

Use of Maternal Glycosylated Hemoglobin Concentration to Estimate the Risk of Congenital Anomalies in the Offspring of Women with Pre-Pregnancy Diabetes Mellitus

Received for publication 9 February 2007 and accepted in revised form 22 March 2007.

Running title: Glycosylated hemoglobin and anomalies

Andrea Guerin, BSc
Schulich School of Medicine & Dentistry, University of Western Ontario,
London, Ontario

Rosane Nisenbaum, PhD
Center for Research on Inner City Health
St. Michael's Hospital, Toronto, Ontario

Joel G Ray, MD MSc FRCPC
Departments of Medicine, Obstetrics and Gynecology and
Health Policy Management and Evaluation,
and the Divisions of General Internal Medicine and Endocrinology and Metabolism,
St. Michael's Hospital, University of Toronto, Toronto, Ontario

Contact:

Joel G Ray
Department of Medicine, St. Michael's Hospital
30 Bond Street
Toronto, Ontario
M5B 1W8
E-mail: rayj@smh.toronto.on.ca

Additional information for this article can be found in an online appendix at
<http://care.diabetesjournals.org>.

Abstract

Objective: To determine the absolute risk of having a congenital anomaly in relation to periconceptional glycosylated hemoglobin concentration (GHb) among women with pre-pregnancy diabetes mellitus (DM).

Research design and methods: Two reviewers independently retrieved all cohort studies through a systematic literature search between 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 standard deviations (SD) of GHb above the mean for non-diabetic, non-pregnant controls. 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 1977 pregnancies. At a periconceptional GHb concentration 0 SD above normal the absolute risk of a pregnancy affected by a congenital anomaly was about 2% (95% confidence interval [CI] 0.0-4.4). At 2 SD above normal, the risk was 3% (95% CI 0.4-6.1), and at 8 SD it was approximately 10% (95% CI 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 HbA_{1c} 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 HbA_{1c} concentration for estimating the absolute risk of a congenital anomaly in the offspring of women with pre-pregnancy DM.

The offspring of women with pre-pregnancy diabetes mellitus (DM) 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>. There is a positive association between poor glycemic control in the periconception period and the risk of such anomalies <1, 6-10>.

Those who counsel women with pre-pregnancy DM currently lack a valid, standardized method to estimate of the risk of a fetal anomaly in relation to the periconceptional glycosylated hemoglobin concentration (GHb), 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 HbA1c)". 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 pre-pregnancy DM; (2) GHb levels were measured in the periconception period, defined as the period from 17 weeks' prior to 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 standard deviation) were provided for a non-diabetic control population. Full text articles deemed eligible were reviewed by A.G and J.R. to ensure that they met the inclusion criteria.

Data abstraction

A.G. and J.R. abstracted data into standardized tables (Tables 1 to 4). 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. 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 standard deviation (SD) from the non-diabetic, non-pregnant control mean value provided in each study, as follows:

$$\text{GHbSD} = \frac{(\text{GHb \% value} - \text{Mean \% GHb control assay value})}{\text{SD GHb control assay}} \quad \text{Formula 1}$$

For example, if a reported GHb % value was 8%, the non-diabetic mean % control value for the assay was 6%, and the SD control value was 1%, then the GHbSD was equal to 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 GHbSD 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 GHbSD category within each study follows a binomial distribution based on the number of births and proportion of anomalies (Appendix 1). A crude odds ratio (OR) and 95% confidence

interval (CI) was estimated according to each 1-unit increase in GHbSD.

Because HbA_{1c} is now the most commonly used measure of GHb, we used the study data to determine the HbA_{1c} values corresponding to each GHbSD. Specifically, a non-weighted mean (SD) population reference value was averaged from those studies that measured HbA_{1c}. Formula 1 was then re-written to derive a series of HbA_{1c} values, as follows:

$$\text{HbA}_{1c} = (\text{GHbSD}) * (\text{SD GHb control assay}) + \text{Mean \% GHb control assay value}$$

Formula 2

Using the GHbSD categories derived from each study, the estimated corresponding HbA_{1c} values were presented accordingly, and the absolute risk of major or minor in association with HbA_{1c} was graphically plotted.

PROC NL MIXED in SAS (version 9.1.3) was used for all analyses. The model and SAS program codes are provided in Appendix 1.

Results

Study and participant characteristics

A total of 45 citations were initially found in PubMed and 33 in Embase. Of the 75 full-text articles that were further examined, seven prospective cohort studies were included in the final analysis <6-9, 13-16> (Table 1). All studies originated from United States, except for one, from Finland <14>. Most study participants had type 1 DM, but one included 20 participants with type 2 DM <6>, together representing 1977 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.

Glycosylated hemoglobin values

A variety of methods were used to measure GHb (Table 1). Four studies measured HbA_{1c} <6, 8, 9, 14, 15>, and the others HbA₁, HbA_{1a+b+c} or "glycosylated hemoglobin". The corresponding GHbSD values are listed in Table 4.

Congenital anomalies

There were 117 structural anomalies (5.9%) reported among 1977 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 GHbSD. The overall absolute risk of malformations ranged from 1.2% (95% CI 0.03-6.5) <15> up to 16.1% (95% CI 8.4-23.8) <13>. About 850 (43%) of all pregnancies and 43 (37%) of all anomalies arose in women who GHbSD was ≤ 4 SD above normal (Table 4).

Association between GHbSD and congenital anomalies

The predicted risk and 95% CI of a major or minor congenital anomaly is presented according to the number of GHbSD above normal (Figure 1a and Appendix 2). Thus, at a periconceptional GHb concentration 0 SD above normal (i.e., equivalent to a woman without DM), the absolute risk of a pregnancy affected by a congenital anomaly was about 2% (95% CI 0.0-4.4), approximately the same as the general population <10>. However, at 2 SD above normal, the absolute risk was 3% (95% CI 0.4-6.1), while at 8 SD above normal it was about 10% (95% CI 2.3-17.8) (Figure 1a).

For each 1-unit increase in the GHbSD the associated risk of any congenital malformation increased by an OR of 1.2 (95% CI 1.1-1.4).

Association between HbA_{1c} and congenital anomalies

A mean (SD) population reference value of 5.5% (0.7%) was averaged from the four studies that measured HbA_{1c} <6, 8, 9, 14, 15>. Thus, solving for Formula 2,

$$\text{HbA}_{1c} = (\text{GHbSD}) * (0.7\%) + 5.5\%$$

For each GHbSD, the corresponding HbA_{1c} concentration and estimated absolute risk of a congenital anomaly is presented in Figure 1b and Appendix 2.

Discussion

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 pre-pregnancy DM (Figures 1a and 1b).

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 GHbSD. Our inclusion of studies spanning nearly two decades would certainly have represented various strategies and degrees of glycemic control, and overall DM care, among participants. Study enrollees may have been motivated to optimize their glycemic control, compared to non-participants. Furthermore, relevant factors, such as maternal age, receipt of counseling before pregnancy, periconceptional folic acid use, ethnicity and DM-related comorbidities were not adjusted for in our analysis. The inclusion of only 1977 pregnancies from seven original studies limited our ability to estimate the absolute risk of congenital anomalies with confidence, especially at higher GHbSD, as seen in Figures 1a and 1b.

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 prior to 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 – 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>.

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 post-meal measures <18>. Postprandial hyperglycemia is common among women with type 2 DM, yet, few affected participants were included herein. The assay 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 GHbSD attempted to minimize such variability. Second, the mean (SD) population HbA_{1c} reference value of 5.5% (0.7%) that we derived is similar to that described in working reports of HbA_{1c} standardization <19-21>, reflecting the non-pregnant assay control

value used by most institutions. Accordingly, the data generated herein may be applicable to centres that can define the performance of their own GHb assay in relation to GHbSD (Figure 1a), or, more specifically, HbA_{1c} (Figure 1b).

Other research

Some high quality studies did not meet the selection criteria, and were not included herein. For example, Rosenn et al assessed GHb and the risk of spontaneous abortion and congenital anomalies among 215 with Type 1 DM <22>. At a GHb concentration greater than 12% (approximately 7 SD above the mean), they observed an increased risk of both adverse outcomes. Mironiuk et al found that elevated maternal HbA_{1c} and the presence of diabetic angiopathy were associated with a 7 times higher risk of fetal malformations compared to women with well controlled type 1 DM <23>.

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 DM, first trimester HbA_{1c} 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 other adverse perinatal outcomes as well.

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 pre-pregnancy and early-pregnancy counseling in women with DM.

Optimizing the GHb (i.e., HbA_{1c}) concentration before conception or the period of organogenesis remains a major goal for women with pre-pregnancy DM <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 DM <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 \leq 4 SD of normal, where the risk curve is rather flat (Figure 1a). This suggests that there may be a small benefit (e.g., a 1-2% absolute risk reduction) upon 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 DM 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 HbA_{1c} <19, 20>. This should facilitate the ease and accuracy of estimating anomaly risk in women with pre-pregnancy DM using the current and future data.

Conclusions

Those who counsel women with pre-pregnancy DM must consider the effects of pregnancy on maternal well being, as well as the impact of DM, 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 periconceptual GHbSD (Figure 1a) and HbA_{1c} (Figure 1b) to estimate the risk of a structural congenital anomaly in the offspring of women with pre-pregnancy DM.

Acknowledgements

Dr. Ray is supported by a Canadian Institutes for Health Research New Investigator Award. This analysis was completed with financial support from the Centre for Research on Inner City Health, the Division of Endocrinology and Metabolism, and the Summer Student Research Programme, St. Michael's Hospital.

The sponsors had no involvement in or control over the design and conduct of the study; the collection, analysis, and interpretation of the data; the preparation of the data; or the preparation, review, and approval of the manuscript.

Each author declares that he/she participated in the design, analysis and writing of the paper, and that each has seen and approved the final version. No author declares a potential conflict of interest.

References

- <1> Ylinen, K, Aula, P, Stenman UH, et al. Risk of minor and major fetal malformations in diabetics with high hemoglobin A_{1C} values in early pregnancy. *BMJ* 1984; 289: 345-6.
- <2> Casson IF, Clarke CA, Howard CV, et al. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. *BMJ* 1997; 315: 275-8.
- <3> Macintosh MC, Fleming KM, Bailey JA, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ* 2006; 333: 177.
- <4> Sadler TW, Hunter ES 3rd, Balkan W, Horton WE Jr. Effects of maternal diabetes on embryogenesis. *Am J Obstet Perinaol* 1988; 5: 319-26.
- <6> Key TC, Giuffrida R, Moore TR. Predictive value of early pregnancy glycohemoglobin in the insulin-treated diabetic patient. *Am J Obstet Gynecol* 1987; 156: 1096-1100.
- <7> Miodovnik M, Mimouni F, Dignan PS, et al. Major Malformations in infants of IDDM women: vasculopathy and early first trimester poor glycemic control. *Diabetes Care* 1988; 11: 713-18.
- <8> Greene MF, Hare JW, Clothery JP, et al. First-trimester hemoglobin A₁ and risk for major malformation and spontaneous abortion in diabetic pregnancy. *Teratology* 1989; 39: 225-31.
- <9> Greene MF. Spontaneous abortions and major malformations in women with diabetes mellitus. *Semin Repro Endo* 1999; 17: 127-36.
- <10> Ray JG, O'Brien TE, Chan WS. Preconception care and the risk of congenital anomalies in the offspring of women with diabetes mellitus: a meta-analysis. *QJM* 2001; 94: 435-44.
- <11> O'Brien TE, Ray JG, Chan WS. Maternal body mass index and the risk of preeclampsia: a systematic overview. *Epidemiology* 2003; 14: 368-74.
- <12> Hox J. *Multilevel Analysis: Techniques and Applications*. New Jersey: Lawrence Erlbaum Associates, 2002.
- <13> Lucas MJ, Leveno KJ, Williams ML, et al. Early pregnancy glycosylated hemoglobin, severity of diabetes, and fetal malformations. *Am J Obstet Gynecol* 1989; 161: 426-31.
- <14> Suhonen L, Hiilesmaa V, Teramo K. Glycaemic control during early pregnancy and fetal malformations in women with Type 1 diabetes mellitus. *Diabetologia* 2000; 43: 79-82
- <15> Kitzmiller JL, Gavin LA, Gin GD, et al. Preconception care of diabetes: glycemic control prevents congenital anomalies. *JAMA* 1991; 265: 731-6.
- <16> Mills JL, Knopp RH, Simpson JL, et al. Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *NEJM* 1998; 318: 671-6.
- <17> Eugene Hoyme H. Minor anomalies: Diagnostic clues to aberrant human morphogenesis. *Genetica* 1993; 89: 307-15.
- <18> Hillman N, Herranz L, Grande C, Vaquero PM, Pallardo LF. What is the relative contribution of blood glucose levels at different time points of the day to HbA_{1c} in Type 1 diabetes? *Diabet Med* 2004; 21: 468-70.
- <19> Sachs DB. Global harmonization of hemoglobin A_{1c}. *Clin Chem* 2000; 51: 681-3.
- <20> Manley S, John WG, Marshall S. Introduction of IFCC reference method for calibration of HbA_{1C}: implications for clinical care. *Diabetic Medicine* 2004; 21:673-6.
- <21> NGSP Clinical Advisory Committee. Harmonizing glycated hemoglobin testing. A better A_{1c} test means better diabetes care. Missouri, 2006. (<http://web.missouri.edu/~diabetes/ngsp.html>)
- <22> Rosenn B, Miodovnik M, Combs A, Khoury J, Siddiqi TA. Glycemic thresholds for spontaneous abortion and congenital malformations in insulin-dependent diabetes mellitus. *Obstet Gynecol* 1994; 84: 515-20.

- <23> Mironiuk M, Kietlinska Z, Jezierska-Kasprzyk K, Piekosz-Orzechowska B. A class of diabetes in the mother, glycemic control in early pregnancy and occurrence of congenital malformations in newborn infants. *Clin Exp Obstet and Gynecol* 1997; 24: 193-7.
- <24> Hanson U, Persson B, Thunell S. Relationship between hemoglobin A1c in early Type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. *Diabetologia* 1990; 33: 100-4.
- <25> Nielsen GL, Moller M, Sorensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. *Diabetes Care* 2006; 29: 2612-6.
- <26> McLeod L, Ray JG. Prevention and detection of diabetic embryopathy. *Commun Genet* 2002; 5: 33-9.
- <27> Feig DS, Palda VA. Type 2 diabetes in pregnancy: a growing concern. *Lancet* 2002; 359: 1690-2.
- <28> Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. *Pediatrics* 2003; 111: 1152-8.

Table 1. Study and participant characteristics, and methods used to measure glycosylated hemoglobin

Study and participant characteristics						Glycosylated hemoglobin (GHb)		
Year <citation>	Design	Study setting; period	No. with type 1/ type 2 DM	Mean (SD) maternal age, years	Definition of periconception period	Assay used	GHb measure	Mean (SD) for non-diabetic, non-pregnant controls, %
1987<6>	Prospective cohort	Single US medical center; 1979-1984	63/20	25.6 (NA)	< 15 weeks' gestation	Spectrophotometric absorption	HbA _{1c}	5.1 (1.1)
1988 <7>	Prospective cohort	US 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 US diabetes center; 1984-1992	599/0	29.1 (NA)	≤ 12 weeks' gestation	Electrophoresis	HbA _{1c}	5.9 (0.57)
1989 <13>	Prospective cohort	Single US 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	HbA _{1c}	4.9 (0.32)
1991 <15>	Prospective cohort	California, US database; 1982-1988	84/0	29.7 (4.4)	Participation prior to conception	High pressure column chromatography	HbA _{1c}	6.2 (0.7)
1988 <16>	Prospective cohort	US	327/0	27.8 (4.0)	Before conception and up to 21 days after conception	Thiobarbituric acid colorimetric method	NA	NA

*Not provided, but number of SD given in paper

**SD estimated from the reported range of values

US United States; SD Standard deviation; NA not available

Table 2. Methods used to detect for congenital anomalies in studies of women with pre-pregnancy diabetes mellitus

Year <citation>	Method(s) described for the systematic detection of congenital anomalies				Were these detection methods equally applied to all women?	Were assessors masked as to the mother's glycemic control?
	Anatomical ultrasound <i>in utero</i>	Maternal serum or amniotic fluid α -fetoprotein	Physical examination of all infants after birth	Autopsy of all fetal and neonatal deaths		
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

NA Not available

Table 3. Type of congenital anomalies detected among the offspring of women with pre-pregnancy diabetes mellitus*

Year <citation>	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

Table 4. Absolute risk of a major or minor congenital anomaly categorized according to periconceptual glycosylated hemoglobin units of standard deviation (GHbSD)

Citation	GHbSD	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 Standard Deviations were available in the original article even though the GHb % values were not

* GHb % value was equal to the mean of control assay

*** Values of GHb Standard Deviations greater than 12 were truncated to 12 in the analyses. NA Not available

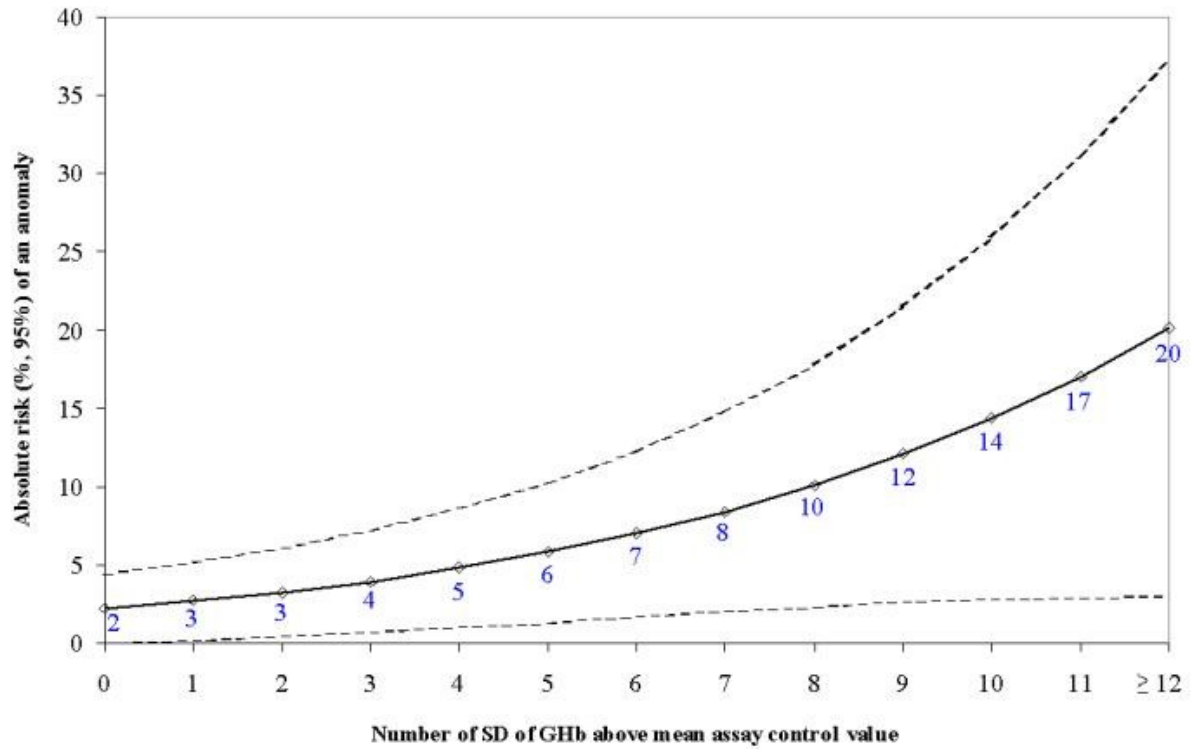
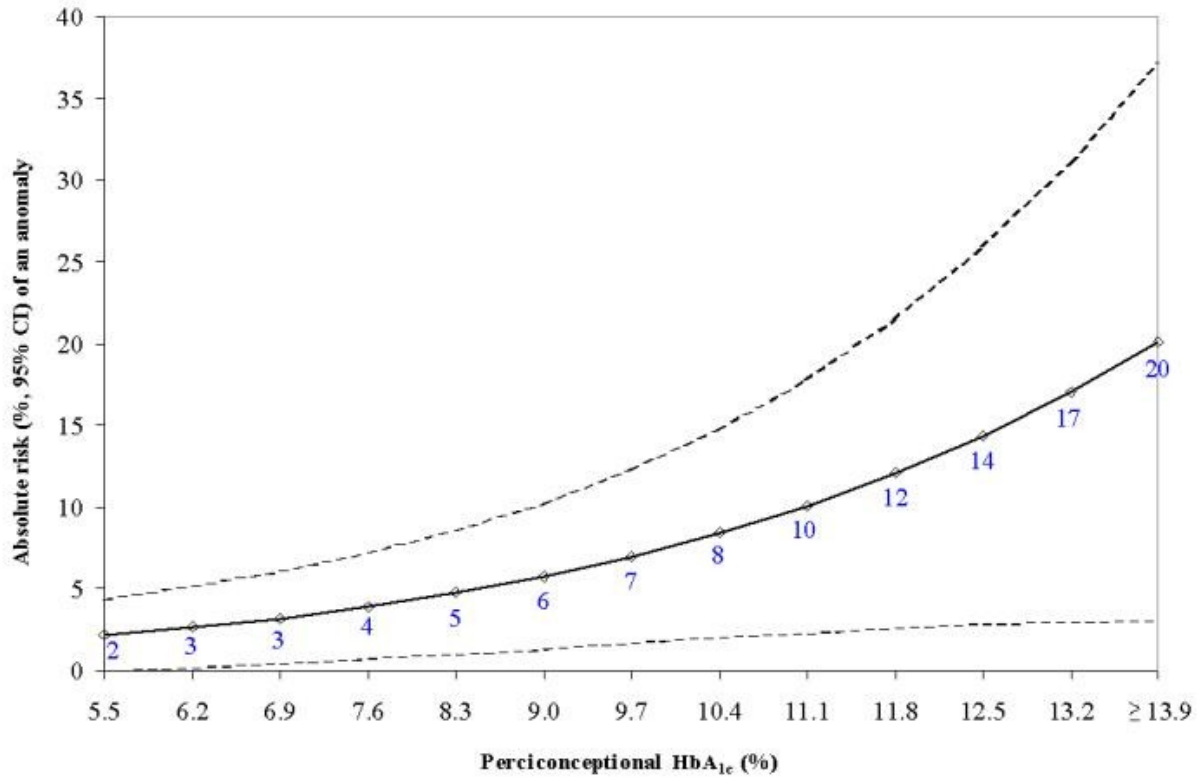


Figure 1a. Risk of a major or minor congenital anomaly according to the number of standard deviations (SD) of glycosylated hemoglobin (GHb) above normal, measured preconceptionally. Data are presented as an absolute risk (solid line and blue values) +/- lower and upper 95% confidence interval (dashed lines)



*Assumes a mean (SD) HbA_{1c} assay reference value of 5.5% (0.7%) among non-diabetic, non-pregnant controls.

Figure 1b. Risk of a major or minor anomaly according to periconceptual HbA_{1c}.* Data are presented as an absolute risk (solid line and blue values) +/- 95% confidence interval (dashed lines)