

# Diabetic Pregnancy Outcome in Malta

## *The outcome of non-gestational diabetic pregnancies in the Maltese Islands*

Charles Savona-Ventura, Marcelle Chircop,  
Alan Ellul, Joseph Azzopardi, Lina Janulova

### Abstract

Diabetes in pregnancy is generally associated with a higher morbidity and mortality for both the mother and child.

**Objective:** The study aims to assess the outcome indicators of diabetic pregnant women and compare these to the remaining obstetric population.

**Research Design and Methods:** Women diagnosed as suffering from diabetes prior to their pregnancy were identified (n = 44) and their outcome indicators were compared to the parameters of the women with a presumed normal carbohydrate metabolism (n = 12260). Women diagnosed with gestational DM (defined as a 2-hour post-load blood glucose of  $>=8.6$  mmol/l; n=236) were excluded from the analysis.

**Results:** The incidence of pre-existing diabetic problems in the Maltese pregnant population is 0.35% of total maternities. Women with pre-existing DM showed themselves to be at a significantly increased risk of developing hypertensive disorders during pregnancy and to require delivery by caesarean section.

### Keywords

diabetes mellitus, pregnancy, outcome, complications

**Charles Savona-Ventura** DScMed, FRCOG

Diabetic Pregnancy Joint Clinic,  
Departments of Obstetrics -Gynaecology and Diabetes,  
St Luke's Teaching Hospital, Gwardamangia, Malta  
Email: charles.savona-ventura@um.edu.mt

**Marcelle Chircop** MD, MRCOG

Diabetic Pregnancy Joint Clinic,  
Departments of Obstetrics -Gynaecology and Diabetes,  
St Luke's Teaching Hospital, Gwardamangia, Malta

**Alan Ellul** MD MSc

Diabetic Pregnancy Joint Clinic,  
Departments of Obstetrics -Gynaecology and Diabetes,  
St Luke's Teaching Hospital, Gwardamangia, Malta

**Joseph Azzopardi** MD, FRCP

Diabetic Pregnancy Joint Clinic,  
Departments of Obstetrics -Gynaecology and Diabetes,  
St. Luke's Teaching Hospital, Gwardamangia, Malta

**Lina Janulova** MD, MSc

National Obstetric Information System,  
Department of Health Information, Gwardamangia, Malta

The infants born to pre-existing DM women were more likely to be macrosomic or preterm and have a low Apgar score at birth. They were also more likely to be of low birth weight and suffer from respiratory distress.

**Conclusions:** It would appear that previously existing diabetes complicating pregnancy remains a high risk situation that increases maternal and infant morbidity in spite of the modern management options.

### Introduction

The St. Vincent's Declaration in 1989 had set the goal of achieving "a pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman".<sup>1</sup> This goal has yet to be reached by many obstetric units who care for diabetic women in the developed world. Disorders of carbohydrate metabolism – Diabetes Mellitus (DM) and Impaired Glucose Tolerance (IGT) – remain one of the most important public health problems in the Maltese population. Cross-sectional population studies carried out in the early 1980s have identified a prevalence rate of DM-IGT of 2.2% in women in the reproductive age of which 0.5% were previously known cases.<sup>2</sup> The present study sets out to assess the outcome of pregnancies in previously diabetic women comparing these outcome indicators with those in normal individuals.

### Material and Methods

The study reviewed the medical data records of all women delivering in the Maltese Islands during 1999-2001 (n = 12540 maternities resulting in 12714 births). The medical data was made available by the National Obstetric Information System managed by the Department of Health Information (Malta). Information pertaining to the incidence of congenital malformations was made available from the Malta Congenital Anomalies Register for years 1999-2000 (total infants born = 8759, inclusive 212 infants of women with pre-DM and GDM). During the two-year period no cases of congenital malformations were registered in infants of women with pre-DM while two cases occurred in infants of GDM women.

The medical records revealed a total of 44 pregnant women who suffered from diabetes mellitus existing prior to the pregnancy (pre-DM). The outcome parameters as established by the WHO-OBSQID project<sup>3</sup> for women with pre-DM were

compared to the parameters of women with presumed or confirmed normal carbohydrate metabolism (n = 12260). The women diagnosed during pregnancy as suffering from GDM were excluded from the analysis (236 women). Statistical significance was tested using the Chi Square test analysis using MedCalc (ver.4.16) statistical package. A probability value of <0.05 was taken to represent a significant correlation.

## Results

The incidence of pre-DM in the Maltese pregnant population was computed as 0.35%. The large majority (75%) of these cases was Type 1 insulin-dependent DM (IDDM) – Table 1. Increasing age resulted in an increase in the incidence of pre-DM in the Maltese pregnant population from 0.27% in the 15-24 years age group to 0.33% in the 25-34 years age group and to 0.63% in the 35-44 years age group. The elderly group was more likely to be suffering from Type 2 diabetes (NIDDM) or IGT with seven cases (63.6%) in this group being older than 35 years. The age-specific incidence of pre-existing Type 1 diabetes during pregnancy was similar in the <35 years age groups (15-24 years: 0.27%; 25-34 years: 0.28%). The rate decreased to 0.19% in women aged 35-44 years suggesting that many Type 1 diabetic patients attempt to complete their pregnancies before 35 years of age.

Pre-DM has been repeatedly associated with maternal and infant complications that contribute towards an adverse maternal and perinatal outcome. Pre-DM women were significantly associated with increased rates of maternal pregnancy-induced hypertension and pre-eclampsia. This group of women was also significantly more likely to require delivery by caesarean section. Intervention to terminate the pregnancy by resorting to induction of labour was significantly less often resorted to because of the very high elective caesarean section rate (Table 2). While there appeared to be a progressive increase in multiple pregnancy rates in pre-DM women, the differences were not statistically significant.

The altered metabolic state brought on by pre-DM is associated with a predisposition to an adverse effect on the neonate. Infants born to pre-DM mothers were statistically more likely to be of low birth weight and premature thus showing a greater predisposition to a lower Apgar score and respiratory

**Table 1: Incidence rates of diabetes in pregnancy**

Pre-existing DM	Number	% pre-DM cases	% total maternities
Type 1 diabetes - IDDM	33	75.0	0.26
Type 2 diabetes - NIDDM	9	20.5	0.07
IGT	2	4.5	0.02
MODY	0	-	-

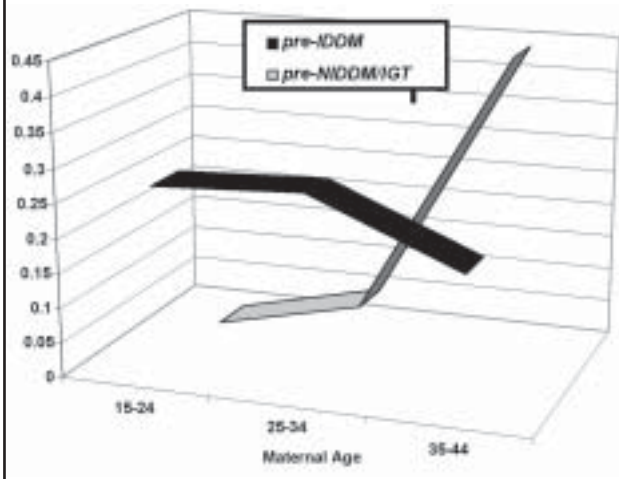
distress after birth. The risks of macrosomia were statistically increased in infants born to pre-DM women, and in spite of the high operative abdominal delivery rate were still more susceptible to shoulder dystocia. There did not appear to be any increased risk of antenatal or neonatal loss, though three infants born as a triplet maternity to a woman with pre-DM and cervical incompetence terminated as late miscarriages (Table 3).

No statistical significance could be demonstrated in the predisposition towards the development of major congenital anomalies, though the incidence of congenital anomalies in infants of the pre-DM women appeared to be markedly increased. The observed increase in the incidence of malformations in pre-DM women may be correlated to the fact that only 40.9% of women received formal pre-conceptional advice while 13.6% had HbA<sub>1c</sub> levels >8.0% in the first trimester of pregnancy - reflecting poor metabolic control during embryogenesis. Throughout pregnancy, half of the pre-DM women attended structured follow-up care and only 6.8% of women had HbA<sub>1c</sub> levels >8.0% in the third trimester of pregnancy. The three cases of congenital malformations included one case of severe caudal regression syndrome and gastroschisis in the male infant of a 27-year old obese women diagnosed prior to her pregnancy as suffering from polycystic ovarian disease with insulin resistance giving rise to impaired glucose tolerance. She was managed by an adequate dietary regimen before and throughout her pregnancy, a regimen that maintained HbA<sub>1c</sub> levels less than 8.0% throughout pregnancy. Another infant suffered from diabetic cardiomegaly. The child was born to a 31-year old Type 2 diabetic drug abuser on

**Table 2: Maternal Outcome Parameters**

Parameter	Normal metabolism		Pre-DM		
	No.	%	No.	%	p value
Multiple births	160	1.3	2	4.6	0.2271
Maternal PIH/PET	809	6.6	12	27.3	<0.0001
Induction of labour	4420	36.3	9	20.5	0.0471
Caesarean section	2887	23.5	30	68.2	<0.0001
Operative vaginal delivery	439	3.6	2	4.3	0.9501
<b>Total</b>	<b>12260</b>		<b>44</b>		

**Figure 1: Age-standardized incidence rates**



methadone managed with metformin and diet prior to pregnancy. The oral hypoglycaemic agent was replaced with an insulin regimen. Control was difficult to achieve since the patient was very unreliable attending rarely for antenatal and metabolic care. She finally presented at 35 weeks of pregnancy with severe polyhydramnios and marked macrosomia birth weight 4330g. The male infant died after the neonatal period. The third mildly malformed male infant with a harelip was born to in a 41-year old non-Maltese woman with Type 2 diabetic who presented for the first time at 32 weeks of gestation with preterm labour.

### Conclusions

Diabetes during pregnancy remains one of the most significant obstetric complications in the Maltese population. The incidence of pre-existing diabetes complicating pregnancy was of the order of 0.35%. This figure is similar, though slightly reduced, to the identified prevalence of DM in the reproductive-age female population that has been estimated by cross-sectional

population studies to amount to 0.5%.<sup>2</sup> The difference can be attributed towards the predisposition of pregnant women to be less than 40 years of age and to the reduced intentional and unintentional fertility rates in the women with DM.

There have been major developments in the care of the pregnant diabetic that has led to a fall in perinatal deaths attributable to the diabetic problem. However adverse maternal and neonatal outcomes are still associated with the pregnant diabetic woman. The diabetic pregnancy remains fraught with risks for the mother through the greater predisposition towards hypertensive disease of pregnancy and pre-eclampsia; and is furthermore associated with a greater morbidity brought on by obstetric interventions. The increased morbidity brought on by obstetric interventions is not restricted to Maltese obstetric practice, but is an observed feature of obstetric practice in European obstetric units. The published DPAD ongoing database collected by the WHO-OBSQID project for various centers in Europe by 2001 included information from 17 countries on 6929 cases of GDM and 2292 cases of pre-DM.<sup>3</sup> The European median for obstetric outcome indicators such as induction of labour and Caesarian delivery was reported as 29.37% and 61.54% respectively. These figures are correspondingly similar in Maltese practice (20.5% and 65.2%). Decisions regarding timing and mode of delivery are often tailored to the patient's metabolic control and state of fetal well-being, conditions that often necessitate earlier intervention. The infant of the diabetic mother similarly suffers from a higher morbidity in the form of a low or high birth weight and the associated complications of prematurity. Infant outcome indicators such as preterm delivery and macrosomia were reported as accounting for 21.43% and 17.46% by the DPAD project;<sup>3</sup> rates that emulate Maltese practice (15.9% and 21.7%). The inability to equate maternal and infant morbidity of diabetic pregnancies to non-diabetic ones emphasizes the difficulties faced in attempting to achieve the goal set by the 1989 St.

**Table 3: Infant Outcome parameters**

Parameter	Normal metabolism		Pre-DM		
	No.	%	No.	%	p value
2 <sup>nd</sup> trimester fetal loss	N/A		3	6.4	n/a
Fetal & neonatal loss	119	1.0	0	-	0.9440
Low birth weight (<2.5 kg)	771	6.2	10	21.3	<0.0001
Preterm birth (<37 weeks)	763	6.2	7	14.9	0.0318
Infant with RDS	269	2.2	8	17.0	<0.0001
Macrosomia (>4.0 kg)	738	6.0	10	21.3	<0.0001
Shoulder dystocia	51	0.4	2	4.3	0.0042
Apgar ≤6 @ 5 min	141	1.1	4	8.5	<0.0001
Congenital anomalies	318*	3.7	3	6.4	0.5696
<b>Total</b>	<b>12350</b>		<b>47</b>		

\* based on 1999-2000 data (total infants = 8547)

Vincent's Declaration that aimed "To achieve a pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman".<sup>1</sup>

Vigilance needs to be maintained to ensure that the metabolic control of the diabetic patient remains optimal. The maintenance of optimal metabolic control in the particularly "fragile" pre-existing diabetic will remain a difficult undertaking that requires the joint co-operation of the patient and the medical team. Until such time as a real-time artificial pancreas that administers insulin in response to blood glucose levels is developed or the various problems related to pancreatic transplantation are resolved, then the management of the pregnant pre-existing diabetic will continue to be sub-optimal. The observed possible predisposition of pre-DM women to give birth to infants with major congenital anomalies reflects the poor pre-conceptional attendance and failure to adequately control the diabetic state at the time of embryogenesis. The risk of early pregnancy loss and teratogenesis in women with pre-existing diabetes has been clearly demonstrated to be attributed to poor glycaemic control during the embryonic period.<sup>4,5</sup> A more broad-based educational program should be undertaken to adequately instruct these young women in the need of seeking to achieve optimal metabolic control pre-conceptionally and throughout early pregnancy.

The rigid metabolic control required to reduce the risks to the pre-DM mother and her infant has been repeatedly defined. The ideal target goals for blood glucose levels have been established to be in the region of 3.9-5.3 mmol/l (fasting); 7.8 mmol/l (1 hour post-prandial); and 6.7 mmol/l (2 hours post-prandial).<sup>6</sup> These levels can only be achieved through strict vigilance and adequate use of insulin supplementation, but are accompanied by significant risks of hypoglycaemia, particularly nocturnal. The current recommendation is that all pregnant diabetic patients are to be regularly followed up jointly by a dedicated multidisciplinary team. In spite of the fact that the Maltese health service does offer such a dedicated clinic, only 50% of pre-DM cases avail themselves of this service. The remainder must be considered to have received sub-standard care considering modern recommendations. The management of the Type 2 diabetic patient presents added problems. These patients are often metabolically adequately controlled with a dietary regimen and oral hypoglycaemic agents. The latter are generally stopped to be eventually replaced by an insulin regimen simply because oral hypoglycaemic agents have been arbitrarily precluded from use during pregnancy due to the fear

of structural or physiological teratogenesis, a belief that they are ineffective during pregnancy, and a fear of maternal side-effects. Their arbitrary replacement with an insulin regimen results in a significant metabolic imbalance at the crucial period of embryogenesis and throughout pregnancy. Few adequate clinical studies have been carried out, but the evidence seems to suggest that oral hypoglycaemic agents, particularly those belonging to the second-generation sulphonylurea group of compounds, have positive therapeutic outcomes in pregnant women.<sup>7,8,9</sup> Metformin similarly has been shown that when used throughout pregnancy in women at high risk of insulin resistance as identified by a previous diagnosis of polycystic ovarian disease reduces the risk of these women to develop gestational diabetes. In a small population study Glueck et al showed that gestational diabetes occurred only in 3 percent (1 of 33) of pregnancies in PCOD women on metformin therapy compared to 31 percent (22 of 72) of pregnancies in PCOD women not receiving metformin.<sup>10</sup> The role of maintaining glycaemic control with oral hypoglycaemic agents during pregnancy is however still *sub judice*.

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