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Time-to-pregnancy and risk of schizophrenia

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Abstract

Schizophrenia has been linked to advanced paternal age, but the explanation is unknown. We questioned whether the incidence of schizophrenia would be related to male reproductive capacity, as reflected in the time taken to conceive. We measured the incidence of schizophrenia in relation to time to conception in a sub-group of 12,269 in the Jerusalem cohort whose mothers, interviewed post-partum, reported that the pregnancy had been intended. Compared with those conceived in less than 3 months, the unadjusted relative risks (RR) of schizophrenia associated with conception-waits of 3–5, 6–11 and 12+ months were 1.10 (95% confidence interval, 0.62–1.94), 1.41 (0.79–2.52) and 1.88 (1.05–3.37) with p for trend=0.035. This trend was attenuated somewhat by adjusting for paternal age, and was observed more strongly in offspring of fathers aged 30+ ($p=.010$). These findings suggest that factors associated with fecundability, either male or female, may contribute to the risk of schizophrenia.

Keywords

time-to-pregnancy; fecundability; paternal age; schizophrenia

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Conflict of Interest

The authors declare that they have no conflicts of interest to report.

Contributors

MGAO designed the study and wrote the first draft of the manuscript. SH and KO undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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Introduction

Originally reported in the 1950s (Johansen, 1958) Malaspina et al (2001) later reported increases in the risk of schizophrenia as paternal age increased, a finding since replicated in multiple studies and populations (Byrne et al 2003; Dallman and Allbeck, 2002; Sipos et al, 2004; Tsuchiya et al, 2005; Zammit et al 2003). It has been postulated that advanced paternal age is associated with accumulated damage to the paternal germline, resulting in genetic or possibly epigenetic damage that is passed on to offspring, thereby conferring risk of schizophrenia. (Torrey et al, 2009) Germline damage and environmental exposures which cause it have been associated with changes in fertility (Aitken & De Iuliis, 2007).

While there have been a variety of studies on the fertility of patients with schizophrenia (Nimgaonkar et al, 1997; Bhatia et al., 2004) the examinations of paternal reproductive health has been limited (Hutchinson et al, 1999). Those studies that have been conducted to date utilize the numbers of offspring as the primary measure (Waddington and Youssef, 1996; Srinivasan and Padmavati, 1997). However, reproductive health is only one factor that influences the total number of offspring produced. Time to pregnancy (TTP) has been used as a standard indicator of reproductive health and fitness, described by Joffe (1997) as a final common pathway for exposures that affect reproduction. It is defined as either the length of the time or the number of menstrual cycles required for a couple to conceive. Prolonged time-to-pregnancy has been associated with smoking, advanced age, and chemical exposures (Boumar et al, 1996; de Cock et al 1994). Reduced fertility as measured by prolonged time-to-pregnancy has also been associated with developmental delay in offspring (Zhu et al 2009).

We postulate that advanced paternal age is associated with accumulated environmental insults over time. If this mechanism may explain (at least in part) the relationship between advanced paternal age and schizophrenia, then it might be associated with changes in reproductive health and fertility. In this study we examine whether TTP is associated with an increased risk of schizophrenia in the offspring using data from the Jerusalem Perinatal Study.

Methods

This study relies on the Jerusalem cohort, a research data resource. During 1964–76, all 92,408 births to residents of Western (Israeli) Jerusalem were surveyed. Items abstracted from the birth certificate included demographic information on the parents and both grandfathers; these were supplemented with data abstracted from medical records, interviews and surveillance of pediatric inpatients. The methods and characteristics of the population have been described (Davies et al 1969, Harlap et al 1977, Harlap et al 2007). In 1974–76 nearly 17,000 mothers were interviewed in hospitals 1–2 days after delivery. Data were collected on maternal health, contraceptive use, infertility and obstetric history. A specific question included “Did you mean to become pregnant?”; those answering in the affirmative were asked “How many months passed from the time you decided to try, until you got pregnant?”

More recently, the offspring and their parents were traced through the Israel’s Population Registry; vital status and dates of death were ascertained until 2005. To study schizophrenia and its related diagnoses, the identification numbers of the traced individuals were linked to Israel’s National Psychiatric Registry. This registry, established in 1950, receives all psychiatric diagnoses, including reports from patients admitted to specialized psychiatric hospitals, psychiatric wards within general hospitals and psychiatric day-care facilities (Lichtenberg et al, 1999). One admission diagnosis and one discharge diagnosis are

recorded, coded with International Classification of Diseases, 10th Revision [ICD-10]; codes from previous revisions are updated to ICD-10. The diagnoses for individuals with psychosis have been validated (Weiser et al, 2005). Linkage of the Jerusalem cohort's offspring and parents with the Psychiatric Registry extracted the dates of admission and discharge and the discharge diagnosis for all episodes (if any) in offspring and parents; then, the names, identity numbers and other identifying information were removed. The anonymous file was analyzed collaboratively in New York and Israel. The study was approved by the Institutional Review Boards in both countries and certified as exempt from the requirement for informed consent.

Statistical Methods

For this study, we defined schizophrenia according to the incidence of one or more hospital admissions for which the ICD-10 code for the discharge diagnosis was F20-F29. The date of diagnosis was considered to be the date of first admission to a psychiatric facility, regardless of the diagnosis at that time. Data were analyzed using SAS, version 9.1. We used Cox proportional hazards models to estimate the relative risk of schizophrenia in offspring conceived after different times to pregnancy, taking into account potential confounding variables. Offspring were followed from birth until the date of diagnosis, death or the cutoff date; at this point they were aged 29–31. Time to event, or death, was modeled in years (i.e. age); survivors were censored on January 1, 2005. Ties were handled with Efron's method. A robust sandwich estimate of the covariance matrix was used to take into account correlation between siblings (Lin and Wei, 1989). Tests for trend were made by treating the time to pregnancy as an ordinal variable recoded 1–4 corresponding to categories 0–2, 3–5, 6–11 or 12+ months. Paternal age was modeled as a continuous variable, in deviations from the mean (31.5); unknowns (0.3%) were assigned to the mean.

Other variables considered for inclusion in the models were those that were significantly related to time to pregnancy and those known to affect schizophrenia in the larger cohort: or parental history of psychiatric hospital admission, the offspring's sex and birth order, paternal and maternal ages, duration of marriage, social class and year of birth, the latter tested because we had observed some under-reporting of schizophrenia in 1976. The final models included only paternal age, year of birth (1976 versus earlier) and parents' history of psychiatric conditions.

Results

There were 16,825 offspring born to mothers who completed post-partum interviews in 1974–1976; of these, 27 (0.75%) were stillborn and 189 (1.1%) remained untraced in 2005. From the remaining 16,509, we excluded 4,140 (25.1%) whose mothers had not intended to become pregnant and 67 (0.4%) with a logical inconsistency between the reported duration of trying to conceive and the date of the end of the previous pregnancy. The excluded subjects had parents who were significantly older, less educated and of lower social class than those who were conceived intentionally; however, they did not differ significantly from the included subjects in the prevalence of schizophrenia in parents or in the incidence of schizophrenia in offspring (data not shown).

As expected, more than half of the subjects were conceived in less than three months and 73% in under six months; but nearly 12% had taken a year or more and 4.4% had taken two years or longer. The longest wait was 120 months. Table 1 shows the distribution of selected variables in categories of time to pregnancy. Offspring conceived after longer waits had older parents with lower social class, but there was no relation of time to pregnancy with offspring's sex or psychiatric conditions in parents. Some 1.1% of offspring had a father with schizophrenia; 0.9% had a mother with schizophrenia; while 1.4% and 1.1% had a

father or mother respectively hospitalized with other psychiatric diagnoses. None of these parental conditions was significantly related to the time taken to conceive.

Table 2 shows how the unadjusted and adjusted relative risk (RR) of schizophrenia varied with time to pregnancy. Compared with the offspring who were conceived most easily, there was a progressively increasing risk of schizophrenia associated with increasing waiting time. The unadjusted RR was almost doubled for those whose parents took a year or more to conceive, compared with the reference category of less than three months. While part of this increase was explained by paternal age, it was not reduced by further adjustment. The tests for trend suggested that the finding was unlikely to be due to chance, although of borderline significance. Table 3 summarizes trend tests in strata of three variables, showing that the increasing risk of schizophrenia associated with increasing time to pregnancy was somewhat stronger in males than in females and in offspring whose parents had psychiatric conditions. It was particularly strong in offspring born older fathers.

Further adjustment for social class, maternal age, sex of offspring or duration of marriage did not change these conclusions; similarly, estimates were virtually unchanged by testing time to pregnancy as a continuous variable, in individual months.

Discussion

Our study demonstrates that time-to-pregnancy, defined as the reported length of time taken for a couple to conceive an intended pregnancy, may be related to the risk of schizophrenia in offspring. To our knowledge, this is the first population-based study to systematically examine this relationship. Longer times to conception, particularly within the highest categories for this variable (12+ months) were associated with modest increases in risk. Our results further indicate that time-to-pregnancy is not likely to be a major explanatory factor of the effect of paternal age in schizophrenia as the effect size is modest and the significance is marginal.

There are several reasons to interpret our results cautiously. First, time to pregnancy is a non-specific measure of the fecundity of a couple. As a result, our study cannot be said to support any particular mechanism and does not indicate whether paternal or maternal factors are involved. There are plausible reasons to suspect that the biological factors which have been implicated in aging in either sex might be involved. Advanced paternal age is strongly associated with reductions in fertility and with other changes in reproductive health and with several indicators of impaired spermatogenesis (Meacham and Murray, 1999). Reviewed by Crow (2000), male germline mutation rates are high due to the frequency of cell division over the lifecourse. Mutation frequency in sperm of men is associated with very strong paternal age effects for a range of conditions (Bazhenova et al, 1984; Glazer et al, 2003; Jones et al, 1975; Rolf and Nieschlag, 2001). Paternal age has been reported to be associated with congenital malformations, cerebral palsy, sporadic Alzheimer disease, pre-eclampsia and spontaneous abortion. (Bertram et al, 1998; Fletch and Foley, 1993; Harlap S et al 2002; Nybo Andersen et al, 2004; Olshan et al, 1994).

Despite the limitations, this study offers additional support for the role of preconceptual factors in the development of schizophrenia. Our finding suggests that some feature of parental reproductive health may contribute to the risk of this disease. Further investigations into this are currently underway to examine this intersection between age, environment, and effects on neurodevelopment of subsequent generations.

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Table 1

Numbers of offspring (N) and percent distribution of selected variables, by time to pregnancy.

	Time to conception (months)					Total
	<3	3–5	6–11	12+		
N	6,342	2,595	1,900	1,432		12,269
Percent	100.0	100.0	100.0	100.0		100.0
Sex						
	Male	52.3	53.3	52.6	51.8	52.5
	Female	47.7	46.7	47.4	48.2	47.5
Age of father (years)						
	<25	17.5	19.0	14.4	9.0	16.4
	25–34	61.6	61.2	62.7	57.5	61.2
	35+	20.4	19.5	22.6	32.6	22.0
Age of mother (years)						
	<25	38.2	38.4	32.8	22.1	35.6
	25–34	53.3	54.4	57.3	58.5	54.8
	35+	8.4	6.9	9.8	19.1	9.5
Social class (occupation of father)						
	High	36.9	45.9	51.6	51.3	42.8
	Medium	41.7	36.7	30.4	33.1	37.9
	Low	21.4	17.5	18.0	15.6	19.3
Year of Birth						
	1974	6.1	5.9	6.1	8.9	6.4
	1975	46.4	45.6	43.2	45.3	45.6
	1976	47.4	48.5	50.7	45.8	48.0
Psychiatric illness in a parent						
		4.6	4.4	4.4	4.4	4.5

Numbers of offspring with and without schizophrenia, adjusted and unadjusted relative risks (RR) and 95% confidence intervals (CI), by time taken to conceive offspring.

Table 2

Variable	Schizophrenia		Unadjusted		Adjusted for paternal age		Further adjusted *	
	+	-	RR	95% CI	RR	95% CI	RR	95% CI
Total offspring	87	12,182						
Time to pregnancy (months)	<3	38	6,304	1	ref	1	ref	Ref
	3-5	17	2,578	1.10	0.62-1.94	1.10	0.62-1.95	1.10
	6-11	16	1,884	1.41	0.79-2.52	1.39	0.78-2.50	1.41
	12+	16	1,416	1.88	1.05-3.37	1.74	0.98-3.12	1.77
Test for trend				1.22	1.02-1.48	1.20	1.00-1.44	1.21
P-value				.035		.053		.047

* Adjusted for paternal age, psychiatric illness in parents and year of birth

Table 3

Numbers of offspring with and without schizophrenia, adjusted* relative risk (RR) and 95% confidence intervals (CI) associated with trend in time to pregnancy, by sex, family history and age of father.

	Schizophrenia		Test for trend		
	-	+	RR*	95% CI	p
Sex of offspring	Male	6,386	53	1.29	1.01–1.64 .038
	Female	5,796	34	1.09	0.81–1.47 .559
Psychiatric illness in parents	None	11,642	74	1.18	0.97–1.45 .106
	Any	540	13	1.37	0.90–2.09 .145
Age of father	<30	6,609	33	0.91	0.67–1.23 .541
	30+	5,519	54	1.36	1.08–1.72 .010

* Adjusted for year of birth and for the other variables in the table.