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# Pregnancy Outcome Among Twins Conceived After Subfertility Treatment Compared With Natural Twins: A Population-Based Study

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Pregnancy outcome and characteristics of women who conceive following subfertility treatment remains a subject of great interest. We analyzed these variables among 199 women who delivered a registerable twin birth compared with 1773 women who delivered a naturally conceived twin birth in a population-based obstetric cohort drawn from around Oxford, England. Treatment was restricted to conceptions involving simple ovulation induction only. Treated mothers were of significantly higher social class and older, more likely to deliver girls and to be delivered by cesarean section, and significantly less likely to be smokers at the time of antenatal booking and to have delivered previous pregnancies. Pregnancy outcome was similar between the two groups for most measures, with the exception of birthweight which was lower in treated twins, though not significantly so. Overall the results are reassuring with respect to outcome in twin pregnancies following simple ovulation induction.

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Effective medical treatments for female subfertility have been in widespread use for more than 30 years. Their use is having an important influence on the occurrence of twinning and higher multiple births. The importance of monitoring the immediate and long-term health of mother and baby where pregnancies follow subfertility and its treatment is recognized, but the data are sparse. There remains concern that some outcomes in the treated groups are poorer than for women with naturally conceived babies. Suitable comparison groups can be difficult to assemble and differentiating the effect of subfertility per se from its successful treatment is problematic. In the United Kingdom, at least, there has been less attention paid to the pregnancies resulting from simple ovulation induction (OI) over the last 30 years, than to pregnancies

following more sophisticated and more recent forms of assisted conception (AC; Beral & Doyle, 1990; Beral et al., 1990; Doyle et al., 1992; Fishel & Jackson, 1989; Rizk et al., 1991; Tan et al., 1992; Thomson et al., 2005). This article considers twin pregnancies following simple OI only, with a suitable population-based comparison group. Few studies have so far included large numbers of twins in the comparison of the subfertile successfully treated with natural conceptions, and many specifically exclude twins from consideration (Basso & Baird, 2003). A meta-analysis recently concluded that for singletons a number of differences in outcome can be detected between babies conceived naturally and those conceived following subfertility treatment, but that this disadvantage is substantially less when comparing twins born in these two categories (Helmerhorst et al., 2004).

We report on characteristics of all twins that were delivered following simple OI compared with all other naturally conceived twins in Oxfordshire and West Berkshire from 1973 to 1989, drawn from the same obstetric population base to form the most appropriate control group. Outcome among the much larger number of singleton babies conceived with OI or naturally in the same obstetric population will be reported subsequently, including comparatively rare events such as cancer incidence on which some interest has focused over the last decade (Lightfoot et al., 2005).

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## Methods

The Oxford Record Linkage Study (ORLS) was assembled from computerized abstracts of hospital inpatient and day-case records, together with birth registrations of all babies born in the area (irrespective of place of residence) and death certificates for them and all other residents of the area. Data for the same individual are linked together. The maternity subset of the ORLS included detailed information on nearly all domiciliary and hospital maternity events in Oxfordshire and West Berkshire from 1965 to 1989. Changes in data collection procedures resulted in less detailed information being available within the ORLS about maternities after this date. From 1973, histories of subfertility and its treatment were recorded in the ORLS maternity statistics using the International Classification of Diseases 9th revision (ICD-9; World Health Organization, 1977) code V23. As part of a continuing study of the relationship between subfertility, its successful treatment and the subsequent health of more than 6500 mothers of this type who gave birth between 1973 and 1989, we identified all multiple births preceded by subfertility treatment and characterized them in detail from the information contained in maternity, gynecological and other general hospital case notes (Murphy et al., 1997; Whiteman et al., 2000).

The treated group was compared with the other natural (untreated) registerable twin births defined from the ORLS files for the study period to comprise controls. The data used for the comparison were those which had been routinely extracted at the time of creation of the ORLS dataset originally. The process of assembling a large comprehensive record-linked dataset involves the loss of information for some individuals because of missing records and technical failures to link. These losses are small but, because of this and also occasionally because an intrauterine death around 28 weeks cannot be registered as a still-birth despite a live co-twin, there is information on a smaller number of twin babies than the recorded number of mothers would imply, and twin deliveries that did not result in any registerable births are not included at all.

## Results

We identified more than 3600 twin deliveries between 1965 and 1989 in the ORLS files, and there were 1972 such deliveries when restricting to registerable births only ( $\geq 28$  weeks gestation) in the period 1973 to 1989. After excluding 30 pregnancies following in vitro fertilization (IVF)/gamete intra fallopian tube transfer (GIFT), 19 following artificial insemination donor (AID) and 3 following artificial insemination husband (AIH), there were 199 following simple OI treatment only. Among the 199 treated twin pairs, the overwhelming majority of women were treated with one or two drugs only, usually clomiphene citrate, alone or in combination with hCG or hMG. Only

**Table 1**  
1973 to 1989 Sex Distribution of Treated and Untreated Twins

	Treated	Untreated	All
Mothers of twins	199	1773	1972
Twin babies	394	3528	3922
Both boys	49 (25.0%)	680 (38.9%)	729 (37.5%)
Both girls	61 (31.1%)	602 (34.5%)	663 (34.1%)
One of each	86 (43.9%)	465 (26.6%)	551 (28.4%)
Sex ratio (M:F)	0.87 (182:210)	1.09 (1838:1687)	1.06 (2020:1897)

Note: Registerable births only; treated exclude IVF, GIFT, AID, AIH.

eight women were recorded as receiving three or more drugs to induce ovulation. Overall over the period 1973 to 1989 about 10% of all twin births followed simple OI. The figure is 12% if the more complicated forms of AC are also included.

Table 1 shows the sex combinations of 1943 pairs, where it was known, comparing 196 conceived following treatment with simple OI only (186 in the cycle of conception and 10 rebounds) with all other

**Table 2**  
Characteristics of the Mothers

	Treated	Untreated	<i>p</i> value for difference
Mothers age (years)	29.0 ( <i>n</i> = 199)	27.8 ( <i>n</i> = 1771)	< .001
Mean height (cms)	163.4 ( <i>n</i> = 149)	162.7 ( <i>n</i> = 1276)	.20
Smoker:			
Yes	21 (13.5%)	296 (23%)	< .01
No	134 (86.5%) ( <i>n</i> = 155)	993 (77%) ( <i>n</i> = 1289)	
Parity:			
0	132 (66.4%)	608 (34.4%)	
1	57 (28.6%)	697 (39.4%)	< .01
2	7 (3.5%)	309 (17.5%)	
3	3 (1.5%)	103 (5.8%)	
$\geq 4$	0 ( <i>n</i> = 199)	53 (2.9%) ( <i>n</i> = 1770)	
Pre-eclampsia:			
Yes	31 (15.6%)	342 (19.3%)	.20
No	168 (84.4%) ( <i>n</i> = 199)	1431 (80.7%) ( <i>n</i> = 1773)	
Social class:			
1	33 (18.7%)	177 (12.3%)	
2	55 (31.1%)	387 (26.8%)	< .05
3	70 (39.5%)	621 (43.1%)	
4	17 (9.6%)	186 (12.9%)	
5	2 (1.1%) ( <i>n</i> = 177)	70 (4.9%) ( <i>n</i> = 1441)	
Baby delivery:			
Caesarean	113 babies (28.9%)	501 (14.4%)	
Forceps	127 babies (32.4%)	1120 (32.2%)	< .05
Other	151 babies (38.6%)	1853 (53.3%)	

**Table 3**  
Outcome Characteristics of the Babies

	Treated	Untreated	<i>p</i> value for difference
Total births (live and still)	394	3523	
Stillbirths	7	54	
Rate per 1000 total births	18	15	.71
Neonatal deaths	4	44	
Rate per 1000 live births	10	13	.69
Congenital malformations	48	372	
Rate per 1000 total births	122	106	.32
Mean birthweight (grams)			
Total births	2425 (386)*	2474 (3474)	.08
Live-born	2440 (381)	2488 (3427)	.07
Nonsmoking mothers	2429 (256)	2503 (2878)	.09
Live-born % < 2500	49.6% (189)	48.1% (1650)	.75
Mean gestation (weeks)	36.6 (394)	36.8 (3528)	.10
% < 37 weeks:	37.1% (146)	35.2% (1243)	.47
Mean Apgar score			
(1 minute)	8.1 (340)	7.9 (3100)	.19
(5 minutes)	9.7 (289)	9.7 (2485)	.97
Mean head circumference (cms)	32.7 (242)	32.9 (1963)	.11
Mean combined placental weight (grams)	983 (106)	987 (996)	.86

Note: \*numbers in brackets are the numbers of babies in each category for whom data were available. The exception is placental weight which relates to twin pairs.

naturally conceived twins. Not surprisingly, unlike-sex pairs are significantly more frequent amongst those treated, reflecting a greater proportion of dizygotic conceptions ( $\chi^2$ , 2df,  $p < 10^{-6}$ ). The sex ratio among the treated group was significantly lower than in the control twins. ( $\chi^2$ , 1df,  $p < .05$ ) with an odds ratio for treated versus untreated of 0.80 (95% CI 0.64–0.99).

Table 2 shows characteristics of the mothers in the two groups. Treated women were slightly older at the birth of their twins, slightly taller and of higher social class. They had delivered far fewer previous births and were much less likely to be smokers at the time of booking, though rates of pre-eclampsia were similar between the two groups. Cesarean section rates were much higher in the treated group but we have no record of the reasons for this.

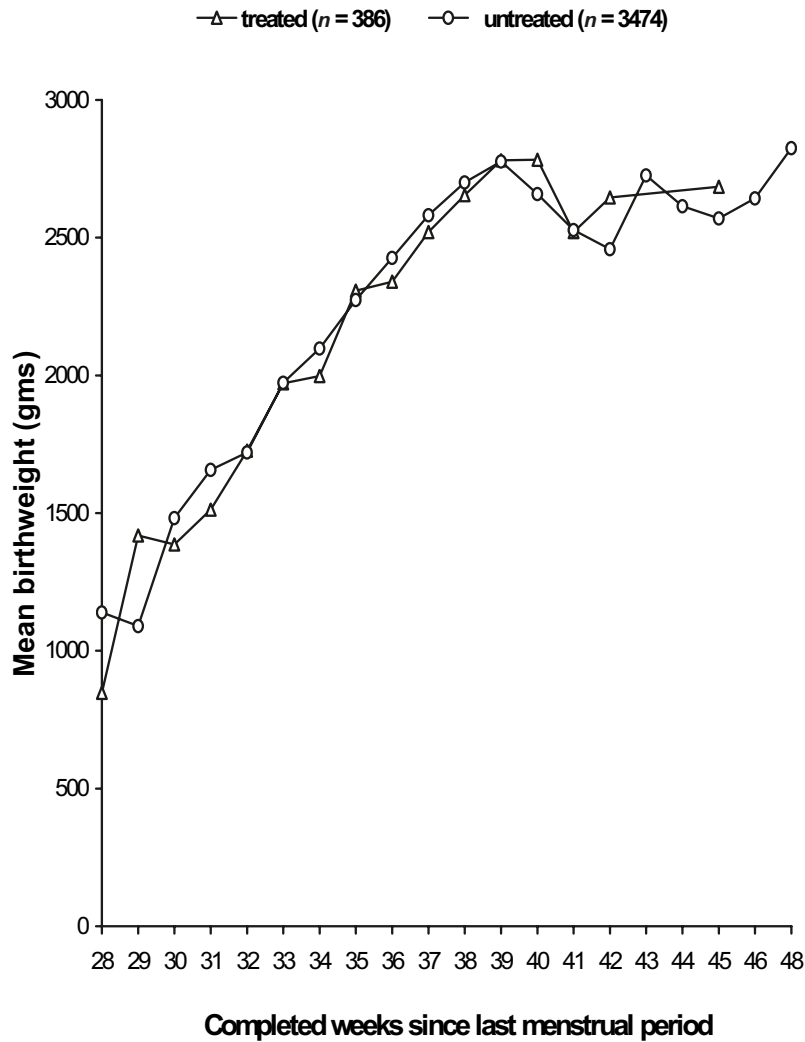
Table 3 shows a variety of outcomes for the babies compared between the treated and untreated groups. Stillbirths and neonatal deaths occurred with similar frequency in the two groups. Although quite large proportions of data were missing, Apgar scores at 1 and 5 minutes and head circumferences of the babies were also very similar, as was total placental weight. The proportions of babies with congenital malformations (presence of any condition coded to the congenital malformation chapters of International Classification of Diseases 8th revision and ICD-9; World Health Organization, 1967, 1977; 740–759) were also very

similar. Mean birthweight amongst both live and stillbirths was about 50 g lower in the treated group and the proportion of low birthweight babies was slightly higher. The mean birthweight for gestation was slightly lower in the treated group than the untreated at most gestational ages, until about 39 weeks (Figure 1). If attention is restricted to nonsmokers only in both groups, the mean birthweight difference was nearly 74 g. Mean gestation was slightly shorter and the proportion of premature deliveries slightly greater in the treated group.

## Discussion

The distribution of types of subfertility treatment experienced by this cohort of subfertile women delivering twin births between 1973 and 1989 is likely to be fairly typical of the experience for Britain as a whole (Dunn & MacFarlane, 1996; Levene et al., 1992). Locally, an assisted conception unit was not in place until 1986, and most twin births followed simple ovulation induction with clomiphene or hMG, with or without hCG to simulate a luteinizing hormone (LH) surge, and to support the established pregnancy. About one twin birth in 10 followed simple OI treatment over the period. That the treated group of women was on average older, less parous, and of higher social class is predictable in terms of who seeks help for subfertility. It is also noteworthy that reported smoking was considerably reduced among treated women whose wish to conceive and deliver a healthy pregnancy would be expected to be greater than average. We have noted elsewhere the particularly low rates of smoking recorded at antenatal booking among women treated with bromocriptine that may have a specific effect on smoking cessation through its dopaminergic agonist actions (Murphy et al., 2002). We think the information recorded is likely to be unbiased by whether conception was natural or treated, and that this represents a truly unselected population-based comparison of treated twins with natural twins. The main limitations of the data lie in our inability to perform multivariate adjustments satisfactorily when considerable amounts of data are missing.

The excess of female births is not entirely unexpected (James, 1986, 1987a, 1987b). James has argued that this inversion of the sex ratio is 'the single most important piece of information about the role of gonadotrophins (and oestrogen) in the determination of the sex ratio'. Hormonal levels induced by treatment or by timing of intercourse to conceive within the cycle are possible explanations (Wilcox et al., 1995). Sex ratio is lower in twins than singletons and for both has been declining since about 1970 in England and Wales as a whole (Shaw, 1989). There is less evidence of this secular decline in Oxfordshire and West Berkshire over the period which emphasizes the importance of having a local control group for comparison (data not shown; Murphy & Seagroatt, 1989). Nonetheless, with a 20% reduction in the odds of a



**Figure 1**

Mean birthweight, by gestational age at delivery, of twins (registrable births) to women with and without treatment for infertility in the cycle of conception\* (including 10 rebounds): 1973–1989 (ORLS linked file).

Note: \* Treated group excludes IVF, GIFT, AID and AIH.

boy being delivered as part of a twin pair in our dataset, this might be information of interest to prospective parents hoping to conceive following treatment for subfertility.

Of most concern is the observation of a 50 g difference in mean birthweight, and slightly earlier gestation of our treated twins, particularly since average smoking was considerably lower among treated women. We are not in a position to unravel why this might be so, but the finding that subfertile (treated) women deliver lighter babies on average has been repeatedly demonstrated (Berkowitz et al., 1990; Ghazi et al., 1991; Hull, 1995; McElrath & Wise, 1997; Scialli, 1986; Venn & Lumley, 1993; Venn & Lumley, 1994). However, few studies have examined birthweight in twins following subfertility treatment and it is less clear that such twin babies are lighter than their naturally conceived counterparts (Beral &

Doyle, 1990; Helmerhorst et al., 2004; Schieve et al., 2002). We do not know what prompted much higher rates of cesarean section but speculate it represents intervention to achieve a safer delivery in part. Nonetheless the outcome in the babies, whether considered as risk of stillbirth, neonatal death, Apgar score, mean placental weight or head circumference seems reassuring. Congenital malformation prevalence also is unremarkable. There has been a particular concern about the risk of neural tube defect (NTD) that might be associated with subfertility (treatment), but there now seems little strong evidence that this is a causal effect with respect to either subfertility or its treatment (Greenland & Ackerman, 1995; Whiteman et al., 2000). However, there remains concern that a variety of major congenital malformations might occur more frequently in babies conceived after more complicated AC interventions

than used for simple OI (Bergh et al., 1999; Hansen et al., 2002). Our cohort was exposed to few such interventions and we restricted our attention to outcomes following simple OI.

Overall the results of this population-based survey are reassuring, and of some biological and social interest. The influence of administration of exogenous hormone stimulating drugs on the sex ratio is an important finding. That women, successfully treated for subfertility do report less smoking but deliver somewhat lower birthweight twin babies, at slightly earlier gestational ages is important from the point of view of both prenatal counselling and postnatal care. As we have shown, it is independent of the much greater frequency with which multiple births occur to women successfully treated for subfertility. The morbidity and mortality associated with any twin birth is substantial and greater than for singletons. However it does not seem to be greater in our subfertile cohort, than in an entirely comparable cohort of natural twin births.

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