono-chorionic and di-chorionic twins due to increased use of ART.

Despite improvements in mortality, multiple births remain at substantially higher risk of poor outcomes compared to singleton births.

Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study

Introduction

Recent decades have seen a major increase in multiple births rates globally[1]. In England and Wales, twin maternities increased from 0.9% of deliveries in the early 1980's to 1.4% in the late 1990's[2 3], and this is similar to patterns described outside the UK[4 5]. Most noticeably, there were dramatic changes in England for triplet and higher order maternities with major increases from around 0.01% of deliveries in the 1980s peaking at 0.05% in the late 1990's. More recent evidence indicates a reversal of this trend with rates of triplet pregnancies declining until 2001[6] to 0.04%.

These rapid temporal increases in multiple births are of key concern. Multiple births have a large impact on health care costs because of the increased health risk compared to singletons. Despite improvements in perinatal outcomes in recent decades, twin and triplet pregnancies are associated with increased risks of obstetric and neonatal complications including preterm birth[7], intrauterine growth restriction[8], twin-twin transfusion syndrome[9] and congenital abnormalities[10]. Consequently while multiple births account for only a small percentage of births, (3% in England and the US), these infants are at greatly increased risk of adverse outcomes, with 16% of neonatal deaths in England being multiple births[2 11].

The increase seen in the rate of multiple birth are generally attributed to the introduction and rises in access to assisted reproductive technologies (ART) and increasing maternal age. However, there is little research assessing whether the widespread increase in the use of ART has led to changes in the rate of multiple births across all socioeconomic groups due to differential access to treatment. Research in the late 1990's[12] highlighted higher rates of multiple births to higher social class families where the father had a higher social class but these analyses excluded those born to single or unemployed parents thus potentially underestimating any socioeconomic inequalities. While standard tables on multiple births and associated mortality are available nationally (www.ons.gov.uk) they do not offer the ability to explore the inter-relationships between factors such as maternal age, and socioeconomic deprivation over time.

Here we combine national data to update temporal trends and explore the effects of socioeconomic deprivation and maternal age on twin and higher order multiple maternity rates in England and associated stillbirth and neonatal mortality.

Methods

Data were obtained on all live births to mothers resident in England between 1 January 1997 and 31 December 2008 by multiplicity of birth, year of birth, maternal age, birth weight, sex, Primary Care Trust and deprivation decile (using the area-level Index of Multiple Deprivation 2004[13] from the UK Office for National Statistics (ONS; www.statistics.gov.uk). Information on stillbirths and neonatal deaths (death of a live-born baby within the first 28 days of life ~~death before 28 days of life~~) for the same period were obtained from the Centre for Maternal Child Enquiries (CMACE; www.cmace.org.uk), which collected neonatal mortality data as part of its national perinatal mortality surveillance work funded by the National Patient Safety Agency. Data included cause of death, gestational age, and super output area of mother's residence (geographical populations of approximately 1500 residents).

Estimating the number of maternities

The birth data we obtained from ONS did not allow multiple births from a single maternity to be linked together. Therefore, the number of multiple maternities (multiple pregnancies resulting in at least one registered live birth or stillbirth) had to be estimated. The number of twin maternities was estimated by calculating the total number of live and still births recorded as being from twin maternities by PCT, mother's age group (5 year bands), year of birth and deprivation decile, resulting in 99660 categories overall. The number of twin births in each category was then divided by two to give the number of twin maternities (rounded up to the nearest whole number to include maternities where one fetus in the pregnancy ended in an unrecorded fetal loss). Similarly for the data on triplets and higher order multiple births the number of maternities was taken as 1/3 of the births from higher order multiple pregnancies (again rounded up to the nearest whole number). Our estimated total number of multiple maternities differed by only 1% from the published total number of multiple maternities in England for 1997-2001[6] (ONS) indicating any underestimation of multiple maternities was negligible.

We measured socioeconomic deprivation by using an area level measure of deprivation, the index of multiple deprivation for 2004[13] at the super output area level. This measure of multiple deprivation is made up of seven domain indices at the super output area level, which relate to income, employment, health and disability, education, skills and training,

barriers to housing and services, and living environment and crime. Super output areas are the smallest areas for which these deprivation data are available and are based on census geography with around 1500 residents in each; although some degree of heterogeneity will exist within them, the small size of the areas ~~(only 1500 residents)~~ limits this. We ranked all super output areas in England by deprivation score and divided them into 10 groups with approximately equal populations of births: 1 (least deprived) to 10 (most deprived). If neonatal mortality was the same for all deprivation groups, a similar proportion of neonatal deaths would be expected in each tenth.

Statistical analysis

The number of *maternities* by multiplicity of birth (singleton, twin, triplet and higher order) and the rate of multiple maternities were calculated by maternal age (5 year bands), deprivation decile and year of birth. Poisson regression models were then used to assess trends in the rate of multiple maternities by maternal age and deprivation decile over time. Interactions were fitted to assess time trends and maternal age differences in the rate of multiple births by socioeconomic deprivation.

The number of *births* was then used to calculate stillbirth and neonatal mortality rates by multiplicity of birth, deprivation decile, year of birth and maternal age. Poisson regression models including interactions were used to explore trends over time by socioeconomic deprivation and maternal age. Analyses were undertaken using STATA v12.

Results

There were 7278707 live births and 32475 stillbirths over the 12 year period of which 210446 births were twins (29 per 1000) and 6795 from a triplet or higher order pregnancy (1 per 1000). This corresponded to 7202637 estimated maternities, of which 106310 were twin maternities (15 per 1000) and 2386 triplet or higher order maternities (3 per *10000*).

Trends in the incidence of multiple maternities

The rate of multiple maternities, i.e. the proportion of all maternities resulting in a multiple birth increased over the 12 year time period by 0.64% per year (95% CI (0.47% to 0.81%)

from 14.7 per 1000 maternities in 1997 to 15.6 per 1000 in 2008 (Table 1). These trends differed between twins and higher order multiple births (Table 1). Univariable analyses showed that the rate of twin maternities increased over time by 0.85% per year (95% CI (0.67% to 1.00%)), while in contrast, there was a consistent year on year reduction of 8.32% per year (95% CI (-7.25% to -9.39%)) in the proportion of triplet and higher order maternities with rates halving over the 12 year period.

The increase in multiple maternities over time was strongly associated with changing patterns of maternal age (Table 2) . There was a steady overall increase in the proportion of all maternities among women aged over 35 years, rising from 13.7% in 1997 to 20.1% in 2008. Since the rate of multiple maternity increased with increasing maternal age (Figure 1) this led to an increase in multiple maternities. Furthermore the data also indicated that for women aged 40 years and over the rate of multiple maternities increased over the period of the study, while for all other age groups there was little change over time. Based on the Poisson multivariable model exploring year of birth and maternal age, women aged 40 years and over were 2.95 times more likely to deliver twins than women under 20 years in 1997 and this increased to 3.57 times more likely in 2007 (1997: RR 2.95; 95% CI (2.69 to 3.22); and in 2008: RR 3.57; 95% CI (3.30 to 3.86)) (P<0.0001). For triplets and higher order births women aged 40 years and over were more than 10 times more likely to deliver triplets or higher order multiples than women under 20 (RR 10.12; 95% CI (7.04 to 14.56)) but numbers were too small to assess trends over time.

Exploring rates by socioeconomic deprivation showed that the rates of multiple maternities decreased with increasing deprivation from 18.0 per 1000 in the least deprived decile to 12.1 in the most deprived decile (Table ~~2~~3). Poisson univariable regression models showed a 33% lower rate of multiple pregnancies in the most deprived decile compared to the least deprived (RR 0.67; 95% CI (0.65~~6~~ to 0.69)). The pattern when based on just twin maternities was similar (RR 0.68; 95% CI (0.65~~6~~ to 0.69)) but a wider gap was seen for triplet and higher order maternities (RR 0.46~~2~~; 95% CI (0.38~~7~~ to 0.56~~48~~)). Multivariable analyses showed that the deprivation gap for all multiple births did not significantly change over time (P=0.97) but did vary with maternal age (Table ~~3~~4; P<0.0001). There was no evidence of a difference in multiple maternity rates in women under 20 years of age (RR comparing most and least deprived deciles: 1.03; 95% CI (0.92 to 1.17)), but there was a widening gap with increasing

age (over 40 years RR 0.66; 95% CI (0.61 to 0.73)) (Figure 2a and 2b). Looking at these patterns by type of multiple birth, showed no evidence of a change in the deprivation effect over time for twins. However there was a significant reduction in the deprivation gap for triplet and higher order pregnancies from a 63% reduced risk of triplets for women from the most deprived decile compared to the least deprived in 1997-2000 compared to a 44% reduced risk in 2005-2008.

Trends in stillbirth and neonatal death among multiple births

Table 4 and 5 show the crude rates for stillbirth and neonatal death by multiplicity for year of birth and deprivation, while table 6 shows the rates from the multivariable model including both time period and deprivation decile. Rates of stillbirth were over twice as high in twin births as in singletons (RR 2.49; 95% CI (2.39 to 2.60)) and 4 times higher in triplets and higher order births (RR 4.40; 95% CI (3.70 to 5.24)). The number of triplet and higher order births were too small for more detailed analysis and so models were fitted for singletons and twin births only. While stillbirth rates among singletons showed no evidence of change over time (Table 4), there was a dramatic reduction in stillbirth rates among twins. Consequently while in 1997-2000, twins were at 2.89 (95% CI (2.69 to 3.10)) times the risk of stillbirth compared to singletons, this had reduced to 2.22 (95% CI (2.06 to 2.40)) by 2005-2008. Babies born to mothers from the most deprived decile showed higher rates of stillbirth for both singletons (RR 1.94 ~~2.03~~; 95% CI (1.84 to 2.05) ~~1.96 to 2.10~~) and twins (RR 1.5 ~~7~~4; 95% CI (1.28 ~~38~~ to 1.85 ~~79~~)) compared to babies born to mothers from the least deprived decile but there was no evidence of a deprivation gap for triplets and higher order births (0.88 ~~72~~; 95% CI (0.39 to 2.00 ~~40 to 1.28~~)). While this relative deprivation gap for stillbirth appears narrower for twins than singletons, (1.5 ~~7~~4 compared to 1.94 ~~2.03~~), the absolute deprivation gap in stillbirth is much wider for twins due to the higher mortality; For twin births there were 4 ~~4~~7.0 additional stillbirths per 10000 births in the most deprived decile compared with the least deprived decile, while for singletons this gap was 27.9 additional stillbirths per 10000 births. There was no evidence of a differential improvement over time in the rate of stillbirths among multiple births between deprivation deciles.

Neonatal mortality was considerably higher for twins (RR 6.30; 95% CI (6.07 to 6.53)) and triplets (RR 15.47; 95% CI (13.73 to 17.43) compared with singletons. Mortality increased

with increasing deprivation for both singletons (most deprived decile versus least deprived decile RR 2.4133; 95% CI (2.225 to 2.5844)) and twin births (RR 1.9385; 95% CI (1.6667 to 2.2606)) but not for triplets (RR 0.891.24; 95% CI (0.51 to 1.5685 to 1.81)). Neonatal mortality rates improved over time for all births (Table 4 and 64), with a greater percentage improvement for neonatal mortality among singletons but a greater absolute improvement among twins, since the rates were much higher.

Discussion

Main findings

We have shown a continued trend of increasing multiple pregnancies in England, both in terms of rates and absolute numbers of deliveries. The findings highlight that this is due to an increase in the rate of twin maternities over the last 12 years. In contrast the rate of triplets and higher order maternities has halved. Substantial differences were seen by socioeconomic deprivation with a lower rate of multiple births among women from the most deprived areas and this was most evident among women over 35 years of age. Stillbirth rates have fallen considerably among twin births unlike the static picture seen for singletons. The recent improvements also observed in neonatal mortality have benefited both singleton and twin births, but wide socioeconomic inequalities exist in mortality for all births.

Possible explanations for findings and comparisons with other work

The observed reduction in the rate of triplet and higher order births continues the pattern observed by Simmons et al[6] up until 2001, and coincides with changes in the regulatory framework in England governing ART. Although the chances of a successful implantation when undergoing fertility treatments such as in-vitro fertilisation or gamete intra-fallopian transfer treatment is significantly improved by increasing the number of embryos or eggs transferred, multiple births, particularly triplets and higher order pregnancies, are at significantly greater risk of poor outcome compared to singletons. Therefore in 2001 the Human Fertilisation and Embryology Authority (http://www.hfea.gov.uk/) introduced regulations to limit the transfer of a maximum of two embryos per cycle, except in

exceptional circumstances. With sporadic compliance, this policy was tightened further in 2004, so that a maximum of two embryos could be transferred to women under the age of 40 with no exceptions, and a maximum of three transferable to women aged 40 and over. Further evidence suggests that in women under 37 years elective single embryo transfer is recommended[14] to improve outcomes. Currently UK fertility units must have a maximum multiple birth rate of 10% (http://www.hfea.gov.uk/). Our findings of a reduction in the rate of triplet and higher order maternities coincide with these changes in regulation. A possible additional factor influencing the rate of triplets could be the increased frequency of fetal reduction in multi-fetal pregnancies in the first trimester. In the UK death of an unborn fetus would not be registered if delivered before 24 weeks of gestation. For those deliveries where a fetal reduction occurred before 24 weeks gestation and the fetus was known to have died the death should not be registered as a stillbirth but there may be some variation in interpretation of the legislation.

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Our data suggest that women from deprived areas, particularly those over 35 years, were less likely to have a multiple birth than women from less deprived areas. While our data cannot determine the reasons for this, one possible explanation is differential access to cycles of assisted reproductive techniques. Carson et al[15] using data from the UK Millennium cohort showed that the income of families of infants conceived through ART was substantially higher than for families of infants resulting from planned or unplanned natural conceptions. A UK survey of Primary Care Trusts has indicated that in the vast majority of Trusts, there is provision for only one cycle of treatment paid for by the NHS (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_101073 2009). Consequently further cycles of treatment need to be paid for by the couple and with charges of between £4000 and £8000 per cycle, this is likely to exclude low income couples. NICE guidelines have recently been updated from those written in 2004 and now recommend up to three cycles of IVF for women under 40 years and 1 cycle for women aged 40-42 years[16] being paid for by the NHS. For those areas under the new commissioning architecture that follow these guidelines, inequalities in access may be reduced with a consequent increase in multiple maternities in the most deprived women. No national data exist to explore access to assisted conception by deprivation and research is needed to assess this issue. Similar socioeconomic inequalities in multiple birth rates are

likely to be seen in developed countries with similar provision of ART but the deprivation gap is likely to be even greater in those countries where ART is only available privately.

We have observed considerable reductions in stillbirth rates over time for multiple births unlike singletons, where rates have remained static for the last decade. This may relate to the introduction of recommendations for changes in antenatal care, including improved early diagnosis and in-utero management of twin-twin transfusion syndrome in mono-chorionic twins. However Glinianaia et al[17] in a smaller UK regional study found no change in stillbirth rates over time for either mono-chorionic or di-chorionic twins but mono-chorionic twins have a considerably higher risk of stillbirth than di-chorionic twins predominantly due to twin-twin transfusion syndrome. The apparent improvement in stillbirth rates we have observed may also be partially explained by a change to the proportion of mono-chorionic versus di-chorionic twins over time. Around 16% of assisted conception multiple pregnancies result in mono-chorionic twins[18] and so a rise in the proportion of multiple births arising from ART would lead to a substantial rise in the proportion of di-chorionic twin births. If this is the explanation it should then be possible to observe an overall reduction in the rate of stillbirth for twins but no improvement in the chorionic specific rates of stillbirth. Since there are no national data on chorionicity we cannot determine to what extent the changes in stillbirth rates are related to changes in the proportion of mono-chorionic twins or to actual improvements in care. However stillbirth rates for twin births improved across all deprivation groups and so it is likely that multiple factors contributed to the observed change in stillbirth rates.

Compared to singletons, there was a smaller deprivation gap in the rate of stillbirth and neonatal death for twins and no significant deprivation gap for triplets and higher order births. However the absolute deprivation gap was wider. Research on explanations for the deprivation gap in neonatal mortality among singleton births has shown it is predominantly explained by increased rates of prematurity and its associated complications[19]. Multiple births are at much higher risk of prematurity with the rate of preterm birth (<37 weeks gestation) being ten times higher among multiple births and with half of all multiple births being born at these gestations[11]. Intrauterine growth restriction is also associated with deprivation[20] and increased complications of prematurity. However it is suggested that both small size and premature delivery in the case of multiple births may be more related to

physiological adaptation to the more limited intra-uterine environment[21] in contrast to the proposed mechanisms in singleton births where maternal or fetal pathology is often implicated. Without further research it is not possible to estimate the extent to which prematurity is responsible for the deprivation gap in neonatal deaths among multiple births.

Strengths and limitations

This study uses national routinely collected data to evaluate trends in multiple birth rates. These data have the advantage of being readily available and having national coverage. They lack detail on the chorionicity of the multiple births and so differences in trends could not be investigated between mono-chorionic and di-chorionic twins. While the focus of increased twinning has been associated with di-chorionic twins relating to assisted conception techniques, data is now indicating that these techniques also lead to increases in mono-chorionic twins and outcomes in these twins are particularly poor[17]. We also did not have information on the use of ART. Whilst information on chorionicity and the use of ART is not currently available nationally, data collection on these factors will commence from January 2013 as part of the MBRRACE-UK programme. This will provide a national picture of chorionicity and ART among stillbirths and infant deaths in the future.

The data we obtained did not link births from the same maternity. Consequently we had to estimate the number of multiple maternities which is prone to error as a result of a lack of data on late fetal losses. Similarly early selective fetocide for congenital anomalies may lead to misclassification of some multiple pregnancies as singleton births. However our sensitivity analyses comparing the overall estimated number of multiple maternities with published data showed that this method estimated the overall number to within 1% of the actual rates and so any impact on the findings presented here is likely to be small. Unfortunately, in the analysis of stillbirths and neonatal deaths we could not take account of the correlated nature of the outcomes of multiple births from the same pregnancy. The confidence intervals presented here are consequently likely to have been narrower had this adjustment been possible, but this is unlikely to have impacted upon our conclusions. National data were also unavailable on gestational age for this time period which prevented exploration or adjustment of mortality for prematurity. Furthermore while national

published data are available, they do not offer the ability to explore interactions between risk factors.

Implications and future research needs

The continuing rise in multiple birth rates and overall increases in births over the last 12 years has had a large impact on the absolute numbers of twin and triplets delivered in England. While there has been a reduction in the rate of triplet and higher order births, which are the most at risk of neonatal death, there are now around 1300 more multiple births a year in England compared to 1997. Since over half of all multiple births are born prematurely[11], increasing healthcare provision and NHS costs for neonatal and longer term care arising from this group of babies will ensue. These high risks for multiple births support the policies in place to reduce the rate of multiple births in the UK and the need to consider reviewing the practice of allowing multiple egg or embryo transfer in older women.

Current national data prevent detailed exploration of socioeconomic inequalities in access to ART in England. However, recently established procedures for national data collection of this information will enable monitoring of such trends in the future. This will also permit an assessment of whether recent changes in the guidelines for provision of assisted conception techniques in the UK, increasing the permitted number of cycles open to women under 39 years, have led to improved access to ART services across all socioeconomic groups.

Table 1 Number of singleton and multiple maternities and rate per 1000 maternities by year of birth and rate ratio compared to 1997, England 1997-2008

	All maternities	Singleton maternities	Multiple maternities								
			All multiples			Twins			Triplets and above		
	N	N	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio
1997	602383	593558	8825	14.7 14.3 to 15.0	1 -	8526	14.2 13.9 to 14.5	1 -	299	0.50 0.44 to 0.56	1 -
1998	596232	587530	8702	14.6 14.3 to 14.9	1.00 0.97 to 1.03	8399	14.1 13.8 to 14.4	1.00 0.97 to 1.03	303	0.51 0.45 to 0.57	1.02 0.87 to 1.20
1999	583714	575172	8542	14.6 14.3 to 14.9	1.00 0.97 to 1.03	8286	14.2 13.9 to 14.5	1.00 0.97 to 1.03	256	0.44 0.39 to 0.50	0.88 0.75 to 1.04
2000	567157	558765	8392	14.8 14.5 to 15.1	1.01 0.98 to 1.04	8136	14.3 14.0 to 14.7	1.01 0.98 to 1.04	256	0.45 0.40 to 0.51	0.91 0.77 to 1.07
2001	558109	549757	8352	15.0 14.6 to 15.3	1.02 0.99 to 1.05	8140	14.6 14.3 to 14.9	1.03 1.00 to 1.06	212	0.38 0.33 to 0.43	0.77 0.64 to 0.91
2002	560122	551598	8524	15.2 14.9 to 15.5	1.04 1.01 to 1.07	8357	14.9 14.6 to 15.2	1.05 1.02 to 1.09	167	0.30 0.26 to 0.35	0.60 0.50 to 0.73
2003	584180	575394	8786	15.0 14.7 to 15.4	1.03 1.00 to 1.06	8649	14.8 14.5 to 15.1	1.05 1.02 to 1.08	137	0.23 0.20 to 0.28	0.47 0.39 to 0.58
2004	601147	591971	9176	15.3 15.0 to 15.6	1.04 1.01 to 1.07	9020	15.0 14.7 to 15.3	1.06 1.03 to 1.09	156	0.26 0.22 to 0.30	0.52 0.43 to 0.63
2005	606808	597618	9190	15.1 14.8 to 15.5	1.03 1.00 to 1.06	9043	14.9 14.6 to 15.2	1.05 1.02 to 1.08	147	0.24 0.21 to 0.28	0.49 0.40 to 0.59
2006	628974	619205	9769	15.5 15.2 to 15.8	1.06 1.03 to 1.09	9620	15.3 15.0 to 15.6	1.08 1.05 to 1.11	149	0.24 0.20 to 0.28	0.48 0.39 to 0.58
2007	648385	638315	10070	15.5 15.2 to 15.8	1.06 1.03 to 1.09	9935	15.3 15.0 to 15.6	1.08 1.05 to 1.11	135	0.21 0.18 to 0.25	0.42 0.34 to 0.51
2008	665426	655058	10368	15.6 15.3 to 15.9	1.06 1.03 to 1.09	10199	15.3 15.0 to 15.6	1.08 1.05 to 1.11	169	0.25 0.22 to 0.30	0.51 0.42 to 0.62

Table 2: Number of singleton and multiple maternities and rate per 1000 maternities by maternal age and rate ratio compared to the youngest age group, England 1997-2008

	All maternities	Singleton maternities	Multiple maternities								
			All multiples			Twins			Triplets and above		
	N	N	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio	N	Rate/1000	Rate ratio
Under 20	507245	503878	3367	6.6 6.4 to 6.9	1 -	3331	6.6 6.3 to 6.8	1 -	36	0.07 0.05 to 0.10	1 -
20-24	1333053	1320339	12714	9.5 9.3 to 9.7	1.44 1.38 to 1.49	12559	9.4 9.3 to 9.6	1.43 1.38 to 1.49	155	0.12 0.10 to 0.14	1.64 1.14 to 2.35
25-29	1964391	1938450	25941	13.2 13.0 to 13.4	1.99 1.92 to 2.06	25462	13.0 12.8 to 13.1	1.97 1.90 to 2.05	479	0.24 0.22 to 0.27	3.44 2.45 to 4.82
30-34	2108007	2069823	38184	18.1 17.9 to 18.3	2.73 2.63 to 2.83	37223	17.7 17.5 to 17.8	2.69 2.60 to 2.79	961	0.46 0.43 to 0.49	6.42 4.60 to 8.96
35-39	1075723	1052170	23553	21.9 21.6 to 22.2	3.30 3.18 to 3.42	22952	21.3 21.1 to 21.6	3.25 3.13 to 3.37	601	0.56 0.52 to 0.61	7.87 5.62 to 11.02
40 and over	214218	209281	4937	23.0 22.4 to 23.7	3.47 3.32 to 3.63	4783	22.3 21.7 to 23.0	3.40 3.25 to 3.55	154	0.72 0.61 to 0.84	10.1 7.05 to 14.56

Table 3: Number of singleton and multiple maternities and rate per 1000 maternities by deprivation decile and rate ratio compared to the least deprived decile, England 1997-2008

Deprivation Decile (1= least deprived)	All maternities	Singleton maternities	Multiple maternities								
			All multiples			Twins			Triplets and above		
			N	Rate /1000	Rate ratio	N	Rate /1000	Rate ratio	N	Rate /1000	Rate ratio
1	720135	707142	12993	18.0 17.7 to 18.4	1 -	12681	17.6 17.3 to 17.9	1 -	312	0.43 0.39 to 0.48	1 -
2	718363	705833	12530	17.4 17.1 to 17.8	0.97 0.94 to 0.99	12175	16.9 16.6 to 17.3	0.96 0.94 to 0.99	355	0.49 0.45 to 0.55	1.14 0.98 to 1.33
3	720421	708292	12129	16.8 16.5 to 17.1	0.93 0.91 to 0.96	11826	16.4 16.1 to 16.7	0.93 0.91 to 0.96	303	0.42 0.38 to 0.47	0.97 0.83 to 1.14
4	721281	709734	11547	16.0 15.7 to 16.3	0.89 0.87 to 0.91	11270	15.6 15.3 to 15.9	0.89 0.87 to 0.91	277	0.38 0.34 to 0.43	0.89 0.75 to 1.04
5	722794	711547	11247	15.6 15.3 to 15.9	0.86 0.84 to 0.88	11015	15.2 15.0 to 15.5	0.87 0.84 to 0.89	232	0.32 0.28 to 0.37	0.74 0.63 to 0.88
6	721632	710992	10640	14.7 14.5 to 15.0	0.82 0.80 to 0.84	10407	14.4 14.1 to 14.7	0.82 0.80 to 0.84	233	0.32 0.28 to 0.37	0.75 0.63 to 0.88
7	720952	710806	10146	14.1 13.8 to 14.3	0.78 0.76 to 0.80	9964	13.8 13.6 to 14.1	0.78 0.76 to 0.81	182	0.25 0.22 to 0.29	0.58 0.49 to 0.70
8	718171	708591	9580	13.3 13.1 to 13.6	0.74 0.72 to 0.76	9383	13.1 12.8 to 13.3	0.74 0.72 to 0.76	197	0.27 0.24 to 0.32	0.63 0.53 to 0.76
9	716909	707727	9182	12.8 12.5 to 13.1	0.71 0.69 to 0.73	9031	12.6 12.3 to 12.9	0.72 0.70 to 0.73	151	0.21 0.18 to 0.25	0.49 0.40 to 0.59
10	721979	713277	8702	12.1 11.8 to 12.3	0.67 0.65 to 0.69	8558	11.9 11.6 to 12.1	0.67 0.65 to 0.69	144	0.20 0.17 to 0.23	0.46 0.38 to 0.56

Table 4 : Stillbirth and neonatal mortality: numbers and rate per 10000 births by multiplicity and year of birth, England 1997-2008

Year of birth	Live births		Stillbirths		Neonatal death		Rate per 10000 births			
							Stillbirths		Neonatal death	
	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1997-2000	2305156	65203	9869	812	6798	1222	42.6	123.0	29.5	187.4
							41.8 to 43.5	114.8 to 131.8	28.8 to 30.2	177.2 to 198.2
2001-2004	2258773	66786	9947	713	5997	1098	43.8	105.6	26.6	164.4
							43.0 to 44.7	98.2 to 113.7	25.9 to 27.2	155.0 to 174.4
2005-2008	2499891	76230	10305	702	5970	1164	41.1	91.2	23.9	152.7
							40.3 to 41.9	847. to 98.3	23.3 to 24.5	144.2 to 161.7

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Table 5 : Stillbirth and neonatal mortality: numbers and rate per 10000 births by multiplicity and deprivation decile, England 1997-2008

Decile of deprivation	Live births		Stillbirths		Neonatal death		Rate per 10000 births			
							Stillbirths		Neonatal death	
	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1	705052	24951	2090	221	1147	290	29.6	87.8	16.3	116.2
							28.3 to 20.9	77.0 to 100.2	15.4 to 17.2	103.6 to 130.4
2	703622	23923	2211	211	1334	340	31.3	87.4	19.0	142.1
							30.0 to 32.7	76.4 to 100.1	18.0 to 20.0	127.8 to 158.1
3	705970	23259	2322	219	1454	323	32.8	93.3	20.6	138.9
							31.5 to 34.1	81.7 to 106.5	19.6 to 21.7	124.5 to 154.9
4	707133	22112	2601	222	1640	320	36.6	99.4	23.2	144.7
							35.3 to 38.1	85.9 to 112.3	22.1 to 24.3	129.7 to 161.5
5	708703	21571	2844	214	1653	366	40.0	98.2	23.3	169.7
							38.5 to 41.5	85.9 to 112.3	22.2 to 24.5	153.2 to 188.0
6	707961	20362	3031	223	1865	363	42.6	108.3	26.3	178.3
							41.1 to 44.2	95.0 to 12.35	25.2 to 27.6	160.8 to 197.6
7	707436	19449	3370	249	2093	365	47.4	126.4	29.6	178.7
							45.8 to 49.0	111.6 to 143.1	28.3 to 30.9	169.4 to 207.9
8	704896	18318	3695	220	2274	378	52.1	118.7	32.3	206.4
							50.5 to 53.9	104.0 to 135.4	31.0 to 33.6	186.6 to 228.2
9	703868	17611	3859	220	2521	364	54.5	123.4	35.8	206.7
							52.8 to 56.3	108.1 to 140.8	34.4 to 37.2	186.5 to 229.1
10	709179	16663	4098	228	2784	375	57.5	135.0	39.3	225.1
							55.7 to 59.2	118.6 to 153.7	37.8 to 40.7	203.4 to 249.0

Table 6: Stillbirth and neonatal mortality: numbers and rate per 10000 births by multiplicity, year of birth and deprivation decile

Year of birth	Deprivation decile	Live births		Stillbirths		Neonatal death		Rate per 10000 births			
								Stillbirths		Neonatal death	
		Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1997-2000	1 Least deprived	239290	8047	709	73	442	96	29.5	89.9	18.5	119.3
								27.4 to 31.8	71.5 to 113.1	16.8 to 20.3	97.7 to 145.7
	2	235080	7567	790	74	540	119	33.5	96.8	23.0	157.3
								31.2 to 35.9	77.1 to 121.6	21.1 to 25.0	131.4 to 188.2
	3	235371	7261	794	83	550	106	33.6	113.0	23.4	146.0
								31.4 to 36.0	91.1 to 140.1	21.5 to 25.4	120.7 to 176.6
	4	233135	7132	869	102	620	116	37.1	141.0	26.6	162.6
								34.7 to 39.7	116.1 to 171.2	24.6 to 28.8	135.6 to 195.1
	5	232029	6723	906	83	617	146	38.9	122.0	26.6	217.2
								36.4 to 41.5	98.3 to 151.2	24.6 to 28.8	184.6 to 255.4
	6	228561	6348	1028	76	652	132	44.8	118.3	28.5	207.9
								42.1 to 47.6	94.5 to 148.1	26.4 to 30.8	175.3 to 246.6
	7	225246	5966	1066	87	738	130	47.1	143.7	32.8	217.9
								44.4 to 50.0	116.5 to 177.3	30.5 to 35.2	183.5 to 258.8
	8	223839	5580	1146	81	770	143	50.9	143.1	34.4	256.3
								48.1 to 54.0	115.1 to 177.9	32.1 to 36.9	217.5 to 301.9
	9	223662	5454	1240	76	863	111	55.1	137.4	38.6	203.5
								52.2 to 58.3	109.8 to 172.1	36.1 to 41.2	169.0 to 245.1
	10 Most deprived	228943	5125	1321	77	1006	123	57.4	148.0	43.9	240.0
								54.4 to 60.5	118.4 to 185.1	41.3 to 46.7	201.1 to 286.4
2001-2004	1 Least deprived	228780	8021	709	84	360	105	30.9	103.6	15.7	130.9
								28.7 to 33.3	83.7 to 128.4	14.2 to 17.4	108.1 to 158.5
	2	227883	7848	702	71	411	105	30.7	89.7	18.0	133.7
								28.5 to 33.1	71.1 to 113.1	16.4 to 19.9	110.5 to 162.0
	3	227298	7543	777	69	421	92	34.1	90.6	18.5	122.0
								31.8 to 36.5	71.6 to 114.8	16.8 to 20.4	99.4 to 149.6
	4	226108	7065	811	56	539	103	35.7	78.6	23.8	145.8
								33.4 to 38.3	60.5 to 102.2	21.9 to 25.9	120.2 to 176.8
	5	225135	6985	934	69	500	110	41.3	97.8	22.2	157.5
								38.7 to 44.1	77.3 to 123.8	20.3 to 24.2	130.6 to 189.8
	6	224169	6413	952	67	602	103	42.3	103.4	26.9	160.6
								39.7 to 45.1	81.4 to 131.4	24.8 to 29.1	132.4 to 194.8
	7	223600	6293	1129	84	664	111	50.2	131.7	29.7	176.4
								47.4 to 53.3	106.4 to 163.1	27.5 to 32.0	146.4 to 212.5
	8	224048	5738	1249	67	769	121	55.4	115.4	34.3	210.9
								52.4 to 58.6	90.8 to 146.6	32.0 to 36.8	176.5 to 252.0
	9	225700	5543	1295	70	839	126	57.1	124.7	37.2	227.3

	10 Most deprived	226052	5337	1389	76	892	122	54.0 to 60.2 61.1 57.9 to 64.4	98.7 to 157.6 140.4 112.1 to 175.8	34.7 to 39.8 39.5 37.0 to 42.1	190.9 to 270.7 228.6 191.4 to 273.0
2005-2008	1 Least deprived	236982	8883	672	64	345	89	28.3 26.2 to 30.5	71.5 56.0 to 91.4	14.6 13.1 to 16.2	100.2 81.4 to 123.3
	2	240659	8508	719	66	383	116	29.8 27.7 to 32.0	77.0 60.5 to 98.0	15.9 14.4 to 17.6	136.3 113.6 to 163.6
	3	243301	8455	751	67	483	125	30.8 28.6 to 33.1	78.6 61.9 to 99.9	19.9 18.2 to 21.7	147.8 124.1 to 176.2
	4	247890	7915	921	64	481	101	37.0 34.7 to 39.5	80.2 62.8 to 102.5	19.4 17.7 to 21.2	127.6 105.0 to 155.1
	5	251539	7863	1004	62	536	110	39.8 37.4 to 42.3	78.2 61.0 to 100.3	21.3 19.6 to 23.2	139.9 116.1 to 168.6
	6	255231	7601	1051	80	611	128	41.0 38.6 to 43.6	104.2 83.7 to 129.7	23.9 22.1 to 25.9	168.4 141.6 to 200.3
	7	258590	7190	1175	78	691	124	45.2 42.7 to 47.9	107.3 86.0 to 134.0	26.7 24.8 to 28.8	172.5 144.6 to 205.7
	8	257009	7000	1300	72	735	114	50.3 47.7 to 53.1	101.8 80.8 to 128.3	28.6 26.6 to 30.7	162.9 135.5 to 195.7
	9	254506	6614	1324	74	819	127	51.8 49.0 to 54.6	110.6 88.1 to 139.0	32.2 30.1 to 34.5	192.0 161.4 to 228.5
	10 Most deprived	254184	6201	1388	75	886	130	54.3 51.5 to 57.2	119.5 95.3 to 149.9	34.9 32.6 to 37.2	209.6 176.5 to 249.0

Table 1: Number (and rate per 1000 maternities) of singleton and multiple maternities, England 1997-2008

	All maternities	Singleton maternities	Multiple maternities					
			All multiples		Twins		Triplets and above	
	N	N	N	Rate/1000	N	Rate/1000	N	Rate/1000
1997	602383	593558	8825	14.7 14.3 to 15.0	8526	14.2 13.9 to 14.5	299	0.50 0.44 to 0.56
1998	596232	587530	8702	14.6 14.3 to 14.9	8399	14.1 13.8 to 14.4	303	0.51 0.45 to 0.57
1999	583714	575172	8542	14.6 14.3 to 14.9	8286	14.2 13.9 to 14.5	256	0.44 0.39 to 0.50
2000	567157	558765	8392	14.8 14.5 to 15.1	8136	14.3 14.0 to 14.7	256	0.45 0.40 to 0.51
2001	558109	549757	8352	15.0 14.6 to 15.3	8140	14.6 14.3 to 14.9	212	0.38 0.33 to 0.43
2002	560122	551598	8524	15.2 14.9 to 15.5	8357	14.9 14.6 to 15.2	167	0.30 0.26 to 0.35
2003	584180	575394	8786	15.0 14.7 to 15.4	8649	14.8 14.5 to 15.1	137	0.23 0.20 to 0.28
2004	601147	591971	9176	15.3 15.0 to 15.6	9020	15.0 14.7 to 15.3	156	0.26 0.22 to 0.30
2005	606808	597618	9190	15.1 14.8 to 15.5	9043	14.9 14.6 to 15.2	147	0.24 0.21 to 0.28
2006	628974	619205	9769	15.5 15.2 to 15.8	9620	15.3 15.0 to 15.6	149	0.24 0.20 to 0.28
2007	648385	638315	10070	15.5 15.2 to 15.8	9935	15.3 15.0 to 15.6	135	0.21 0.18 to 0.25
2008	665426	655058	10368	15.6 15.3 to 15.9	10199	15.3 15.0 to 15.6	169	0.25 0.22 to 0.30

Table 2: Number of singleton and multiple maternities and rate per 1000 maternities by deprivation decile, England 1997-2008

Deprivation Decile (1= least deprived)	All maternities	Singleton maternities	Multiple maternities					
			All multiples		Twins		Triplets and above	
			N	Rate /1000	N	Rate /1000	N	Rate /1000
1	720135	707142	12993	18.0 (17.7 to 18.4)	12681	17.6 (17.3 to 17.9)	312	0.43 (0.39 to 0.48)
2	718363	705833	12530	17.4 (17.1 to 17.8)	12175	16.9 (16.6 to 17.3)	355	0.49 (0.45 to 0.55)
3	720421	708292	12129	16.8 (16.5 to 17.1)	11826	16.4 (16.1 to 16.7)	303	0.42 (0.38 to 0.47)
4	721281	709734	11547	16.0 (15.7 to 16.3)	11270	15.6 (15.3 to 15.9)	277	0.38 (0.34 to 0.43)
5	722794	711547	11247	15.6 (15.3 to 15.9)	11015	15.2 (15.0 to 15.5)	232	0.32 (0.28 to 0.37)
6	721632	710992	10640	14.7 (14.5 to 15.0)	10407	14.4 (14.1 to 14.7)	233	0.32 (0.28 to 0.37)
7	720952	710806	10146	14.1 (13.8 to 14.3)	9964	13.8 (13.6 to 14.1)	182	0.25 (0.22 to 0.29)
8	718171	708591	9580	13.3 (13.1 to 13.6)	9383	13.1 (12.8 to 13.3)	197	0.27 (0.24 to 0.32)
9	716909	707727	9182	12.8 (12.5 to 13.1)	9031	12.6 (12.3 to 12.9)	151	0.21 (0.18 to 0.25)
10	721979	713277	8702	12.1 (11.8 to 12.3)	8558	11.9 (11.6 to 12.1)	144	0.20 (0.17 to 0.23)

Table 3: Rate ratio (95%CI) of multiple maternities for most deprived versus least deprived decile by maternal age adjusted for year of birth

Maternal age	Deprivation gap: Most deprived tenth versus least deprived Rate ratio	95%CI
Under 20	1.04	(0.92 to 1.17)
20-24	0.97	(0.92 to 1.03)
25-29	0.94	(0.90 to 0.97)
30-34	0.88	(0.85 to 0.91)
35-39	0.81	(0.78 to 0.85)
40 and over	0.66	(0.61 to 0.73)

Table 4 Stillbirth and neonatal mortality numbers and rate per 10000 births by multiplicity, year of birth and deprivation decile

Year of birth	Deprivation decile	Number of births		Number of deaths				Rate per 10000 births			
		All births		Stillbirths		Neonatal death		Stillbirths		Neonatal death	
		Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins	Singleton	Twins
1997-2000	1 Least deprived	239999	8120	709	73	442	96	28.5 26.5 to 30.7	89.9 71.5 to 113.1	17.8 16.2 to 19.5	118.2 96.8 to 144.4
	2	235870	7641	790	74	540	119	32.4 30.2 to 34.7	96.8 77.1 to 121.6	22.1 20.3 to 24.1	155.7 130.1 186.4
	3	236165	7344	794	83	550	106	32.5 30.4 to 34.9	113.0 91.1 to 140.1	22.5 20.7 to 24.5	144.3 119.3 to 174.6
	4	234004	7234	869	102	620	116	36.0 33.7 to 38.4	141.0 116.1 to 171.2	25.7 23.7 to 27.8	160.4 133.7 to 192.4
	5	232935	6806	906	83	617	146	37.7 35.4 to 40.3	122.0 98.3 to 151.2	25.7 23.8 to 27.8	214.5 182.4 to 252.3
	6	229589	6424	1028	76	652	132	43.5 40.9 to 46.2	118.3 94.5 to 148.1	27.6 25.6 to 29.8	205.5 173.3 to 243.7
	7	226312	6053	1066	87	738	130	45.8 43.2 to 48.7	143.7 116.5 to 177.3	31.7 29.5 to 34.1	214.8 180.9 to 255.1
	8	224985	5661	1146	81	770	143	49.6 46.8 to 52.6	143.1 115.1 to 177.9	33.4 31.1 to 35.8	252.6 214.4 to 297.6
	9	224902	5530	1240	76	863	111	53.8 50.9 to 56.8	137.4 109.8 to 172.1	37.4 35.0 to 40.0	200.7 166.7 to 241.8
	10 Most deprived	230264	5202	1321	77	1006	123	56.1 53.1 to 59.2	148.0 118.4 to 185.1	42.7 40.1 to 45.4	236.5 198.1 to 282.2
2001-2004	1 Least deprived	229489	8105	709	84	360	105	29.8 27.7 to 32.1	103.6 83.7 to 128.4	15.1 13.7 to 16.8	129.6 107.0 to 156.9
	2	228585	7919	702	71	411	105	29.6 27.5 to 31.9	89.7 71.1 to 113.1	17.4 15.8 to 19.1	132.6 109.5 to 160.5
	3	228075	7612	777	69	421	92	32.9 30.7 to 35.3	90.6 71.6 to 114.8	17.8 16.2 to 19.6	120.9 98.5 to 148.3
	4	226919	7121	811	56	539	103	34.6 32.3 to 37.1	78.6 60.5 to 102.2	23.0 21.1 to 25.0	144.6 119.2 to 175.5
	5	226069	7054	934	69	500	110	40.0 37.6 to 42.7	97.8 77.3 to 123.8	21.4 19.6 to 23.4	155.9 129.4 t o188.0
	6	225121	6480	952	67	602	103	41.1 38.5 to 43.8	103.4 81.4 to 131.4	26.0 24.0 to 28.1	159.0 131.0 to 192.8
	7	224729	6377	1129	84	664	111	48.8 46.1 to 51.8	131.7 106.4 to 163.1	28.7 26.6 to 31.0	174.1 144.5 to 209.7
	8	225297	5805	1249	67	769	121	54.0 51.1 to 57.1	115.4 90.8 to 146.6	33.3 31.0 to 35.7	208.4 174.4 to 249.1
	9	226995	5613	1295	70	839	126	55.6 52.7 to 58.8	124.7 98.7 to 157.6	36.0 33.7 to 38.6	224.5 188.5 to 267.3
	10 Most deprived	227441	5413	1389	76	892	122	59.6 56.6 to 62.8	140.4 112.1 to 175.8	38.3 35.9 to 40.9	225.4 188.7 to 269.1

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2005-2008	1 Least deprived	237654	8947	672	64	345	89	27.2 (25.2 to 29.4)	71.5 (56.0 to 91.4)	14.0 (12.6 to 15.5)	99.5 (80.8 to 122.4)
	2	241378	8574	719	66	383	116	28.7 (26.7 to 30.9)	77.0 (60.5 to 98.0)	15.3 (13.9 to 16.9)	135.3 (112.8 to 162.3)
	3	244052	8522	751	67	483	125	29.7 (27.7 to 31.9)	78.6 (61.9 to 99.9)	19.1 (17.5 to 20.9)	146.7 (123.1 to 174.8)
	4	248811	7979	921	64	481	101	35.8 (33.6 to 38.2)	80.2 (62.8 to 102.5)	18.7 (17.1 to 20.5)	126.6 (104.2 to 153.8)
	5	252543	7925	1004	62	536	110	38.5 (36.2 to 41.0)	78.2 (61.0 to 100.3)	20.6 (18.9 to 22.4)	138.8 (104.1 to 198.2)
	6	256282	7681	1051	80	611	128	39.8 (37.5 to 42.3)	104.2 (83.7 to 129.7)	23.1 (21.4 to 25.0)	166.7 (143.1 to 203.4)
	7	259765	7268	1175	78	691	124	44.0 (41.5 to 46.6)	107.3 (86.0 to 134.0)	25.9 (24.0 to 27.9)	170.6 (134.2 to 193.7)
	8	258309	7072	1300	72	735	114	49.0 (46.4 to 51.7)	101.8 (80.8 to 128.3)	27.7 (25.7 to 29.8)	161.1 (134.2 to 193.7)
	9	255830	6688	1324	74	819	127	50.4 (47.8 to 53.2)	110.6 (88.1 to 139.0)	31.2 (29.1 to 33.4)	189.9 (159.6 to 226.0)
	10 Most deprived	255572	6276	1388	75	886	130	53.0 (50.3 to 55.8)	119.5 (95.3 to 149.9)	33.8 (31.7 to 36.1)	207.1 (174.4 to 246.0)

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1,P3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P6
Objectives	3	State specific objectives, including any prespecified hypotheses	P6
Methods			
Study design	4	Present key elements of study design early in the paper	P7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*P7*
Bias	9	Describe any efforts to address potential sources of bias	P7
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P8
		(*b*) Describe any methods used to examine subgroups and interactions	P8
		(*c*) Explain how missing data were addressed	P7,P8
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	P7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P8,P9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P8,P9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	P8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	P8-P10

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	P7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P8-10
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P13-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P14
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.