Before, Between & Beyond Pregnancy
The National Preconception Curriculum and Resources Guide for Clinicians

Annotated Articles Guiding Preconception Care of Women with Diabetes

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Preconception Glycemic Control

Nielsen, GL., Sorensen, HT., Nielsen, PH., Sabroe, S., Olsen, J. Glycosylated hemoglobin as predictor of adverse fetal outcome in type 1 diabetic pregnancies. Acta Diabetol 1997; 34(3): 217-222. http://www.springerlink.com/content/xatebg03v1yxtn1x/fulltext.pdf

Greene, MF., Hare, JW., Cloherty, JP., Benacerraf, BR., Soeldner, JS. First-trimester Hemoglobin A1 and risk for major malformation and spontaneous abortion in diabetic pregnancy. Teratology 1989; 39: 225-231.

Synopsis: In 1989, Greene, et al., evaluated the link between glycemic control and fetal loss and malformation in a prospective evaluation of all diabetic women presenting to care at <12 weeks between Dec 1983-Dec 1987. The women's HbA1c levels were determined at the first visit prenatal visit and every month thereafter. Ultrasound was performed on all women at 16-19 weeks by an examiner blinded to first trimester HbA1c levels, and anomalies were assessed in the neonatal period by pediatricians prior to discharge from the hospital. Malformations were considered major if they were fatal, required surgery, or were of major anatomic or cosmetic importance.

A total of 303 women fulfilled study criteria. 21 were excluded for insufficient outcome data. Of these, two women had spontaneous abortions at outside hospitals (mean HbA1c: 13.3), 9 women transferred to other physicians (mean HbA1c: 9.6), 10 were completely lost to follow-up (mean HbA1c: 12), and one underwent amniocentesis for AMA and subsequently terminated the pregnancy due to Turner's syndrome (she was included in analysis for 1st trimester loss but not in the calculation for malformations).

Using women with a HbA1c ≤ 6 SD above the mean (9.3%) as the referent group, the risk ratio for fetal loss and malformations were calculated

First trimester A1c	Risk ratio major malformation (95%CI)	Risk ratio for spontaneous loss

		(95%CI)
<9.3 (<6 SD above non-DM mean 5.9)	1.0 (still accounted for 3/20 major malformations)	1.0 (still accounted for 14/52 losses)
9.4 – 11	1.7 (0.4 – 1.7)	0.7 (0.3 – 1.6)
11.1 – 12.7	1.4 (0.3 – 8.3)	1.98 (1.03 – 3.38)
12.8 – 14.4	12.8 (4.7 – 35)	2.9 (1.4 – 5.8)
>14.4	13.2 (4.3 – 40)	3.0 (1.3 – 7.0)

In summary, the overall risk for major malformation was 8% which is similar to that reported in prior studies of diabetic patients. Examining a wide range of control, the data showed that HbA1c values below 12.5 SD above the mean resulted in a major malformation rate of 4%, which is comparable to "low risk" diabetic groups seen by prior investigators. They found a risk ratio for fatal malformations was approximately 24 with HbA1c > 12.5 SD above the mean.

The authors concede that with no "non-diabetic" control group, they are unable to compare risk in well controlled diabetics to non-diabetics. Also, their incidence of spontaneous loss was 17.2 overall which is likely an underestimation since the women who were lost to follow up had high hgA1c values and pregnancy loss is a common reason for failure to return to care. Nonetheless, this study supports other studies that indicate that achieving good early glycemic control can reduce fetal loss and congenital malformations.

More recently, Nielsen and colleagues conducted a retrospective review to determine if there is a level of glycemic control below which no further improvement in outcome is seen; was seen with adjustment for maternal age and White classification.

The records of women with Type 1 diabetes who were cared for from 1980 to 1992 were evaluated. They defined "healthy outcome" as all pregnancies ending with healthy take-home babies, including minor, non-disabling malformations. "Adverse outcome" was defined as pregnancy ending with spontaneous abortion, lethal or major malformations including all those requiring surgery or those causing lasting disability. A total of 184 women with type 1 diabetes were admitted representing 271 unselected pregnancies. Median time of first prenatal visit was 12.5 weeks (range 6-25).

The researchers reported an increase in the odds ratio for adverse outcome of 1.4 for each percent increase in the HbA1c value (e.g..from 6.6-7.6).

In an analysis of 60 pregnancies with HbA1c measurement in the two months prior to pregnancy, they found the following:

HbA1c	**Healthy (n=49)**	**Adverse (n=11)**	**OR (95% CI)**
<6.5	15	1	1.0
6.6 – 7.8	15	2	1.4 (0.1 – 18)
7.9 – 9.3	12	3	3.0 (0.2 – 36)
>9.4	7	5	6.9 (0.6 – 76)

In an analysis of 161 pregnancies with HbA1c measurements between weeks 0-12 of pregnancy, they found the following:

HbA1c	**Healthy (n=144)**	**Adverse (n=17)**	**OR (95% CI)**
<6.5	54	2	1.0
6.6 – 7.8	39	5	3.1 (0.5 – 18)
7.9 – 9.3	41	5	2.8 (0.5 – 16)
>9.4	10	5	13.2 (2.1 – 82)

The authors noted a trend toward improved outcome with improved control which furthered the earlier work of Greene, et al. Their findings support the current recommendation for obtaining glycemic control with a HbA1c <7 at the time of conception to reduce risk for adverse outcome.

Posted March, 2008; reviewed April 27, 2009