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The End of Reproductive Life in Mothers of Twins: Epidemiologic Analysis of a Large Data Base

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Abstract. A case-control study was conducted on the termination of menstrual life on mothers of twins. It involves a much larger data base and finer analyses, and makes use of the same methodology of a previous study. The time interval between the twin and the last confinement proved to be shorter in twin-bearing mothers than in a matched set of controls with singletons only after blocking of the effect of birth order, and despite the similarity of maternal age at delivery and confinements numbers. Mothers of like-sex twins only appeared to terminate reproductive life earlier than controls. The separate study of maternal age at twin confinement shows that the earlier the twin birth the shorter the menstrual life thereafter. Both like-sex twin births and early maternal age at delivery of a twin pair have the same shortening effect on subsequent menstrual life without clear evidence of additivity of effects as if both occurrences were alternatives with similar biological effects. Comparison of the results of the current study with those of our earlier analysis shows consistency on above results. However, the current study could not reproduce previous results on the role of unlike-sex twins or late maternal age at delivery on time to last confinement; yet, they cannot be discarded. It is suggested that increased power of interaction analyses and tighter matching of controls with respect to sex might improve the conclusions of subsequent studies.

Key words: Twinning, Menopause, Fertility, Historical demography

INTRODUCTION

In a study on the termination of menstrual life in mothers of twins at Isle-aux-Coudres, Quebec [8], we found that mothers of unlike-sex (ULS) twins had a longer

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time interval (TI) to last confinement than controls; on the contrary, the TI proved to be shorter in mothers of like-sex (LS) twins than in appropriate controls. We had then speculated that mothers of twins experience two opposite types of ovarian dysfunctions that postpone menopause in the former and accelerate aging of the ovary in the latter.

We here want to restudy this double problem on a much larger data base, while attempting to refine our analysis of the previously reported phenomenons.

MATERIALS AND METHODS

The data are population-based. Again, they belong to the Quebec population but span over a period starting with colonization (1608) and ending in 1730. The population civil registers, kept by the Catholic Church, are the first-hand material of the study. Exactly 52,183 confinements were reported during the above time period. This represents all of the confinements which occurred in the whole Quebec population during the time period.

The data base is part of an impressive endeavor that the Groupe de Recherches en Démographie Historique (PRDH) of the University of Montreal has started in 1968, the aim of which is a complete register of the Quebec population from colonization to 1850. At last, linkage of birth, marriage and death certificates will have borne on more than 2 million records. The civil acts of Quebec have a reputation for general reliability but are nonetheless subject to well known defects. To date, data have been collected, validated by multiple devices, analyzed mostly from a demographic standpoint, and published [5].

For the time period studied, the PRDH register contains 725 twin pairs belonging to 651 families. The latter contain 5,834 offspring 1,460 of which are multiple births, the rest being singletons. All variables directly known from the civil acts or estimated therefrom may be used: this is the case of birth and marriage dates, parental ages at various occasions, birth orders of offspring, birth places of parents, dates of specific family events, and all types of information useful to either control for confounding or investigate interactions in epidemiological studies.

In a study of the TI until last confinement, the whole of this data base cannot be used as not all mothers will have attained menopause status by 1730, date at which family reconstruction ends. Truncation is unavoidable, and the current study deals with mothers born prior to 1680 so that they could have reached the age of 50 years at the very least. This reduces the data base available from 725 to 341 twin pairs. Even though the corresponding mothers have theoretically attained the age of 50 years, ascertainment of age is not possible for each and every of them. For example, only 23% of mothers of twins are known to still be alive past age 49 years. This information is obtained from citations or signatures at the moment of various demographic events, most of which are birth events reported by civil acts; this means that for 77%, survival until age 50 years may not be ensured. Since our objective is to study the TI between the birth of twins and the last confinement, the question was raised whether to include all the same or to put away those families without confirmed maternal survival. We have decided to include them because not doing so would have introduced a bias. Since ascertainment of survival at age 50 years is done mainly through recognition of late confinements, ruling out mothers on the basis of this criterion would have selected the sample for unusually long TIs until last confinement. As a matter of fact, what is needed is a criterion independent of confinement events only exceptionnally available in the present data base. In the following, accordingly, case mothers (with one twin pair) will be represented by 341 marriages celebrated in Canada at a known date.

As the study relies upon an analytical case/control methodology and on a pair-matched design [11], a similar number of control mothers were ascertained within the same target population. Controls were matched to cases for exact maternal birth cohort, exact birth order of the index confinement, and country of birth (Canada or France) of mothers. On the basis of the matching criteria 340 mothers with singletons were found. These three variables are here considered as confounders and thus controlled for. Variables investigated for possible interaction with TI were maternal age at confinement of the twins and the sex of the twin pairs. Differences between the total number of twin confinements and numbers appearing in tables could not be avoided; they are ascribed to a deficit of information on the stratification variable, such as maternal age and sex of twin pairs. However, they do not affect the sample size substantially.

The TI between the index and last confinement is the logical independent variable. It is the difference between maternal age at both confinements. In order to allow for the large sample size, a distinctive feature of the current study, most analyses bore on ungrouped data and also on the polytomization of the independent variable. However, to conform most closey with our previous study, estimates of the risk of a twin confinement in mothers with a given TI were also computed on dichotomized data treated within 2 by 2 contingency tables. Eventually, categories for TI were: less than 10, and equal or greater than 10 years. Actually, all TIs were computed in completed months. As to maternal age at index confinement, we have been keeping with previous usage [6-8] and considered groupings of less than, and equal or greater than, 30 years old.

Though the study involves a matched design, experience with our previous study [8] shows that an analysis not allowing for matching is not necessarily disruptive of matching for the confounding variables studied and that identical results are obtained from matched and unmatched analyses. We thus judged that the cross-product odds ratio is an appropriate surrogate that we actually used across all computations of risks, and for interaction estimation. More specifically, results on TI are presented according to maternal age groups at confinement and according to sex categories (LS and ULS) of twins.

Statistical tests are standard [10]. Statistical estimates of risk were provided by the computation of the odds ratio [11]. Haldane's testing of the odds ratio and confidence limits (corrected for small sample size) were also relied upon [4]. Woolf's method was used to test heterogeneity between the results of the current and the previous study [3]. Given the conclusions of our previous study, we would have been legitimized to rely on single-tailed tests to assess departure from the null hypothesis. However, bilateral confidence intervals were still used throughout. Thus, save for chi-square, all testings must be considered as very conservative.

RESULTS

Descriptive Features

The data base has several features worth specifying before undertaking its analysis. First, in relation to the potential bias mentioned above as to the relevance of studying only mothers whose survival at age 50 years had been ascertained, it should be said that both control and case mothers agree in the proportion for whom survival cannot be ascertained: this is estimated as 77% in cases and 75% in controls. Thus, suspected incompleteness of reproductive life after index confinement is not different between cases and controls.

The distribution of LS, ULS, and unspecified-sex twins in the whole sample is 59%, 35% and 6%, respectively. Discarding unspecified-sex pairs, Weinberg's formula [1] yields percent estimates of MZ and DZ twins of 25% and 75%, respectively. This is no different than the proportions actually found in the Isle-aux-Coudres (IAC) data base [8].

Table 1 - Maternal age at birth of like- and unlike-sex twins and singletons

Maternal age	All twins	Like-sex twins	Unlike-sex twins	Unspecified sex twins	Singletons
<20	10	10			24
20-24	44	25	13	6	50
25-29	75	35	39	1	82
30-34	86	55	25	6	68
35-39	88	49	31	8	74
40- +	38	26	11	1	42
Total	341	200	119	22	340
Mean	31.6	31.7	31.4		30.5
S.D.	6.45	6.80	5.86		7.25

The distribution of maternal age at index confinement is shown in Table 1. Though data are categorized within six classes, a Kolmogorov-Smirnov test on the distribution of ungrouped ages of cases and controls yielded an observed D = 0.09, not significant at the 5% level. Chi-square for grouped data is not significant either, thus underscoring identical mean maternal ages at index confinement. Separation of LS and ULS twin pairs was undertaken, and the distributions of maternal age at confinement (Table 1) were also compared with that of controls. There is no difference in maternal age at confinement of LS and ULS twins and controls on a

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Kolmogorov-Smirnov test carried out on ungrouped data even though no DZ twins were born before age 20 years of mothers. However, grouping of data within the six classes appearing in Table 1 shows a significant departure of maternal age at confinement of ULS twins from that of controls; chi-square was 13.3 with 5 d.f. ($P = 0.02$). The youngest age group contributed most to significance and, when discarded, the chi-square value stood within chance variation ($P = 0.37$).

Table 2 - Distribution of the number of confinements in mothers of twins and mothers of singletons

Number of confinements	All twins	Like-sex twins	Unlike-sex twins	Unspecified sex twins	Singletons
<5	39	22	13	4	29
5-9	146	83	54	9	124
10-14	140	88	44	8	164
>15	16	7	8	1	23
Total	341	200	119	22	340
Mean	9.0	9.0	9.1		9.7
S.D.	3.42	3.41	3.41		3.42

Table 2 presents the distribution of the number of confinements in case and control mothers as well as in mothers bearing LS and ULS twins. As the distributions presented with clear negative asymmetry on normality testing by Fisher's cumulants method, confinements were grouped and subjected to a chi-square test which proved to be nonsignificant across all comparisons. The mean number of confinements is thus statistically similar in all subgroups tested.

Analysis

Table 3 features the distribution of TI in cases and controls. The corresponding Figure 1 sketches the TI broken down into 5-year classes. Given the large data base, we first performed a fine analysis of ungrouped data: the observed D value of the Kolmogorov-Smirnov test was equal to 0.12 and significant at $P = 0.01$. Data were also categorized within a 2 by 2 table similar to that reported in our first study [8]. A relative risk of 1.68 stood up that proved to be significant at $P = 0.01$. The distribution of TIs thus appears shorter in twin-bearing mothers than in mothers with singletons only, even after blocking on the effect of birth order, and despite the similarity of maternal age and confinement number in the two groups.

Next, an analysis of the TI was carried out breaking down the case group into sex categories (Table 4 and Fig.2). Kolmogorov-Smirnov testing on data grouped within 16 classes, a rather conservative test for grouped data, yielded an observed $D = 0.13$ at $P < 0.05$ and $D = 0.08$ (n.s.) for LS and ULS twins, respectively. Data

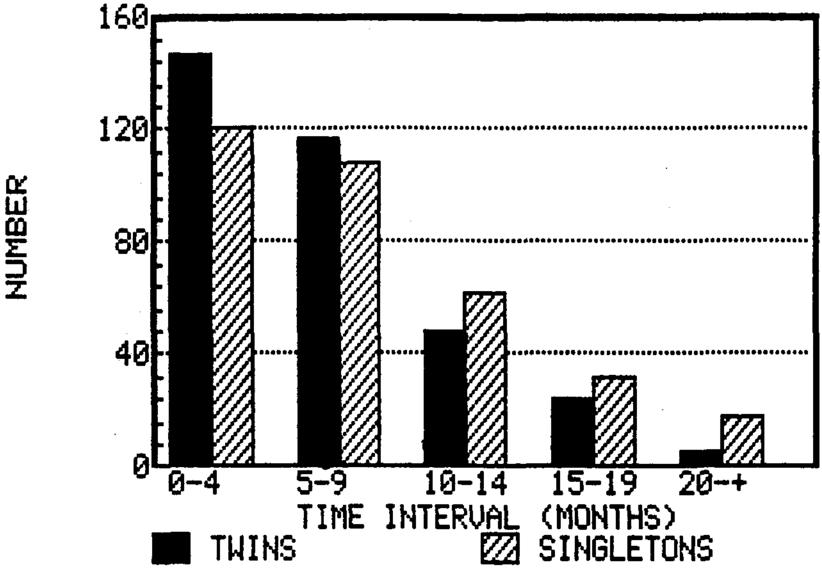

Fig. 1. Distribution of time interval to last confinement in cases and controls.

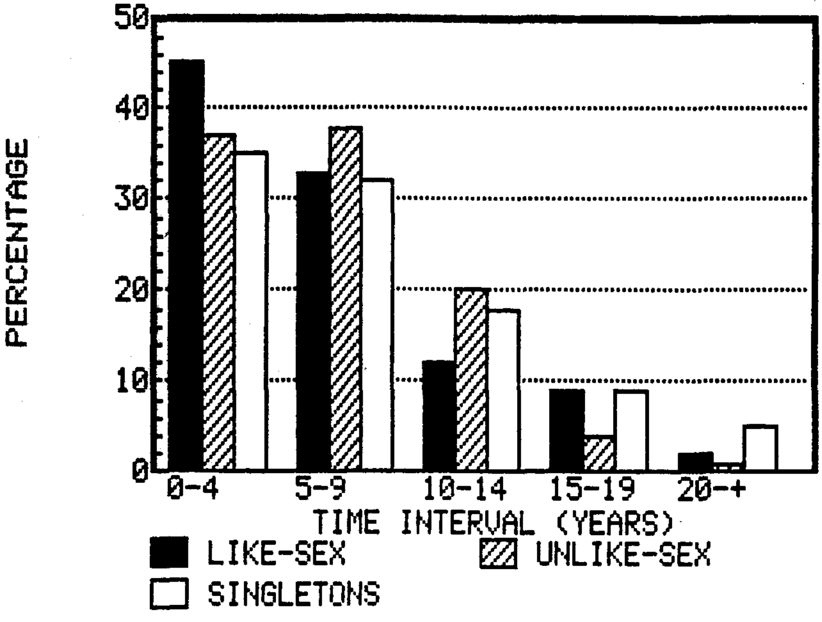

Fig. 2. Distribution of time interval to last confinement in cases by sex of twin pairs and in controls.

Table 3 - Distribution of time interval to last confinement in mothers of twins and mothers of singletons

Interval (months/years)	Mothers of twins	Mothers of singletons
0	67	53
1-24 / 0-2	26	21
25-48 / 2-4	54	46
49-72 / 4-6	47	36
73-96 / 6-8	30	45
97-120/ 8-10	40	27
121-144/10-12	13	23
145-168/12-14	22	23
169-192/14-16	13	16
193-216/16-18	13	13
217-240/18-20	6	9
241-264/20-22	5	10
265-288/22-24	2	9
289-312/24-26	3	6
313-336/26-28		2
337-360/28-30		1
Total	341	340
Mean (yr)	6.4	8.0
S.D.	5.88	6.93
<10 yr	264	228
>10 yr	77	112

Relative risk: 1.68 (P=0.01)
99% CI: 1.08 - 2.62

were then categorized in a four-cell table. Results show that LS twins only differ from controls at the P = 0.01 level. Since time to last confinement is up to maternal age at index confinement and that ULS twins differed from controls because of lack of confinements before age 20 years, the distribution of maternal age at the time of index confinement was truncated at age 20 years and a new relative risk computed; the relative risk for the ULS twin group fell by 27% to 1.19 with 95% confidence limits from 0.74 to 1.91. This shows clearly that TI does not differs between ULS twins and controls, but that mothers of LS twins used to terminate reproductive life rather early after confinement.

Table 4 - Distribution of time interval to last confinement in mothers of like- and unlike-sex twins and mothers of singletons

Interval (months/years)	Like-sex twins	Unlike-sex twins	Unspecified-sex twins	Singletons
0	41	18	8	53
1-24 / 0-2	18	7	1	21
25-48 / 2-4	31	19	4	46
49-72 / 4-6	27	20		36
73-96 / 6-8	20	8	2	45
97-120/ 8-10	18	17	5	27
121-144/10-12	6	7		23
145-168/12-14	11	11		23
169-192/14-16	7	6		16
193-216/16-18	8	4	1	13
217-240/18-20	6			9
241-264/20-22	3	1	1	10
265-288/22-24	1	1		9
289-312/24-26	3			6
313-336/26-28				2
337-360/28-30				1
Total	200	119	22	340
Mean (yr)	6.4	6.7		8.0
S.D.	6.21	5.30		6.93
<10 yr	155	89		228
>10 yr	45	30		112
	Like-sex twins	Unlike-sex twins		
Relative risk:	1.69 (P=0.01)	1.46 (n.s.)		
99% CI:	1.00 - 2.84			
95% CI:		0.90 - 2.31		

Besides sex of twin pairs, maternal age at confinement is the second potentially interactive variable. Table 5 controls for it while depicting TIs distribution for the two large age groupings used in our latest study of the subject. Kolmogorov-Smirnov testing of the case/control distributions falls short of significance for both age groups but the merging of data in 2 by 2 tables attained the 5% significance level only for index confinements occurring prior to maternal age 30 years. Stratification analyses were also carried out according to finer classes of the younger age group which was broken down into three subgroups as shown in Table 6, and relative risks computed. Though statistical significance is lacking by Woolf's heterogeneity chi-square, an emerging trend shows that the earlier the twin confinement, the stronger the association of short TIs with twin confinement incidence.

Table 5 - Distribution of time interval to last confinement according to maternal age at birth and case/control status

Interval (months/years)	<30 years at birth		>30 years at birth	
	Twins	Singletons	Twins	Singletons
0	5	13	62	40
1-24 / 0-2	7	5	19	16
25-48 / 2-4	15	11	39	35
49-72 / 4-6	11	7	36	29
73-96 / 6-8	9	17	21	28
97-120/ 8-10	20	9	20	18
121-144/10-12	7	14	6	9
145-168/12-14	16	14	6	9
169-192/14-16	12	16	1	
193-216/16-18	11	13	2	
217-240/18-20	6	9		
241-264/20-22	5	10		
265-288/22-24	2	9		
289-312/24-26	3	6		
313-336/26-28		2		
337-360/28-30		1		
Total	129	156	212	184
Mean (yr)	10.4	12.1	4.6	3.9
S.D.	6.40	7.54	3.87	3.81
<10 yr	67	62	197	166
>10 yr	62	94	15	18
	<30 years at birth		>30 years at birth	
Relative risk:	1.64 (P=0.05)		1.42 (n.s.)	
95% CI:	1.02 - 2.61		0.70 - 2.87	

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Breaking down the data base by maternal age groups and sex of twin pairs (Table 7) does not add much to the significance of previous results and is presented here for the sake of completeness. The order of magnitude of the relative risk of a LS twin confinement occurring early during reproductive life is retained but is of borderline significance because of smaller sample size. Confidence intervals for the three other subgroups do not point to any new results.

Table 6 - Association between time interval to last confinement and a twin birth occurring prior to maternal age <30 years

Time interval (yr)	Cases	Controls	Relative risk
	Maternal age: < 20 yr		
<10	3	3	
>10	7	21	2.87
	Maternal age: 20 - 24 yr		
<10	21	18	
>10	23	32	1.61
	Maternal age: 25 - 29 yr		
<10	43	41	
>10	32	41	1.34
Total	129	156	

DISCUSSION

A return to the IAC study is a prerequisite to comment the PRDH study results. Table 8 sums up the relative risks and confidence intervals for the IAC and PRDH studies, taking into account crude and adjusted analyses. First, let us recall the main conclusions of our previous study.

The crude analysis of TI at IAC proved to be nonsignificant. However, the age-adjusted analysis revealed two opposite trends (cancelling out each other in the crude analysis), the first showing that young twin-bearing mothers have rather short TIs, the second pointing to longer TIs in older twin-bearing mothers. These results were statistically significant at the 5% level. The sex-adjusted analysis, instead, gave no significant result. However the trend for LS twins was similar to that elicited by younger maternal age while that characterizing ULS twins was in a direction similar to that reported for older maternal age. When both age and sex were simultaneously controlled for, only LS twins born to younger mothers and ULS twins born to older mothers showed significance, but not LS twins born to older mothers and ULS twins born to younger mothers.

The IAC data base was small and the computed confidence intervals imprecise. Be this at it may, major trends emerged. The PRDH study involves a much larger data base. Nonetheless, statistical power is still at a loss when interaction comes to be tested. However, results presented in Table 8 still make use of 95% rather than 90% confidence intervals (CI) because of high error rates with low power [12].

Because the same methodology was used in both our studies, heterogeneity was tested by Woolf's chi-square. Although the crude analysis of TIs in the PRDH data base appears different from that of the IAC study, the pooled RR-value remains highly significant but is of a rather modest magnitude (RR = 1.6). Low power is the likely reason for the null hypothesis not being rejected in our first study; this is confirmed by the lack of heterogeneity between the two studies. The CI rules out

Table 7 - Distribution of time interval to last confinement according to maternal age at birth, sex of twin pairs and case/control status

Interval (months/years)	Maternal age <30 yr			Maternal age >30 yr		
	Like-sex twins	Unlike-sex twins	Singletons	Like-sex twins	Unlike-sex twins	Singletons
0	2	1	13	39	17	40
1-24 / 0-2	3	3	5	15	4	16
25-48 / 2-4	13	2	11	18	17	35
49-72 / 4-6	5	6	7	22	14	29
73-96 / 6-8	5	3	17	15	5	28
97-120/ 8-10	9	10	9	9	7	18
121-144/10-12	2	5	14	4	2	9
145-168/12-14	6	10	14	5	1	9
169-192/14-16	6	6	16	1		
193-216/16-18	6	4	13	2		
217-240/18-20	6		9			
241-264/20-22	3	1	10			
265-288/22-24	1	1	9			
289-312/24-26	3		6			
313-336/26-28			2			
337-360/28-30			1			
Total	70	52	156	130	67	184
Mean (yr)	10.7	10.3	12.1	4.0	3.8	4.6
S.D.	7.04	5.15	7.54	4.15	3.34	3.81
<10 yr	37	25	62	118	64	166
>10 yr	33	27	94	12	3	18

	<30 years at birth		>30 years at birth	
	Like-sex	Unlike-sex	Like-sex	Unlike-sex
Relative risk:	1.69 n.s.	1.40 n.s.	1.05 n.s.	2.05 n.s.
95% CI:	0.96-2.98	0.75-2.62	0.49-2.24	0.63-6.65

Table 8 - Comparisons of relative risks (RR) and 95% confidence intervals (CI) from the two studies

	Isle-aux-Coudres study	PRDH study	Pooled
	Crude analysis		
RR	1.1 n.s.	1.7 (P<0.01)	1.6 (P<0.01)
CI	0.5 - 2.1	1.2 - 2.4	1.2 - 2.1
Hetero X			1.4 n.s.
	Age-adjusted analysis		
Maternal age <30 yr			
RR	2.7 (P=0.05)	1.6 (P=0.05)	1.8 (P<0.01)
CI	1.0 - 7.6	1.0 - 2.6	1.2 - 2.7
Hetero X			0.4 n.s.
Maternal age >30 yr			
RR	0.2 (P<0.05)	1.4 n.s.	
CI	0.05 - 0.9	0.7 - 2.9	
Hetero X			5.4 (P<0.05)
	Sex-adjusted analysis		
Like-sex twin			
RR	1.6 n.s.	1.7 (P<0.01)	1.7 (P<0.01)
CI	0.7 - 3.7	1.1 - 2.5	1.2 - 2.4
Hetero X			0.0 n.s.
Unlike-sex twins			
RR	0.7 n.s.	1.2 n.s.	1.3 n.s.
CI	0.3 - 1.7	0.7 - 1.9	0.8 - 1.9
Hetero X			2.1 n.s.
	Simultaneous adjustment analysis		
Like-sex/<30 yr			
RR	3.3 (P=0.05)	1.7 (P=0.05)	1.9 (P=0.01)
CI	1.0 - 11.0	1.0 - 3.0	1.1 - 3.2
Hetero X			1.1 n.s.
Unlike-sex/<30 yr			
RR	1.3 n.s.	1.4 n.s.	1.4 n.s.
CI	0.3 - 5.7	0.8 - 2.6	0.8 - 2.5
Hetero X			0.0 n.s.
Like-sex/>30 yr			
RR	0.4 n.s.	1.1 n.s.	0.9 n.s.
CI	0.1 - 2.3	0.5 - 2.2	0.5 - 1.8
Hetero X			1.0 n.s.
Unlike-sex/>30 yr			
RR	0.2 (P<0.05)	2.1 n.s.	
CI	0.03 - 0.8	0.6 - 6.7	
Hetero X			6.4 (P<0.05)

large effects beyond 2.1. However, from a statistical standpoint the parametric RR of the current study stands within the CI of the IAC study and, yet, is compatible with it. Both studies, therefore, agree on the magnitude of the main effect, that is, the confinement of twins is modestly associated with a short (10 years or less) TI to last confinement.

When time comes to analyze effect modifications by maternal age, we find that the order of magnitude of the RR is similar, and significant for ages less than 30 years in both studies. The pooled RR is highly significant and excludes very large effects as well as the null value. Again, heterogeneity between studies is notably absent. However, effect modification by maternal age greater than 30 years at confinement is different in both studies.

Like-sex twins are associated with short TIs in the present study with a point estimate of the RR of the same order of magnitude to that computed for the IAC study. The greater precision of the current study confirms the association of LS twins with short TIs, and heterogeneity is markedly absent. The effect by ULS twins is significant in neither studies and the pooled RR also lacks significance.

At last, when both potentially interactive variables are considered simultaneously, only the RR for LS twins born to younger mothers proves to be significant in the current study, a result similar to that found at IAC. Further, the pooled relative risk is slightly increased (and significant at the $P < 0.01$ level) over that reported for the main effect or in the subgroup of mothers aged less than 30 years at index confinement. Again, heterogeneity is notably absent. On the other hand, results for ULS twins born to older mothers seem at variance with that of the IAC study.

From the comparison of both studies and the greatest precision of the current one, it appears very likely that both LS twins and young maternal age at index confinement are associated with short TIs. The effect of the simultaneous blocking of both interactive variables on the risk of a twin birth remains modest with a RR of 2 and no greater than 3.2 as judged by the upper limit of the combined CI. On the other hand, older maternal age at index confinement proves to have different effects in both studies.

The current study has confirmed several results put forward on the basis of the IAC data base, except for few inconsistencies that should be resolved by further studies. Low power of interaction analyses may be a case in point here, and ought to be improved in the future. However, the consistency of several results among both studies rules out the effects of an uncontrolled potential confounder. Further, the effect of LS and young maternal age are neither additive nor multiplicative in effects. It rather seems that both occurrences as well as their unique involvement have about the same overall effect on TIs.

From a biological standpoint, we would be tempted to reiterate the conclusions of our previous work. Short TIs are associated with like-sex twins or young maternal age at birth of a twin pair, both features resulting from related biological mechanisms, that is, premature ovarian aging and ovarian failure, both being associated with premature menopause. That early childbearing may induce infertility is possible. But that early childbearing may result from a displaced peak of the fecundity potential followed by its early and abrupt dampening, is also a distinct possibility [9]. As twins are usually born to advanced age mothers, it is tempting to relate this occurrence to the approaching menopause [1,2]. Thus, precocious menopause and, therefore, short TIs may conceivably accelerate the birth of a twin pair. That LS twins per se result from ovarian failure associated with early menopause may also be concluded from our two studies. That the biological mechanism leading to it is distinct from that due to early maternal age at confinement per se is not obvious as interaction is minimal and additivity of effects unclear.

The case of ULS twins and older maternal age poses a different problem. The inconsistencies between the two studies do not allow confirmation of an elongated reproductive life in mothers of ULS twins and/or in those with advanced age at twin birth. Nevertheless, an effect of late maternal age at confinement opposite to that of LS twins, and of ULS twins opposite to that of early maternal age cannot be ruled out. Thus, slow oocyte depletion – the postulated mechanism referred to in our previous study to explain later age at last confinement in ULS twin-bearing mothers – should be tested further. As a matter of fact, inconsistencies might be resolved by an increased effort toward tighter matching of controls, particularly with respect to the sex of twin pairs in group and subgroup analyses, and by larger sample sizes allowing for interaction testing.

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