Human Reproduction Update 1999, Vol. 5, No. 2 pp. 179–187 © European Society of Human Reproduction and Embryology

The epidemiology of multiple births

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On the basis of MEDLINE and manual searches, we examined the main papers in the English literature regarding risk factors for spontaneous (i.e. not related to fertility drug use) multiple births. The constant frequency of monozygotic (MZ) pregnancies over time and in different geographical areas suggests that the determination of MZ twins is largely unchanged over time, and that a genetic mechanism may have a role. In contrast, temporal and geographical trends observed in dizygotic (DZ) pregnancies suggest that environmental factors play a role in determining this condition. At present, maternal age and hereditary components are the best-defined determinants for spontaneous multiple births.

Key words: epidemiology/multiple births/risk factors

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Introduction

Twin pregnancies are the result of a complex interaction of genetic and environmental determinants. Their frequency is now increasing, after a decreasing trend lasting 30–40 years. To explain these trends, maternal age, parity, race, nutrition, fecundity and, for the increasing trend particularly the use of fertility drugs, have all been associated with the risk of multiple pregnancy. The role of these factors, however, may differ for dizygotic (DZ) and monozygotic (MZ) pregnancies, and in different populations.

Available epidemiological evidence on risk factors for multiple birth is scanty and partially controversial. Using a MEDLINE and manual search, we examined the main papers in the English literature published since 1976 on the epidemiology of multiple births.

We have focused our interest on spontaneous multiple births, with specific attention having been paid to considering separately the evidences regarding DZ and MZ pregnancies. We have considered only the epidemiology of clinically detected twin pregnancy. The incidence at conception of multiple birth may in fact be much higher than at birth, the loss of only one twin now being considered more common than was originally thought (Landy and Keith, 1998).

In order to offer to the reader information on the papers considered in this review, the type of study and particularly the adjustment for the potential confounding effect of age and fertility treatment in the analysis of results are presented in Table I. Great caution should be taken in the interpretation of findings reported in the text, or in the tables of studies which have not considered in their analysis the role of age and fertility treatment use.

Time patterns

Both the number of twin live births and the rate of twin births per 1000 live births have risen fairly steadily since the 1970s (Tong and Short, 1998). This recent rise in twinning incidence reflects chiefly an increased use of fertility drugs [which greatly increases the risk of multiple ovulation and subsequent multiple pregnancies (Schenker *et al*., 1981; Webster and Elwood, 1985; Derom *et al*., 1993)] and change in the age distribution of women at childbirth, with more women giving birth at older ages (National Center for Health Statistics, 1992).

In the United States in the late 1980s there were 22 twin live births per 1000 live births, an increase of 22% over the value of 18 in the early 1970s (National Center for Health Statistics, 1992). A rising proportion of twin births since the 1970s has

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also been noted in England and Wales (Botting *et al*., 1987), and in Denmark the national incidence of multiple pregnancies increased 1.7-fold during 1980–1994 (Westergaard *et al*., 1997). It should be noted that the proportional increase in the number of triplets during the past 10 years is far greater than that of twins (Orlebeke *et al*., 1993; Luke, 1994).

This rise in the frequency of twin births follows a decline in rates from 1950 to the late 1960s and early 1970s (James, 1982). In Sweden, after the 1930s a marked decrease in the twinning rate took place. During the 1960s the twinning rate has been only about half what it was 200 years earlier (Fellman and Eriksson, 1993). In Italy, between 1955 and 1983 the frequency of multiple births declined by about 25% (from 12.6 per 1000 deliveries to 9.6 per 1000 deliveries), and the downward trend was constant until the early 1970s, when rates tended to level off and increase slightly (Parazzini *et al*., 1991).

These findings were largely attributable to trends in DZ rates, MZ births being approximately constant over the past few decades (James, 1980b, 1982; Botting *et al*., 1987; Parazzini *et al*., 1991; Westergaard *et al*., 1997).

It is difficult to estimate the actual trends in spontaneous multiple births in the absence of diffusion of fertility treatments. If assisted reproduction techniques may be assumed to be rarely exercised on women aged <20 years, then the natural twinning rate had increased in them since about 1980 (James, 1995). However, there are some suggestions that the twin rates should be still declining. For example, assuming that assisted reproduction is rare in illegitimate births, the trends of multiple births in Italy showed that multiple births in legitimate births declined until 1980, but increased thereafter, being 10.7 per 1000 births in 1989. Conversely, multiple birth rates in illegitimate births tended to be slightly higher than in legitimate births from 1960 to 1985, but in 1989 continued to decline and occurred at a rate of 9.1 per 1000 births (Parazzini *et al*., 1994). To monitor temporal trends in the frequency of twins may offer clues to understand the aetiological factors for multiple conception. Further, it represents a useful indicator of changing environmental factors which may impact on reproduction/fecundability, together with the monitoring of sperm counts (Parazzini *et al*., 1998), males to females ratio at birth (Davis *et al*., 1998) and spontaneous abortion rates (Parazzini *et al*., 1996b).

Table I. Characteristics of studies considered in this paper

Reference	Country/State	Population (total births/ twin births)	Type of study	Age taken into account	Patients treated for infertility excluded
Royal College of General Practitioners (1976)	Great Britain	16 539/149	Cohort	Yes	No
Rothman (1977)	Massachusetts	8616/97	Cohort	Yes	No
Allen (1978)	USA	54 000/570	Cohort	Yes	No
Bracken (1979)	Connecticut	3552[a]/58	CC	No	No
Harlap (1979)	Israel	16 583/238	Cohort	Yes	Yes
Vessey *et al.* (1979)	Great Britain	4565/60	Cohort	No	No
Hemon *et al.* (1981)	France	673[a]/673	CC	Yes	Yes
Nylander (1981)	Scotland	49 000/608	HS	Yes	No
Nylander (1981)	Nigeria	6010/290	HS	Yes	No
Rao *et al.* (1983)	India	11 103/96	Cohort	Yes	No
Webster and Elwood (1985)	England	102[a]/111	CC	No	Yes
Campbell *et al.* (1987)	Scotland	1534/384	VS	Yes	No
Murphy *et al.* (1989)	Scotland	3410/Not reported	Cohort	No	No
Murphy and Botting (1989)	Great Britain	Not reported	VS	Yes	No
Allen and Parisi (1990)	Italy	2 261 058/21 000	VS	Yes	No
Bonnelykke (1990)	Denmark	1606[a]/1,003	CC	Yes	Yes
Akerman and Fischbein (1991)	Sweden	14 972/145	Cohort	No	No
Parazzini *et al.* (1991)	Italy	2 467 965/23 236	VS	Yes	No
Murphy and Seagroatt (1992)	Great Britain	Not reported	VS	Yes	No
Parazzini *et al.* (1993)	Italy	308[a]/103	CC	Yes	Yes
Ashley *et al.* (1994)	Jamaica	10 408/99	Cohort	Yes	Yes
Luke (1994)	USA	Not reported	VS	Yes	No
Parazzini *et al.* (1994)	Italy	Not reported	VS	Yes	No
Kapidaki *et al.* (1995)	Greece	380[a]/380	CC	Yes	Yes
Lichtenstein *et al.* (1996)	Sweden	31 586/359	VS	Yes	No
Parazzini *et al.* (1996a)	Italy	395[a]/133	CC	Yes	Yes
Westergaard *et al.* (1997)	Denmark	119 345/1637	VS	Yes	No

[a]Controls.
CC = case control study; HS = hospital statistics; VS = analysis of vital statistics.

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Table II. Twinning rates according to maternal age

Reference	Country	Population (total births/ twin births)	Twins/1000 births		
			Dizygotic	Monozygotic	All
Royal College of General Practitioners (1976)	Great Britain	16 539/149			7.0[a]/7.8[b] (<25 y) 10.2/11.9 (25–34 y) 34.3/19.5 (≥35 y)
Harlap (1979)	Israel	16 583/238	3.6 (<20 y) 5.8 (20–24 y) 11.3 (25–29 y) 8.3 (30–34 y) 17.3 (35–39 y) –	5.4 (<20 y) 5.1 (20–24 y) 5.0 (25–29 y) 5.1 (30–34 y) 7.3 (35–39 y) 7.4 (≥40 y)	9.0 (<20 y) 10.9 (20–24 y) 16.3 (25–29 y) 13.4 (30–34 y) 24.6 (35–39 y) 7.4 (≥40 y)
Nylander (1981)	Scotland	49 000/608			10.1[c]/9.3[d] (15–24 y) 18.8/13.7 (25–34 y) 28.6/16.8 (≥35 y)
Nylander (1981)	Nigeria	6010/290	32.3 (≤29 y)	4.2 (≤29 y)	26 (<25 y) 46 (25–29 y)
			72.8 (≥30 y)	4.7 (≥30 y)	77 (30–34 y) 71 (35–39 y) –(≥40 y)
Rao *et al.* (1983)	India	11 103/96	1.9 (<25 y) 5.9 (25–29 y) 10.7 (30–34 y) 12.0 (≥35 y)	3.7 (<25 y) 4.6 (25–29 y) 1.1 (30–34 y) 1.0 (≥35 y)	5.6 (<25 y) 10.5 (25–29 y) 11.8 (30–34 y) 13.3 (≥35 y)
Parazzini *et al.* (1991) Italy		2 467 965/ 23 236	2.5 (<19 y) 4.2 (20–24 y) 5.4 (25–29 y) 7.3 (30–34 y) 8.1 (35–39 y) 6.0 (40–44 y) – (≥45 y)	3.6 (<19 y) 3.6 (20–24 y) 4.2 (25–29 y) 4.1 (30–34 y) 4.5 (35–39 y) 3.8 (40–44 y) 4.7 (≥45 y)	6.1 (<19 y) 7.8 (20–24 y) 9.6 (25–29 y) 11.4 (30–34 y) 12.6 (35–39 y) 9.8 (40–44 y) 4.7 (≥45 y)
Ashley *et al.* (1994)	Jamaica	10 408/99			5 (<20 y) 10 (20–24 y) 11 (25–29 y) 11 (30–34 y) 16 (≥35 y)
Luke (1994)	USA	Not reported			18[e]/13[f] (15–19 y) 31/23 (25–29 y) 35/32 (35–39 y) 10/26 (45–49 y)
Westergaard *et al.* (1997)	Denmark	119 345/1637			1.2[g]/1.1[h] (<30 y) 1.9/1.1 (≥30 y)

[a]Former pill users; [b]never pill users; [c]illegitimate pregnancies; [d]legitimate pregnancies; [e]black women; [f]white women; [g]parae 1; [h]parae ≥2.

Seasonal variation in reproductive cycles is a well-recognized phenomenon in both humans and animals (Bulmer, 1970; Cole *et al.*, 1976; Chan *et al.*, 1982). Seasonality statistics for multiple gestations are limited and somewhat conflicting. The birth rate for twins has been reported to be highest in May–June (Bonnelykke *et al.*, 1987), October (Elwood, 1978), November (James, 1976) or December (Kamimura, 1976; James, 1980a; Bonnelykke *et al.*, 1987), depending on the population studied. However, no significant seasonal variation in twinning rates has been found in the Aberdeen study

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(Nylander, 1981). Elster and Bleyl (1991) analysed birth data on 1050 sets of triplets delivered in the United States between 1985 and 1988. Seasonality in the number of triplet births was noted, and this differed significantly from that of the entire US population: a large peak in triplet births was seen in the spring, and a smaller peak in late summer.

Racial factors and geographical distribution

The incidence of twin pregnancy varies from country to country, the highest rates being reported in Nigeria, and the lowest in Japan (Golding, 1990). As a broad generalization, it can be stated that 'the DZ twinning rate is about eight per thousand in Caucasoids, about twice as large in Negroes and less than half as large in Mongoloids' (Bulmer, 1970).

Differences between racial and ethnic groups are due primarily to differences in DZ twinning rates. The rate of MZ twinning is fairly constant throughout the world (National Center for Health Statistics, 1992).

In the United States, in all the years for which data are available, the twinning rate for black births exceeds the rate for white births. Twin birth rates for American Indian, Chinese, Japanese, Filipino and other Asian and Pacific Islander births were 13–31% lower than for white births, and 26–42% lower than for black births, despite a generally higher proportion of births to older mothers and lower incidence of teenage births; the twinning rate was lower for almost all age groups (National Center for Health Statistics, 1992).

Several factors have been investigated to explain racial differences in DZ twinning incidence. These include genetic predisposition, which is inherited primarily through the mother, and undernourishment (Danforth, 1990). It has been suggested that malnutrition may play a role in the high frequency of twinning in East-Nigerian Blacks (Cox, 1964), and Nylander suggested that some substance in the diet of West-Nigerian tribe (e.g. yams, a staple) may cause high serum concentrations of follicle-stimulating hormone (Nylander, 1978).

In Sweden, the twinning rate during this century has been considerably lower in towns than in rural communities. In Finland, since the turn of the century the twinning rate in rural communities has been about 1–2‰ units higher than in towns. These differences were not explained by differences in mean maternal age and parity (Eriksson *et al*., 1976).

Risk factors

Maternal age

Bulmer indicated that the twinning rate increased more than 4-fold, or by 300%, between the ages 15 and 37 years, when parity was held constant (Bulmer, 1970).

Several other studies have reported increasing twinning rates with maternal age up to 35–39 years. The increase was due to increases in DZ twinning rates only, MZ rates being fairly constant (Table II).
Similar results also emerged from case-control studies (Kapidaki *et al*., 1995) and studies which reported mean age of mothers of twins and singletons (Hemon *et al*., 1981; Bonnelykke, 1990; Akerman and Fischbein, 1991).

This pattern has been attributed to the rise in the level of gonadotrophins with age, with maximum stimulation of follicles occurring at ages 35–39 years, and a subsequent decline in ovarian function at older ages. No obvious reason has been identified to explain the decreasing rates of DZ births found in women of 40 years or more. Selective mechanisms, such as the greater frequency of abortions in multiple pregnancies in older women, and genetic and environmental factors, can all be suspected, but these hypotheses are merely speculative.

Socioeconomic, constitutional factors and maternal lifestyle habits

No association emerged in a study conducted in Scotland between social class and twinning rates, but higher rates of twinning were observed in women of lower social class in Nigeria (Nylander, 1981). These differences might be explained in terms of different dietary habits of women in the lower social classes (Nylander, 1981). Murphy and Botting examined like and unlike sex twinning rates in Great Britain by social class over the period 1974–1985: twinning rates were higher in the manual group than in the non-manual one over the whole considered period (Murphy and Botting, 1989). No consistent association between education and risk of twin pregnancies emerged from case-control studies (Kapidaki *et al*., 1995; Parazzini *et al*., 1996a).

With regard to marital status, studies in the Nordic countries (Eriksson and Fellman, 1967a,b) and USA (Allen and Schachter, 1970, 1971; Myrianthopoulos, 1970) have shown differences in DZ twinning rates between married and unmarried mothers. Therefore, it has been suggested that unmarried mothers comprise a select group from the standpoint of fecundity. They may be more apt to give birth to twins because of a higher polyovulation rate.

In a study conducted in Scotland, the rates per 1000 births of twins were 12.3 and 14.9 respectively among legitimate and illegitimate births (Nylander, 1981), and Murphy and Seagroatt showed this relation for DZ twins in Great Britain (Murphy and Seagroatt, 1992). However, other studies conducted in Italy and Jamaica did not confirm these findings (Ashley *et al*., 1994; Parazzini *et al*., 1994).

Rates of multiple births according to maternal height in selected studies are set out in Table III. There is a suggestive direct, albeit somewhat inconsistent, association between greater maternal height and risk of DZ twins. However, in a case-control study conducted in Greece, the odds ratios (OR) of DZ and MZ twins were respectively 1.7 and 1.6 for women with a height of 165–169 cm, but 1.2 and 1.1 for women with a height ≥170 cm, in comparison with those with a height of 160–164 cm (Kapidaki *et al*., 1995).

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Table III. Twinning rates according to maternal height and weight

Reference	Country	Population (total births/twin births)	Twins/1000 births		
			Dizygotic	Monozygotic	All
Maternal height					
Harlap (1979)	Israel	16 583/238			11.3 (<160 cm) 13.1 (160–164 cm) 11.4 (≥165 cm)
Nylander (1981)	Scotland	49 000/608	6.5 (short) 6.9 (medium) 7.3 (tall)	1.9 (short) 1.8 (medium) 2.2 (tall)	12.0 (short) 12.0 (medium) 12.9 (tall)
Nylander (1981)	Nigeria	18 400/1052	44.7 (short) 50.7 (medium) 57.6 (tall)	5.1 (short) 4.3 (medium) 4.3 (tall)	51.4 (short) 57.7 (medium) 67.4 (tall)
Maternal weight					
Harlap (1979)	Israel	16 583/238			10.7 (<20[a]) 11.1 (20–49) 12.6 (50–79) 12.8 (≥80)

[a]Pre-pregnant weight centile (within height).

Higher rates of twins in overweight women were reported (Harlap, 1979; Hemon *et al*., 1981) (Table III). In a case-control study conducted in Italy, the OR of DZ and MZ twins were respectively 1.3 and 1.5 for women with a body mass index (BMI, kg/m^2) ≥19, in comparison with those with a BMI <19; however, the finding was not statistically significant (Parazzini *et al*., 1996a).

Heavy smokers tended to be at increased risk of multiple pregnancy in two case-control studies conducted in Greece and Italy (Kapidaki *et al*., 1995; Parazzini *et al*., 1996a), both for DZ and MZ twins, but this finding was not statistically significant. Likewise, the risk of multiple pregnancy tended to be higher in women drinking ≥15 alcoholic drinks per week in an Italian population (Parazzini *et al*., 1996a). In a Greek study, each cup of coffee per day was associated with a 1.2-fold increment in the relative risk. Restriction of the analysis to DZ twins of different gender increased the relative risk to 1.3 for each cup of coffee consumed daily (Kapidaki *et al*., 1995). However, in an Italian study (Parazzini *et al*., 1996a), the risk was significant only for MZ pregnancies, with an increase of about 3-fold in women drinking ≥3 cups per day.

History of multiple pregnancies in first-degree relatives and parental consanguinity

In an Italian case-control study, the OR of DZ and MZ pregnancies were 2.4 and 2.7 in women reporting a history of multiple pregnancies in first-degree relatives compared with those who did not (Parazzini *et al*., 1996a). Hemon *et al*. showed this relationship only for DZ twins (Hemon *et al*., 1981). In an Indian population, the total and MZ twinning rates declined with closeness of consanguinity, whereas the DZ twinning rates showed a non-significant positive trend (Rao *et al*., 1983). Lichtenstein *et al*. showed an increased risk of giving birth to twins in women who were themselves twins (Lichtenstein *et al*.,1996). In particular, DZ mothers had an increased risk of giving birth to DZ twins, while MZ mothers had an increased risk of having MZ twins. Parisi *et al*. analysed the incidence of twinning in the families of twins, and indicated that a propensity to MZ twinning, as well as to DZ twinning, may be inherited through the maternal line (Parisi et al., 1983). They also found a paternal role in DZ, but not in MZ twinning (Parisi et al., 1983).

The possible polygenic nature of twinning was proposed by Stern (1973), though another suggestion was that twinning in humans is recessive and sex-linked (Bulmer, 1970). If it is assumed that twinning is due to the non-dominance and/or homozygosity of genes, then one would expect to find the twinning rate to be related to the rate of consanguineous marriages in a population; however, no data are available on this aspect.

In summary, there is consistent evidence that a history of multiple pregnancies in first-degree relatives is associated with an increased risk of twin pregnancies, though this association seems to be more evident for DZ twins.

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Table IV. Twinning rates according to parity

Reference	Country	Population (total births/twin births)	Twins/1000 births Dizygotic	Monozygotic	All
Royal College of General Practitioners (1976)	Great Britain	16 539/149			9.7[a]/10.4[b] (nulliparae)
					10.2/11.1 (parae)
Vessey *et al.* (1979)	Great Britain	4565/60			4.4[c] (nulliparae)
					14.6 (parae)
Nylander (1981)	Scotland	49 000/608			11.0[d]/9.7[e] (0)
					17.7/12.9 (1–2)
					32.6/16.2 (≥3)
					14.9/12.3 (all parities)
Nylander (1981)	Nigeria	6010/290	36.6 (0,1)	4.3 (0,1)	19 (0)
					42 (1)
			69.2 (≥2)	4.7 (≥2)	60 (2)
					73 (3)
					75(≥4)
Rao *et al.* (1983)	India	11 103/96	0.9 (0)	2.4 (0)	3.3 (0)
			3.8 (1,2)	6.2 (1,2)	10.1 (1,2)
			6.5 (3,4)	1.4 (3,4)	7.9 (3,4)
			11.9 (≥5)	0.5 (≥5)	12.4 (≥5)
Allen and Parisi (1990)	Italy	2 261 058/21 000	5.7 (1)	4.2 (1)	
			5.2 (2)	4.1 (2)	
			5.9 (3)	4.6 (3)	
			6.7 (4)	4.4 (4)	
			8.4 (≥5)	5.2 (≥5)	
Ashley *et al.* (1994)	Jamaica	10 408/99			6 (0)
					9 (1)
					11 (2)
					9 (3)
					19 (≥4)

[a]Former pill users; [b]never pill users; [c]planned pregnancies in oral contraceptive users; [d]illegitimate pregnancies; [e]legitimate pregnancies.

Reproductive history

Twinning rates per 1000 births, according to parity, in selected studies are shown in Table IV.

A positive relationship emerged between parity and frequency of DZ twinning (Nylander, 1981; Rao *et al.*, 1983; Allen and Parisi, 1990). Similar results also emerged in studies which have analysed the mean parity of women who delivered twin or singleton births. The mean number of births was 4.1 and 3.5 respectively in women who delivered DZ twins and in those who delivered singletons in a study conducted in the USA (Allen, 1978), 2.2 and 1.7 in a study conducted in France (Hemon *et al.*, 1981), and 0.9 and 0.8 in a Danish study (Bonnelykke, 1990). Conversely, Rao *et al.* and Bonnelykke suggested a negative association between MZ pregnancies and multiparity (Rao *et al.*, 1983; Bonnelykke, 1990) (data not shown in Table IV).

Findings from case-control studies related to outcome of previous pregnancies and frequency of multiple births are detailed in Table V. No clear association with previous miscarriages or induced abortions was evident.

Table V. Odds ratios of twin births according to history of spontaneous or induced abortion

Reference	Country	Population (twin births/ controls)	Odds ratios[a] Dizygotic	Monozygotic
Miscarriages				
Parazzini *et al.* (1993)	Italy	103/308	1.4 (≥1)	0.8 (≥1)
Kapidaki *et al.* (1995)	Greece	380/380	1.1 (≥1)	1.5 (≥1)
Induced abortions				
Parazzini *et al.* (1993)	Italy	103/308	0.9 (≥1)	0.7 (≥1)
Kapidaki *et al.* (1995)	Greece	380/380	1.4 (1)	1.4 (1)
			1.5 (≥2)	0.5 (≥2)

[a]Reference category: no spontaneous or induced abortions.

Table VI. Twinning rates according to oral contraceptive use

Reference	Country	Population (total births/twin births)	Twins/1000 births All	
Royal College of General Practitioners (1976)	Great Britain	16 539/149	Nulliparae	10.4 (No)
				9.7 (Former use)
			Parae	11.1 (No)
				10.2 (Former use)
Rothman (1977)	Massachusetts	8616/97		11 (0[a])
				9 (1–3)
				5 (4–6)
				13 (7–12)
				12 (13–24)
				14 (≥25)
Harlap (1979)	Israel	16 583/238		12.7 (No)
				11.8 (0–2[b])
				12.2 (≥3)
Vessey *et al.* (1979)	Great Britain	4565/60	Nulliparae	16.3 (No)
				6.9 (Former use)
			Parae	18.0 (No)
				13.6 (Former use)
Campbell *et al.* (1987)	Scotland	1534/384	No relationship[c]	
Murphy *et al.* (1989)	Scotland	3410/nr	No relationship with dizygotic births[d]	

[a]Total duration of prior oral contraceptive use (months). [b]Months between stopping oral contraceptive use and conception; [c]No versus former use; [d]Women exposed to oral contraception 2 months or less before conception versus 3 or more months before conception (included never used).
nr = not reported

Table VII. Odds ratios of twin births according to oral contraceptive use

Reference	Country	Population (twin births/controls)	Odds ratios[a] Dizygotic	Monozygotic	All
Bracken (1979)	Connecticut	58/3552	2.9*[b] (≤2 months)	1.7 (≤2 months)	2.0* (≤2 months)
					1.1[c] (3–12 months)
Hemon *et al.* (1981)	France	673/673	0.5* (Yes)		0.7* (Yes)
Webster and Elwood (1985)	England	111/102	2.3 (Yes)		1.1 (Yes)
Parazzini *et al.* (1993)	Italy	103/308	0.9 (Yes)	0.8 (Yes)	0.8 (Yes)
Kapidaki *et al.* (1995)	Greece	380/380	0.9 (Yes)	0.7 (Yes)	

[a]Reference category: no or contraceptive users; [b]Reference category: oral contraceptive use ≥3 months before conception; [c]Reference category: oral contraceptive use >12 months before conception.
*$P \leq 0.05$.

These associations have not always been confirmed. No association emerged between parity and risk of twin pregnancy in a case-control study in Greece (Kapidaki *et al.*, 1995). Otherwise, in a case-control study conducted in Italy (Parazzini *et al.*, 1996a), in comparison with nulliparae, the OR of DZ and MZ twins was 0.9 and 0.8 for women reporting one previous birth and 0.5 and 0.8 for those reporting two or more births.

It has been suggested that mothers of DZ twins have increased fecundity, as reflected in the apparent ease of conception, but the relationship between parity and multiple pregnancy can be interpreted in terms of non-adjustment or incomplete adjustment for the confounding effect of age and socioeconomic factors, particularly in developing countries.

A later age at first pregnancy has been reported to increase the risk of twin pregnancy in a case-control study conducted in Greece (Kapidaki *et al.*, 1995). However, this finding can be explained in terms of confounding factors, such as not complete adjustment for age or different socioeconomic conditions in women with early or late age at first pregnancy.

Oral contraceptive use

Several studies have been published on the relationship between oral contraception (OC) and risk of multiple pregnancy. Tables VI and VII show the results respectively from studies which have presented twinning rates according to OC use and case-control studies on the relationship between OC use and risk of multiple births.

Some studies suggest a lower risk—about half—of multiple births in recent OC users but others note an increase—from 3- to 6-fold—or no association.

It is possible that an increase occurs only during a short period after discontinuation of OC and concerns both MZ twins—on account of delayed conception and implantation—and DZ twins through a mechanism involving the rebound increase of pituitary gonadotrophins.

On the other hand, Hemon *et al*. suggested that the higher incidence of chromosomal abnormalities among spontaneous abortions of OC users or their lower fertility might explain the lower DZ twinning rate after OC discontinuation (Hemon *et al*., 1981).

Conclusions

Epidemiological observations suggest that the causes of MZ and DZ twins are multifactorial, and include genetic and environmental elements. The constant frequency of MZ pregnancies over time and in different areas, and the lack of association between maternal age and frequency of MZ, suggests that MZ twins are largely determined by genetic mechanisms; the trends in DZ pregnancies suggest that environmental factors play a role here. The existence of a family component and of social differences in DZ twinning rate may also suggest a potential generation predisposition, though it is difficult to disentangle the role of environmental and generational factors in explaining the association between race and family history and risk of twins. At present, maternal age and the hereditary components are the best-defined determinants of risk of multiple births. Other determinants of twinnings are race, parity/fecundity and nutrition. All these factors should be always considered in studies on the epidemiology of twinnings.

There is a greater risk of complications of pregnancy and delivery in multiple births, and a consequently higher rate of neonatal problems (MacGillivray, 1986). Thus, it is important to clarify the causes of this condition, through aetiological studies on the risk factors for spontaneous multiple births, which take into account the confounding effect of maternal age and treatments for infertility, to identify variations attributable to other causes, and to research into the prevention of preterm delivery and low birth weight.

Acknowledgements

The authors wish to thank Ivana Garimoldi and Judy Baggott for editorial assistance, Carmen Mezzanotte, and Marina Parazzini for her help in the preparation of the manuscript.

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Received on October 12, 1998; accepted on February 12, 1999