# The Effects of Assisted Reproduction on the Trends and Zygosity of Multiple Births in England and Wales 1974–99

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Assisted reproductive techniques have led to an increase in the proportion of maternities that are multiple. Though predominantly dizygotic, they are at greater risk of monozygotic division than those spontaneously conceived. England and Wales data 1974–99 on stillbirths and livebirths were analysed for 4 periods: 1974–80 (pre-assisted reproduction; 1982–8; 1989–91 (pre-redefinition of stillbirth); 1993–9 (post-redefinition of stillbirth). For twin data, Weinberg's rule was applied to estimate the proportions that were mono- (MZ) and dizygotic (DZ). Compared with the period before assisted reproduction, the most recent period shows an increase in twin maternities of 3.81 per 1000 comprised of 3.22 (95% CI 3.10 to 3.33; $p < 0.0001$) DZ and 0.60 (95% CI 0.51 to 0.68; $p < 0.0001$) MZ twins. It is estimated that 15.7% of assisted reproduction twins are MZ. Higher order multiple births showed an increase of 3.06 (95% CI 2.85 to 3.29; $p < 0.0001$) per 10,000 maternities. Stillbirth rates in MZ twins are of the same order of magnitude as those in higher order multiple births but higher than those in DZ twins. The improvement in stillbirth rates over the 26 year study period is of the same order magnitude in singletons, DZ and MZ twins and higher order multiples. Assisted reproduction has led to a significant increase in the proportion of MZ twins. These are at high risk of fetal death and this needs to be considered when local stillbirth and perinatal mortality rates are used in auditing obstetric services.

The registration of all stillbirths became a legal requirement in 1927, an enactment that followed the report of an investigation into the factors involved in the cause of fetal death (Holland, 1922). Since then the annual stillbirth rate has shown a steady decrease and it has been used to monitor the provision and quality of obstetric services. Within the overall stillbirth rate, multiple births have higher rates than singleton births (Campbell & MacGillivray, 1988; Kiely, 1990) and, within multiple births, monozygous (MZ) have higher rates of fetal loss than dizygous (DZ) conceptions (Potter, 1963; Nylander, 1979).

The past two decades have witnessed a rapid increase in assisted reproduction and an accompanying rise in the proportion of multiple births (Botting et al., 1987). In response to these developments, we report an examination of the trends in multiple birth rates, the contribution of MZ and DZ twins to the overall stillbirth rate and estimate the proportion of assisted reproductions that are associated with monozygotic division.

## Materials and Methods

A descriptive epidemiological study based on national birth registration data was carried out. Annual birth registration statistics for England and Wales, published by the Office for Population Censuses and Surveys (OPCS) that subsequently became the Office for National Statistics (ONS), were used (Office for National Statistics, 1974–1999). These statistics show the number of maternities, stillbirths and live births according to plurality, sex and, for twins, whether of like- or unlike-sex.

The period covered was 1974 to 1999. This period is conveniently, though arbitrarily, divided into 1974 to 1980, 1982 to 1988, 1989 to 1991 and 1993 to 1999. This sub-division arose because in 1981, following industrial action by the Registrars of Births, Deaths and Marriages, no national statistics were published for multiple births. In 1992 there was a change in the definition of stillbirth for registration purposes from a gestational age of 28 to 24 weeks. Although the statistics for 1992 were published, it is appropriate to view 1992 in isolation because of this definitional change. The intermediate period 1982–1991 was a period of rising twinning rates and it was sub-divided further into 1982 to 1988 and 1989 to 1991 so that, for comparison purposes, 1989 to 1991 represented the last 3 years before the redefinition of a stillbirth.

To examine stillbirth trends in MZ and DZ twins, Weinberg's rule was applied to the data (Weinberg, 1902). The rule assumes that twins of unlike-sex are DZ and, by chance, there will be an equal number of DZ twins of like-sex. From the total number of twin pairs and the number of unlike-sex pairs, it is possible to estimate the number of MZ and DZ twin pairs.

Risk ratios (Kelsey et al., 1986) for MZ compared with DZ twins were calculated as:

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$$\frac{\text{Probability [2 fetal deaths of MZ twins]/ Total MZ twin pairs}}{\text{Probability [2 fetal deaths of DZ twins]/ Total DZ twin pairs}}$$

and

$$\frac{\text{Probability [1 fetal death and 1live birth in MZ twins]/Total MZ twin pairs}}{\text{Probability [1 fetal death and 1 live birth in DZ twins]/Total DZ twin pairs}}$$

using EpiInfo 6 statistical package and the Student *t* test for comparing the difference between two proportions.

## Results

The MZ, DZ, total twinning and higher order multiple rates for the four time periods are shown in Table 1.

Comparing the fourth (1993–99) with the first (1974–80) period, there has been a 40% increase in the overall twinning rate comprised of a 57% increase in the DZ rate and a 15% increase in the MZ rate. Among higher order multiple births there has been a 3–4 fold increase in rates between the first and third periods. The annual trend in MZ, DZ, total twinning and higher order multiple birth rates is shown in Figure 1.

It is generally accepted that recent increases in the proportion of multiple birth maternities reflect the increasing application of assisted reproductive technology resulting predominantly in dizygotic pregnancies. Nevertheless, pregnancies resulting from assisted reproduction are at increased risk of monozygotic division compared with those conceived spontaneously. It is possible to estimate the relative proportions of MZ and DZ twins among assisted reproduction if two assumptions are made. The first assumption is that, in this national population, the MZ and DZ twinning rates in the 1st period, 1974–80, are representative of the twinning rates before assisted reproduction technologies became available. The second assumption is that the increase in the MZ and DZ twinning rates in the 2nd, 3rd

**Table 1**

Trends in Multiple Birth per 1000 Maternities

| | Period 1 1974–80 | Period 2 1982–88 | Period 3 1989–91 | Period 4 1993–99 | Difference Period 2 — Period 1 (95% CI) | Difference Period 3 — Period 1 (95% CI) | Difference Period 4 — Period 1 (95% CI) |
|---|---|---|---|---|---|---|---|
| MZ twins | 3.94 | 4.24 | 4.38 | 4.54 | 0.30 (0.22–0.39); $p < 0.0001$ | 0.44 (0.33 to 0.54); $p < 0.0001$ | 0.60 (0.51 to 0.68); $p < 0.0001$ |
| DZ twins | 5.69 | 6.08 | 7.02 | 8.90 | 0.40 (0.30–0.50); $p < 0.0001$ | 1.33 (1.20 to 1.46); $p < 0.0001$ | 3.22 (3.10 to 3.33); $p < 0.0001$ |
| All twins | 9.63 | 10.33 | 11.39 | 13.44 | 0.70 (0.57–0.83); $p < 0.0001$ | 1.77 (1.60 to 1.94); $p < 0.0001$ | 3.81 (3.67 to 3.95); $p < 0.0001$ |
| Higher order multiples* | 1.27 | 1.78 | 3.01 | 4.34 | 0.51 (0.35–0.68); $p < 0.0001$ | 1.74 (1.49 to 2.01); $p < 0.0001$ | 3.06 (2.85 to 3.29); $p < 0.0001$ |

*per 10,000 maternities.

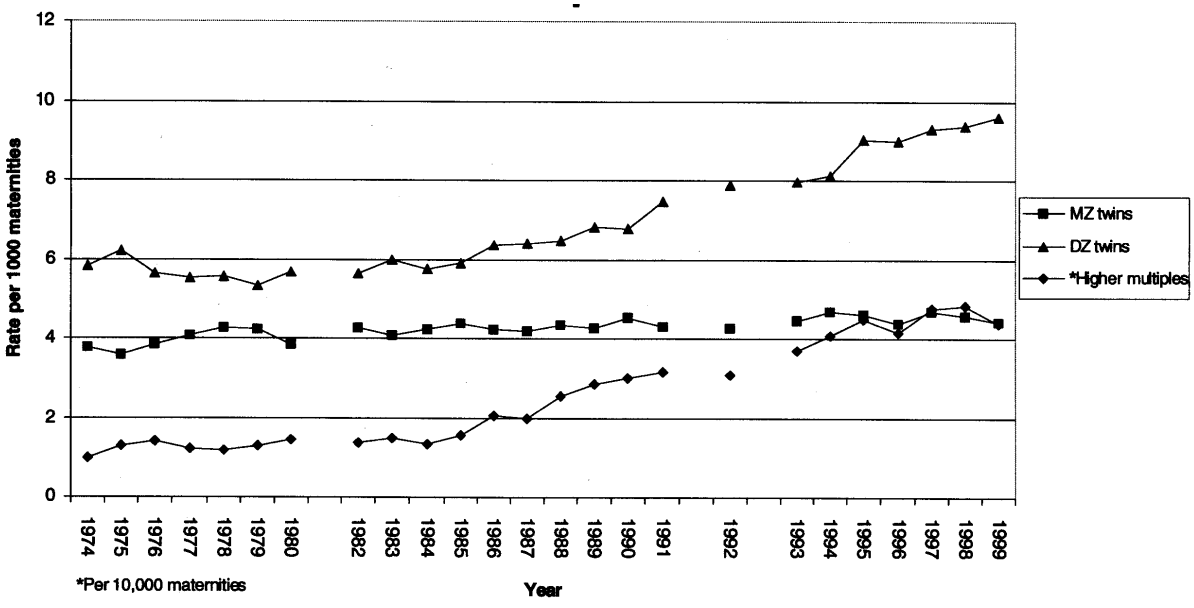


**Figure 1**

Trends in multiple birth rates.



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and 4th periods compared with the first time period is due to assisted reproduction.

Comparing the 4th with the 1st period, of the 4,496,257 total maternities in 1993–99, 40,024 were DZ and 20,404 were MZ twins. Applying the DZ and MZ rates for 1974–80 to the 1993–1999 total maternities, there would have been 25,584 DZ and 17,715 MZ maternities. Therefore, 14,440 (40,024 minus 25,584) DZ and 2,689 (20,404 minus 17,715) MZ maternities in 1993–1999 may be attributed to assisted reproduction. From this it is estimated that 15.7% (2,869 out of 17,129) of assisted conception twin maternities lead to MZ twins. Applying the upper and lower values of the 95% confidence intervals shown in Table 1, the probable range of assisted reproduction twin maternities that are MZ is 13.2% to 19.0%.

Similarly, if the 3rd is compared with the 1st period, the probable range of assisted reproduction twin maternities that are MZ is 24.9% with a range of 17.0% to 33.8%.

Comparison of the stillbirth rates in singletons, MZ and DZ twins and higher order multiple births are given in Table 2 and the annual trend in these stillbirth rates is shown in Figure 2.

The higher stillbirth rates for singleton and all categories of multiple births in the fourth period compared with the third period is predominantly attributable to the change in the definition of a stillbirth. MZ twins have stillbirth rates of similar magnitude to the rates in higher order multiple births and both have significantly higher rates than DZ twins.

The higher stillbirth rate in MZ compared with DZ twins is comprised of two components that is, when both conceptuses are fetal deaths and when one conceptus is a fetal death and the other is a livebirth. For each of these components, MZ are at greater risk than DZ twins. The risk ratio of MZ compared with DZ twins for the two components and for each of the time periods is shown in

**Table 2**

Trends in Stillbirth Rates per 1000 Total Births in Singletons, Twins and Higher Order Multiple Births

| | Period 1 1974–80 | Period 2 1982–88 | Period 3 1989–91 | Period 4 1993–99 |
|---|---|---|---|---|
| Singletons | 9.0 | 5.2 | 4.4 | 5.1 |
| DZ twins | 15.3 | 11.1 | 8.1 | 10.5 |
| MZ twins | 45.3 | 26.8 | 24.1 | 27.4 |
| Higher order multiple births | 49.1 | 26.4 | 19.8 | 23.9 |
| All births | 9.4 | 5.5 | 4.6 | 5.5 |

**Table 3**

Risk Ratio (95% CI) for MZ Compared to DZ Twins

| | Period 1 1974–80 | Period 2 1982–88 | Period 3 1989–91 | Period 4 1993–99 |
|---|---|---|---|---|
| 2 fetal deaths | 11.4 (8.5 to 15.4) | 14.8 (9.4 to 23.5) | 35.3 (13.0 to 96.0) | 13.7 (10.0 to 18.8) |
| 1 fetal death and 1 livebirth | 1.7 (1.6 to 1.9) | 1.6 (1.4 to 1.7) | 1.8 (1.6 to 2.2) | 1.6 (1.5 to 1.8) |

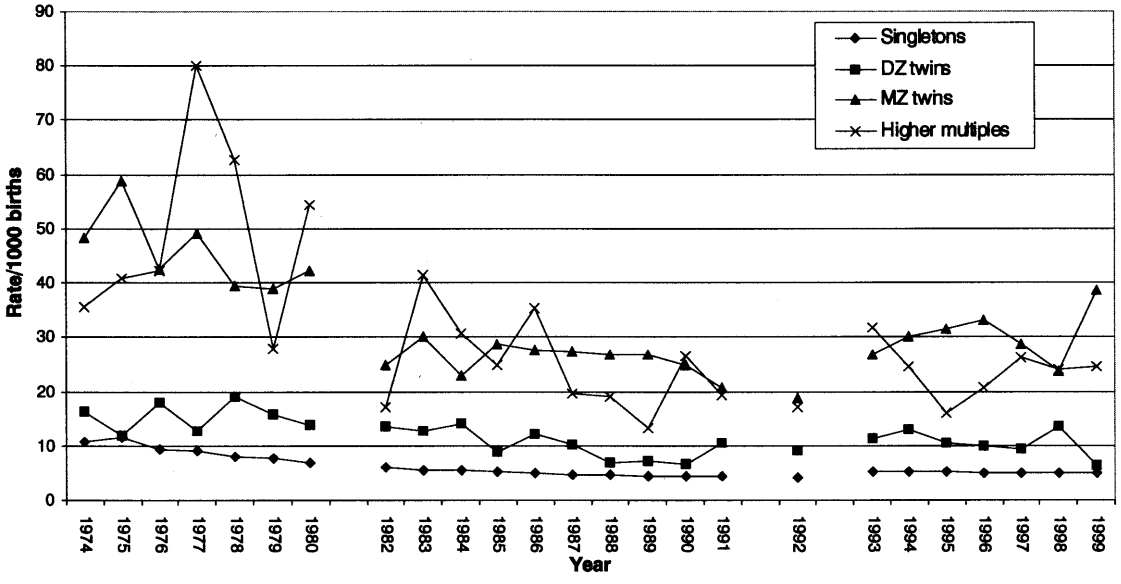


**Figure 2**

Trends in stillbirth rates.



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Table 3. In all four periods, there is more than a 10-fold increase in risk for MZ compared with DZ twins for both conceptuses to die in utero and a 60% to 80% increase in risk for one of the conceptuses to die in utero.

## Discussion

The recent increase in the proportion of maternities resulting in multiple births is well known (Dunn & Macfarlane, 1996; Macfarlane & Mugford, 2000; Wood, 1997). Weinberg's rule was applied to examine the differential contribution of MZ and DZ twins to the increase. The validity of Weinberg's rule has been questioned. However, as a result of the blood typing of twins it is generally accepted that the rule holds good for large samples but that there is a small but significant excess of like-sex twins among DZ twins. (James, 1979)

An unexpected consequence of assisted reproduction is the increase in MZ twins.

Therefore the assumptions made in estimating the proportion of MZ twins among assisted reproduction maternities require substantiation. MZ twinning rates are remarkably constant over time and show little racial variation (Little & Thompson, 1988). Therefore the assumption that the recent increase in MZ twinning rates is the result of assisted reproduction is reasonable. In contrast, DZ twinning rates show significant racial differences and is affected by other factors, notably maternal age (Bulmer, 1970; Elwood, 1978; James, 1972; Nylander, 1981). The recent trend towards increasing age at birth may have contributed to the rise in DZ twinning rates. If so, less of the rise can be attributed to assisted reproduction and the proportion of MZ twins attributable to assisted reproduction will have been underestimated. Alternatively, if the increase in the DZ twinning as a result of assisted reproduction reversed the downward trend in DZ twinning observed before the use of assisted reproduction techniques (Botting et al., 1987), then the proportion of MZ twins attributed to assisted reproduction will have been over-estimated.

Comparing Period 4 with Period 1, the proportion of MZ estimated among assisted reproduction twins was 15.7%. However, there was the change of the definition of stillbirth between these comparison periods with the gestational age at which a stillbirth had to be registered being lowered from 28 to 24 weeks. As MZ twins have a lower mean gestational age at delivery than DZ twins, part of the increase in MZ twinning could be attributed to this definitional change. If so, the 15.7% would be an overestimate. However, comparing Period 3 with Period 1 when there had been no change in definition, the estimated proportion of MZ twins among assisted reproduction twins was even greater at 24.9%. Both estimates are greater than those reported elsewhere. Following artificial induction of ovulation, 13% of the twin pairs were MZ (Derom et al., 1987). In another report, the incidence of monochorionicity among multiple gestations following assisted reproduction technologies was 9.8% (Wenstrom et al., 1993). In the national study of deliveries and children born after in-vitro fertilisation in Sweden, Weinberg's rule was applied to the 1068 twin births for which the sex of both twins was known and 3.4% were estimated to be MZ (Bergh et al., 1999). The wide variation in the several estimates of the proportion of MZ twinning among assisted reproduction maternities requires further investigation. One possible factor may arise from differences in the methods of assisted reproduction used.

A major bias in an analysis of national statistics, and one that will affect the interpretation of the trends we have reported, arises from both the accuracy and the completeness of registration of stillbirths. The problems arise when the stillbirth is of indeterminate sex. Although the sex may be registered 'indeterminate' on the stillbirth certificate, it is coded in the national statistics as 'male'. Sometimes, the Registrars of Births and Deaths allow the parents the choice of what sex is registered (Pharoah, 1999).

Furthermore, the legal requirement is that a stillbirth is registered if it is expelled from the mother after 24 weeks (previously 28 weeks) and not the gestational age at death. Nevertheless, in some cases, the parents have not been informed that there has been a fetal death of one twin and only a singleton birth is registered (Heys, 1996; Pharoah & Cooke, 1997). As fetal death of one or both twins is more common among MZ than DZ twins, these anomalies will lead to the under-registration of MZ twins. If such under-registration of MZ twins was more prevalent in Period 1 than in the subsequent time periods of the study, the estimate of MZ twinning due to assisted reproduction will have been artificially inflated.

There is an almost three-fold increase in fetal death rate in MZ compared with DZ twins that is highly significant both clinically and statistically (Table 2). There appears to be a spectrum of severity of damage in MZ twins. At the severe end of the spectrum both twins die in-utero and the risk ratio of MZ compared to DZ twins is very high. The risk ratio is also increased for one fetus to die in-utero (Table 3). At the less severe end of the spectrum there are two livebirths but neonatal mortality is higher in MZ twins and if one twin survives infancy it is at greatly increased risk of cerebral palsy (Pharoah, 2001). Twin to twin transfusional problems are the most plausible explanation for MZ being at greater risk than DZ twins. If so, those that are monochorionic within the group of MZ twins will be at exceptionally high risk.

Thus, fetal death of a MZ twin has important implications for serious mortality and morbidity of the co-twin and therefore, for parental counselling (Pharoah & Adi, 2000). It has also implications for the monitoring of obstetric services at Health District level. A small increase in the registration of fetal deaths will have a disproportionate effect on stillbirth and perinatal mortality rates. Efforts are underway to improve the registration of fetal deaths (Gompels & Davies, 1999) but, until the rules of registration are universally applied, examination of trends and inter-district comparisons are liable to misinterpretation.

## References

Bergh, T., Ericson, A., Hillen, J. S., Nygren, K-G., & Wennerholm, U-B. (1999). Deliveries and children born after in-vitro fertilisation in Sweden 1982–95: A retrospective cohort study. *Lancet, 354,* 1579–1585.



https://doi.org/10.1375/twin.4.6.417 Published online by Cambridge University Press

Botting, B. J., MacDonald Davies, I., & Macfarlane, A. J. (1987). Recent trends in the incidence of multiple births and associated mortality. *Archives of Disease in Childhood, 62,* 941–950.

Bulmer, M. G. (1970). *The biology of twinning in man.* Oxford: Clarendon Press.

Burn, J., & Corney, G. (1988). Zygosity determination and the types of twinning. In I. MacGillivray, D. M. Campbell, & B. Thompson (Eds.), *Twinning and twins* (pp. 8–25). Chichester: John Wiley Ltd.

Campbell, D. M., & MacGillivray, I. (1988). Outcome of twin pregnancies. In I. MacGillivray, D. M. Campbell & B. Thompson (Eds.), *Twinning and twins* (pp. 179–205). Chichester: John Wiley Ltd.

Derom, C., Derom, R., Vlietinck, R., Van Den Berghe, H., & Thiery, M. (1987). Increased monozygotic twinning rates after ovulation induction. *Lancet, i*, 1236–1238.

Dunn, A., & Macfarlane, A. J. (1996). Recent trends in the incidence of multiple births and associated mortality in England and Wales. *Archives of Disease in Childhood, 75,* F10–F19.

Elwood, J. M. (1978). Maternal and environmental factors affecting twin births in Canadian cities. *British Journal of Obstetrics and Gynaecology, 85,* 351–358.

Gompels, M. J., & Davies, D. (1999). Fetus papyraceus is being registered increasingly in Wessex. *British Medical Journal, 319,* (letter), 1271.

Heys, R. F. (1996). Selective abortion. *British Medical Journal, 313,* (letter), 1004.

Holland, E. (1922). The causation of foetal death. *Reports on Public Health and Medical Subjects No.7.* London: HMSO.

James, W. H. (1972). Secular changes in dizygotic twinning rates. *Journal of Biosocial Science, 4,* 427–434.

James, W. H. (1979). Is Weinberg's differential rule valid? *Acta Geneticae Medicae et Gemellologiae, 28,* 69–71.

Kelsey, J. L., Thompson, W. D., & Evans, A. S. (1986). *Methods in observational epidemiology.* Oxford: University Press.

Kiely, J. L. (1990). The epidemiology of perinatal mortality in multiple births. *Bulletin of the New York Academy of Medicine, 66,* 618–637.

Little, J., & Thompson, B. (1988). Descriptive epidemiology. In I. MacGillivray, D. M. Campbell, & B. Thompson (Eds.), *Twinning and twins* (pp. 37–66). Chichester: John Wiley Ltd.

Macfarlane, A., & Mugford, M. (2000). *Birth counts. Statistics of pregnancy and childbirth.* London: The Stationery Office.

Nylander, P. P. S. (1979). Perinatal mortality in twins. *Acta Geneticae Medicae et Gemellologiae, 28,* 363–368.

Nylander, P. P. S. (1981). The factors that influence twinning rates. *Acta Geneticae Medicae et Gemellologiae, 30,* 189–202.

Office for National Statistics (1974–1999). *Birth Statistics. Series FM1; Nos 1–28.* London: HMSO.

Pharoah, P. O. D., & Cooke, R. W. I. (1997). Registering a fetus papyraceous. *British Medical Journal, 314,* (letter), 441–442.

Pharoah, P. O. D. (1999). Anomalies occur in registrations of fetal deaths in multiple pregnancies. *British Medical Journal, 319,* (letter), 188.

Pharoah, P. O. D. (2001). Cerebral palsy in the surviving twin associated with infant death of the co-twin. *Archives of Disease in Childhood*, *84*, F111-F116.

Pharoah, P. O. D., & Adi, Y. (2000). Consequences of in-utero death in a twin pregnancy. *Lancet*, *355*, 1597–1602.

Potter, E. L. (1963). Twin zygosity and placental form in relation to the outcome of the pregnancy. *American Journal of Obstetrics and Gynecology, 87,* 566–577.

Weinberg, W. (1902). Beiträge zur Physiologie und Pathologie der Mehrlingsgeburten beim Menschen. *Archiv für die gesamte Physiologie des Menschen und der Tiere, 88,* 346–430.

Wenstrom, K. D., Syrop, C. H., Hammett, E. G., & Van Voorhis, B. J. (1993). Increased risk of monochorionic twinning associated with assisted reproduction. *Fertility and Sterility, 60,* 510–513.

Wood, R. (1997). Trends in multiple births, 1938–1995. *Population Trends, 87,* 29–35.



https://doi.org/10.1375/twin.4.6.417 Published online by Cambridge University Press