

Congenital Malformations, Stillbirths, and Infant Deaths Among Children of Women With Schizophrenia

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Background: Women with schizophrenia have increased exposure to risk factors for congenital malformations, stillbirths, and infant deaths among their children. However, the occurrence of these outcomes is unknown.

Methods: The risks of stillbirth and infant death among 2230 children of women with schizophrenia were compared with the risks among 123 544 children in the general population. The risk of congenital malformations among 746 children of women with schizophrenia were compared with the risk among 56 106 children in the general population. The year of birth, the sex of the child, the mother's age, and parity were included in the analyses as potential confounders. We had no information about socioeconomic status, smoking status, substance abuse, or psychotropic medication use.

Results: Children of women with schizophrenia had increased risk of postneonatal death (relative risk [RR], 2.76;

95% confidence interval [CI], 1.67-4.56). This was largely explained by an increased risk of sudden infant death syndrome (RR, 5.23; 95% CI, 2.82-9.69). There was no statistically significant increased risk of stillbirth (RR, 1.51; 95% CI, 0.94-2.40) or neonatal death (RR, 1.26; CI, 0.77-2.06). Children of women with schizophrenia had a marginally statistically significant increase in the risk of congenital malformations (RR, 1.70; 95% CI, 1.04-2.77).

Conclusions: Children of women with schizophrenia have a considerable increased risk of death caused by sudden infant death syndrome. However, the results should be interpreted in the light of failure to adjust for socioeconomic status, substance abuse, smoking status, and psychotropic medication use.

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THE RISK OF congenital malformations, stillbirths, and infant deaths among children of women with schizophrenia has rarely been investigated. Most studies have been based on small sample sizes. However, there is some evidence that the children of schizophrenic women have an increased risk of these outcomes.^{1,2} An increased risk of stillbirth and infant death might be suspected, as schizophrenic women are often smokers and substance abusers, and tend to live in poor socioeconomic conditions.² If it was known that children of women with schizophrenia have an increased risk of stillbirth or infant death, it might be possible to prevent some of these deaths in the future.

It might be suspected that the prevalence of congenital malformations is increased in children of women with schizophrenia because of the administration of antipsychotic drugs during pregnancy.^{3,4} A common genetic or environmental

cause between schizophrenia and congenital malformations has also been suggested.^{5,6} If it is found that children of women with schizophrenia have an increased prevalence of congenital malformations, it may be of interest to research in the etiology of schizophrenia.

The aim of this study was to investigate the risk of congenital malformations, stillbirths, and infant deaths among children of women with schizophrenia.

RESULTS

The distribution of the potential confounders among women with schizophrenia and control women is shown in **Table 1**.

CONGENITAL MALFORMATIONS

Among children born to women with schizophrenia in 1983-1992, 16 children delivered by 15 women had a total of 20 malformations (**Table 2**). These malformations were either conspicuous or po-

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SUBJECTS AND METHODS

DATA SOURCES

Data were created by a linkage between the Danish Psychiatric Central Register,⁷ the Danish Medical Birth Registry,⁸ and the National Registry of Congenital Malformations,⁹ which are nationwide registers covering the total Danish population. The Danish Psychiatric Central Register holds computerized information about all admissions to psychiatric departments in Denmark reported by psychiatrists since 1969.⁷ The Danish Medical Birth Registry holds information about all births in Denmark since 1973, reported by the midwives on structured coding sheets.⁸ Based on linkage between birth notification forms and death certificates, the register contains information about stillbirths and infant deaths. The National Registry of Congenital Malformations was established in 1983. The information is based on standardized reports by physicians about malformations diagnosed during the first year of life.⁹ In addition to the children registered in the National Registry of Congenital Malformations, some children were registered in the Danish Medical Birth Registry as having congenital malformations as a cause of death.

SUBJECTS

The study group comprised all single births ($n=2230$) by women with schizophrenia ($n=1544$) in Denmark during the study period of 1973 to 1993. Data concerning congenital malformation were available for the years 1983 to 1992. In that period, the study group consisted of 746 births to 584 women with schizophrenia. Women with schizophrenia were defined as all women who were admitted at least once as inpatients to a Danish psychiatric department during 1969 to 1993 with the diagnosis schizophrenia (*International Classification of Diseases, Eighth Revision [ICD-8]*).

The women in the control group were all women who gave birth to a single child in Denmark on 1 of 3 randomly selected days each month. If these women gave birth more than once in the study period, all their single births were

included. For the years 1973-1993 the control group comprised 123 544 births by 72 840 women. For the years 1983-1992 it comprised 56 106 births by 38 589 women.

STATISTICAL ANALYSIS

Statistical analyses were performed using the SAS system version 6.12 (SAS Institute, Cary, NC). Adjusted relative risks (RRs) with 95% confidence intervals (CIs) for the outcomes in children of schizophrenic women compared with controls were computed in an additive model with the logarithm as link function. Two-tailed P values were obtained by likelihood ratio tests. Because the year of birth, the sex of the child, the mother's age (<20 , $20-34$, ≥ 35 years), and parity (primipara, multipara) could be associated with the outcomes of interest, these variables were included in the analyses as potential confounders. Information about parity was available only for the years 1978 to 1993, whereas information about the number of previous pregnancies was available for the entire study period and was used as a proxy for parity. The deliveries of women with schizophrenia were previously found to differ from those of control women according to birth weight (<2500 g, ≥ 2500 g) and gestational age (<37 weeks, ≥ 37 weeks).¹⁰ As preterm birth and low birth weight are strongly associated with neonatal mortality,¹¹ these variables were included when the risk of death was analyzed. Differences in the deliveries of women with schizophrenia who gave birth before or after their first admission to a psychiatric department were investigated. It was also determined whether the estimates changed after exclusion of births to women with schizophrenia who had their first psychiatric admission during pregnancy, in the first 3 months after pregnancy, or at the death of a child.

Some women gave birth more than once in the study period. Deliveries of the same woman cannot be considered as independent events. To adjust for this potential problem, adjusted relative risks were also computed using the General Estimation Equation (GEE). This method takes into account that repeated observations over subjects are correlated.¹²

Neonatal death was defined as death of a liveborn infant during the first month of life. Postneonatal death was defined as death between the age of 1 month and 1 year.

tentially life threatening, meaning that they would probably have been diagnosed in all children. As shown in **Table 3**, there was a small increase of marginal statistical significance in the risk of having at least 1 congenital malformation among children of women with schizophrenia. There was no evident excess of malformations in any specific organ system, although the frequency of malformations in eyes or ears was greater in children of women with schizophrenia (Table 2). There was no statistically significant difference between children of women with schizophrenia who gave birth before or after their first admission to a psychiatric department ($P=.91$). Exclusion of births to women who had their first psychiatric admission during or in the first 3 months after pregnancy did not change the results. Analysis of data using GEE left the RRs and CIs essentially unchanged.

STILLBIRTHS

There were 18 stillbirths among children of women with schizophrenia for the period 1969-1993 (**Table 4**). Two of these were delivered by the same woman. As seen in Table 3, the RR of stillbirth was not significantly increased in children of women with schizophrenia. After adjustment for birth weight, the RR decreased to 1.14 (95% CI, 0.72-1.81). Because a substantial number of stillbirths in the control group had missing gestational ages, it was not possible to adjust for gestational age. There was no difference between births occurring before or after the mothers' first psychiatric admission ($P=.63$). Exclusion of births to women with schizophrenia who had their first admission during or in the first 3 months after pregnancy did not change the results. Analysis of data using GEE left the RRs and CIs essentially unchanged.

Table 1. Distribution of Confounders in Schizophrenic and Control Women (1973-1993)

Confounder	% of Women		χ^2	df	P
	Schizophrenic Group (n = 2230)	Control Group (n = 123 544)			
Year of birth					
1973-1979	49.6	36.5	233.55	2	.001
1980-1986	30.5	29.4			
1987-1993	19.9	34.1			
Sex of child					
Boy	52.6	51.6	0.74	1	.39
Girl	47.4	48.4			
Maternal age, y					
<20	4.5	4.5	73.15	2	.001
20-34	83.8	88.5			
≥35	11.7	7.0			
No. of previous pregnancies					
0 or not reported*	34.4	35.4	30.41	3	.001
1	32.7	34.1			
2	16.5	17.9			
≥3	16.4	12.6			
Parity (1978-1993)					
Primiparous or not reported†	51.6	46.4	15.02	1	.001
Multiparous	48.4	53.6			
Gestational age, wk					
<37	7.2	4.7	18.86	2	.001
37-40	68.6	68.3			
>40	24.2	27.0			
Birth weight, g					
<2500	8.3	4.9	74.70	2	.001
2500-3999	81.9	81.5			
≥4000	9.8	13.6			

*In 1973-1990 it was possible to distinguish between not reported and no previous pregnancies. There was 0.05% not reported in both the schizophrenia group and the control group.

†Information about parity was only available in 1978-1993. In 1978-1990 it was possible to distinguish between primiparity and not reported parity. There was 0.08% not reported in the schizophrenia group and 0.06% not reported in the control group.

Estimation of RR excluding children born with malformations did not change the results.

NEONATAL DEATHS

There were 16 neonatal deaths among children of women with schizophrenia (**Table 5**). Two of these children were delivered by the same woman. As seen in Table 3, the risk of neonatal death was not significantly increased in children of women with schizophrenia. After adjustment for birth weight and gestational age, the RR decreased to 0.88 (95% CI, 0.54-1.45). There was no difference between births given before and after the mothers' first psychiatric admission ($P = .46$). The estimates did not change after exclusion of children whose mothers had their first psychiatric admission in relation to pregnancy or death of child. Analysis by GEE did not change the results. After exclusion of children born with malformations, the RR of neonatal death was essentially unchanged.

POSTNEONATAL DEATHS

There were 16 children delivered of 16 women with schizophrenia who died during the postneonatal period (**Table 6**). The risk of postneonatal death was increased among children of women with schizophrenia

(Table 3). The RR remained unchanged after adjustment for gestational age and birth weight. There was no difference between births occurring before or after the women's first psychiatric admission ($P = .61$). After exclusion of children of women who had their first psychiatric admission in relation to pregnancy or death of child, the RR decreased to 2.34 (95% CI, 1.34-4.07). Analysis by GEE failed to change the results. After exclusion of children with malformations for the years 1983-1992, the RR of postneonatal death increased from 4.14 (95% CI, 2.04-8.42) to 5.71 (95% CI, 2.66-12.26). After exclusion of children who died of sudden infant death syndrome (SIDS), the adjusted RR of postneonatal death was 1.59 (95% CI, 0.71-3.59).

As seen in Table 3, children of women with schizophrenia had a statistically significant increased risk of SIDS. Adjustment for birth weight and gestational age failed to change the results. There was no difference in risk between children delivered before or after the mothers' first psychiatric admission ($P = .90$). Analysis by GEE made no difference.

COMMENT

We found a small increase in the risk of congenital malformations in children of women with schizophrenia. Jablensky et al¹ reported similar findings. Sobel¹³ re-

ported an increased risk of congenital malformations among children of women with schizophrenia, but no statistical analysis was performed. Paffenbarger et al¹⁴ found no difference in the frequency of congenital malformations between the offspring of women with postpartum psychoses and the offspring of control women, but no data were provided. Miller et al¹⁵ found no difference in risk of congenital malformations among children of female psychiatric patients compared with children born to the general population. McNeil et al¹⁶ found no difference in the frequency of malformations including minor physical anomalies among children of women with schizophrenia compared with children of control women.

We found an increased risk of postneonatal death, which was largely explained by SIDS, among children of women with schizophrenia. There was no statistically significant increased risk of stillbirth or neonatal death. Most previous studies that investigated fetal or infant death were small studies without adjustment for potential confounders. Some found a tendency toward an increased risk of fetal, perinatal, or neonatal death among children of women with schizophrenia or other mental diseases.^{13,14,17-19} Others found a tendency toward a lower risk.^{20,21} Modrzejewska²² found an increased risk of stillbirth and infant death among 553 children of parents with schizophrenia. Also, Jablensky et al¹ reported an increased risk of infant death.

This study is considerably larger than previous studies investigating these outcomes, and it is the only study in which adjustment for some of the potential confounders was possible. Unfortunately, we had no information about socioeconomic status, smoking status, substance abuse, and psychopharmacological treatment, which may lead to residual confounding. Small differences in risks could not be detected in this data set because of the relatively few events. It is possible that there would be statistically significant differences in the risks of stillbirth and neonatal death in a larger data set.

The control group was a random sample of all births in Denmark during the study period, which minimized the risk of selection bias. Probably some of the women with schizophrenia were also included in the control group. If that was the case for 10% of the women with schizophrenia, their deliveries would amount to approximately 0.2% of the births in the control group, which would be of minimal importance. The women with schizophrenia were selected by the criteria that they were admitted and correctly diagnosed with schizophrenia at least once during 1973 to 1993. It is not known how many patients with schizophrenia were never admitted as inpatients, but probably it is a minority.²³ It could be suspected that complications during pregnancy or delivery, or infant death, might lead to an increased risk of psychiatric admission for schizophrenia. This could lead to selection bias. However, exclusion of births to women who had their first admission in relation to pregnancy, delivery, or death of a child did not essentially change the results. Munk-Jørgensen²³ validated the ICD-8 diagnosis of schizophrenia in the Danish Psychiatric Central Register, and found a positive predictive value of the diagnosis of approximately 90%. This means that the ma-

Table 2. Number of Congenital Malformations in Children of Schizophrenic and Control Women

Region	No. (%) ^a of Malformations	
	Schizophrenic Group	Control Group
Nervous system	1 (0.13)	62 (0.11)
Eyes or ears	3 (0.40)	48 (0.09)
Face	2 (0.27)	153 (0.27)
Heart or circulatory system	5 (0.67)	174 (0.31)
Respiratory system	0	16 (0.03)
Digestive system	1 (0.13)	45 (0.08)
Genitals or urinary system	2 (0.27)	164 (0.29)
Extremities, muscles, or bones	5 (0.67)	310 (0.55)
Others or unspecified	1 (0.13)	45 (0.08)

^aAll malformations in a specific region in percentage of all children. If a child had more than 1 malformation in a specific region, each malformation was counted separately.

jority of patients in this study probably were correctly diagnosed as having schizophrenia. There were relatively few births to women with schizophrenia late in the study period (Table 1), which may be explained by the inclusion criteria. Inclusion in the study required an admission with schizophrenia during 1969 to 1993, and a delivery during 1973 to 1993. The chance of having experienced both these events was higher for women who gave birth early in the study period.

The National Registry of Congenital Malformations was found to have a completeness of more than 90% according to the cleft lip and palate registration.⁹ Other malformations in the registry have never been validated. However, a considerable underreporting has been shown.²⁴ There is no reason to believe that there was a selectively higher reporting of malformations among children of women with schizophrenia, as their reported malformations were of such types that they would probably also have been diagnosed in other children. The general validity of the registration of causes of death for infants in Denmark is not known,²⁵ but was approximately 85% of deaths based on autopsy findings.²⁶ The diagnosis of SIDS cannot easily be validated. There were regional differences in the frequencies of SIDS. These differences were probably partly explained by differences in autopsy rates and interpretations of autopsy findings, which may not reflect genuine differences in rates.²⁶ As there are probably also regional differences in the incidence of schizophrenia,²⁷ it cannot be excluded that some of the observed increased risk of SIDS in children of women with schizophrenia was explained by these regional differences.

We previously found that children of women with schizophrenia generally had lower birth weight and lower gestational age.² These differences did not explain the increased risk of postneonatal death and SIDS. We also found a tendency toward a lower Apgar score in the children of women with schizophrenia,²⁸ which might indicate that the children were in poorer condition at birth and thus at increased risk of death. It is not known how many of these children actually lived with their mothers, but it is likely that the women with schizophrenia were less capable of taking care of their infants com-

Table 3. Relative Risks of Congenital Malformations, Stillbirths, Neonatal and Postneonatal Deaths, and Sudden Infant Death Syndrome in Children of Women With Schizophrenia Compared With Control Women*

	Proportion of Controls, %	Relative Risk (95% Confidence Interval)		P
		Crude	Adjusted	
Congenital malformations	1.2	1.75 (1.07-2.86)	1.70† (1.04-2.77)	.05
Stillbirth	0.5	1.63 (1.02-2.60)	1.51‡ (0.94-2.40)	.11
Neonatal death	0.5	1.39 (0.85-2.29)	1.26‡ (0.77-2.06)	.38
Postneonatal death	0.3	2.75 (1.67-4.54)	2.76‡ (1.67-4.56)	<.001
Sudden infant death syndrome	0.1	4.74 (2.56-8.76)	5.23‡ (2.82-9.69)	<.001

*For congenital malformations, n = 746 in schizophrenic group and n = 56 106 in the control group; all others, n = 2230 in the schizophrenic group and n = 123 544 in the control group.

†Adjusted for year of birth, sex of child, mother's age, and parity.

‡Adjusted for year of birth, sex of child, mother's age, and number of previous pregnancies.

Table 4. Primary Causes of Death in Stillborn Children of Schizophrenic and Control Women

Cause of Death	No. (%)* Stillbirths	
	Schizophrenic Group	Control Group
Congenital malformations	3 (0.13)	70 (0.06)
Maternal disease	0	20 (0.01)
Preeclampsia	1 (0.05)	28 (0.02)
Placental or umbilical cord conditions	7 (0.31)	293 (0.24)
Fetal anoxia or hypoxia	2 (0.09)	81 (0.07)
Other reasons	1 (0.05)	27 (0.02)
Unknown reasons	4 (0.18)	93 (0.08)
Total	18 (0.81)	612 (0.50)

*Percentage of all children.

Table 5. Primary Causes of Death in Children Who Died Neonatally

Cause of Death	No. (%)* of Neonatal Deaths	
	Schizophrenic Group	Control Group
Congenital malformations	6 (0.27)	211 (0.17)
Complications during pregnancy and delivery	4 (0.18)	127 (0.10)
Neonatal anoxia and hypoxia	4 (0.18)	191 (0.16)
Immaturitas	1 (0.04)	42 (0.03)
Infections	0	29 (0.02)
Others	1 (0.04)	38 (0.03)
Total	16 (0.72)	638 (0.52)

*Percentage of all children at risk.

pared with other women. Their children might therefore be in a poorer nutritional condition and have poorer general health compared with other children. Women with schizophrenia may also have an inadequate reaction if their children become ill, which might lead to insufficient medical treatment and increased risk of death. Maternal substance abuse and especially maternal smoking are known risk factors for SIDS.²⁹⁻³³ As women with schizophrenia are more likely to be smokers or substance abusers compared with other women,^{2,10} this could explain some of the increased risk of SIDS in this study. In a Dan-

Table 6. Primary Causes of Death in Children Who Died Postneonatally

Cause of Death	No. (%)* of Postneonatal Deaths	
	Schizophrenic Group	Control Group
Congenital malformations	3 (0.14)	102 (0.08)
Infections	2 (0.09)	46 (0.04)
Sudden infant death syndrome	10 (0.46)	124 (0.10)
Others	1 (0.04)	52 (0.04)
Total	16 (0.73)	324 (0.26)

*Percentage of all children at risk.

ish study, Geertinger and Theilade³⁴ found that schizophrenia and SIDS had a tendency to occur in the same families. They suggested a genetic association between schizophrenia and SIDS, which might be an explanation for the findings in this study. However, co-occurrence in families might also be caused by shared environmental risk factors. It is also possible that some of the SIDS deaths were disguised homicides, which may occur more frequently among children of women with schizophrenia.

It might be suspected that the occurrence of congenital malformations and infant deaths was increased among children of women with schizophrenia due to the administration of antipsychotic drugs during pregnancy or lactation. Altshuler et al⁴ concluded in a meta-analysis that first-trimester exposure to low-potency antipsychotic medications may lead to a small increase in the risk of congenital malformations. Little is known about risks associated with prenatal exposure to high-potency antipsychotic drugs and of newer antipsychotic drugs. However, most studies found that administration of haloperidol during pregnancy did not increase risk of congenital malformations.^{3,4} There may be an association between genetic or environmental risk factors contributing to schizophrenia and to congenital malformations. This hypothesis was supported by the findings of an increased prevalence of minor physical abnormalities or congenital malformations among people with schizophrenia^{35,36} and also among their relatives.^{5,37}

We found no difference in the risk of death or congenital malformations between children who were born

before or after their mothers' first psychiatric admission. This is probably due to the environmental risk factors such as smoking and socioeconomic disadvantages that may be present before the first admission.³⁸⁻⁴⁰ It also suggests that use of antipsychotic drugs during pregnancy is not a major risk factor for these outcomes.

The most important clinical implication of our findings is that pregnant women with schizophrenia, like other pregnant women, should be encouraged to refrain from smoking. Another clinical implication is that women with schizophrenia who keep custody of their children should have access to close supervision by health personnel to secure the well-being of the child and thereby prevent potentially avoidable infant deaths.

The association between congenital malformations and schizophrenia was weak in this study, a finding that should be tested in future studies. The association between schizophrenia and SIDS might be explained by common etiological factors and should be further investigated.

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