

Gestational diabetes as possible risk factor for Type I childhood-onset diabetes in the offspring

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Abstract

Epidemiological, clinical, as well as experimental findings obtained during the past two decades in Germany suggest that gestational diabetes might be a predisposing factor for increased risk of Type I childhood-onset diabetes in the offspring, which could therefore be prevented—at least in part—by systematic diagnostic screening and correction of maternal hyperglycemia during pregnancy.

Introduction

The incidence rates of Type I childhood-onset diabetes show rapid increases in many parts of the world [1, 2, 3]. Such rapid increases during short periods cannot be explained by genetic but rather by epigenetic environmental risk factors. It is more and more accepted that disturbances of the intrauterine metabolic and hormonal environment may lead to a “programming” of infant and adult diseases [4, 5]. Gestational diabetes (GD) is well known to be such a detrimental condition, leading to increased risk for the offspring to develop overweight or the metabolic Syndrome X in later life [5–10]. A possible increased risk of Type I diabetes in the offspring of GD mothers was hardly considered until now, in general.

Experimental observations

Some experimental data in perinatally hyperinsulinemic offspring of gestational diabetic mother rats clearly indicate an increased risk even to develop Type I-like diabetes:

- 1) In maternal-side F1 and even F2 offspring of streptozotocin (STZ)-treated gestational diabetic mother rats (F0) spontaneous GD, basal hyperinsulinemia from birth into adulthood, indicating persisting basal overstimulation of the pancreatic β -cells, and, most important, a severe insulin deficient Type I-like diabetes after a single low dose STZ-treatment were observed in contrast to the offspring of control mothers [6]. Multiple low dose STZ-treatment is a well known model for Type I-like diabetes in rats accompanied by cell mediated immune responses which closely resemble the autoimmune processes associated with infantile Type I diabetes in the human.
- 2) Indeed, offspring of GD mother rats responded to multiple low dose STZ-treatment with increased spleen cell cytotoxicity to syngeneic β -cells as compared to control rats [11]. Note, Botazzo et al. [12] have emphasized that overstimulation and hyperactivity of endocrine cells in general and of β -cells in particular may lead to an increased expression of HLA class II antigens. If an additional noxious agent, e.g. a virus or STZ, gives rise to the production of autoantigens, a strong autoimmune response can result, leading to overt Type I diabetes. Permanent basal hyperactivity of pancreatic β -cells in GD offspring—as indicated by persisting basal hyperinsulinaemia from birth to adulthood—may be the result of a neuroendocrine “malprogramming” acquired during fetal

and neonatal life of the hypothalamo-pancreatic neuroendocrine axis [5, 6, 10, 13–15].

- 3) As a model for perinatal elevation of insulin characteristic for GD offspring, exogenous insulin treatment of newborn rats, even when only intrahypothalamically performed, was followed by persisting basal hyperinsulinemia, decreased glucose tolerance, and increased susceptibility to low dose STZ Type I-like diabetes in later life [5, 13–16].

Epidemiological and clinical observations

Noteworthy, a low insulin response to glucose load, which is well known to indicate increased Type I diabetes risk, was observed not only in the offspring of GD mother rats [6, 7] but also in children of GD mothers in humans [17]. It should be further mentioned that epidemiological studies revealed a clear-cut predominance of familial Type II diabetes aggregation on the maternal side of infantile and juvenile Type I diabetics [18]. Familial type II diabetes aggregation on the maternal side is also a risk factor for GD [19, 20].

With regard to these data it should be kept in mind that already during the 1970s and 1980s a pilot project in East-Germany (former GDR) aimed to prophylactically correct for the continuously increasing rates of GD (see below). The diabetics of all ages living in East Germany were annually recorded by the Ministry of Health up to 1989. In addition, the incidence rates of pregnant diabetics, in particular of gestational diabetics, were recorded by five obstetric centers. In 1973, a special screening and health care system for pregnant diabetics was initiated in East Berlin. The aim was to achieve strict normoglycemia for pregnant women during pregnancy. Similar measures were then successively introduced in other districts of East Germany [5, 21]. In this context, several remarkable findings were obtained:

- 1) The prevalence rate of diabetic children under 10 years of age who were born in East Berlin between 1973 and 1982, i.e. following the introduction of systematic diagnostic screening and therapeutic measures for pregnant women with diabetes had been significantly decreased to less than 1/3 as compared to the prevalence rate in those children born in the decade before [22].
- 2) Between 1979 and 1983 significantly more gestational diabetics, especially non-insulin-dependent pregnant diabetics, were then screened and consequently treated not only in East Berlin but also in Halle and Leipzig compared to the other dis-

tricts of the former GDR. Interestingly enough, a significant lower prevalence rate (1/3) of infantile-onset diabetics born during this period was then found not only in Berlin but also in Halle and Leipzig as compared to the other districts of East Germany [21].

- 3) Even a significant inverse correlation could be demonstrated for the 15 districts of the former GDR between the rates of diagnosed and treated pregnant diabetics and the prevalence rates of diabetic children under 5 years of age who were born during this period [22].

With regard to the observations mentioned above, the following recent data on the development of Type I childhood-onset diabetes (analyzed by Poisson Regression) and gestational diabetes in Germany during the past decade seem to be most important (Table I: next page):

- 1) In 1987–89, i.e. before the reunification of Germany, the incidence rates of Type I diabetic children under 10 years of age were 5.01 (95%-CI: 4.49–5.57) per 10^5 person-years (py) in East Germany and 9.38/ 10^5 py (95%-CI: 8.31–10.54) in West Germany (Baden-Württemberg; $p < 0.001$, χ^2 -test), and in children under 5 years of age 3.00/ 10^5 py in East Germany and 5.81/ 10^5 py in West Germany ($p < 0.001$), i.e. about two times lower in East Germany than in West Germany [23–26].
- 2) On the other hand, in 1995–97 in East Germany the incidence rate of Type I diabetic children under 5 years of age was even slightly, but not significantly, higher in East Germany (10.81/ 10^5 py) than in West Germany (9.52/ 10^5 py) [2, 26].
- 3) Thus, the incidence rate for Type I diabetic children under 5 years of age increased between 1987–89 and 1995–97 from 3.00/ 10^5 py up to 10.81/ 10^5 py in East Germany (3.6-fold) but only from 5.81/ 10^5 py up to 9.52/ 10^5 py in West Germany (1.64-fold). Hence, after the breakdown of a centralized special health care for pregnant diabetics and gestational diabetics, respectively, in East Germany the increase rate was more than 2.2-times higher than in West Germany ($p < 0.001$). Moreover, the incidence in East Germany is likely to be underestimated, because completeness of ascertainment of new diabetic children was lower in East Germany than in West Germany during 1995–97 [2, 26].
- 4) Finally, in parallel, the frequencies of GD seem to have more than doubled. GD was calculated to occur in about 5–6% of pregnant women in Ger-

many in the 1980s [27]. On the other hand, recent data suggest that the prevalence of GD is meanwhile about 13% [28], while no general screening exists. Most alarming, it was calculated that more than 80% of GD cases are not screened and treated [28, 29].

Conclusion

From all the experimental and epidemiological data presented, we speculate that gestational diabetes might be an important predisposing factor for increased risk to develop Type I childhood-onset diabetes mellitus in the offspring. Increased disposition might be due to perinatally acquired “malprogramming” and vulnerability due to the diabetic intra-uterine environment offspring of GD are exposed to. Specific mechanisms seem to include neuroendocrine alterations and should be further clarified in future studies. However, most of all our observations indicate that an increased risk to develop Type I childhood-onset diabetes in the offspring of GD mothers could be preventable—at least in part—by systematic or even general screening of hyperglycemia and even glucose intolerance in pregnant

Table 1. Incidence rates of Type I diabetes in children under 5 years of age in West Germany (Baden-Württemberg) and East Germany (former GDR) in 1987–1989 and in 1995–1997.

Calendar years	Region	No. of cases	Person-years at risk	Incidence rate (95%-CI)	IRR (95%-CI) East vs. West Germany by period	p	IRR (95%-CI) 1995-97 vs. 1987-89 by region	p	Ratio (95%-CI) of Incidence increases East vs. West Germany	p
1987–89	West	89	1,531,025	5.81 (4.67–7.15)	1		1			
	East	100	3,333,986	3.00 (2.44–3.65)	0.52 (0.39–0.69)	< 0.001	1			
1995–97	West	166	1,744,457	9.52 (8.12–11.08)	1		1.64 (1.27–2.12)	< 0.001	1	
	East	135	1,248,453	10.81 (9.07–12.80)	1.14 (0.91–1.43)	0.270	3.61 (2.78 - 4.67)	< 0.001	2.20 (1.53–3.17)	< 0.001

IRR: incidence rate ratio, p: p-value of χ^2 -test (Poisson Regression Analysis)

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