Fertility in Women With Type 1 Diabetes

A population-based cohort study in Sweden

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OBJECTIVE — The purpose of this study was to assess fertility in women with type 1 diabetes and the risk of congenital malformations in their offspring.

RESEARCH DESIGN AND METHODS — This was a register-based cohort study in Sweden. All 5,978 women hospitalized for type 1 diabetes at age ≤16 years identified in the Swedish Inpatient Register during 1965–2004 were followed until the end of 2004 through linkage to nationwide registers. A standardized fertility ratio (SFR), the ratio of observed to expected number of live births, with 95% CIs, was used to express the relative fertility rate. The proportion of newborns with congenital malformations was compared with that of the general population.

RESULTS — We observed 4,013 live births (SFR 0.80 [95% CI 0.77–0.82]). The SFRs for those who had retinopathy, nephropathy, neuropathy, or cardiovascular complications were 0.63, 0.54, 0.50, and 0.34, respectively. Stratified analyses by year of first hospitalization showed that the reduced fertility was confined to women first hospitalized before 1985, but the presence of complications was associated with subfertility in all calendar-year strata. The proportions of newborns with congenital malformations decreased from 11.7% during 1973–1984 to 6.9% during 1995–2004 but were consistently higher than the corresponding figures for the general population.

CONCLUSIONS — Women with type 1 diabetes have reduced fertility, but it appears that normalization has occurred among women with uncomplicated disease and an onset in the past 20 years. Our results suggest that the stricter metabolic control exercised in the past 20 years may have helped prevent subfertility. However, although the risk of congenital malformations has decreased, it is still higher than that for the general population.

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Previous small-scale studies of women with diabetes showed reproductive abnormalities such as delayed menarche and increased incidence of menstrual cycle irregularities (1) and delayed ovulation (2). With the refinement of insulin therapy, improved fertility might be expected, although fertility among type 1 diabetic women reportedly remained below that for the nondiabetic population in the 1980s (3). The presence of type 1 diabetes in pregnant women has been associated with adverse effects on the fetal outcomes of pregnancy, such as congenital malformations (4). An increased risk of congenital malformations among diabetic women has been reported (5). To our knowledge, there is no recent population-based epidemiological study on fertility rates over time among women with type 1 diabetes and the risk of congenital malformations in their offspring. In 1989, the St. Vincent Declaration set treatment goals for type 1 diabetes (6), one of which was to achieve equal pregnancy outcomes among women with diabetes compared with those without. To study whether this goal of the St. Vincent Declaration has been reached, we estimated fertility among women with type 1 diabetes and the risk of congenital malformations in their offspring in a nationwide population-based cohort study.

RESEARCH DESIGN AND METHODS

— With minor exceptions, in-hospital medical services in Sweden have been exclusively public, administered by the county councils and overseen by the National Board of Health and Welfare. Because patients have been obliged to use the hospitals in their county of residence, in-hospital care registration is, in practice, population-based and referable to the county where the patient lives. The Swedish Inpatient Register was established by the National Board of Health and Welfare in 1964–1965, but most counties joined the registration later, with the last one joining in 1987, when the Register became nationwide. Each record in the register corresponds to one hospital admission and contains, in addition to the patient's national registration number (NRN), a unique identifier assigned to all Swedish residents, the dates of admission and discharge, as well as codes for surgical procedures and discharge diagnoses. Codes that specifically differentiated between type 1 and type 2 diabetes, however, were introduced first with ICD 10 in 1997.

Women in Sweden who were first hospitalized for diabetes at age ≤16 years (thus almost exclusively all of whom had type 1 diabetes) were identified from the Inpatient Register. The NRNs permitted exact record linkages with the Register of Total Population, the Migration Register, and the Causes of Death Register. Fifty-eight records had NRNs that could not be found in any of these registers. Because these records could not be linked to any currently or previously existing person,

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Abbreviations: NRN, national registration number; SFR, standardized fertility ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

they were excluded. Further excluded were 110 patients with a recorded date of emigration or death before or on entry into the cohort and 2,276 patients born after December 31, 1988, who thus had not attained the age of 16 years before closure of follow-up. Our final cohort included 5,978 patients.

Information on the number of live births was obtained via linkage to the Swedish Multi-Generation Register. This register provides information on all first-degree relatives for residents born in Sweden in 1932 or later (index person). To be included in the register, the index person had to be alive in 1960 or born thereafter. Adoptions and other nonbiological relations are flagged (7).

Through linkage to the Swedish Medical Birth Register, information on congenital malformations of live newborns was obtained. The Medical Birth Register has received standardized information on all hospital births since 1973, including maternal demographic data, maternal reproductive and medical history, complications and treatments provided during pregnancy, delivery, and the neonatal period, and neonatal medical conditions. Antenatal, obstetric, and neonatal data are recorded on standardized records starting with the first antenatal visit and collected until the mother and child are discharged from the hospital after delivery. This Register includes >99% of all births in Sweden (8). This study was approved by the Regional Ethics Committee at Karolinska Institutet.

Statistical analysis

Cohort members were followed from age 16 until age 48 years, emigration, death, or the end of follow-up (31 December 2004), whichever occurred first. Standardized fertility ratios (SFRs), the ratio of the observed to the expected numbers of live births, were used as a measure of relative fertility, using age- and calendar year–matched Swedish women at large as a reference. CIs (95%) were calculated by assuming that the number of observed events followed a Poisson distribution (9,10). The expected number of births was calculated by multiplying the person-years experienced among the diabetic women in strata of age (1 year) and calendar year (1 year) by the stratum-specific fertility rates in the Swedish female population. The latter rates were calculated through dividing the number of live births in each stratum by the corresponding female midyear populations.

Complications of diabetes were identified through cross-linkage within the Inpatient Register. Stratified analyses were performed by the presence of diabetes complications, calendar period or age at index hospitalization for type 1 diabetes, and calendar period or age at follow-up. Person-time experienced before the onset of complications was allocated to the complication-negative strata. Thus, only diabetes complications diagnosed before live birth were reported in this study.

To isolate the independent effects of explanatory variables, we estimated relative effects on the standardized fertility ratios using a multivariable Poisson regression model with the log of the expected number as the offset, assuming multiplicative effects between outcome and explanatory variables. Pearson's χ^2 test was used to check the goodness of fit of the model (9). The Pearson's χ^2 statistic for the multivariate model was 93 with 43 degrees of freedom, which indicated a slight overdispersion of the model. A scale parameter, the square root of the Pearson's χ^2 divided by the degrees of freedom, was thus used to correct SEs.

The proportions of live newborns with congenital malformations of mothers with type 1 diabetes or the general Swedish female population were calculated by dividing the number of newborns with congenital malformations by the total number of live newborns. For the type 1 diabetes cohort, we also calculated Wald 95% CIs for the observed proportion on the basis of normal theory approximation. If the CIs did not include the proportion of the corresponding general Swedish female population, their difference was deemed to be statistically significant.

Maternal death was defined as the death during pregnancy or within 42 days after live birth and was identified through linkage to the Causes of Death Register (ICD-7 codes 640–689, ICD-8 codes 630–678, ICD-9 codes 630–676, and ICD-10 codes O00–O99).

RESULTS

— On average, the 5,978 cohort members were followed for 13.3 years, yielding 79,774 person-years (Table 1). Retinopathy, nephropathy, neuropathy, and cardiovascular complications were recorded in 34.4, 14.8, 9.4, and 7.5%, respectively, among women who were first hospitalized for type 1 diabetes before 1985 and in 5.2, 1.9, 1.4, and 0.9% among those hospitalized in 1985 and thereafter. During follow-up, 4,013 live births were noted. The mean age at first live birth during the entire observation period was 25.8 years, and it increased from 21.1 in the period 1970–1979 to 23.9, 26.1, and 27.5 for periods 1980–1989, 1990–1999, and 2000–2004, respectively.

The overall observed number of live births was smaller than expected (SFR 0.80 [95% CI 0.77–0.82]) (Table 2). There was no important variation of SFR by age at first hospitalization for diabetes. On the other hand, relative fertility increased monotonically with calendar year of first hospitalization ($P_{trend} < 0.01$) and was close to the expected rate among women with a first hospitalization after 1984. In accordance with this trend, relative fertility increased with calendar year of follow-up ($P_{trend} < 0.01$), albeit the fertility was still significantly below expectation in 2000–2004. Also consistent with improved fertility in successive subcohorts according to calendar time of first hospitalization for diabetes was a decreased relative fertility with attained age; the oldest age-group (40–48 years) exhibited a 43% reduction compared with the age- and period-matched women in the background population. The SFRs for those who were ever hospitalized for retinopathy, nephropathy, neuropathy, and cardiovascular complications were 0.63 [0.58–0.68], 0.54 [0.47–0.62], 0.50 [0.41–0.61], and 0.34 [0.22–0.51], respectively (Table 2).

Moreover, we grouped our cohort into women who were first hospitalized before 1985 and those who were hospitalized in 1985 and thereafter and then further stratified by calendar year at follow-up, attained age, and presence of diabetes complications (Table 3). This analysis showed that the subfertility observed in the group hospitalized before 1985 remained through all calendar years of follow-up but that SFRs fell considerably with attained age at follow-up. With the exception of a significant deficit in fertility among the oldest women, those who were first hospitalized in 1985 or later exhibited essentially normal fertility rates in virtually all substrata. However, similar to the subcohort included before 1985, the presence of diabetes complications was associated with a substantially decreased fertility (SFR 0.77 [95% CI 0.60–0.98]) also in the subcohort included in 1985 or later.

In a Poisson regression model with mutual adjustments for calendar year and age at first hospitalization for diabetes, the

Table 1—*Characteristics and fertility of the women who were first hospitalized for type 1 diabetes at age ≤16 years, 1965–2004, Sweden*

Patient characteristics	Total	Calendar year at first hospitalization for type 1 diabetes before 1985	Calendar year at first hospitalization for type 1 diabetes during or after 1985
n	5,978	2,773	3,205
Calendar year at entry	1990	1983	1997
Follow-up duration (years)	13.3 ± 8.9	20.5 ± 6.6	7.1 ± 5.1
Person-years accumulated	79,774	56,888	22,886
Percentage of women ever experiencing (%)			
Retinopathy*	18.7	34.4	5.2
Diabetic nephropathy†	7.9	14.8	1.9
Neuropathy‡	5.1	9.4	1.4
Cardiovascular complications§	4.0	7.5	0.9
No. of live births	4,013	31,24	889
Age at first delivery (years)	25.8	26.3	24.2

Data are means or means ± SD unless otherwise indicated. *Retinopathy defined by ICD-7 codes 260.20, 260.21, and 260.29; ICD-8 codes 250.01, 250.02, and 250.03; ICD-9 codes 250E; and ICD-10 codes E10.3, E11.3, E12.3, E13.3, and E14.3. It included aneurysm, inter-retinal edema, intraocular pathologic neovascularization, simplex retinopathy, and proliferative retinopathy. †Diabetic nephropathy defined by ICD-7 code 260.30; ICD-8 code 250.40; ICD-9 code 250D; and ICD-10 codes E10.2, E11.2, E12.2, E13.2, and E14.2. It included persistent proteinuria, from microalbuminuria progressing to albuminuria; reduced glomerular filtration rate; and end-stage renal disease. ‡Neuropathy defined by ICD-7 codes 260.40 and 260.49; ICD-8 code 250.05; ICD-9 code 250F; and ICD-10 codes E10.4, E11.4, E12.4, E13.4, and E14.4. It included third nerve palsy, mononeuropathy, mononeuropathy multiplex, diabetic amyotrophy, a painful polyneuropathy, autonomic neuropathy, thoracoabdominal neuropathy, and unspecified diabetic neuropathy. §Including ischemic heart diseases defined by ICD-7 code 420, ICD-8 codes 410–414, ICD-9 codes 410–414, and ICD-10 codes I20–I25; diseases of arteries, arterioles, and capillaries defined by ICD-7 codes 450–456, ICD-8 codes 440–448, ICD-9 codes 440–448, and ICD-10 codes I70–I79, I98.8, and I99; and surgery for cardiovascular diseases (Swedish codes for surgical procedures 8800–8839 and 8861–8869 before 1997 and PA–PG for 1997 and thereafter).

presence or absence of diabetes complications, and the duration of type 1 diabetes, the relative fertility was significantly lower for those who were first hospitalized for type 1 diabetes before 1985, compared with those hospitalized in 1985 and thereafter (online Appendix 1 [available at http://dx.doi.org/10.2337/dc06-2574]). Hence, this effect was independent of the presence or absence of recorded diabetes complications. The presence of such complications was associated with a markedly reduced relative fertility, independent of calendar year at first hospitalization for diabetes. Age at first hospitalization was unrelated to relative fertility in univariable analysis but was inversely related to relative fertility in multivariable analysis. In both univariable and multivariable analysis, a longer duration of type 1 diabetes was associated with lower relative fertility.

We identified 3,979 live births during the period 1973–2004, and among them 3,815 were found also in the Medical Birth Register. The overall proportion of live newborns with congenital malformations was 7.4% [95% CI 6.6–8.3], which was significantly higher than the corresponding proportion of 4.2% observed in the general population. For the type 1 diabetes cohort, the proportion was highest during 1973–1984 (11.7%), and then it dropped to 7.3 and 6.9% for calendar periods 1985–1994 and 1995–2004, respectively. However, in all three calendar periods, the proportions were consistently higher than the corresponding figures for the general population (online Appendix 2).

We did not observe any maternal deaths during the entire follow-up period. The expected number, based on one previous Swedish study (11), was only 0.3, however.

CONCLUSIONS — To our knowledge, this is the first population-based epidemiological study on fertility rates over time among women with type 1 diabetes. Overall, the fertility among women with type 1 diabetes recorded between 1965 and 2004 was reduced by 20%. Importantly, the lowest SFRs were observed among women who had their first hospitalization for diabetes in the earliest years, and SFRs increased monotonically with calendar year of first hospitalization to become statistically indistinguishable from 1.0 after 1984. The presence of diabetic microvascular or cardiovascular complications was associated with particularly low fertility, essentially regardless of year of first hospitalization. Although the proportions of live newborns with congenital malformations of mothers with type 1 diabetes had decreased for the last 30 years, it was still twice that of the general Swedish female population in most recent years.

Our analyses indicated that the improvement in fertility in the subcohort with calendar year of first hospitalization after 1984 was essentially independent of complication status, age at first hospitalization, and duration of diabetes. This suggests that this cohort effect is real and is probably attributable to interventions that were used increasingly across successive subcohorts defined by year of first recorded hospitalization for diabetes. The improvement in the intervention includes stricter metabolic control, better control of blood pressure, and more frequent use of drugs active in blocking the renin-angiotensin system, which may decrease the development and progression of diabetic nephropathy and possibly retinopathy as well as endothelial function that may contribute to fertility. As the improvement was equally evident among women with and without recorded diabetes complications, this result implies that metabolic control was improved in patients independent of complications. However, women with manifest complications always had lower fertility than those without these complications. The national program for treatment of diabetes launched in 1990 prescribed that all women who planned to become pregnant were to follow a stricter insulin treatment plan, and this measure may have played a critical role (12). According to this program, women have been advised to use

Table 2—*SFRs and corresponding 95% CIs among women first hospitalized for type 1 diabetes at age ≤16 years, stratified by calendar year and age at first hospitalization, calendar year and age at follow-up, or type of complications,1965–2004, Sweden*

	Live births		
	Expected	Observed	SFR (95% CI)
Total	5,040	4,013	0.80 (0.77–0.82)
Age at first hospitalization for type 1 diabetes			
≥5 years	393	319	0.81 (0.72–0.91)
6–10 years	1,372	1,122	0.82 (0.77–0.87)
11–16 years	3,275	2,572	0.79 (0.76–0.82)
P_{trend}			0.30
Calendar period at first hospitalization for type 1 diabetes			
1965–1969	408	237	0.58 (0.51–0.66)
1970–1974	1,001	686	0.69 (0.63–0.74)
1975–1979	1,486	1,114	0.75 (0.71–0.80)
1980–1984	1,253	1,087	0.87 (0.82–0.92)
1985–1989	694	671	0.97 (0.89–1.04)
1990–1994	166	189	1.14 (0.98–1.31)
1995–2004	31	29	0.92 (0.62–1.32)
P_{trend}			<0.01
Calendar period at follow-up			
1965–1979	212	158	0.75 (0.63–0.87)
1980–1989	1,014	688	0.68 (0.63–0.73)
1990–1999	2,368	1,916	0.81 (0.77–0.85)
2000–2004	1,446	1,251	0.87 (0.82–0.91)
P_{trend}			<0.01
Attained age at follow-up			
16–19 years	205	184	0.90 (0.77–1.04)
20–24 years	1,327	1,158	0.87 (0.82–0.92)
25–29 years	1,925	1,569	0.82 (0.78–0.86)
30–34 years	1,215	873	0.72 (0.67–0.77)
35–39 years	332	209	0.63 (0.55–0.72)
40–48 years	35	20	0.57 (0.35–0.88)
P_{trend}			<0.01
Diabetic retinopathy*			
No	4,009	3,364	0.84 (0.81–0.87)
Yes	1,030	649	0.63 (0.58–0.68)
Diabetic nephropathy*			
No	4,660	3,807	0.82 (0.79–0.84)
Yes	380	206	0.54 (0.47–0.62)
Diabetic neuropathy*			
No	4,837	3,911	0.81 (0.78–0.83)
Yes	203	102	0.50 (0.41–0.61)
Cardiovascular complications*			
No	4,970	3,989	0.80 (0.78–0.83)
Yes	70	24	0.34 (0.22–0.51)

The age- and calendar year–matched Swedish women at large were used as a reference population. The SFRs are thus inherently adjusted for attained age and calendar year. *Person-time experienced before the onset of complications was allocated to the complication-negative strata.

contraceptive measures when they have poor metabolic control.

Earlier findings showed that women with type 1 diabetes more often are nulliparous or have fewer pregnancies than women without diabetes (3,13). Before 1990, it was common practice to advise against pregnancies if the woman had simplex retinopathy or microalbuminuria. In the most recent decade, however, women with such complications have not been discouraged to become pregnant, but strict metabolic control has been zealously enforced. Insufficient metabolic control affects the homeostasis of the hypothalamus-pituitary-ovary axis, which in turn could result in delayed menarche and menstrual disturbances (14,15). Indeed, patients with diabetes complications have shown a higher incidence of menstrual disorders compared with those without complications (1). Delayed menarche and early onset of menopause shorten the reproductive years by 17% (15). Reduced fertility may also be due to impaired activity of the IGF axis seen in type 1 diabetes (16). Animal models with lower IGF-I and higher IGF binding protein-1 levels showed reduced fertility (17,18). It is fairly well established that

Table 3—*SFRs and corresponding 95% CIs, stratified by calendar period at follow-up, attained age at follow-up, and presence of any diabetes complications, among women first hospitalized for type 1 diabetes at age ≤16 years, grouped by calendar period at first hospitalization before 1985 or in 1985 and thereafter, 1965–2004, Sweden*

	Calendar year at first hospitalization before 1985			Calendar year at first hospitalization during or after 1985		
	Live births			Live births		
	Expected	Observed	SFR (95% CI)	Expected	Observed	SFR (95% CI)
Calendar period at follow-up						
1965–1979	212	158	0.75 (0.63–0.87)	—	—	—
1980–1989	1,010	679	0.67 (0.62–0.73)	5	9	1.93 (0.88–3.67)
1990–1999	2,056	1,594	0.78 (0.74–0.81)	311	322	1.03 (0.92–1.15)
2000–2004	870	693	0.80 (0.74–0.86)	576	558	0.97 (0.89–1.05)
Attained age at follow-up						
16–19 years	139	114	0.82 (0.68–0.99)	66	70	1.06 (0.83–1.34)
20–24 years	983	799	0.81 (0.76–0.87)	345	359	1.04 (0.94–1.16)
25–29 years	1,565	1,208	0.77 (0.73–0.82)	360	361	1.00 (0.90–1.11)
30–34 years	1,096	775	0.71 (0.66–0.76)	120	98	0.82 (0.67–1.00)
35–39 years	330	208	0.63 (0.55–0.72)	2	1	0.54 (0.01–2.99)
40–48 years	35	20	0.57 (0.35–0.88)	—	—	—
Presence of diabetes complications*						
No	3,071	2,440	0.79 (0.76–0.83)	805	822	1.02 (0.95–1.09)
Yes	1,077	684	0.64 (0.59–0.68)	87	67	0.77 (0.60–0.98)

The age- and calendar year–matched Swedish women at large were used as reference. The SFRs are thus inherently adjusted for attained age and calendar year.
*Including ophthalmic complications, diabetic nephropathy, neurological complications, and cardiovascular complications.

adverse pregnancy outcomes, including spontaneous abortion (19) and still births (5,20), are more common among women with type 1 diabetes than among women without this disease. Both hyperglycemia and low IGF-1 can explain the development of micro- and macrovascular complications as well as impaired fertility. Psychosocial mechanisms may also contribute; as a chronic disease, type 1 diabetes could negatively affect patients' attitudes toward having children (13).

The teratogenic mechanism in infants of diabetic mothers is complicated and not known completely. A number of potential factors, such as hyperglycemia and ketosis, as well as other factors in the diabetic process, may play different roles (21). The susceptibility to teratogenic factors occurs mainly during the period of organogenesis, which corresponds to the first 8 weeks of gestation (22). Hyperglycemia at the time of conception and organogenesis are major teratogenic factors (23). An animal study showed that dysmorphogenesis in embryos is caused by high blood glucose through an interaction of oxidative stress and inositol depletion (24).

The strengths of our study include the cohort design, the population-based approach, and the use of information from virtually complete national registers rather than reliance on self-reports. Because almost all NRNs in our cohort were verified in the registers, follow-up was practically complete and without bias.

Caveats to be highlighted include the lack of any specific diagnostic codes that distinguished between type 1 and type 2 diabetes in the Swedish Inpatient Register before 1997. Although the admixture of type 2 diabetes should be negligible among patients hospitalized before the age of 17, we may have missed some women with late-onset type 1 diabetes. We were also unable to identify patients whose diabetes was managed entirely on an outpatient basis, but because it has been consistently recommended in Sweden that all pediatric patients with new-onset type 1 diabetes be hospitalized at least once in their early course for insulin treatment and education on diabetes control (25,26), we believe that the proportion of missed cases is negligible. Left truncation before the start of registration probably led to misses of the true first hospitalization in some of the earlier patients. Hence, the second (or third or higher) hospitalization might then have been misinterpreted as the first. If it is assumed that the number of hospitalizations during childhood and adolescence is related to severity of the diabetes, we may to some extent and have inadvertently selected patients with more severe forms of the disease in the early part of this study. This selection could have contributed to a spuriously strong finding toward improvement over time. Another limitation of our study is that the proportion of women with diabetes complications in our cohort was low. The prevalence of mild diabetic neuropathy may have been underestimated as the onset is insidious and easily overlooked at young ages. The prevalence of complications may also be underestimated because of nonspecific reporting in the Inpatient Register. Thus, it is likely that patients with more than one type of complication have been registered as having multiple complications, which then was not recorded in our study. However, severe diabetes complications were recorded. The underascertainment of complications might have falsely lowered the fertility in the group without complication because this group may be mixed with some patients with undiagnosed complications.

It must also be emphasized that, because of early censoring in the substrata included in the cohort in more recent periods, the number of observed births in these substrata was limited. The trend toward improved fertility was less certain in these groups. Swedish women in general have tended to delay childbearing to older ages for social reasons. The mean ages at first birth for periods 1970–1979, 1980–1989, 1990–1999, and 2000–2004 were

24.5, 25.9, 27.2, and 28.6 years, respectively. The mean age of first birth has increased by no less than 3 years in the past 20 years (http://www.scb.se/statistik/BE/BE0701/2005I01/Ålder%20första%20barn%20regionalt%201970-2004.xls); thus, the fertility in the reference population has gone down. Although a similar trend in the average age at first live birth was observed in the diabetic cohort, the younger mean age before 1990 in women with type 1 diabetes may be due to the advice to the older women to avoid pregnancy if they have had some mild complications, which increase with the duration of diabetes.

In summary, women hospitalized for type 1 diabetes for the first time before 1985, especially those with diabetes complications, had reduced fertility compared with the matched general Swedish female population. Women with type 1 diabetes first hospitalized after 1985 had reduced fertility only if they had diabetes complications. Thus, our population-based results suggest that the new strategy with more rigorous metabolic control instituted in the mid- or late 1980s has been successful also with regard to fertility. However, the risk of congenital malformations in live newborns of mothers with type 1 diabetes is higher than that of mothers in the general Swedish population although a decreasing trend has been observed in the last 30 years. To reach the aims of the St. Vincent Declaration, it is important to offer women with type 1 diabetes strict metabolic control to prevent or postpone the occurrence of diabetes complications, including subfertility. Prevention of congenital malformations in offspring of mothers with type 1 diabetes should also be emphasized. Corresponding methods for the improvement of pregnancy outcomes should be designed and implemented.

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