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Health Characteristics of Mothers of Twins

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Abstract. Mothers of twins, as compared with mothers of singletons, are taller, and for a given height are heavier; they have slightly earlier menarche and menopause. Our recent studies have shown that mothers of DZ twins are at greater risk of cancer of the pancreas (but not for cancers of other sites), as well as of death due to diabetes, other endocrine diseases, and allergies. These findings are consistent with the clinical and epidemiological literature. We have also found that singleton siblings of twins are slightly heavier at birth than children born into sibships consisting of singletons only. The need for further research on the characteristics and long-term health of mothers of twins is indicated.

Key words: Twin bearers, Menarche, Menopause, Cancer, Diabetes, Endocrine diseases, Birthweight

In white populations, twins occur in about 1% of all deliveries, but the frequency varies from one population to another and from year to year. The variation in the twinning rate occurs in dizygotic (DZ) twinning; monozygotic (MZ) twinning is virtually constant. DZ twinning varies by maternal age (reaching a peak between 35 and 39 years) and by race. Among the Yoruba of Nigeria, the rate is as high as 57 per 1,000 maternities, while in Japan the rate is low — around 2 per 1,000 maternities [1].

Mothers of DZ twins have been found to have a higher level of gonadotropic hormones, particularly FSH, than mothers of singletons [8]. The question arises as to whether such a raised hormone level would be reflected in different reproductive and health characteristics. It has been shown, among other observations, that mothers of DZ twins are taller, and for a given height heavier than mothers of singletons [3]. They also have a slightly earlier menarche and a slightly earlier menopause [12,13].

This paper reports findings on the cancer experience of mothers of unlike sexed (necessarily DZ) twins and mortality from causes other than cancer.

We carried out a study to determine whether women who bore DZ twins or other

polyzygous multiple births have a cancer incidence or cancer mortality different from that of a matched group of mothers of singletons only. The study was conducted using study subjects identified from the records of the Connecticut Twin Registry, Tumor Registry, and vital records with the collaboration of Dr. M.S. Honeyman and J.T. Flannery [14].

A total of 3982 women born between 1885 and 1935 who had borne unlike sexed twins or other polyzygous multiple births in Connecticut during 1925-1959 were identified. A comparison group of 3982 women matched pair-wise on year of childbirth, age, number of previous children, race, and national origin was obtained using vital records. The two cohorts of women were searched in the Connecticut Tumor Registry for the incidence and mortality of cancers of all sites. Causes of death excluding cancers were also investigated using death certificate information [15]. Deaths recorded in the state of Connecticut for the period 1959-1977 have been collated in one computer tape, referred to as the Death Tape. The period covered on the Death Tape includes death coding according to two revisions of the Manual of International Classification of Disease (ICD Seventh and ICD Eighth Revisions). From 1959 through 1966 the 7th revision was used, from 1967 through 1977, the 8th.

One of the hypotheses to be tested with respect to cancer was that there might be an excess incidence of breast cancer and cancers of the reproductive system among mothers of DZ twins. This hypothesis was suggested by the fact that the Japanese women have both a low rate of DZ twinning and a low rate of breast cancer [10].

This hypothesis was not supported in our data. There was, however, a significant excess incidence of cancer of the pancreas among mothers of DZ twins; RR (relative risk) = 3.2, exact 2-tail $P = 0.026$, exact 95% confidence limits 1.12 to 11.16. Cancers of the colon and rectum, liver and gallbladder, were also elevated; stomach cancer was lower in mothers of DZ twins.

The relative risk for cancers of all sites combined was 1.1, showing no significant difference in the two cohorts of women. With respect to non-cancer deaths, a statistically significant risk in mothers of multiple births in ICD Group III (Allergic, Endocrine System, Metabolic and Nutritional Diseases) was observed. The RR is 2.4, exact 2-tail $P = 0.024$, exact 95% CL 1.1 to 5.6. Of the 24 deaths among mothers of DZ twins, 17 were due to diabetes, one to bronzed diabetes, two to diseases of the adrenal gland, one of the thyroid gland, and three of asthma. Of the 10 deaths in ICD Group III among mothers of singletons only 9 were due to diabetes, and one to asthma. Deaths in ICD Group VIII, respiratory diseases were also somewhat elevated in mothers of twins. RR = 2.1, exact 2-tail $P = 0.088$, exact 95% CL 0.91 to 5.3. Of the 19 deaths in mothers of twins, 8 were due to bronchitis and emphysema; no deaths from these causes were reported in the 9 deaths among mothers of singletons. Interestingly, in ICD Group IX, diseases of the digestive system, the RR was 0.6. However, much of the lower risk for mothers of twins was because of the deaths due to cirrhosis. Of the 11 deaths in the twin mothers group, 2 were due to cirrhosis, while 8 of 18 in the singleton group were due to cirrhosis. For all causes combined, the RR was 1.16, again showing no difference in mothers of DZ twins and mothers of singletons only.

What conclusions might be drawn from these findings? What leads for further research do they suggest?

1) We conclude that the hormonal factors that may be associated with DZ twinning are not significantly involved in the etiology of cancer of the breast nor cancers of the

reproductive system. Possible explanations for this are: a) The gonadotropins may be overshadowed by other factors and/or occur in amounts too small to produce cancers of the breast and reproductive system; b) the gonadotropins may not reach the target cells of the breast or reproductive organs; or c) the effects of the hormones are nullified in these sites.

2) We conclude that the findings indicating an elevated risk of cancers of the pancreas, gallbladder and liver among mothers of DZ twins are not likely to be due to chance and are consistent with observations of other investigators. Epidemiologists Wynder et al. [11] and McMichael and Potter [7] have suggested hormonal influences on cancers of the digestive system. In particular, we point out that Wynder observed that the age-adjusted mortality rate from cancer of the pancreas is lowest among the Japanese. (Soma et al [10] reported lower FSH among the Japanese). Further evidence in support of the plausibility of our findings comes from autopsy data. Soloway and Sommers [9] found excessive gonadotropic activity among women but not among men with pancreatic duct cell carcinoma. The possible role of gonadotropic hormones in the etiology of cancer of the pancreas comes from an early report of high FSH in the urine of diabetics [5] and the association of diabetes and pancreatic cancer among women only [11].

3) The elevated risk of death due to diabetes and other endocrine diseases among mothers of DZ twins is not surprising in view of the known association between cancer of the pancreas and diabetes. More directly, however, Gedda et al [6] found that diabetes is more common in parents and grandparents of DZ twins and more frequent in the maternal line. Burch [2] has hypothesized that there might be an association between Klinefelter's syndrome, DZ twinning, and diabetes mellitus. An association between maternal thyroid disease and twinning has also been reported [4].

In sum, we believe that the elevated risk of cancer of the pancreas and the elevated risk of death due to diabetes and other endocrine diseases are not likely to be due to chance, are biologically plausible, and are consistent with the epidemiologic and clinical literature. We conclude that these findings may reflect some underlying pathophysiology that is associated with higher levels of gonadotropic hormones.

Mothers of DZ twins who have markers such as a higher level of gonadotropic hormones can contribute to epidemiologic studies concerned with elucidating the etiology of cancer, diabetes and other diseases.

From the large data set collected several years ago through the cooperation and participation of mothers of Twins Clubs, we have been examining birthweights of non-twin children of mothers who have also borne twins. This line of investigation is relevant because of our finding with respect to diabetes, and the well known fact that children of diabetic mothers are heavier at birth than offspring of nondiabetic women.

Table 1 presents data on birthweights of singleton children of women who have borne twins or other multiple births, and compares these birthweights with those of children born into sibships containing singleton children only. (This analysis is restricted to babies whose birthweights were reported as ranging between 1358 and 5660 g.)

Table 1 shows that for birth orders 1-6, the birthweights of singleton children born into sibships containing multiple births are consistently greater than for those in singleton sibships. This pattern holds for all birth orders and for both males and females. By covariance analysis, for birth order 1, we controlled for weight, height, and age of mother (at time of reporting), and at first birth (Table 2). Singletons, both male and female, born into families containing one or more sets of twins, are heavier at birth than children born

TABLE 1 - Birthweights (g) of Singletons by Kind of Sibship

Birth order	Sex	Sibships containing						Difference in means (g)
		Twins and other multiple births			Singletons only			
		\bar{x}	SE	(N)	\bar{x}	SE	(N)	
1	M	3402	12.4	(1796)	3348	11.1	(2127)	54
	F	3265	12.3	(1603)	3227	11.1	(1928)	38
2	M	3491	17.2	(963)	3421	11.3	(2025)	70
	F	3338	15.9	(913)	3299	11.3	(1920)	39
3	M	3516	19.2	(743)	3464	13.2	(1612)	52
	F	3361	19.0	(749)	3311	13.0	(1509)	50
4	M	3499	22.9	(532)	3474	18.0	(957)	25
	F	3407	22.5	(487)	3339	16.8	(892)	68
5	M	3526	31.8	(295)	3490	24.8	(522)	36
	F	3408	32.5	(285)	3340	25.1	(446)	68
6	M	3584	45.9	(160)	3530	36.4	(238)	54
	F	3419	40.3	(156)	3320	35.6	(254)	99

TABLE 2 - Birthweights (g) of Singletons Born into Sibships Containing Twins Compared with Sibships of Singletons Only: Analysis of Covariance *

Birth Order 1	Sibships containing				Difference in means	P-value
	Twins		Singletons only			
	\bar{x}	SE	\bar{x}	SE		
Male	3392 ± 12		3353 ± 11		39	0.009
Female	3261 ± 12		3232 ± 11		29	0.038

* Adjusting for: Mother's weight, Height, Age at time of first birth, and Age at time of reporting.

into sibships consisting of singletons only, though the difference is greater for males.

The implications of the findings are not obvious, but as suggested by Corney et al [3] in reporting on mother's height and birthweight of twin offspring, they support the possible association between pituitary gonadotropins and DZ twinning, and they may reflect the possible association between diabetes and DZ twinning.

We hope to continue our investigations on the epidemiology of twin-proneness and long-term health outcomes of mothers of twins.

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