TABLE 1. Reported perinatal mortality in pregnancies complicated by diabetes compared with that in the general population

	Study Design	Type of patient	No of Patients/ Pregnancies	PNM rate in the Diabetic population per 1000	PNM in the general population per 1000	RR/OR
Hawthorne (1997)	Prospective	All diabetic pregnancies	111/113	48	8.9	5.38
Casson IF (1997)	Retrospective	Insulin dependent Diabetes of pregnancy	355/462	36.1	8.3	4.34
Cundy T (2000)	Prospective	Type 1 diabetes Type 2 diabetes	160 256	12.5 46.1	12.5	
Hawthorne G (2000)	Prospective	Pregestational diabetes	304	42.8	10	4.4
Platt MJ (2001)	Retrospective	Type 1 diabetes	547	43	8.5	5
Vaarasmaki M (2002)	Retrospective	Type 1 diabetes	954	13.6	6.2	2.2
Wood SL (2003)	Retrospective	Prediabetic pregnancies after diagnosis of diabetes	406 593	19.7* 33.7*	5.5	3.5-6
Lauenborg J (2003)	Retrospective	Type 1 diabetes	1361	18*		
Diabetes and Pregnancy Group France (2003)	Prospective cross-sectional	Pregestational diabetes	435	44	7	6.2
Evers IM (2004)	Prospective	Type 1 diabetes	323	27.8	8	3.5

*This report refers to stillbirths only and not to perinatal mortality.

THE CASE OF PERINATAL MORTALITY

Recent studies show that the infants of women with pregestational diabetes have a 4- to 6-fold increased risk of PNM reaching 28 to 48 per 1000[3-14]. However, the true PNM rate in this population is difficult to asses because it includes women with type 1 and type 2 diabetes and excludes some women with previously undiagnosed type 2 diabetes misdiagnosed as having GDM.

There are only a few published reports on PNM in type 2 diabetes. Cundy et al[7] reported a rate of 46 fetal deaths per 1000 pregnancies over a 12-year period, significantly higher than the 12.5/1000 reported for type 1 or the 8.9/1000 reported for GDM. Most of the increased mortality rate was explained by late fetal deaths related to maternal obesity, advanced age, hypertension and low socioeconomic class. However, as the study sample consisted mostly of native Maori women and immigrants from the Pacific Islands residing in New Zealand, the findings cannot be generalized to more heterogeneous populations. Other maternal comorbidities including obesity, higher maternal age, higher frequency of hypertension, and low socioeconomic class were also present in these women and probably contributed to the increased mortality rate. These women also presented for care later than women with type 1 disease and many were smokers. Many women with type 2 diabetes suffer from massive obesity, which has been associated with an increased risk of late fetal death, fetal macrosomia, and preterm delivery.

Other studies reported a PNM rate ranging from 4/1000 to 81/1000. Some studies showed no significant difference in PNM between patients with type 2 and type 1 diabetes[15,16] whereas one study reported four perinatal deaths in 113 patients with type 2 and none in 46 patients with type 1 disease[17]. Other neonatal outcomes were also examined in this study. There were no significant differences in the rates of macrosomia, cesarean section, shoulder dystocia, or neonatal hypoglycemia between mothers with type 1 and those with type 2 diabetes. If this finding is confirmed in other studies and if, in fact, the outcomes of women with type 2 diabetes are similar to those of women with type 1 diabetes, women with type 2 diabetes and their infants should receive similar concern to that shown to women with type 1 diabetes.

Just as infants born of mothers with type 1 diabetes are at increased risk of congenital anomalies, so are the infants of women with type 2 diabetes. Major congenital anomalies affect 4-12% of infants of mothers with overt diabetes, a percentage that is 3- to 5-fold greater than that in the offspring of nondiabetic mothers, and these anomalies are a leading cause of PNM in this population. Moreover, poorer attendance at prepregnancy care, later booking for prenatal care, and poorer glycemic control during organogenesis are thought to contribute to the higher rate of congenital malformations.

What can be done to reduce PNM in diabetic pregnancies?

Prior to the introduction of insulin in 1921, juvenile female diabetics rarely survived to puberty, and those who did suffered from sterility, abortions, intrauterine fetal death, and a maternal mortality rate of nearly

50%. Insulin treatment has practically eliminated maternal mortality but, although PNM has dramatically declined, it still remains high. Failure to achieve glycemic control at the time of conception and during the early weeks of gestation is associated with an increased risk of spontaneous abortions and congenital malformations.

Langer[18] postulated that distinct thresholds of mean glucose values are associated with different fetal complications such as stillbirth, spontaneous abortion, congenital anomalies, fetal macrosomia, and metabolic and respiratory complications. For each complication, a different targeted threshold from normality must be achieved to eliminate complications. This fundamental observation provides an explanation for differences in the reported results of perinatal outcome obtained in distinct centers, usually demonstrating a low congenital malformation rate on the one hand but a high neonatal death rate on the other. Kitzmiller[2] demonstrated a 10-fold reduction (from 10.9% to 1.2%) in the congenital anomaly rate achieved by moderate reduction of mean blood glucose value with preconception education and treatment of women with pre-gestational diabetes. Karlsson and Kjellmer1 found that PNM decreased from 24% when the mean blood glucose was above 150 mg% to 16% with a glucose level of 100-150 mg% and to 3.8% with daily glucose below 100 mg%. These results were supported by Pedersen, Roversi and Möller[19-21], demonstrating that rigorous control of diabetes during pregnancy significantly reduces the PNM rate.

The findings of a series of nonrandomized studies in the mid-1980s on the importance of strict glycemic control before and during early pregnancy in preventing the increased risk of PNM led to the 1989 St. Vincent meeting in Italy of European representatives and diabetes experts, held under the auspices of the World Health Organization (WHO) and the International Diabetes Federation. The result was the St. Vincent Declaration, which set the 5-year goal to "achieve pregnancy outcome in the (pre-gestational) diabetic woman that approximates that of the non-diabetic women"[22]. Several years later, the Diabetes Control and Complications Trial (DCCT) reported that intensified glycemic control (with HbA_{1c} 4.7 SD above the mean compared with 6.3 SD in the conventional group) was associated with improved perinatal outcome similar to that of the nondiabetic population[23].

Furthermore a meta-analysis f the impact of preconception counseling showed a significant reduction in the pooled rate of major malformations in women receiving preconception care (2.1%) compared with controls (6.5%) (RR: 0.36; 95% CI: 0.22-0.6)[24]. A large-scale Pregnancy Program Project Grant funded by the NIH23 from 1978-1993 enrolled women prior to pregnancy or during the first trimester. Preconception care and strict glycemic control were implemented. A retrospective comparison analysis of the period before the study (1973-1978) and the study period showed that the congenital malformation rate decreased from 14% to 2.2%. As preconception enrollment increased over the years, PNM progressively decreased from 7% (before the study period) to 3-2% (from 1978-1988) to 0% (from 1988-1993). Reducing the rate of congenital anomalies is associated with a substantial reduction in PNM[23].

CONCLUSION

The year 2004 marks the 15th anniversary of the St. Vincent Declaration and cumulative data indicate that pregnancy outcomes remain poor among women with diabetes, even in top-rated medical centers throughout Western Europe.

Research from England, France, Scotland and very recently from the Netherlands revealed an undesirably high rate of both perinatal mortality and malformations.

Thus, all of these nationwide studies show that the goals of the St. Vincent Declaration for outcome of pregnancy in women with diabetes are still not being met.

Although most women planned their pregnancies and prepared well (that is, they had good glycemic control and adequate folic acid supplementation), outcome was still not comparable to that of the general population. The risks of congenital malformations, macrosomia, and pre-eclampsia were increased threefold to 12-fold, and neonatal morbidity, especially hypoglycemia, was also extremely high.

There is no doubt that specialist centers with substantial skill in the care of diabetic pregnancies achieve outcomes that fall within reach of the St. Vincent Declaration. We believe that preconception counseling for pre-gestational diabetes and strict glycemic control using intensified management in diabetic pregnancies (both GDM and pre-GDM) will be associated with a significant reduction of PNM in pregnancies complicated by diabetes, by preventing both the excessive congenital anomaly rate and reducing metabolic complications.

We sought to raise this very important issue for critical evaluation and discussion in order to determine whether a prospective, multinational, multicenter audit is warranted, aimed at helping the United States, European Union and/or WHO community to achieve the unfulfilled, 15-year-old Declaration and improve pregnancy outcome in diabetic women.

REFERENCES

1. Karlsson K, Kjellmer I. The outcome of diabetic pregnancies in relation to the mother's blood sugar level. Am J Obstet Gynecol. 1972;112: 213-20.
2. Kitzmiller JL, Cloherty JP, Younger MD, Tabatabaii A, Rothchild SB, Sosenko I, et al. Diabetic pregnancy and perinatal morbidity. Am J Obstet Gynecol. 1978;131:560-80.