

## INFERTILITY TREATMENT AND MULTIPLE BIRTH RATES IN BRITAIN, 1938–94

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**Summary.** Trends in multiple birth rates are thought to have been substantially affected by subfertility treatments in the last 25 years, but there are few quantitative assessments of this. This paper examines trends in twin and higher multiple birth rates separately in Scotland, England and Wales and compares their course with corresponding multiple birth rates in the Oxford Record Linkage Study area, where the proportions following subfertility treatment are documented. National data on prescriptions for subfertility treatments reinforce the view that they have had a major effect on the trends, and currently perhaps 60% of triplet and higher order births and 15% of twins follow their use in Britain.

### Introduction

Simple ovulation induction (OI) and more complicated forms of assisted conception (AC) are now in widespread use. The current national proportions of triplet and higher multiple births that follow OI and AC are known with greater accuracy than the proportions of twins, at least in Britain (Levene, Wild & Steer, 1992; Parazzini *et al.*, 1991; Tuppin, Blondel & Kaminski, 1993). Twinning rates declined inexplicably from the 1950s world-wide, but have generally increased since around 1970 (Editorial, 1976). This pattern is dominated by the dizygotic component. Monozygotic twinning has steadily increased since around 1950 (Murphy & Seagroatt, 1992). To examine the impact of OI and AC, twinning, triplet and higher multiple birth rates within England and Wales and Scotland are contrasted separately. At the national level only a few point estimates of the impact of OI and AC exist for any multiple birth type. The national changes were therefore calibrated against trends in multiple births in Oxfordshire and West Berkshire, where continuous assessment of the impact of subfertility treatment is possible. Trends in the amount of medical treatment of subfertility available nationally and locally are also described.

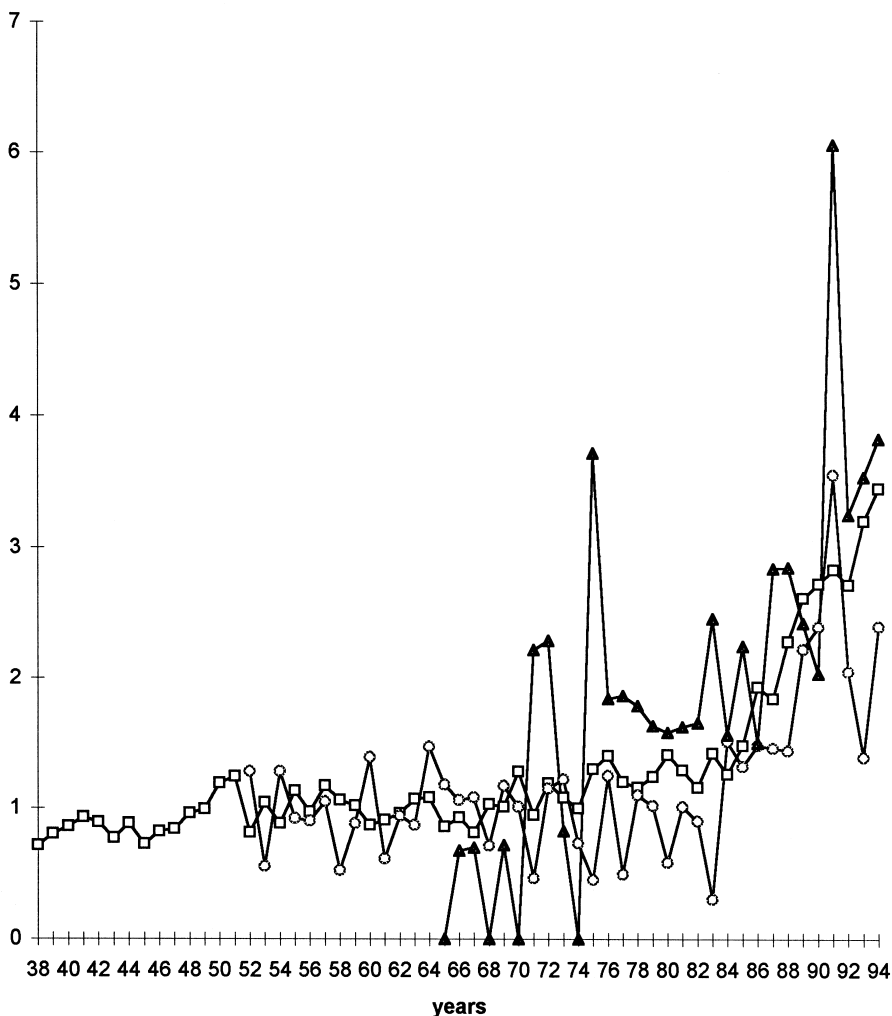
## Methods

For Scotland, England and Wales birth data were extracted from the publications of the respective Registrars General from 1938 (or 1939 in Scotland) to 1994. Multiple birth rates were age-standardised indirectly using the 1970 England and Wales twin and higher multiple birth rates in 5-year age groups from 15–19 to 45+. For Scotland age-adjustment is possible only from 1952. The 1981 data for England and Wales are unreliable due to industrial action involving the Registrars of births, marriages and deaths and values for those years are plotted as averages of 1980 and 1982 data.

National data for England on prescriptions by class of drugs used in the treatment of subfertility, were obtained from 1980 to 1994 from the Prescription Pricing Authority (PPA). These data cover prescriptions dispensed by general practitioners or community pharmacies only. The approximate total prescribing was estimated, assuming Oxfordshire to be representative, by comparing prescriptions dispensed for Clomiphene citrate in the hospital pharmacies of Oxfordshire Family Health Service Authority (FHSA) in the years 1991–94, with the numbers dispensed through the outlets in Oxfordshire FHSA from which the PPA collects its data.

Local multiple birth and infertility treatment data were available from the Oxford Record Linkage Study (ORLS). In the ORLS, currently, all NHS hospital and domiciliary deliveries in Oxfordshire and West Berkshire irrespective of mother's residence are captured in a detailed maternity file from 1965 to 1988. Private deliveries have, historically, taken place in NHS institutions and are included. From 1989 to 1994, data for Oxfordshire and West Berkshire residents who gave birth at home or in hospital in these two districts were obtained from the Office of Population Censuses and Surveys (OPCS). Twin and higher multiple birth rates were age-adjusted for residents of Oxfordshire and West Berkshire giving birth within these two districts for 1965–94 as nationally above. An approximation was necessary for 1989 and 1993. Comparison of OPCS and ORLS records for 1968–88 suggests that less than 10% of Oxfordshire/West Berkshire residents gave birth outside those districts throughout the entire period. Greater variation exists for births to non-residents within Oxfordshire and West Berkshire but they are not considered here. There were 100–200 sets of twins born annually to residents in these districts, and total maternities ranged from a high of 15,000 in 1965 to a low of 10,000 in the mid-1970s. Information on the proportion of multiple births in Oxfordshire/West Berkshire which followed subfertility treatment was available from two sources. From 1973, hospital maternities in the two districts preceded by a history of subfertility (treatment) were noted on the ORLS maternity file (Hey *et al.*, 1994). As part of a cohort study of the relationship between subfertility, its successful treatment and the subsequent health of the 5500 mothers identified in this way between 1973 and 1985, the hospital casenotes of all registrable multiple births to Oxfordshire/West Berkshire residents were examined to determine which followed subfertility treatment. For 1986–94 it is known which deliveries were preceded by subfertility treatment from the computerised obstetric data system (ODS), which captures all births at the John Radcliffe Hospital in Oxford (Yudkin, Wood & Redman, 1987). These comprise about half of all births in Oxfordshire and West Berkshire combined. The validity of the information about subfertility treatment on the ODS for the period considered is thought to be very high. A postal questionnaire study of twin mothers and controls who gave birth at this hospital in 1990 achieved a 90% response

—□— England & Wales —○— Scotland —▲— Oxfordshire & West Berks

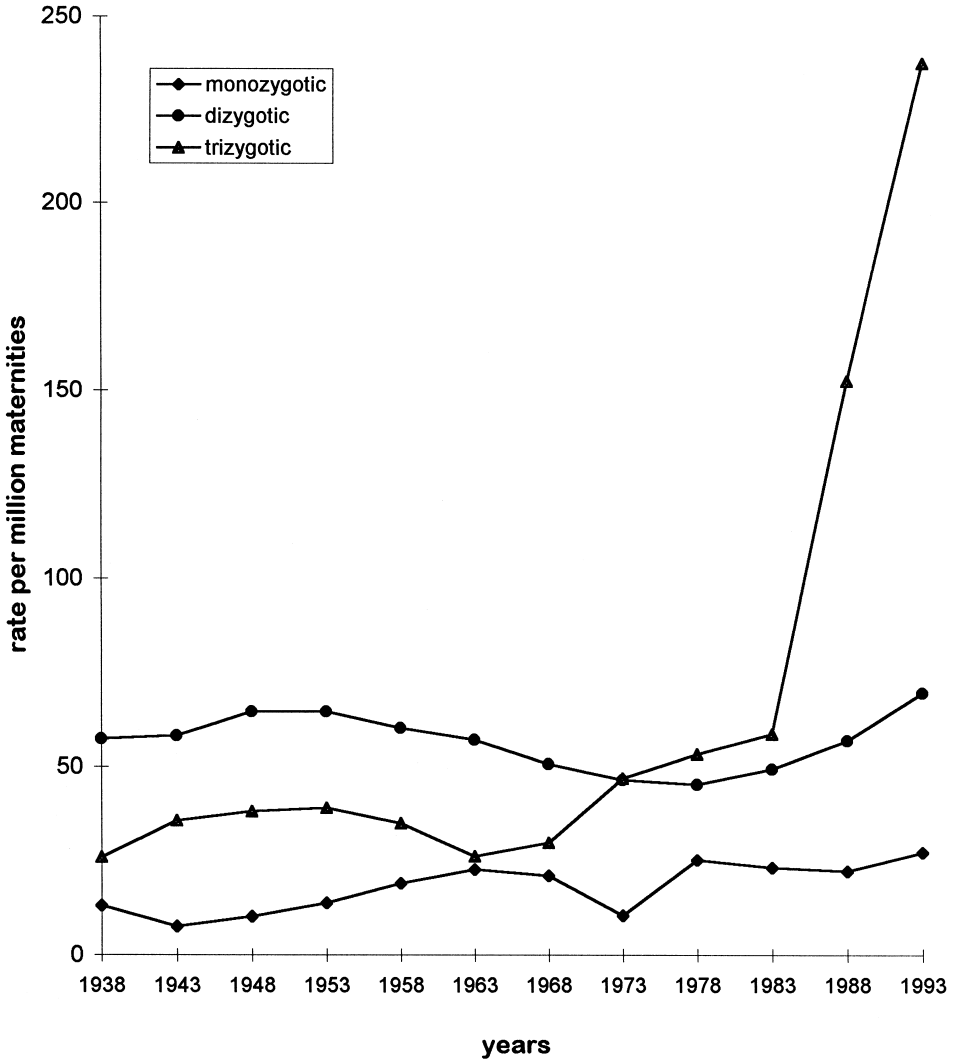


**Fig. 1.** Age-standardised triplet and higher order birth rates per 10,000 maternities in England and Wales (1938–94), Scotland (1952–94) and to residents in Oxfordshire and West Berkshire (1965–94).

rate and showed very high levels of agreement with the subfertility treatment information held about the same women on the ODS.

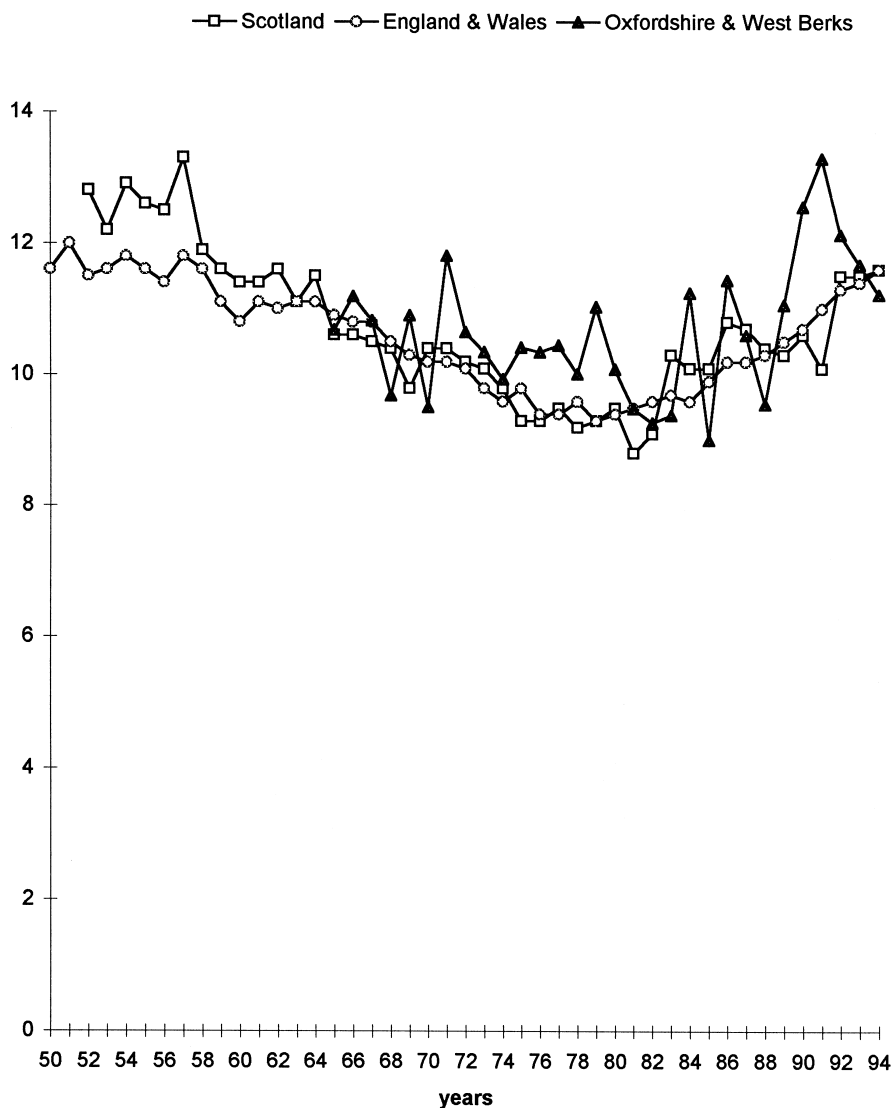
### Results

Figure 1 shows age-adjusted triplet and higher multiple birth rates in England and Wales, Scotland and Oxfordshire and West Berkshire. There is a clear increase in the



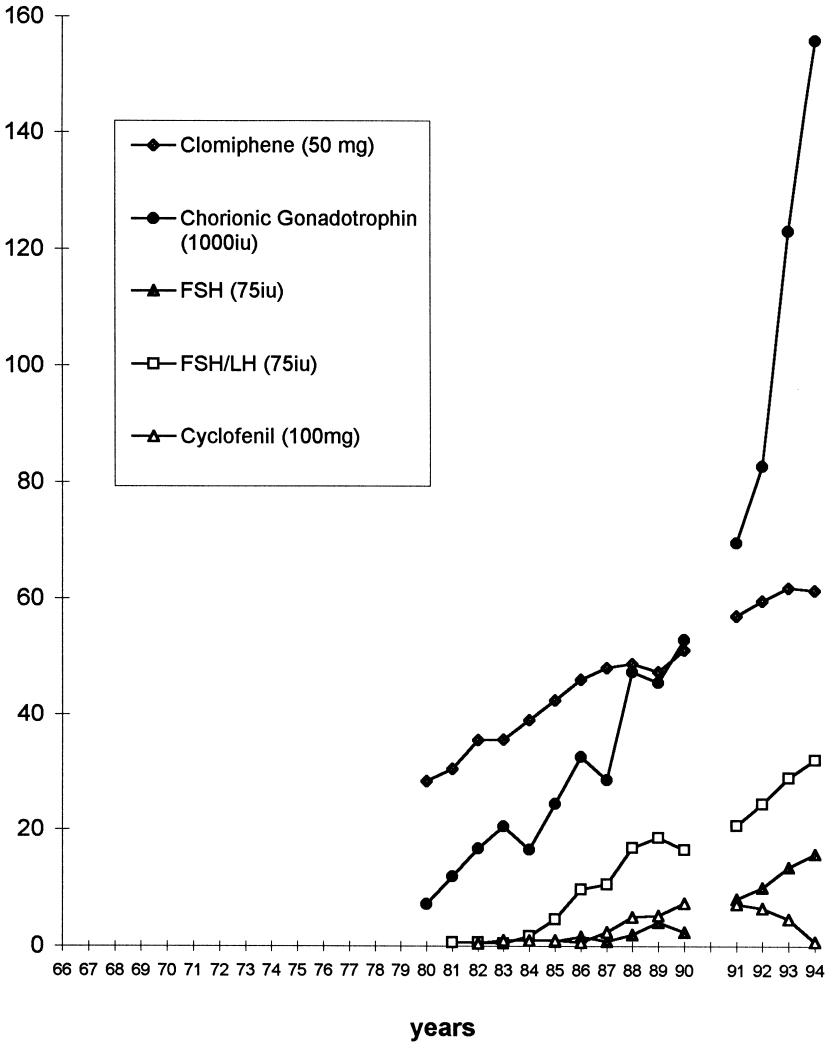
**Fig. 2.** Crude triplet rates per million maternities by zygoty in England and Wales 1938–94. (1938–40, 1982–84, 1991–94, otherwise quinquennia; data for 1981 unavailable).

rates for England and Wales from about 1970 (and perhaps throughout the entire period) with an acceleration in the 1980s and 1990s. Scotland in contrast shows a decline from 1952 (and from 1939 in the crude data which are not shown) to the mid-1980s before steeply increasing in a similar fashion to England and Wales. Oxfordshire and West Berkshire rates show much greater annual variation because there are so few triplet and higher order births per year. The rates appear initially lower than the national average but from the early 1970s appear to be usually higher. The difference between the indirectly standardised rate in Oxfordshire/West Berkshire



**Fig. 3.** Age-standardised twin rates per 1000 maternities in England and Wales (1950–94), Scotland (1952–94) and to residents in Oxfordshire and West Berkshire (1965–94).

averaged over the 20 years 1975–94 and the corresponding rate in the remainder of Great Britain over the same period was tested. This difference just reached statistical significance ( $p < 0.05$ ) and provides some evidence that the apparent transition to higher rates locally is unlikely to be due to chance. Hospital casenotes indicated 18 of the 27 triplet and higher multiple births to residents in these districts in the period 1973–85 followed subfertility treatment, in each case using simple OI apparently. Overall between 1991 and 1994 the ODS indicates this pattern of about two-thirds



**Fig. 4.** Numbers of prescriptions (thousands) for drugs used in subfertility treatments, dispensed from outlets making returns to the Prescription Pricing Authority, England 1980–94 (Crown copyright reserved). Figures up to 1990 are based on fees and on a sample of 1/200 prescriptions dispensed by community pharmacists and appliance contractors only. Figures from 1991 are based on items, and cover all prescriptions dispensed by community pharmacists, appliance contractors, dispensing doctors and prescriptions submitted by prescribing doctors for items personally administered.

treated was maintained at the John Radcliffe, perhaps being lower in Oxfordshire/West Berkshire combined.

The higher multiple birth patterns in England and Wales were explored further and Fig. 2 shows crude triplet rates by zygosity for 1938–94. Zygosity was estimated by Allen's extension of Weinberg's method (Allen, 1960). The general shape of the triplet

rate is dictated by variation in the trizygotic component and monozygotic and dizygotic triplet patterns have resembled closely the corresponding twinning.

Figure 3 shows age-adjusted twin rates for Oxfordshire and West Berkshire, England and Wales and Scotland. The national trends are very similar throughout. The local rates are higher than the national throughout the 1970s and again from 1989. Amongst the subfertility cohort between 1973 and 1985 an average of 8.3% of twins followed subfertility treatment (always simple OI), with no evidence of a trend in the proportion during the period. Between 1986 and 1988 the estimated average at the John Radcliffe was 13% and in 1990 it is known that 40% of twins followed subfertility treatment (roughly equal proportions of AC and OI). Between 1991 and 1994 about 18% of twins followed subfertility treatment at the John Radcliffe. The proportion in Oxfordshire and West Berkshire as a whole might have been lower.

Figure 4 shows the national trend in prescriptions for the major classes of drugs used in the medical treatment of subfertility. The year 1966 was chosen as the origin because it was the year in which Clomiphene citrate was first licensed for use. There has been a steady increase in the use of all except Cyclofenil. If the experience of Oxfordshire is generalisable then national PPA data undercount total prescriptions of Clomiphene citrate by about 10% in the 1990s, since about 900 prescriptions per year were dispensed through PPA outlets and about 100 through hospital pharmacies. It is not known if this is equally true of the other drugs.

### **Discussion**

This paper presents national data from the civil birth registration systems together with estimates of the trend in amounts of medical subfertility treatment available in England. Prescription data can only be a guide to treatment. Local maternity data, of similar provenance, validity and accuracy as the national, were used, and data about the proportions of individuals whose pregnancies followed subfertility treatment. There have been few definitional changes over the entire period considered, and they would not affect the trends markedly. Stillbirth was re-defined in 1992, to occur at 24 rather than 28 weeks of completed gestation, which might possibly influence the proportions of multiple (particularly higher multiple) births being defined as the next higher registrable multiple birth since there are no restrictions by gestation for registering live births. The only geographical definition change was to the boundaries of Oxfordshire/West Berkshire in 1974. Although there have been some changes to NHS maternity provision within the area, by confining attention to residents giving birth locally, it is felt that multiple birth trends and related patterns of successful subfertility treatment are described accurately over 30 years and in an unselected way. At national and local level the figures are based on births and no adjustment was possible for vanishing multiple conceptions or selective reduction of higher order pregnancies. Nevertheless it is considered all the trends can be taken at face value.

The early trends in triplet and higher multiple birth rates for Scotland and England and Wales differ. Declines throughout the century have been described in Scandinavia and Italy, and England and Wales appears to be the odd one out (Fellman & Eriksson, 1993; Parisi & Caperna, 1981). The zygosity pattern, however, is unremarkable in comparison to the few other countries for which it has been estimated (Parisi &

Caperna, 1981). Adjustment was made for the principal factor (age), affecting the risk of these births in the past, and the steep rise seen in the 1980s throughout Britain must largely represent the effects of AC on these births. It is primarily confined to the married (Murphy & Seagroatt, 1992; Murphy, 1995). However, whereas simple OI seems likely to have increased their occurrence in England and Wales in the 1970s, no such effect was readily apparent in Scotland. The lower Scottish rates in the 1990s may be related to different practices of embryo or oocyte replacement during AC. Equally puzzling is the contrast between the two parts of Britain earlier in the century, given the similarity of their trends in twinning rates (Fellman & Eriksson, 1993; Parisi & Caperna, 1981). It emphasises how little is understood about the factors involved.

The available national data about medical subfertility treatment qualitatively support the impression that the major factor affecting triplet and higher multiple births now is medical practice. So do the data for Oxfordshire and West Berkshire. Clomiphene and FSH/LH were used in Oxford since 1968, soon after each was available for the treatment of subfertility and earlier than elsewhere in the country. An in-vitro fertilisation (IVF) service was introduced in Oxford in 1985 and will have contributed substantially to the local higher multiple birth rate since 1987. The area saw the introduction of the most modern techniques of subfertility treatment early enough for the local multiple birth rates to become established at a higher rate than the national average. Thus a bigger impact of simple OI on triplet and higher multiple rates locally was seen than observed nationally (Levene *et al.*, 1992). With overall 8% of twins following simple OI from 1973 to 1985 this area was above the average for England and Wales of 6% for 1980–85 (Botting, Macfarlane & Price, 1990) more probably resembling Nottingham in 1981–82, where 11–14% of twins followed OI (Webster & Ellwood, 1985). Assuming the higher twinning rates throughout Oxfordshire/West Berkshire in the 1990s are due to subfertility treatment, perhaps 15% of twins nationally now follow treatment and the natural twinning rate might still be in decline.

### Acknowledgments

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