Use of Maternal GHb Concentration to Estimate the Risk of Congenital Anomalies in the Offspring of Women with Prepregnancy Diabetes

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OBJECTIVE — We sought to determine the absolute risk of having a congenital anomaly in relation to periconceptional GHb concentration among women with prepregnancy diabetes.

RESEARCH DESIGN AND METHODS — Two reviewers independently retrieved all cohort studies through a systematic literature search between January 1985 and May 2006. For each study, the absolute risk of having a pregnancy affected by a major or minor structural anomaly (diagnosed either antenatally or up to 28 days after conception) was calculated according to the number of SDs of GHb above the mean for nondiabetic, nonpregnant control subjects. A multilevel logistic-normal model was used to pool the data, which were expressed in tabular and graphic formats.

RESULTS — In seven cohort studies, there were 117 anomalies among 1,977 pregnancies. At a periconceptional GHb concentration 0 SD above normal, the absolute risk of a pregnancy affected by a congenital anomaly was ~2% (95% CI 0.0–4.4). At 2 SD above normal, the risk was 3% (0.4–6.1), and at 8 SD it was ~10% (2.3–17.8). For each 1-SD unit increase in GHb, the associated risk of a congenital malformation increased by an odds ratio of 1.2 (95% CI 1.1–1.4). The risk in relation to A1C followed the same pattern.

CONCLUSIONS — Using data from a limited number of published studies, a practical aid was developed to optimize use of the GHb and A1C concentrations for estimating the absolute risk of a congenital anomaly in the offspring of women with prepregnancy diabetes.

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The offspring of women with prepregnancy diabetes are at increased risk of having a structural congenital anomaly (1–3). It is hypothesized that hyperglycemia exerts a teratogenic effect on the developing fetus (4,5). There is a positive association between poor glycemic control in the periconcep-tion period and the risk of such anomalies (1,6–10).

Those who counsel women with prepregnancy diabetes currently lack a valid, standardized method to estimate of the risk of a fetal anomaly in relation to the periconceptional GHb concentration, a measure of glycemic control (10). We undertook a meta-analysis to determine the absolute risk of congenital anomalies in relation to periconceptional GHb.

RESEARCH DESIGN AND METHODS

Literature search

Two investigators independently searched PubMed and Embase databases from January 1985 to May 2006. The following search expression was used: "(diabetes OR diabetes mellitus) AND (anomaly OR congenital anomaly OR malformation OR congenital malformation OR organ system OR birth defect) AND (periconception OR periconceptional OR preconception OR preconceptional OR perinatal OR first trimester) AND (glycosylated hemoglobin OR HbA_{1c})". All searches were limited to English language and human studies. The bibliographic references of all articles were searched for additional papers.

The abstract of each article was read and determined for eligibility according to the following criteria: *1*) a cohort study comprising at least 20 women with prepregnancy diabetes; *2*) GHb levels were measured in the periconception period, defined as the period from 17 weeks before conception up to the completion of the first trimester of pregnancy (i.e., up to 16 weeks' gestation); *3*) the associated number of congenital malformations was provided at each category of GHb concentration; and *4*) reference values for the GHb (i.e., assay mean and SD) were provided for a nondiabetic control population. Full-text articles deemed eligible were reviewed by A.G. and J.G.R. to ensure that they met the inclusion criteria.

Data abstraction

A.G. and J.G.R. abstracted data into standardized tables. Information about the study and participant characteristics, as well as the GHb assay used, was included in Table 1. The methods used to detect congenital anomalies were incorporated into Table 2. We considered any major or minor structural anomaly diagnosed either antenatally or up to 28 days after conception. We only counted those pregnancies (in the numerator and denominator) that did not result in spontaneous abortion, as determined by the authors of each study.

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

Anomalies were further broken down according to major anatomical systems (Table 3).

As presented in Table 4, we standardized the reported GHb values across studies by converting values into units of SD from the nondiabetic, nonpregnant control mean value provided in each study, as follows: GHb SD = (GHb % value − mean % GHb control assay value)/SD GHb control assay.

For example, if a reported GHb % value was 8%, the nondiabetic mean % control value for the assay was 6%, and the SD control value was 1%, then GHb SD = 2. The mid-point GHb was used when GHb values were reported as an interval; if a lower or upper limit for GHb was provided, then that value was used.

Statistical analysis

The association between the GHb SD and the proportion (i.e., absolute risk) of major or minor anomalies was meta-analyzed using a multilevel model, a modification of our previous method (11). Specifically, we fitted the logistic-normal model (12), where the number of anomalies for each GHb SD category within each study follows a binomial distribution based on the number of births and proportion of anomalies (online appendix 1 [available at http://dx.doi.org/10.2337/dc07-0278]). A crude odds ratio (OR) and 95% CI was estimated according to each 1-unit increase in GHb SD.

Because A1C is now the most commonly used measure of GHb, we used the study data to determine the A1C values corresponding to each GHb SD. Specifically, a nonweighted mean ± SD population reference value was averaged from those studies that measured A1C. The previous equation was then rewritten to derive a series of A1C values, as follows: A1C = (GHb SD) × (SD GHb control assay) + mean % GHb control assay value.

Using the GHb SD categories derived from each study, the estimated corresponding A1C values were presented accordingly, and the absolute risk of major or minor, in association with A1C, was graphically plotted.

PROC NLMIXED in SAS (version 9.1.3) was used for all analyses. The model and SAS program codes are provided in online appendix 1.

RESULTS — A total of 45 citations were initially found in PubMed and 33 in Embase. Of the 75 full-text articles that

Table 1—*Study and participant characteristics and methods used to measure GHb*

Study and participant characteristics						GHb		
Year (reference)	Design	Study setting; period	No. with type 1/type 2 diabetes	Mean ± SD maternal age (years)	Definition of periconception period	Assay used	GHb measure	Mean ± SD for nondiabetic, nonpregnant control subjects (%)
1987 (6)	Prospective cohort	Single U.S. medical center; 1979–1984	63/20	25.6 ± NA	<15 weeks' gestation	Spectrophotometric absorption	A1C	5.1 ± 1.1
1988 (7)	Prospective cohort	U.S. university; 1978–1986	134/0	25.0 ± NA	Recruited during first trimester of pregnancy	1978–1980: high-performance liquid chromatography; 1981–1986: column chromatography	HbA_1	NA*
1989 (8,9)	Prospective cohort	Large U.S. diabetes center; 1984–1992	599/0	29.1 ± NA	≤12 weeks' gestation	Electrophoresis	A1C	5.9 ± 0.57
1989 (13)	Prospective cohort	Single U.S. hospital; 1980–1985	87/0	NA	<16 weeks' gestation	Ion exchange chromatography	HbA_{1a+b+c}	6.0 ± 1.0†
2000 (14)	Prospective cohort	Finnish university hospital; 1988–1997	663/0	NA	5–10 weeks' gestation	High-performance liquid chromatography	A1C	4.9 (0.32)
1991 (15)	Prospective cohort	California, U.S. database; 1982–1988	84/0	29.7 ± 4.4	Participation prior to conception	High-pressure column chromatography	A1C	6.2 ± 0.7
1988 (16)	Prospective cohort	U.S.	327/0	27.8 ± 4.0	Before conception and up to 21 days after conception	Thiobarbituric acid colorimetric method	NA	NA

*Not provided, but the number of SD was given in paper. †SD estimated from the reported range of values.

Table 2—*Methods used to detect for congenital anomalies in studies of women with prepregnancy diabetes*

	Method(s) described for the systematic detection of congenital anomalies					
Year (reference)	Anatomical ultrasound in utero	Maternal serum or amniotic fluid α-fetoprotein	Physical examination of all infants after birth	Autopsy of all fetal and neonatal deaths	Were these detection methods equally applied to all women?	Were assessors masked as to the mother's glycemic control?
1987 (6)	Some	No	Yes	No	No	NA
1988 (7)	Yes	No	Yes	Yes	Yes	NA
1989 (8,9)	Yes	No	Yes	Yes	Yes	Yes
1989 (13)	No	No	Yes	NA	Yes	Yes
2000 (14)	No	No	Yes	No	Yes	NA
1991 (15)	No	No	No	No	NA	NA
1988 (16)	No	No	Yes	No	Yes	Yes

were further examined, 7 prospective cohort studies were included in the final analysis (6–9,13–16) (Table 1). All studies originated from U.S., except for one, which was from Finland (14). Most study participants had type 1 diabetes, but one included 20 participants with type 2 diabetes (6), together representing 1,977 pregnancies (Table 1). The exact number of women who had more than one pregnancy was not known. In one study, participants were divided according to receipt of preconception care (6); since the postconception group included pregnancies up to 20 weeks' gestation, only preconception participants were included herein.

Table 2 describes the various screening methods used to detect congenital anomalies in the neonates. In all studies, infants were examined at birth, with the exception of one study (15). Other methods of identifying anomalies, such as anatomical ultrasonography or neonatal autopsy, were not performed. No study described the use of maternal serum screening or amniocentesis as screening methods but was mostly done in the era before these modalities were commonly available.

GHb values

A variety of methods were used to measure GHb (Table 1). Four studies measured A1C (6,8,9,14,15), and the others HbA_1, HbA_{1a+b+c}, or "glycosylated hemoglobin." The corresponding GHb SD values are listed in Table 4.

Congenital anomalies

There were 117 structural anomalies (5.9%) reported among 1,977 pregnancies. The majority involved the cardiac (36.8%), central nervous (20.8%), and urogenital systems (13.6%) (Table 3).

The number of congenital anomalies varied by study and according to GHb SD. The overall absolute risk of malformations ranged from 1.2% (95% CI 0.03–6.5) (15) up to 16.1% (8.4–23.8) (13). About 850 (43%) of all pregnancies and 43 (37%) of all anomalies arose in women whose GHb SD was ≤4 SD above normal (Table 4).

Association between GHb SD and congenital anomalies

The predicted risk and 95% CI of a major or minor congenital anomaly is presented according to the number of GHb SD above normal (Fig. 1*A* and online appendix 2). Thus, at a periconceptional GHb concentration 0 SD above normal (i.e., equivalent to a woman without diabetes), the absolute risk of a pregnancy affected by a congenital anomaly was ~2% (95% CI 0.0–4.4), which is approximately the same as the general population (10). However, at 2 SD above normal, the absolute risk was 3% (0.4–6.1), while at 8 SD above normal it was ~10% (2.3–17.8) (Fig. 1*A*). For each 1-unit increase in the GHb SD, the associated risk of any congenital malformation increased by an OR of 1.2 (95% CI 1.1–1.4).

Association between A1C and congenital anomalies

A mean ± SD population reference value of 5.5 ± 0.7% was averaged from the four studies that measured A1C (6,8,9,14,15). Thus, solving for the second above-listed equation: A1C = (GHb SD) × (0.7%) + 5.5%.

For each GHb SD, the corresponding A1C concentration and estimated absolute risk of a congenital anomaly is presented in Fig. 1*B* and online appendix 2.

CONCLUSIONS — Using data from a limited number of published cohort studies, we developed a practical tool to assist clinicians in estimating the absolute risk of a major or minor congenital anomaly in the offspring of women with prepregnancy diabetes (Fig. 1*A* and *B*).

Limitations and strengths

We used strict criteria to select studies for our review, and, accordingly, we may have overlooked those studies whose format did not allow us to estimate the GHb SD. Our inclusion of studies spanning nearly two decades would certainly have represented various strategies and degrees of glycemic control, as well as overall diabetes care, among participants. Study enrollees may have been motivated to optimize their glycemic control compared with nonparticipants. Furthermore, relevant factors, such as maternal age, receipt of counseling before pregnancy, periconceptional folic acid use, ethnicity, and diabetes-related comorbidities, were not adjusted for in our analysis. The inclusion of only 1,977 pregnancies from seven original studies limited our ability to estimate the absolute risk of congenital anomalies with confidence, especially at higher GHb SD, as seen in Fig. 1*A* and *B*.

In this review, GHb was differentially measured across a fairly broad periconceptional period; although most were assessed in the first trimester of pregnancy, some were done before conception. The method used to screen for congenital anomalies was also not uniform across studies. Since most anomalies were detected at birth, pregnancies resulting in early spontaneous or therapeutic abortion would have been missed, as would those malformations identified after the neonatal period. A major congenital anomaly—

Table 3—*Type of congenital anomalies detected among the offspring of women with prepregnancy diabetes

Year (reference)	No. of congenital anomalies according to anatomical location						
	Central nervous system or caudal dysgenesis	Cardiac	Gastrointestinal	Musculoskeletal	Urogenital	Orofacial cleft	Other
1987 (6)	4	2	2	0	1	0	0
1988 (7)	3	9	1	4	0	0	3
1989 (8,9)	3	3	1	3	8	1	0
1989 (13)	5	2	0	4	1	0	3
2000 (14)	5	13	4	5	4	0	0
1991 (15)	2	7	3	0	1	0	0
1988 (16)	4	10	0	0	2	1	1
Total number (% of all anomalies)	26 (20.8)	46 (36.8)	11 (8.8)	16 (12.8)	17 (13.6)	2 (1.6)	7 (5.6)

*More than one anomaly may be present in an affected offspring.

that leading to either death or serious handicap necessitating surgical correction or medical therapy (10)—would be more easily detected in utero than a minor birth defect. We might be criticized for combining major and minor anomalies together, but some studies included herein did not distinguish between them. There exists no hard and fast rule to define the impact of one type of anomaly over another, in terms of the social and psychological consequences for parents and child. Moreover, in the presence of two or three minor anomalies, 11 and 90% of infants have an associated major malformation, respectively, which is often occult in nature (17).

Table 4—*Absolute risk of a major or minor congenital anomaly categorized according to periconceptional GHb SD*

Reference	GHb SD	GHb (%)	No. congenital anomalies	No. births	Absolute risk of a congenital anomaly (%)
3	2	NA*	0	29	0.0
3	3	NA*	3	42	7.1
3	4	NA*	6	63	9.5
6	2	7.5	0	8	0.0
6	3	8.5	0	15	0.0
6	5	10.5	2	25	8.0
6	7	12.5	1	15	6.7
6	9	14.5	3	14	21.4
6	10	15.5	3	6	50.0
13	0†	6.1	0	17	0.0
13	2	8	4	28	14.3
13	4	10	6	26	23.1
13	5	11.2	4	16	25.0
14	14‡	9.4	4	61	6.6
14	2	5.6	1	47	2.1
14	4	6.2	7	170	4.1
14	8	7.5	8	252	3.2
14	12	8.7	6	133	4.5
15	2	6.1	0	37	0.0
15	3	8.2	1	31	3.2
15	4	9.3	0	10	0.0
15	6	10.3	0	5	0.0
16	2	NA*	6	125	4.8
16	3	NA*	5	114	4.4
16	4	NA*	4	88	4.5
8,9	14‡	13.6	10	31	32.3
8,9	15‡	14.4	5	12	41.7
8,9	6	9.3	10	266	3.8
8,9	8	10.2	10	193	5.2
8,9	11	11.9	8	97	8.2

*GHb SDs were available in the original article even though the GHb percent values were not. †GHb percent value was equal to the mean of control assay. ‡Values of GHb SDs >12 were truncated to 12 in the analyses.

The use of GHb as a measure of glycemic control is not without limitations. For example, it has been suggested that GHb better represents fasting glucose levels than postmeal measures (18). Postprandial hyperglycemia is common among women with type 2 diabetes, yet, few affected participants were included herein. The assays for measuring GHb have not been universally standardized (19,20), which may pose a limitation with regard to between-study variability and the applicability of these data to other clinical centers. However, our use of the GHb SD attempted to minimize such variability. Second, the mean ± SD population A1C reference value of 5.5 ± 0.7% that we derived is similar to that described in working reports of A1C standardization (19–21), reflecting the nonpregnant assay control value used by most institutions. Accordingly, the data generated herein may be applicable to centers that can define the performance of their own GHb assay in relation to GHb SD (Fig. 1*A*) or, more specifically, A1C (Fig. 1*B*).

Other research

Some high-quality studies did not meet the selection criteria and were not included herein. For example, Rosenn et al. (22) assessed GHb and the risk of spontaneous abortion and congenital anomalies among 215 individuals with type 1 diabetes. At a GHb concentration >12% (~7 SD above the mean), they observed an increased risk of both adverse outcomes. Mironiuk et al. (23) found that

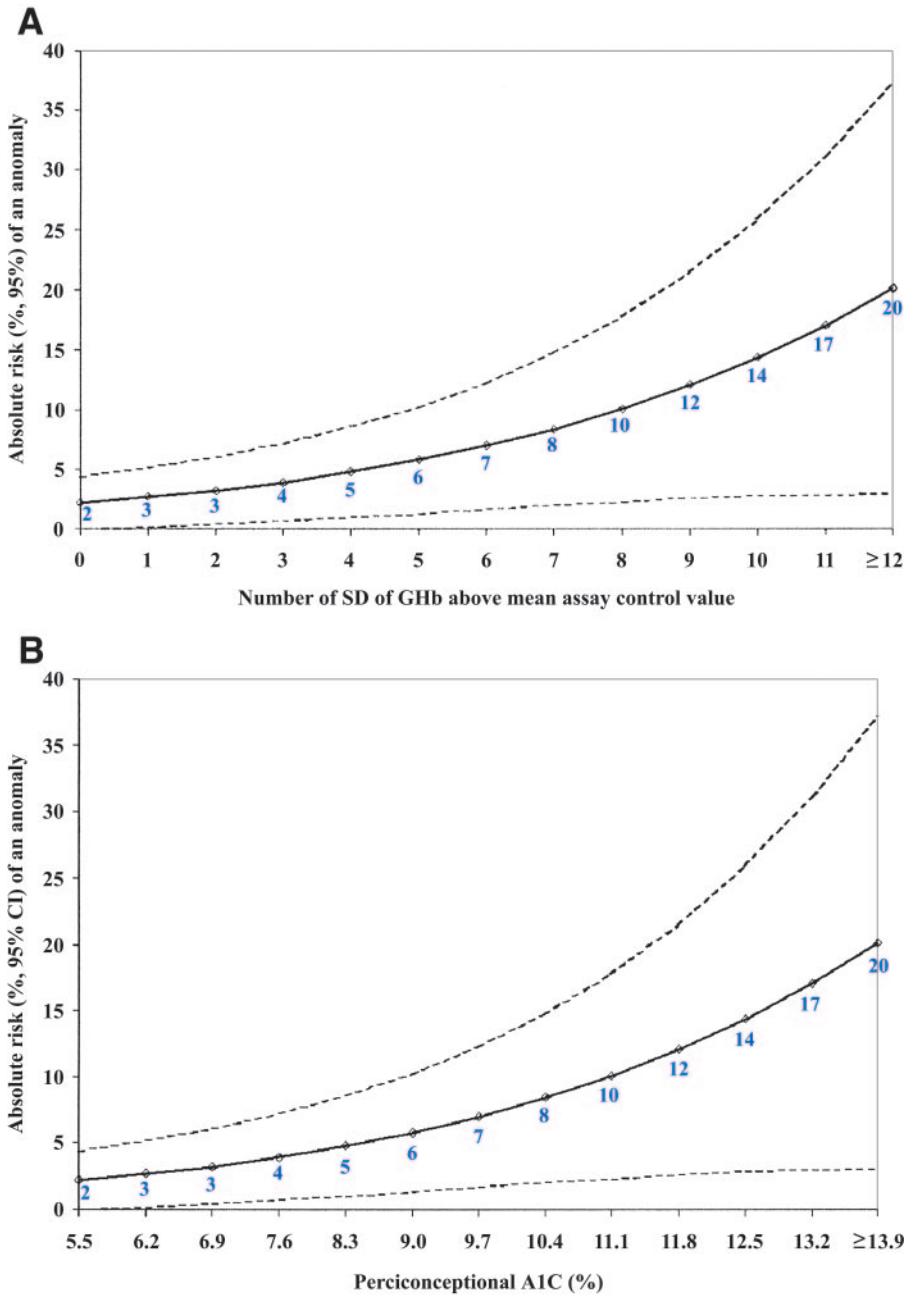

Figure 1—A*: Risk of a major or minor congenital anomaly according to the number of SDs of GHb above normal, measured periconceptionally. Data are presented as an absolute risk (solid line and blue values) ± lower and upper 95% CIs (dashed lines).* B*: Risk of a major or minor anomaly according to periconceptional A1C. *Data are presented as an absolute risk (solid line and blue values) ± 95% CIs (dashed lines).*

elevated maternal A1C and the presence of diabetic angiopathy were associated with a seven times higher risk of fetal malformations compared with women with well-controlled type 1 diabetes.

While authors have reported a single GHb threshold above which the risk of fetal anomalies is increased (1,24), this was done using an arbitrary cut point. Rather, the data presented herein suggest that this risk continuously rises in a curvilinear fashion with increasing GHb and that no pregnancy can be deemed "at risk" or "risk free." Even the presence of mild periconceptional hyperglycemia is not without some degree of risk (14). Moreover, within a large Danish cohort of women with type 1 diabetes, first trimester A1C was strongly correlated with adverse perinatal outcomes, extending beyond structural anomalies to include early and late fetal loss and neonatal death (25). Thus, GHb may serve as a useful indicator of the risk of not only structural malformations but also other adverse perinatal outcomes.

Implications

Several factors are clearly important in determining the risk of a congenital anomaly, such as maternal age, weight, and use of periconceptional folic acid supplements (10). This review provides the best available data for expressing that risk, as it related to maternal glycemic control. Together, they can be used to optimize prepregnancy and early pregnancy counseling in women with diabetes.

Optimizing the GHb (i.e., A1C) concentration before conception or the period of organogenesis remains a major goal for women with prepregnancy diabetes (10,26). In a recent meta-analysis, preconception care (with improved glycemic control) was associated with a significantly lower risk of congenital anomalies among women with diabetes (10). This is reinforced by the current observation that an elevated GHb in the periconceptional period heightens the risk of structural anomalies, many of which involve the cardiac and central nervous systems. At the same time, nearly half of the study participants included herein had a GHb ≤4 SD of normal, where the risk curve is rather flat (Fig. 1*A*). This suggests that there may be a small benefit (e.g., a 1–2% absolute risk reduction) on lowering the GHb concentration below this threshold.

Future research

Ongoing studies are needed to determine the optimal time at which GHb should be measured for the estimation of anomaly risk, as well as the additional utility of routine capillary glucose testing. Given the increasing prevalence of type 2 diabetes in pregnancy (27), more data are needed about the use of GHb to estimate anomaly risk in this population, especially since maternal obesity may be an independent risk factor for fetal malformations (28).

There is an ongoing international effort to standardize the measurement of A1C (19,20). This should facilitate the ease and accuracy of estimating anomaly risk in women with prepregnancy diabetes using the current and future data.

In conclusion, those who counsel women with prepregnancy diabetes must consider the effects of pregnancy on maternal well being, as well as the impact of diabetes, including glycemic control, on both

mother and fetus (26). Counseling that is evidence based and informed, considering preexisting measures of maternal health and glycemic control, is essential. We have developed a tool that uses periconceptional GHb SD (Fig. 1*A*) and A1C (Fig. 1*B*) to estimate the risk of a structural congenital anomaly in the offspring of women with prepregnancy diabetes.

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