Hong Kong J Gynaecol Obstet Midwifery 2024;24(2):66-76 | https://doi.org/10.12809/hkjgom.24.2.371

Predictors for adverse pregnancy outcomes in women with pre-gestational diabetes: a retrospective study

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Objective: To identify predictors for adverse pregnancy outcomes among women with pre-gestational diabetes.
Methods: We retrospectively reviewed medical records of women with pre-gestational diabetes who attended the Tuen Mun Hospital between 1 January 2012 and 30 December 2022 for antenatal care and delivery. Composite adverse early perinatal outcomes included spontaneous fetal loss before 24 weeks and congenital malformations. Composite adverse maternal outcomes included pre-eclampsia and Caesarean section. Composite adverse neonatal outcomes included preterm delivery <37 weeks, small and large for gestational age, shoulder dystocia, hypoglycaemia, Apgar score <7 at 5 minutes, arterial cord blood pH <7.0, admission to a neonatal intensive care unit, stillbirth, and death within 28 days of life. Factors associated with adverse pregnancy outcomes were identified.
Results: Among 245 women included in analysis, there were 10 spontaneous pregnancy losses before 24 weeks, four stillbirths, and 41 congenital malformations, which resulted in four terminations of pregnancy. The glycated haemoglobin (HbA1c) level at the first antenatal visit was a predictor for composite adverse early perinatal outcomes (adjusted odds ratio [aOR]=1.27, p=0.013). The rate of congenital anomaly increased threefold from 10% when the HbA1c level was <5.6% to 37.1% when the HbA1c level was >9.1% (p=0.003). Predictors for composite adverse maternal outcomes were a pre-pregnancy body mass index ≥25 kg/m^2 (aOR=2.04, p=0.033) and chronic hypertension (aOR=3.59, p=0.009), whereas the predictor for composite adverse neonatal outcomes were the HbA1c level before delivery (aOR=1.57, p=0.025). Pre-pregnancy medical care was associated with a lower maternal HbA1c level at the first antenatal visit (6.8% vs 8.2%, p=0.002) and earlier gestational age at the first antenatal visit (8 vs 12 weeks, p<0.001), compared with no pre-pregnancy medical care.
Conclusion: Maternal glycaemic control and body mass index are the major modifiable risk factors for adverse pregnancy outcomes in women with pre-gestational diabetes. Pre-pregnancy medical care should emphasise lowering the HbA1c level and bodyweight at early pregnancy to avoid adverse pregnancy outcomes.

Keywords: Congenital abnormalities; Diabetes mellitus; Glycated hemoglobin; Pregnancy complications

Introduction

The worldwide prevalence of pre-gestational diabetes has increased from 0.5% to 1% during the period 1990 to 2020 and ranges from 0.5% to 2.4% among different populations[1]. Factors associated with pre-gestational diabetes include obesity, type 2 diabetes, and advanced maternal age[1]. Pregnancies with pre-gestational diabetes are associated with an increased risk of adverse pregnancy outcomes including spontaneous abortion, congenital anomalies (cardiac malformations, neural tube defect, sacral agenesis, and caudal regression syndrome[2,3]), pre-eclampsia, Caesarean section, preterm delivery, macrosomia, low Apgar score at 5 minutes, neonatal hypoglycaemia, hyperbilirubinaemia, neonatal respiratory distress syndrome, stillbirth, neonatal death, and admission to a neonatal intensive care unit[4-8]. Pregnancy care for women with pre-gestational diabetes improves the maternal and perinatal outcomes[9,10].

Risk factors for adverse pregnancy outcomes in women with pre-gestational diabetes include a high glycated haemoglobin (HbA1c) level at the periconceptional period and in late pregnancy, a high pre-pregnancy body mass index (BMI), excessive gestational weight gain, lack of preconception care, nulliparity, low socioeconomic status, smoking, and the presence of microvascular disease (including diabetic nephropathy and retinopathy)[10-14]. We aimed to identify predictors associated with adverse

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pregnancy outcomes among women with pre-gestational diabetes in Hong Kong.

Materials and methods

We retrospectively reviewed medical records of women with pre-gestational type 1 or type 2 diabetes who attended the Tuen Mun Hospital between 1 January 2012 and 30 December 2022 for antenatal care and delivery. Women with more than one pregnancy during the study period were analysed independently. Women were excluded if they had incomplete clinical data, diabetes first recognised during pregnancy, multiple pregnancies, or delivery in other hospitals.

According to our protocol, combined antenatal and diabetic care was provided weekly to fortnightly throughout the pregnancy by a multidisciplinary team that comprises obstetricians, endocrinologists, diabetes midwife specialists, and dietitians. Women were educated on the importance of good glycaemic control, proper techniques of capillary blood glucose monitoring (and insulin injection if required), and dietary advice. Diabetic control was assessed by daily self-monitoring of capillary blood glucose and the 3-monthly HbA1c level. Fetal outcomes were assessed using morphology scans, serial growth scans, and cardiotocography. Women were offered delivery from 38 weeks onward.

Pregnancy outcomes included spontaneous pregnancy loss before 24 weeks, termination of pregnancy, congenital malformations, and stillbirth. Maternal outcomes included polyhydramnios, pre-eclampsia, gestation, mode of delivery, primary postpartum haemorrhage, and admission to an intensive care unit. Neonatal outcomes included sex, birthweight, large and small for gestational age[15,16], Apgar scores, umbilical cord arterial blood pH, admission to a neonatal intensive care unit, shoulder dystocia, birth trauma (including brachial plexus injury and bone fracture), neonatal hypoglycaemia, neonatal hyperbilirubinaemia requiring phototherapy, transient tachypnoea, respiratory distress syndrome, cerebral palsy, and death within 28 days of life.

Composite adverse early perinatal outcomes included spontaneous fetal loss before 24 weeks and congenital malformations. Composite adverse maternal outcomes included pre-eclampsia and Caesarean section. Composite adverse neonatal outcomes included preterm delivery <37 weeks, small and large for gestational age, shoulder dystocia, hypoglycaemia, Apgar score <7 at 5 minutes, arterial cord blood pH <7.0, admission to a neonatal intensive care unit, stillbirth, and death within 28 days of life.

Women with or without composite adverse pregnancy outcomes were compared using the Student's *t* test or Mann-Whitney *U* test for continuous variables and the Chi-squared test or Fisher's exact test for categorical variables. Univariate and multivariate logistic regression analyses were performed to determine predictors for adverse pregnancy outcomes. Data analysis was performed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], United States). A p value of <0.05 was considered statistically significant.

Results

Over the 11 years, the number of pre-gestational diabetes cases has increased from 4.05 to 5.83 per 1000 deliveries per year (Table 1). Of 389 women with pre-gestational diabetes managed in our unit, 144 were excluded because of diabetes first recognised during pregnancy (n=111), incomplete clinical data (n=11), unknown pregnancy outcomes (n=3), delivery in other hospitals (n=13), and multiple pregnancies (n=6). The remaining 245 women were included in the analysis.

Most (92.2%) of the women were Chinese. The median maternal age at delivery was 34 (interquartile range [IQR]=30-37) years (Table 2). Most (96.3%) pregnancies were conceived naturally; 45.3% were nulliparous. The median interval from diagnosis of diabetes to pregnancy was 4 (IQR=2-7) years; 91.0% had type 2 diabetes and

Table 1. Numbers of pregnant women with pre-gestational diabetes per 1000 deliveries from 2012 to 2022

Year	No. of pregnant women with pre-gestational diabetes per 1000 deliveries		
	Type 1 diabetes	Type 2 diabetes	Total
2012	0.35	3.69	4.05
2013	0.59	3.74	4.34
2014	0.37	3.67	4.03
2015	0.18	3.87	4.05
2016	0.35	2.46	2.81
2017	0.38	3.23	3.61
2018	0.19	4.28	4.48
2019	0.41	4.31	4.72
2020	0.99	5.43	6.42
2021	0	5.66	5.66
2022	1.03	4.8	5.83

9.0% had type 1 diabetes. In addition, 65.3% had a BMI ≥25 kg/m^2 (33.9% overweight, 31.4% obese); 84.5% received pre-conception diabetic care; 11% had diabetic retinopathy; 13.5% had diabetic nephropathy; 0.4% had diabetic neuropathy; and 22.9% had chronic hypertension. Only 4.5% of the women were taking pre-conception folic acid. The median gestational age at booking visit was 8 (IQR=7-12) weeks. Dietary control was practised by 10.2% and 12.2% of women before and during pregnancy, respectively. Insulin use increased from 14.3% before pregnancy to 86.9% during pregnancy. At the first antenatal visit, the median HbA1c level was 7.0% (IQR=6.1-8.4%); 80 (32.7%) women had a HbA1c level <6.5%. At delivery, the median HbA1c level was 6.3% (IQR=5.9%-7.0%); 60 (26.0%) women had a HbA1c level <6.0%.

Among the 245 women, there were 10 (4.1%) spontaneous pregnancy losses before 24 weeks, four (1.6%) stillbirths, and 41 (16.7%) congenital malformations, which resulted in four (1.6%) terminations of pregnancy (Table 3). Details of the four stillbirths and one death within 28 days of life are shown in Table 4, whereas details of the 41 cases of congenital malformations are shown in Table 5. In women with pregnancy beyond 24 weeks (n=231), the median gestational age at delivery was 37 (IQR=36-38) weeks; 59 (25.5%) women had preterm delivery; 44 (19.0%) had pre-eclampsia; and 145 (62.8%) had a Caesarean section. With regard to neonates, the median birthweight was 3180 (IQR=2750-3620) g; 93 (40.3%) were large for gestational age; 19 (8.2%) were macrosomic (birthweight ≥4000 g); one (0.4%) had an Apgar score <7 at 5 minutes; one (0.4%) had umbilical cord arterial pH <7.0; one (0.4%) had shoulder dystocia; 61 (26.9%) had hypoglycaemia; 31 (13.7%) required admission to a neonatal intensive care unit; and one (0.4%) died within 28 days of life.

The HbA1c level at the first antenatal visit was a predictor for composite adverse early perinatal outcomes (adjusted odds ratio [aOR]=1.27, p=0.013, Table 6). The rate of congenital anomaly increased threefold from 10% when the HbA1c level was <5.6% to 37.1% when the HbA1c level was >9.1% (p=0.003, Table 7). Predictors for composite adverse maternal outcomes were a pre-pregnancy BMI ≥25 kg/m^2 (aOR=2.04, p=0.033) and chronic hypertension (aOR=3.59, p=0.009), whereas the predictor for composite adverse neonatal outcomes were the HbA1c level before delivery (aOR=1.57, p=0.025) [Table 6].

Pre-pregnancy medical care was associated with a lower maternal HbA1c level at the first antenatal visit (6.8% vs 8.2%, p=0.002) and earlier gestational age at the first antenatal visit (8 vs 12 weeks, p<0.001), compared with no pre-pregnancy medical care.

Discussion

In the present study, predictors for adverse pregnancy outcomes were the HbA1c level at the first antenatal visit, pre-pregnancy BMI, chronic hypertension, and the HbA1c level before delivery. The rate of congenital anomaly was associated with the HbA1c level at the first antenatal visit, whereas pre-pregnancy medical care was associated with a lower HbA1c level and an earlier gestational age at the first antenatal visit.

The rate of congenital anomalies in our cohort was 16.7%, which is similar to the 14.4% reported in a study in Canada in 2021, which includes major and minor anomalies identified according to the International Classification of Diseases, 10th revision. In our cohort, 32.7% of women had a HbA1c level <6.5% during the periconceptional period; periconceptional HbA1c level was associated with congenital anomalies.

Women with pre-gestational diabetes are at four- to five-fold increased risk of stillbirth[17]. Maternal hyperglycaemia causes fetal hyperinsulinaemia, acidosis, and hyperlacticaemia leading to fetal distress[18]. Maternal and fetal hyperglycaemia may cause angiopathy that affects the uteroplacental blood vessels and leads to fetal hypoxia[19]. The rate of stillbirth in our cohort was 1.6%, which is similar to the rate reported in other studies[20,21]. Maternal blood glucose control is an important modifiable risk factors for stillbirth in mothers with diabetes. In our three cases of stillbirth (presumably related to poor glycaemic control), the HbA1c level at the first antenatal visit ranged from 7.1% to 8.8%, and the HbA1c level at delivery ranged from 6.2% to 8.1%. This highlights the importance of glycaemic control.

In our study, the HbA1c level at the first antenatal visit was associated with early pregnancy loss and congenital anomalies; the findings are consistent with those reported in studies in 1980s[22] and in Japan[23] and the United States[24]. High maternal HbA1c level is a major teratogenic agent, which affects the signalling pathways involved in organogenesis and fetal development. These results highlight the importance of periconceptional glycaemic control and pre-pregnancy medical care in reducing adverse pregnancy outcomes, as recommended by the American Diabetes Association[8].

Table 2. Characteristics of women with pre-gestational diabetes (n=245)

Characteristic	Value*
Maternal age at delivery, y	34 (30-37)
Ethnicity	
Chinese	226 (92.2)
Southeast Asian	17 (6.9)
African	2 (0.8)
Education level	
Primary	10 (4.1)
Secondary	176 (71.8)
Tertiary	59 (24.1)
Nulliparity	111 (45.3)
Previous Caesarean section	71 (29.0)
Type 1 diabetes	22 (9.0)
Type 2 diabetes	223 (91.0)
Smoking	18 (7.3)
Drinking	2 (0.8)
Natural conception	236 (96.3)
Planned pregnancy	125 (51.0)
Duration of diabetes, y	4 (2-7)
Pre-pregnancy body mass index, kg/m^2	26.9 (23.6-31.3)
25-29.9 (overweight)	83 (33.9)
≥30 (obese)	77 (31.4)
Pre-conception medical care	207 (84.5)
Pre-pregnancy diabetic treatment	
Dietary control alone	25 (10.2)
Oral medication	122 (49.8)
Insulin	35 (14.3)
Oral medication and insulin	27 (11.0)
Pre-conception folic acid	11 (4.5)
Diabetic retinopathy	27 (11.0)
Diabetic nephropathy	33 (13.5)
Diabetic neuropathy	1 (0.4)
Chronic hypertension	56 (22.9)
Gestational age at first antenatal visit, wk	8 (7-12)
Glycated haemoglobin at first antenatal visit, %	7.0 (6.1-8.4)
<6.5	80 (32.7)
≥6.5	165 (67.3)
Glycated haemoglobin at delivery, % (excluding cases of miscarriage and pregnancy termination)	6.3 (5.9-7.0)
<6.0	60 (26.0)
≥6.0	171 (74.0)
Diabetic treatment during pregnancy	
Dietary control only	30 (12.2)
Oral medication	1 (0.4)
Insulin	213 (86.9)
Oral medication and insulin	1 (0.4)
Increment in insulin during pregnancy, units/day	22 (7-42)

* Data are expressed as median (interquartile range) or No. (%) of patients

Table 3. Pregnancy, maternal, and neonatal outcomes of women with pre-gestational diabetes

Outcome	Value*
Pregnancy outcome	**n=245**
Spontaneous pregnancy loss before 24 weeks	10 (4.1)
Termination of pregnancy	4 (1.6)
Stillbirth	4 (1.6)
Livebirth	227 (92.7)
Pregnancy with congenital malformation	41 (16.7)
Maternal outcome	**n=231**
Polyhydramnios	14 (6.1)
Pre-eclampsia	44 (19.0)
Gestational age at delivery, wk	37 (36-38)
Preterm delivery <37 weeks	59 (25.5)
Preterm delivery <34 weeks	21 (9.1)
Mode of delivery	
Normal vaginal delivery	73 (31.6)
Instrumental delivery	13 (5.6)
Caesarean section	145 (62.8)
Primary Caesarean section	84 (36.4)
Primary postpartum haemorrhage (≥500 ml)	64 (27.7)
Intensive care unit admission	4 (1.7)
Neonatal outcome	**n=231**
Male sex	139 (60.2)
Birthweight, g	3180 (2750-3620)
Macrosomia (≥4000 g)	19 (8.2)
Birthweight percentiles	
Large for gestational age	93 (40.3)
Small for gestational age	11 (4.8)
Apgar score	**n=227**
1 minute	8 (8-8)
5 minutes	9 (9-9)
Low Apgar score <7 at 5 minutes	1 (0.4)
Umbilical cord arterial pH <7.0	1 (0.4)
Admission to neonatal intensive care unit	31 (13.7)
Shoulder dystocia	1 (0.4)
Birth trauma (brachial plexus injury, bone fracture)	0
Neonatal hypoglycaemia	61 (26.9)
Neonatal hyperbilirubinaemia requiring phototherapy	86 (37.9)
Transient tachypnoea of the newborn	7 (3.1)
Respiratory distress syndrome	18 (7.9)
Cerebral palsy	1 (0.4)
Neonatal death within 28 days	1 (0.4)

* Data are expressed as median (interquartile range) or No. (%) of patients

Table 4. Details of four stillbirths and one neonatal death

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Age at delivery, y	34	31	38	27	43
Race	Chinese	Chinese	Chinese	Southeast Asian	Chinese
Education level	Secondary	Secondary	Secondary	Secondary	Secondary
Smoker	No	No	No	No	No
Gravidity	2	1	2	3	3
Parity	1	0	1	2	0
History of pregnancy loss	No	No	No	No	Two (2nd trimester)
Consanguineous relationship	No	No	No	No	No
Previous Caesarean section	Yes	No	Yes	No	No
Type of diabetes	2	1	2	2	2
Duration of diabetes, y	3	13	3	0.5	2
Planned pregnancy	No	No	No	Yes	No
Method of conception	Natural	Natural	Natural	Natural	Natural
Pre-pregnancy body mass index, kg/m^2	28.6	17.3	32.8	35.7	26.0
Pre-pregnancy medical care	No	Yes	Yes	Yes	Yes
Comorbidity	Chronic hypertension, hyperlipidaemia, nephropathy, polycystic ovarian syndrome	No	Chronic hypertension, hyperlipidaemia	Chronic hypertension	History of loop electrosurgical excision procedure for cervical intraepithelial neoplasia III, cervical incompetence (cerclage performed), polycystic ovarian syndrome
Gestational age at first antenatal visit, wk	17	6	10	11	9
Glycated haemoglobin, %					
Pre-pregnancy	-	11.1	6.2	10.1	-
First trimester	-	8.8	7.1	7.9	5.8
Second trimester	7.5	7.1	6	6.9	5.7
Third trimester	6.2	8.1	5.9	8.1	-
Diabetic treatment before conception	No	Insulin	Oral hypoglycaemic agent	Oral hypoglycaemic agent	Oral hypoglycaemic agent
Presence of folate supplementation	No	No	No	No	No
Aspirin use	Yes	No	No	No	No
Diabetic treatment during pregnancy					
At first trimester	No	Insulin	Oral hypoglycaemic agent	Insulin	Insulin
At second trimester	Insulin	Insulin	Oral hypoglycaemic agent	Insulin	Insulin
At third trimester	Insulin	Insulin	Oral hypoglycaemic agent	Insulin	-
Compliance to antenatal follow-up/treatment	Poor, occasional hyperglycaemia	Poor, occasional hypoglycaemia	Good	Poor, occasional hyperglycaemia	Good

Table 4. (cont'd)

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5
Antenatal ultrasound finding	Polyhydramnios	Large for gestational age	Large for gestational age	Large for gestational age	Normal
Antenatal complication	No	Threatened preterm labour at 28 weeks	No	No	Antepartum haemorrhage, preterm premature rupture of the membranes, intrauterine infection
Mode of delivery (indication)	Vaginal delivery	Vaginal delivery	Caesarean section (previous Caesarean section)	Caesarean section (macrosomia)	Vaginal delivery
Gestational age at stillbirth/delivery, wk	30	35	34	36	25
Birthweight at delivery, g	1486 (50th-90th centile)	2600 (50th-90th centile)	2940 (>90th centile)	4220 (>90th centile)	670 (10th-50th centile)
Perinatal/neonatal outcome	Stillbirth	Stillbirth	Stillbirth	Stillbirth	Neonatal death
Likely cause of stillbirth/ neonatal death	Suboptimal glycaemic control	Suboptimal glycaemic control	Congenital leukaemia	Suboptimal glycaemic control	Prematurity, respiratory distress syndrome, necrotising enterocolitis, sepsis, disseminated intravascular coagulation, neonatal death at day 14
Postmortem examination	Right microtia, aortopulmonary window, 11 pairs of ribs	No	Placental histopathology: B-lymphoblastic leukaemia	No	No

Table 5. Details of the 41 cases of congenital malformations

Classification by the International Classification of Diseases, 10th revision	No. (%) of cases
Q00-07: Congenital malformations of the nervous system	1 (2.4)
Q05: Spina bifida	1 (2.4)
Q10-Q18: Congenital malformations of eye, ear, face, and neck	2 (4.9)
Q17: Other congenital malformations of ear	2 (4.9)
Q17.2: Microtia	1 (2.4)
Q17.4: Misplaced ear	1 (2.4)
Q20-Q28: Congenital malformations of the circulatory system	36 (87.8)
Q21: Congenital malformations of cardiac septa	23 (56.1)
Q21.0: Ventricular septal defect	7 (17.1)
Q21.1: Atrial septal defect	14 (34.1)
Q21.3: Tetralogy of Fallot	1 (2.4)
Q21.4: Aortopulmonary septal defect	1 (2.4)
Q25: Congenital malformations of great arteries	9 (22.0)
Q25.0: Patent ductus arteriosus	6 (14.6)
Q25.4: Other congenital malformations of aorta	1 (2.4)
Q25.5: Atresia of pulmonary artery	1 (2.4)
Q25.6: Stenosis of pulmonary artery	1 (2.4)
Q26: Congenital malformations of great veins	1 (2.4)
Q26.1: Persistent left superior vena cava	1 (2.4)
Q27: Other congenital malformations of peripheral vascular system	3 (7.3)
Q27.0: Congenital absence and hypoplasia of umbilical artery	3 (7.3)

* Data are presented as No. (%) of pregnancies

Table 5. (cont'd)

Classification by the International Classification of Diseases, 10th revision	No. (%) of cases
Q30-Q34: Congenital malformations of the respiratory system	0
Q35-37: Cleft lip and cleft palate	1 (2.4)
Q36: Cleft lip	1 (2.4)
Q36.9: Cleft lip, unilateral	1 (2.4)
Q38-Q45: Other congenital malformations of the digestive system	1 (2.4)
Q42: Congenital absence, atresia, and stenosis of large intestine	1 (2.4)
Q42.2: Congenital absence, atresia, and stenosis of anus with fistula	1 (2.4)
Q50-Q56: Congenital malformations of genital organs	3 (7.3)
Q53: Undescended testicle	2 (4.9)
Q53.1: Undescended testicle, unilateral	1 (2.4)
Q53.2: Undescended testicle, bilateral	1 (2.4)
Q55: Other congenital malformations of male genital organs	1 (2.4)
Q55.4: Other congenital malformations of vas deferens, epididymis, seminal vesicles, and prostate	1 (2.4)
Q60-Q64: Congenital malformations of the urinary system	8 (19.5)
Q60: Renal agenesis and other reduction defects of kidney	1 (2.4)
Q60.3: Renal hypoplasia, unilateral	1 (2.4)
Q61: Cystic kidney disease	1 (2.4)
Q61.0: Congenital single renal cyst	1 (2.4)
Q62: Congenital obstructive defects of renal pelvis and congenital malformations of ureter	4 (9.8)
Q62.0: Congenital hydronephrosis	4 (9.8)
Q63: Other congenital malformations of kidney	2 (4.9)
Q63.1: Lobulated, fused, and horseshoe kidney	1 (2.4)
Q63.2: Ectopic kidney	1 (2.4)
Q65-Q79: Congenital malformations and deformations of the musculoskeletal system	15 (36.6)
Q66: Congenital deformities of feet	2 (4.9)
Q66.4: Talipes calcaneovalgus	1 (2.4)
Q66.8: Other congenital deformities of feet	1 (2.4)
Q67: Congenital musculoskeletal deformities of head, face, spine, and chest	1 (2.4)
Q67.5: Congenital deformity of spine	1 (2.4)
Q69: Polydactyly	8 (19.5)
Q69.1: Accessory thumb(s)	6 (14.6)
Q69.2: Accessory toe(s)	2 (4.9)
Q72: Reduction defects of lower limb	2 (4.9)
Q72.3: Congenital absence of foot and toe(s)	1 (2.4)
Q72.4: Longitudinal reduction defect of femur	1 (2.4)
Q76: Congenital malformations of spine and bony thorax	2 (4.9)
Q76.6: Other congenital malformations of ribs	2 (4.9)
Q80-Q89: Other congenital malformations	2 (4.9)
Q85: Phacomatoses, not elsewhere classified	1 (2.4)
Q85.0: Neurofibromatosis (non-malignant)	1 (2.4)
Q89: Other congenital malformations, not elsewhere classified	1 (2.4)
Q89.2: Congenital malformations of other endocrine glands	1 (2.4)
Q90-Q99: Chromosomal abnormalities, not elsewhere classified	0

Table 6. Predictors for adverse pregnancy outcome in women with pre-gestational diabetes

Outcome	With adverse outcome*	Without adverse outcome*	Odds ratio (95% confidence interval)	p Value	Adjusted odds ratio (95% confidence interval)	p Value
Composite adverse early perinatal outcome	n=51	n=194				
Advanced maternal age	22 (43.1)	86 (44.3)	0.953 (0.51-1.78)	0.879	1.01 (0.52-1.96)	0.981
Type 1 diabetes	4 (7.8)	18 (9.3)	0.832 (0.27-2.58)	>0.99	0.79 (0.23-2.80)	0.720
Pre-pregnancy overweight/obesity	34 (66.7)	126 (64.9)	1.08 (0.56-2.1)	0.819	1.15 (0.55-2.40)	0.705
Pre-conceptional folic acid	21 (41.2)	82 (42.3)	0.96 (0.51-1.79)	0.888	1.08 (0.22-5.31)	0.927
Glycated haemoglobin at first antenatal visit	7.3 (6.6-9.2)	6.9 (6.1-8.1)	1.25 (1.05-1.50)	0.015	1.27 (1.05-1.53)	0.013
Composite adverse maternal outcome	n=153	n=78				
Advanced maternal age	71 (46.4)	29 (37.2)	1.46 (0.84-2.56)	0.181	1.16 (0.62-2.18)	0.647
Type 1 diabetes	10 (6.5)	11 (14.1)	0.43 (0.17-1.05)	0.059	0.66 (0.22-1.99)	0.457
Pre-pregnancy overweight/obesity	111 (72.5)	39 (50.0)	2.64 (1.50-4.67)	0.001	2.04 (1.06-3.94)	0.033
Nulliparity	69 (45.1)	36 (46.2)	0.96 (0.55-1.66)	0.879	1.04 (0.56-1.94)	0.907
Chronic hypertension	47 (30.7)	6 (7.7)	5.32 (2.16-13.10)	<0.001	3.59 (1.38-9.31)	0.009
Use of aspirin	72 (47.1)	30 (38.5)	1.42 (0.82-2.48)	0.213	1.28 (0.69-2.38)	0.439
Glycated haemoglobin at first antenatal visit	7.2 (6.3-8.6)	6.7 (5.9-7.7)	1.16 (0.97-1.39)	0.099	1.19 (0.96-1.49)	0.120
Glycated haemoglobin before delivery	6.3 (6.0-7.1)	6.2 (5.9-6.8)	1.14 (0.87-1.50)	0.338	1.07 (0.76-1.51)	0.684
Composite adverse neonatal outcome	n=155	n=76				
Advanced maternal age	62 (40.0)	38 (50.0)	0.67 (0.38-1.16)	0.150	0.65 (0.36-1.20)	0.166
Type 1 diabetes	14 (9.0)	7 (9.2)	0.98 (0.38-2.54)	0.965	0.85 (0.28-2.58)	0.772
Pre-pregnancy overweight/obesity	105 (67.7)	45 (59.2)	1.45 (0.82-2.55)	0.202	1.66 (0.85-3.25)	0.137
Chronic hypertension	40 (25.8)	13 (17.1)	1.69 (0.84-3.39)	0.139	1.47 (0.69-3.12)	0.324
Glycated haemoglobin at first antenatal visit	7.2 (6.2-8.8)	6.8 (6.0-7.6)	1.32 (1.09-1.60)	0.005	1.15 (0.91-1.43)	0.238
Glycated haemoglobin before delivery	6.4 (6.0-7.3)	6.1 (5.8-6.5)	1.75 (1.25-2.46)	0.001	1.57 (1.06-2.33)	0.025

* Data are presented as No. (%) of participants or median (interquartile range)

Table 7. Association of congenital anomaly with maternal glycated haemoglobin at first antenatal visit in women with pre-gestational diabetes

Glycated haemoglobin at first antenatal visit, %	% of congenital anomaly
<5.6	10
5.7-6.5	10.1
6.6-7.8	16.7
7.9-9.1	14
>9.1	37.1

In our study, maternal pre-pregnancy BMI and chronic hypertension were predictors for adverse maternal outcomes. Maternal obesity is associated with hypertensive disorders and Caesarean sections in mothers with diabetes[25]. Chronic hypertension is a well-established risk factor for pre-eclampsia. Although chronic hypertension is considered a non-modifiable risk factor, optimising pre-pregnancy BMI and strict compliance with low-dose aspirin for pre-eclampsia prevention are recommended for reduction of maternal complications.

The HbA1c level at delivery was a predictor of adverse neonatal outcomes. Hyperinsulinaemia causes excessive fetal growth and macrosomia and is associated with shoulder dystocia, birth trauma, respiratory distress syndrome, neonatal hypoglycaemia, hyperbilirubinaemia, and polycythaemia[26]. In our study, the median HbA1c level at delivery was 6.3%. In our cohort, 40.3% of neonates had excessive growth; 8.2% had macrosomia; 26.9% had neonatal hypoglycaemia; and 37.9% had jaundice requiring phototherapy. There was room for improvement in glycaemic control because only 26.0% of women could reduce their HbA1c level to <6.0% at delivery, which was the optimal level recommended by the American Diabetes Association[8].

We recommend that women of reproductive age with diabetes should be educated about the importance of periconceptional folate intake, optimisation of BMI, and glycaemic control to the HbA1c level of <6.5% before conception. Effective contraception should be conducted until the general health condition and the HbA1c level are optimised[8]. Compliance with pre-pregnancy medical care can reduce congenital malformations, early HbA1c level, and adverse maternal and fetal outcomes[9,10,27,28]. Pregnant women with pre-gestational diabetes should be managed by a multidisciplinary team to facilitate timely and personalised care in dietetic counselling, insulin injection technique and titration, early dating by ultrasound for timely start of low-dose aspirin regimen for pre-eclampsia prevention, and routine obstetric care. In hindsight, more aggressive glycaemic control should have been aimed, and women should have been made aware of the HbA1c target of <6.0%. Daily self-monitoring of blood glucose should be emphasised to women with pre-gestational diabetes[29].

To the best of our knowledge, this is the first study to identify predictors of adverse pregnancy outcomes in women with pre-gestational diabetes in Hong Kong. Nonetheless, there were limitations to our study. It was a retrospective cohort study, and some data were missing. The pre-pregnancy BMI was self-reported. Analyses for each adverse outcome were not performed because of the small sample sizes; this can be overcome by inclusion of women from multiple centres. The presence of maternal hypoglycaemia was not recorded, although it could lead to adverse outcomes.

Conclusion

Predictors for adverse pregnancy outcomes were HbA1c level, pre-pregnancy BMI, and chronic hypertension. Women should be educated about the pre-pregnancy medical care for diabetes and the aggressive glycaemic control throughout pregnancy to optimise maternal, fetal, and neonatal outcomes.

Contributors

TCL, PLS, and LTK designed the study. TCL, PLS, and DYC acquired and analysed the data. TCL drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have no conflicts of interest to disclose.

Funding and support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the Central Institutional Review Board of Hospital Authority (reference: CIRB-2023-052-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures and for publication.

Acknowledgement

We thank Dr SF Wong and Ms TL Lo for setting up the multidisciplinary pregnancy diabetic clinic. We also thank the endocrine team and dieticians in our hospital for the holistic care given to pregnant women with pre-gestational diabetes.

References

1. Chivese T, Hoegfeldt CA, Werfalli M, et al. IDF Diabetes Atlas: the prevalence of pre-existing diabetes in pregnancy: a systematic review and meta-analysis of studies published during 2010-2020. Diabetes Res Clin Pract 2022;183:109049. Crossref
2. Tinker SC, Gilboa SM, Moore CA, et al. Specific birth defects in pregnancies of women with diabetes: National Birth Defects Prevention Study, 1997-2011. Am J Obstet Gynecol 2020;222:176.e1-176.e11. Crossref
3. Garne E, Loane M, Dolk H, et al. Spectrum of congenital anomalies in pregnancies with pregestational diabetes. Birth Defects Res A Clin Mol Teratol 2012;94:134-40. Crossref
4. Davidson AJF, Park AL, Berger H, et al. Association of improved periconception hemoglobin A1c with pregnancy outcomes in women with diabetes. JAMA Netw Open 2020;3:e2030207. Crossref
5. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ 2004;328:915. Crossref
6. 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. Crossref
7. Murphy HR, Howgate C, O'Keefe J, et al. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. Lancet Diabetes Endocrinol 2021;9:153-64. Crossref
8. ElSayed NA, Aleppo G, Aroda VR, et al. Management of diabetes in pregnancy: standards of care in diabetes-2023. Diabetes Care 2023;46(Suppl 1):S254-S266. Crossref
9. Wahabi HA, Alzeidan RA, Esmaeil SA. Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis. BMC Public Health 2012;12:792. Crossref
10. Wahabi HA, Fayed A, Esmaeil S, et al. Systematic review and meta-analysis of the effectiveness of pre-pregnancy care for women with diabetes for improving maternal and perinatal outcomes. PLoS One 2020;15:e0237571. Crossref
11. Sato T, Sugiyama T, Kurakata M, et al. Pregnancy outcomes in women with type 1 and type 2 diabetes mellitus in a retrospective multi-institutional study in Japan. Endocr J 2014;61:759-64. Crossref
12. Lepercq J, Le Ray C, Godefroy C, Pelage L, Dubois-Laforgue D, Timsit J. Determinants of a good perinatal outcome in 588 pregnancies in women with type 1 diabetes. Diabetes Metab 2019;45:191-6. Crossref
13. Cyganek K, Hebda-Szydlo A, Skupien J, et al. Glycemic control and pregnancy outcomes in women with type 2 diabetes from Poland. The impact of pregnancy planning and a comparison with type 1 diabetes subjects. Endocrine 2011;40:243-9. Crossref
14. Buhary BM, Almohareb O, Aljohani N, et al. Glycemic control and pregnancy outcomes in patients with diabetes in pregnancy: a retrospective study. Indian J Endocrinol Metab 2016;20:481-90. Crossref
15. Fok TF, So HK, Wong E, et al. Updated gestational age specific birth weight, crown-heel length, and head circumference of Chinese newborns. Arch Dis Child Fetal Neonatal Ed 2003;88:F229-F236. Crossref
16. Lok IWY, Kong MCW, To WWK. Updated gestational age specific birthweight reference of Hong Kong Chinese newborns and comparison with local and international growth charts. Open J Obstet Gynecol 2021;11:940-54. Crossref
17. Mackin ST, Nelson SM, Kerssens JJ, et al. Diabetes and pregnancy: national trends over a 15 year period. Diabetologia 2018;61:1081-8. Crossref
18. Lauenborg J, Mathiesen E, Ovesen P, et al. Audit on stillbirths in women with pregestational type 1 diabetes. Diabetes Care 2003;26:1385-9. Crossref
19. Rackham O, Paize F, Weindling AM. Cause of death in infants of women with pregestational diabetes mellitus and the relationship with glycemic control. Postgrad Med 2009;121:26-32. Crossref
20. Murphy HR, Bell R, Cartwright C, et al. Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study. Diabetologia 2017;60:1668-77. Crossref
21. Mackin ST, Nelson SM, Wild SH, et al. Factors associated with stillbirth in women with diabetes. Diabetologia 2019;62:1938-47. Crossref
22. 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;39:225-31. Crossref
23. Nakanishi K, Kanagawa T, Fujikawa K, Ishii K, Waguri M. Congenital malformation and hemoglobin A1c in the first trimester among Japanese women with pregestational diabetes. J Obstet Gynaecol Res 2021;47:4164-70. Crossref
24. Dude AM, Badreldin N, Schieler A, Yee LM. Periconception glycemic control and congenital anomalies in women with pregestational diabetes. BMJ Open Diabetes Res Care 2021;9:e001966. Crossref
25. Langer O, Yogev Y, Xenakis EM, Brustman L. Overweight and obese in gestational diabetes: the impact on pregnancy outcome. Am J Obstet Gynecol 2005;192:1768-76. Crossref
26. Negrato CA, Mattar R, Gomes MB. Adverse pregnancy outcomes in women with diabetes. Diabetol Metab Syndr 2012;4:41. Crossref
27. Gizzo S, Patrelli TS, Rossanese M, et al. An update on diabetic women obstetrical outcomes linked to preconception and pregnancy glycemic profile: a systematic literature review. ScientificWorldJournal 2013;2013:254901. Crossref
28. Murphy HR, Roland JM, Skinner TC, et al. Effectiveness of a regional prepregnancy care program in women with type

1 and type 2 diabetes: benefits beyond glycemic control. Diabetes Care 2010;33:2514-20. Crossref
29. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390:2347-59. Crossref