Neonatal Morbidity and Gestational Diabetes: Coincidence or Consequence of the 2011 Protocol

Morbilidade Neonatal na Diabetes Gestacional: Coincidência ou Consequência do Consenso de 2011

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Gestational diabetes is one of the diseases associated with pregnancy with higher rate of complications. Despite being a transitory condition, short and long term complications related to gestational diabetes have been described. There is scientific evidence to say that good metabolic control decreases perinatal complications. In 2011, new criteria was proposed for its diagnosis, which made possible its diagnosis during the 1st trimester of pregnancy. The aim of this study is to compare neonatal morbidity in two groups of women with gestational diabetes diagnosis before and after the latest Portuguese guidelines for diabetes and pregnancy were published (February 2011).

Material and Methods: We included all newborns born in Maternidade Bissaya Barreto whose mother, followed at our maternity between 2008 and 2013, had unifetal pregnancy complicated by diabetes. We used a perinatal database and analysed the impact of the new guidelines in perinatal morbidity over two periods of three years.

Results: There were 774 women who met the inclusion criteria. We found that gestational diabetes was diagnosed earlier, insulin therapy was more frequent. Neonatal morbidity was increased, and there were more cases of neonatal hypoglycemia and congenital anomalies, and newborns became smaller for gestational age.

Discussion: The increase in neonatal morbidity was associated with early diagnosis and rigorous metabolic control.

Conclusion: To analyse national data will be fundamental to understand this unexpected increase in morbidity.

Keywords: Diabetes, Gestational; Infant, Newborn, Diseases; Pregnancy Complications

RESUMO

Introdução: A diabetes gestacional constitui uma das doenças associada à gravidez com maior taxa de complicações. Apesar de ser uma condição habitualmente transitória, estão reconhecidas as suas complicações a curto e longo prazo. Há evidência científica para afirmar que um bom controlo metabólico reduz as complicações perinatais. Em 2011, foram propostos novos critérios para o seu diagnóstico, o que o tornou possível logo no primeiro trimestre de gravidez. Neste trabalho, propomo-nos comparar a morbilidade neonatal entre dois grupos de recém nascidos filhos de mulheres com diabetes gestacional submetidos a dois protocolos diferentes.

Material e Métodos: Estudo observacional analítico, retrospetivo descritivo de recém nascidos de mães com diabetes gestacional com gravidez unifetal seguida na Maternidade Bissaya Barreto no período de 2008 a 2013. Utilizou-se a informação clinica de recém nascidos e mães com diabetes gestacional armazenada em base de dados. Analisaram-se as repercussões clínicas da utilização do novo consenso comparando dois períodos de três anos.

Resultados: Analisaram-se 774 díades mãe-filho. No segundo período a diabetes gestacional foi diagnosticada mais precocemente e a terapêutica com insulina foi instituída com mais frequência. Registou-se um aumento significativo da morbilidade neonatal, com mais casos de hipoglicémia neonatal e de anomalias congénitas e maior taxa de recém nascidos leves para a idade gestacional.

Discussão: O aumento da morbilidade neonatal, nos últimos anos, associou-se de um modo positivo à precocidade do diagnostico de diabetes gestacional e ao rigor do controlo metabólico.

Conclusão: Analisar os dados nacionais será fundamental para compreender este inesperado e preocupante aumento da morbilidade.

Palavras-chave: Complicações na Gravidez; Diabetes Gestacional; Doenças do Recém-Nascido

INTRODUCTION

Gestational diabetes mellitus (GDM) relates to an impaired glucose tolerance during pregnancy with varying severity ranging from mild forms of impaired glucose tolerance to pre-existing although undiagnosed diabetes previous to pregnancy.[1–3]

GDM is currently diagnosed with fasting plasma glucose test at the first prenatal visit. With a normal level, a 75g oral glucose tolerance test (OGTT) is usually carried out between the 24th and the 28th week of pregnancy. Most patients (70-85%) with GDM are adequately treated with diet and physical exercise, even though insulin therapy has to be initiated for some pregnant mothers.[3–8]

A universal GDM screening is currently used in Portugal[9] supported by the fact that 30 to 50% of women do not present with any risk factors for the condition.[8,10,11]

This diagnostic approach for GDM is supported by clinical studies such as the *Hyperglycemia and Adverse Pregnancy Outcomes* (HAPO)[12] showing a linear positive correlation between blood glucose level and pregnancy complications in women with no GDM.[2,5,6,9,11–15]

GDM is considered as one of the pregnancy complications mostly associated with higher perinatal

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morbidity[5,6,11,13,16] mainly when incorrectly treated. Neonatal hypoglycaemia, respiratory distress syndrome, prematurity and hyperbilirubinaemia[3,8,17–19] are the most frequently found disorders in newborn infants and high blood pressure, pre-eclampsia and hydramnios in pregnant mothers.[5,6,13,18–20]

Apart from GDM association with short-term morbidity, a medium and long-term association with diabetes and metabolic syndrome in mothers, as well as obesity, glucose metabolism disorders and cardiovascular disease in children is well documented.[9,16,21,22]

A varying prevalence of GDM has been found depending on the population and criteria being used.[16,22,23] An estimated 5.8% prevalence has been found in Portugal in 2013,[24] 1.7 times higher when compared to what has been found in 2007-2008.[7,25]

This study aimed mainly at the analysis of the influence of a new diagnostic approach to GDM in perinatal morbidity and mortality.

MATERIAL AND METHODS

This was an analytical and observational study involving a retrospective analysis of a clinical database regarding a group of pregnant mothers with diabetes having attended the MBB (*Maternidade Bissaya Barreto*) Maternity over a six-year period (2008-2013).

Inclusion criteria: singleton pregnancy in a mother with GDM followed and admitted to give birth at the MBB. A two-step GDM screening process had been followed over the first three years of the study (O'Sullivan test – 50g oral glucose followed by blood glucose level obtained 1 hour later) between the 24th and the 28th week of pregnancy, followed by a diagnostic test (100 g OGTT). Upon February 2011, GDM has been diagnosed by following a single-step process either with a fasting blood glucose determination obtained over the first trimester of pregnancy or using an OGTT carried out between the 24th and the 28th week of pregnancy.

A 75g OGTT should be offered to every woman with GDM six to eight weeks after delivery, according with the recommendations of the World Health Organization, aimed at a postpartum reclassification.[9]

The following variables regarding mothers were analysed: age, personal history of GDM, body weight and pre-gestational BMI. As regards pregnancy, the following variables were analysed: risk factors for the presence of GDM (family history of diabetes, history of gestational diabetes, over 35 years of age, multiparity and previous history of foetal macrosomia, recurrent pregnancy loss, congenital anomalies or intrauterine foetal death (IUFD), gestational age (GA) at diagnosis, gestational weight gain according with the standard values defined in 2009 by the Institute of Medicine (IM),[26] insulinisation rate and GA at insulin therapy onset and obstetric complications. The following variables regarding newborn infants were analysed: GA at birth and mode of birth, birth weight (BW), gender, perinatal morbidity (need for resuscitation, birth trauma, congenital malformations and metabolic complications) and mortality.

The following definitions regarding pregnant mothers were used:

Apart from GDM, any event with an impact on pregnancy outcomes has been considered as pathology of pregnancy: high blood pressure, pre-eclampsia, urinary tract infections (UTI), cholestasis, threatened preterm labour (TPTL) and premature rupture of membranes (PROM).

The presence of maternal overweight or obesity was defined with pre-gestational BMI over 25 kg/m^2 and 30 kg/m^2, respectively. Insulin therapy has been used according with the recommendations of the Portuguese Consensus Report on Diabetes and Pregnancy (*Relatório de Consenso sobre Diabetes e Gravidez*).[9]

Birth weight has been assessed by qualified nurses on the first minutes after birth, using a Seca$^{(R)}$ scale. Olsen growth curves[27] were used for the classification of newborn infants as regards BW percentiles (P) and GA, as follows: small for gestational age (SGA) – BW < 10th P, appropriate for gestational age (AGA) - BW: 10th-90th P and large for gestational age (LGA), BW > 90th P.

The following definitions regarding newborn infants were used:

- Hypoglycaemia: defined as the presence of capillary blood glucose under 40 mg/dL (2.2 mmol/L) at any moment during hospital stay, regardless of the GA and postnatal age. The presence of asymptomatic hypoglycaemia led to an improved support to breastfeeding and/or to the use of an oral 10% glucose solution (2 ml/kg) and new blood glucose determination obtained around one hour later. Persistent neonatal hypoglycaemia whether or not symptomatic usually led to being admitted to the neonatal intensive care unit (NICU) for clinical monitoring and IV infusion of 10% glucose.
- Hyperbilirubinaemia (obtained by dry chemistry methods): neonatal jaundice with an indication for phototherapy based on the approach used at the MBB,[28] based on GA and time since delivery. Infants with pathological jaundice were excluded from the study.
- Hypoxic-ischaemic encephalopathy (HIE): neurological symptoms (hypotonia, absent suck reflex, irritability, seizures or coma) due to birth asphyxia (Apgar score [AS] <7 at 5 minutes and need for resuscitation), leading to metabolic acidosis (pH < 7.00, base excess ≤ -16 mmol/L within 1 hour after birth) and ultrasound brain abnormalities.
- Hypocalcaemia (obtained by dry chemistry methods): calcium level under 2 mmol/L in blood serum.
- Combined morbidity: presence of one of the following: AS <7 at 5 minutes, HIE, seizures, hypoglycaemia, hypocalcaemia, hyperbilirubinaemia, polycythaemia, respiratory distress, Erb's palsy or clavicular fracture or the need for admission to the intensive or intermediate care unit (due to medical reasons).

Perinatal morbidity and mortality in this population has been compared to the remaining newborn infants admitted to the MBB over the same period. ICD9 codes have been used for the classification of patient´s medical records and these were coded by a neonatologist working

at the Department; data were based on the Portuguese adaptation of the DRG (Diagnosis-related Group) system [GDH (*Grupos de Diagnósticos Homogéneos*)].

The *Statistical Package for the Social Sciences* - SPSS version 20 software was used for the statistical analysis and a 0.05 level of significance has been considered. A bivariate analysis was used for the identification of differences among groups; Mann-Whitney test has been used for the comparison between continuous variables and Chi-square / Fisher test were used for the comparison between categorical variables. Odds ratio (OR) and adjusted odds ratio (aOR) were obtained upon logistic regression of statistically significant variables.

Exclusion criteria: pregnant mothers with twin pregnancies and those not followed or having not been admitted to give birth at the MBB were excluded from the study.

RESULTS

A total of 17,211 infants were born at the MBB over the study period and the presence of GDM was found in 970 pregnant mothers. Upon application of the exclusion criteria, 774 mother and newborn dyads were included in the study and divided into two study periods [2008-2010 (n = 421) *vs.* 2011-2013 (n = 353)].

The number of pregnant mothers with risk factors for GDM has decreased over the past three years (Table 1), even though with no statistical significance, except for the presence of previous birth defect, which has increased from 0.7 to 3.7%. The presence of a higher number of pregnant mothers with abnormal fasting glucose, higher need for insulin therapy and higher rate of TPTL and PROM have been found more recently. A non-significant increase in prematurity and in the number of caesarean births has been found.

Higher combined morbidity was found in group 2 (Table

Table 1 – Perinatal morbidity and mortality: mother and child

			Group 1 2008 - 2010 n = 421 (%)	Group 2 2011 - 2013 n = 352 (%)	*p*	OR (95% confidence interval)
Mother	Maternal age		33.1 (± 4.7)	32.8 (± 5.3)	0.451	
	BMI ≥ 30 kg/m²		105 (25.7)	85 (24.4)	0.679	
	Overweight		233 (57.1)	196 (56.3)	0.828	
	Risk factors		349 (82.9)	278 (78.8)	0.143	
	History of GDM(*)		64 (15.2)	36 (10.2)	**0.039**	0.633 (0.410 - 0.979)
	Previous neonatal anomaly(*)		3 (0.7)	13 (3.7)	**0.004**	5.327 (1.506 - 18.848)
Pregnancy	GA at GDM diagnosis		29.3 (± 5.9)	21.7 (± 5.1)	**< 0.001**	7.692 (6.712 - 8.673)
	Abnormal fasting glucose		19 (4.6)	144 (40.8)	**< 0.001**	14.179 (8.54 - 23.541)
	Pathology of pregnancy		85 (20.2)	112 (31.7)	**< 0.001**	1.837 (1.325 - 2.547)
	Weight gain during pregnancy		10.4 (± 5.2)	9.9 (± 5.4)	0.295	
	Gestational hypertension		41 (9.7)	35 (9.9)	0.935	
	PEC		7 (1.7)	10 (2.8)	0.269	
	TPTL		9 (2.1)	20 (5.3)	**0.010**	2.749 (1.236 - 6.118)
	PROM		16 (3.8)	42 (11.9)	**< 0.001**	3.418 (1.886 - 6.194)
	Insulin therapy		105 (24.9)	147 (41.6)	**< 0.001**	2.148 (1.582 - 2.916]
	GA at insulin onset		29.3 (± 6.6)	26.6 (± 7.0)	**0.002**	2.699 (1.006 - 4.392)
	GA at birth		38.5 (± 1.4)	38.3 (± 1.7)	0.115	
	Prematurity		23 (5.5)	29 (8.2)	0.128	
	Caesarean birth		129 (30.6)	128 (36.3)	0.098	
	Assisted birth		244 (58.0)	200 (56.7)	0.716	
Newborn infant	Olsen growth curves	SGA	39 (9.7)	37 (10.5)	0.593	
		LGA	22 (5.2)	16 (4.5)	0.687	
	BW		3237 (± 534)	3105 (± 548)	**0.001**	132.270 (55.438 - 209.102)
	Weight > 4,000 g		24 (5.7)	17 (4.8)	0.584	
	Apgar < 7 at 5 minutes		1 (0.2)	1 (0.3)	0.899	
	Need for resuscitation		11 (2.6)	11 (3.1)	0.670	
	Hypoglycaemia		6 (1.4)	23 (6.5)	**< 0.001**	4.835 (1.946 - 12.013)
	HBRB		46 (10.9)	45 (12.8)	0.425	
	RDS		5 (1.2)	11 (3.1)	0.060	
	Combined		63 (15)	76 (21.5)	**0.019**	1.559 (1.078 - 2.255)
	Birth trauma		3 (0.7)	1 (0.3)	0.408	
	Anomalia congénita		21 (5.0)	37 (10.5)	**0.004**	2.23 (1.280 - 3.887)
	NICU		26 (6.2)	22 (6.3)	0.966	
	Perinatal mortality		0 (0)	4 (1.1)	**0.043**	1.011 (1.000 - 1.023)

(*) – Nulliparous mothers were excluded; OR: odds ratio

BMI: body mass index; GDM: gestational diabetes; GA: gestational age; PEC: pre-eclampsia; TPTL: threatened preterm labour; PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age (according with Olsen growth curves); BW: birth weight; HBRB: hyperbilirubinaemia; RDS: respiratory distress syndrome; NICU: neonatal intensive care unit

1), mainly due to a significant increase in the number of infants with neonatal hypoglycaemia. A non-significant increase in the number of patients with respiratory distress and hyperbilirubinaemia has also been found. Even though with higher expression (8.2%), prematurity has not significantly increased with the new approach (group 2) and a significant increase in the total number of birth defects has been found in group 2 (10.5%), half of these having been considered as major disorders.

Hypoglycaemia (Table 2 and Fig. 1) was mainly associated with an earlier onset GDM (before the 10th week of pregnancy in 24.15% of pregnant mothers), with

Table 2 – Variables related to hypoglycaemia

		HYPOGLYCAEMIA				
	(%)	Yes n = 29	No n = 744	*p*	OR	$_{a}$OR
Mother	Maternal age (years)	32.3 (± 6.2)	33.1 (± 4.9)	0.548		
	BMI (kg/m^2)	28.1 (± 6.6)	27 (± 5.3)	0.381		
	BMI > 30 kg/m^2	8 (27.6)	182 (25.1)	0.759		
	Abnormality of glucose	2 (6.9)	38 (5.1)	0.670		
DRG	GA at diagnosis (weeks)	21.3 (± 9.2)	26.0 (± 7.6)	**0.011**	1.737 (1.160 - 8.260)	0.833 (0.800 - 0.868)
	Diagnosis before the 10th week	7 (24.1)	65 (8.7)	**0.005**	3.324 (1.368 - 8.076)	0.097 (0.030 - 0.321)
	Abnormal fasting glucose	13 (44.8)	149 (20.3)	**0.002**	3.185 (1.499 - 6.766)	6.353 (3.498 - 11.539)
	Insulin therapy	11 (37.9)	241 (32.4)	0.532		
	GA at insulin onset (weeks)	27 (± 7.8)	27.8 (± 6.9)	0.747		
	Insulin before the 10th week	0 (0)	5 (0.7)	0.658		
	HbA1c (mmol/mol)	5.2 (± 0.53)	5.2 (± 0.57)	0.752		
Pregnancy	Poor weight gain	11 (37.9)	261 (35.1)	0.753		
	Excess weight gain	8 (27.6)	184 (25.0)	0.753		
	Gestational hypertension	6 (20.7)	70 (9.4)	**0.045**	2.512 (0.989 - 6.376)	
	Caesarean birth	11 (37.9)	246 (33.1)	0.585		
	Prematurity	4 (13.8)	47 (6.3)	0.112		
	GA at birth (weeks)	37.7 (± 2.2)	38.4 (± 1.5)	0.076		
	GA < 35th week	2 (6.9)	13 (1.7)	**0.049**	4.165 (0.895 - 19.380)	
Newborn infant	Birth weight (g)	2968 (± 644)	3188 (± 534)	0.080		
	Birth weight > 4 kg	1 (3.4)	40 (5.4)	0.649		
	SGA	3 (10.3)	73 (9.8)	0.893		
	LGA	2 (6.9)	36 (4.8)	0.608		
	Need for resuscitation	0 (0)	22 (3.0)	0.347		
	NICU	6 (20.7)	42 (5.6)	**0.001**	4.360 (1.685 - 11.284)	
	RDS	3 (10.3)	13 (1.7)	**0.001**	6.488 (1.742 - 24.165)	
	Neurological symptoms	2 (6.9)	3 (0.4)	**< 0.001**	18.296 (2.935 - 114.050)	
	Birth defect	3 (10.3)	55 (7.4)	0.554		
	Mortality	1 (3.4)	2 (0.3)	0.109		

BMI: body mass index; GA: gestational age; SGA: small for gestational age; LGA: large for gestational age (according with Olsen growth curves); NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; OR: odds ratio; $_{a}$OR: adjusted odds ratio

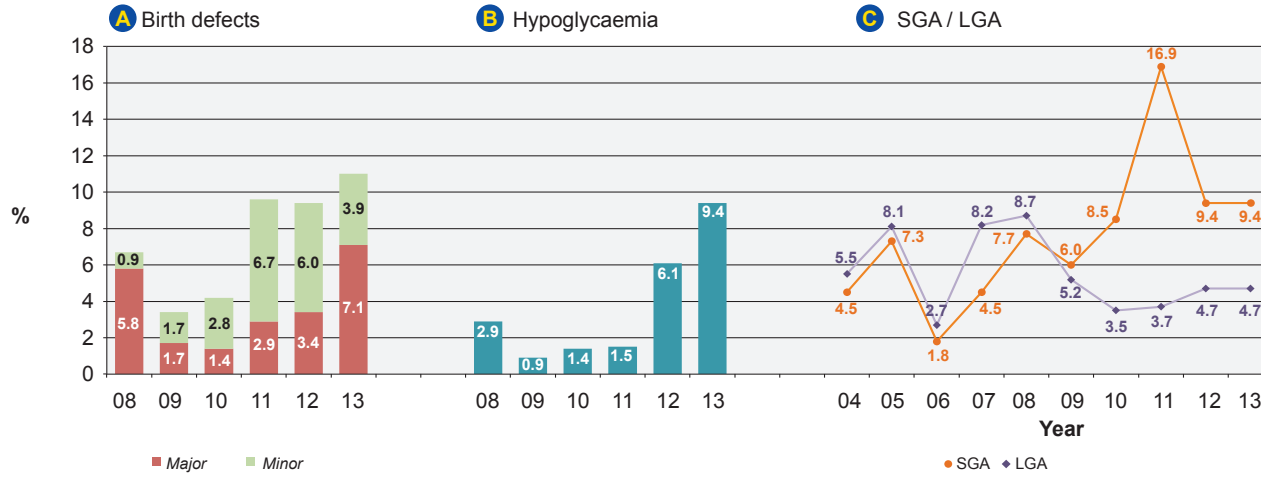

Figure 1 – Neonatal morbidity over the years

SGA: small for gestational age; LGA: large for gestational age

the presence of impaired fasting glucose and gestational hypertension. Even though more frequent in preterm, SGA and LGA newborn infants, this association was not statistically significant. Hypoglycaemia was more frequently found in newborn infants admitted to the NICU, with RDS and neurological symptoms. Upon logistic regression analysis, a statistically significant association between GA at the time of GDM diagnosis and the presence of hypoglycaemia remained, mainly when diagnosed before the tenth week of pregnancy and with impaired fasting glucose.

Birth defects (Table 3) were more frequently found in newborn infants from mothers having been diagnosed with GDM before the tenth week of pregnancy and on insulin therapy, mainly when early initiated (before the tenth week). Birth defects explained for the admission of a significant number of newborn infants (17.2% *vs.* 5.3%) to the NICU. Congenital heart (n = 10) and skeletal (n = 8) defects were most frequently found, followed by birth defects in kidney and urinary tract. When analysing the profile of birth defects over the years (Fig. 1), a varying rate of birth defects has been found, even though following an increasing trend over the past three years. Upon logistic regression analysis, a statistically significant association with adjusted OR between the need for insulin therapy and the presence of birth defects remained, mainly when insulin therapy was initiated before the tenth week of GA.

A decreasing trend regarding the presence of foetal macrosomia and LGA and an increasing trend regarding SGA have been found (Fig. 1). Despite the reduction in the prevalence of LGA newborn infants (and of foetal macrosomia) and considering the associated variables (Table 4), a significant association has been found between these and the presence of maternal obesity – mean BMI of 31.1 *vs.* 26.8 kg/m^2, multiparity, history of previous LGA newborn infants and the need for insulin therapy. Excess weight gain during pregnancy is usually a determinant factor for giving birth to LGA newborn infants and, due to this fact, non-normal births are more frequent, mostly caesarean births. Maternal excess gain weight is a determinant for LGA newborn infants, while poor maternal weight gain has been associated with SGA newborn infants (Table 4). A statistically significant association between LGA newborn infants and maternal pre-gestational BMI, previous foetal macrosomia and an excess gain weight during pregnancy has remained upon logistic regression analysis, while a statistically significant association remained between SGA newborn infants and the presence of poor maternal weight gain during pregnancy, in addition to the presence of gestational hypertension.

Despite of an increased morbidity, the number of hospital admissions to the NICU remained unchanged (around 6%) and prematurity, RDS (1.1% with the need for ventilation), birth defects and hyperbilirubinaemia with the need for intensive phototherapy were the main reasons for hospital admission. The number of hospital admissions due to an infectious pathology should be mentioned and two babies died (due to neonatal infection with group-B *Streptococcus* and *Escherichia coli*) and in both no infectious pathology

Table 3 – Variables associated with birth defects

		BIRTH DEFECT				
		Yes n = 58	No n = 716	*p*	OR	$_a$OR
Mother	Maternal age (years)	33.4 (± 5.1)	33 (± 4.5)	0.601		
	Age > 35 years	23 (39.7)	268 (37.4)	0.737		
	BMI (kg/m^2)	26.8 (± 5.9)	27.1 (± 5.4)	0.785		
	BMI > 30 kg/m^2	8 (14.8)	182 (25.9)	0.070		
	Previous child w/ birth defect	2 (3.4)	14 (2.0)	0.442		
	Previous IUFD	1 (1.7)	9 (1.3)	0.762		
	Abnormality of glucose metabolism	2 (3.4)	38 (5.3)	0.761		
Pregnancy / DRG	GA at diagnosis (weeks)	24.2 (± 8.5)	25.9 (± 7.7)	0.124		
	Diagnosis before 10th week	10 (17.2)	63 (8.8)	**0.034**	2.159 (1.042 - 4.475)	
	Abnormal fasting glucose	15 (25.9)	148 (21)	0.384		
	Insulin	28 (48.3)	224 (31.3)	**0.008**	2.050 (1.196 - 3.513)	1.929 (1.115 - 3.340)
	GA at insulin onset (weeks)	28.4 (± 6.9)	27.7 (± 6.9)	0.590		
	Insulin before 10th week	2 (3.4)	3 (0.4)	**0.006**	8.488 (1.389 - 51.853)	5.667 (0.905 - 35.494)
	HbA1c (mmol/mol)	5.2 (± 0.61)	5.2 (± 0.60)	0.566		
Birth	Caesarean birth	24 (41.4)	233 (32.5)	0.169		
	Prematurity	2 (3.4)	50 (7)	0.301		
	GA at birth (weeks)	38.2 (± 2.0)	38.4 (± 1.5)	0.448		
Newborn infant	Birth weight (g)	3125 (± 709)	3182 (± 530)	0.551		
	Need for resuscitation	3 (5.2)	19 (2.7)	0.314		
	NICU	10 (17.2)	38 (5.3)	**< 0.001**	3.72 (1.743 - 7.902)	
	RDS	4 (6.9)	12 (1.7)	**0.007**	4.32 (1.354 - 13.91)	
	Mortality	0 (0)	4 (0.6)	0.568		

OR: odds ratio; $_a$OR: adjusted odds ratio
BMI: body mass index; IUFD: intra-uterine foetal death; GA: gestational age; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome

Table 4 – Nutritional status at birth and associated variables

NUTRITIONAL STATUS						
LARGE FOR GESTATIONAL AGE (excluding SGA newborn infants)		**Yes n = 38**	**No n = 650**	***p***	**OR**	**$_a$OR**
Mother	BMI (kg/m^2)	31.1 (± 4.8)	26.8 (± 5.3)	**< 0.001**	0.825 [- 5.926 - 2.594]	
	BMI > 30 kg/m^2	20 (54.1)	153 (23.6)	**< 0.001**	3.791 (1.937 - 7.419)	2.942 (1.661 - 5.955)
	Previous GDM	10 (36.3)	83 (12.1)	0.11		
	Previous neonatal macrosomia	8 (21.6)	39 (5.9)	**< 0.001**	4.246 (1.825 - 9.878)	4.062 (1.619-10.192)
	Multiparity	3 (7.9)	11 (1.7)	**0.004**	5.057 (1.349 - 18.952)	
	Abnormality of glucose metabolism	4 (10.5)	36 (4.9)	0.126		
Pregnancy	Excess weight gain	23 (60.5)	169 (23.6)	**< 0.001**	4.968 (2.529 - 9.759)	5.204 (2.555 -10.601)
	Poor weight gain	1 (2.6)	272 (37.0)	**< 0.001**	0.046 (0.006 - 0.338)	
	Weight gain, in kg	12.6 (± 5.2)	10.0 (±5.3)	**0.019**	1.042 [-6.783 - 2.569]	
	Pathology of pregnancy	17 (44.7)	160 (24.2)	**0.005**	2.501 (1.291 – 4.844)	2.380 (1.163 - 4.868)
	Gestational hypertension	5 (13.2)	59 (8.9)	0.478		
	PEC	1 (2.6)	12 (1.6)	0.855		
	Hydramnios	5 (13.2)	24 (3.3)	**0.002**	4.495 (1.613 – 12.525)	
	TPTL	1 (2.6)	28 (3.8)	0.710		
	PROM	5 (13.2)	53 (7.2)	0.174		
	Abnormal fasting glucose	11 (28.9)	140 (21.0)	0.253		
	Insulin (Y/N)	20 (52.6)	232 (31.5)	**0.007**	2.414 (1.253 – 4.649)	
	Caesarean birth	27 (71.1)	230 (31.3)	**< 0.001**	5.4 (2.633 – 11.074)	
	Assisted birth	31 (81.6)	413 (56.1)	**0.002**	3.464 (1.506 – 7.967)	
	Prematurity	4 (10.5)	48 (6.5)	0.336		
Newborn infant	GA < 35th week	2 (5.3)	14 (1.9)	0.156		
	Birth weight (g)	4242 (± 541)	3122 (± 485)	**< 0.001**	89.634 (-1300.72 - 938.441)	
	Need for resuscitation	2 (5.3)	20 (2.7)	0.358		
	Asphyxia	1 (2.6)	0 (0.0)	**< 0.001**	1.027 (0.975 – 1.082)	
	Ventilation	1 (2.6)	3 (0.4)	0.062		
	NICU	4 (10.5)	44 (6.0)	0.258		
	Hypoglycaemia	2 (5.3)	27 (3.7)	0.615		
	RDS	2 (5.3)	14 (1.9)	0.156		
	Combined	11 (28.9)	128 (17.4)	0.070		
	Mortality	1 (2.6)	3 (0.4)	0.062		
SMALL FOR GESTATIONAL AGE (excluding LGA infants)		**Yes n = 75**	**No n = 660**	***p***	**OR**	**$_a$OR**
GA	Abnormality of glucose metabolism	7 (9.2)	33 (4.7)	0.094		
	Diagnosis before 10th week	5 (6.6)	68 (9.7)	0.370		
	Abnormal fasting glucose	12 (16.0)	151 (21.5)	0.265		
Pregnancy	Poor weight gain	41 (53.9)	232 (36.2)	**< 0.001**	2.353 (1.459 – 3.794)	2.433 (1.500 - 3.946)
	Excess weight gain	15 (20.0)	154 (23.6)	0.486		
	Gestational hypertension	12 (15.8)	59 (8.9)	0.055		1.976 (1.003 - 3.895)
	PEC	4 (5.3)	12 (1.8)	0.051		
	TPTL	2 (2.6)	26 (3.9)	0.572		
	PROM	4 (5.3)	54 (7.7)	0.437		
	Caesarean birth	28 (36.8)	229(32.8)	0.478		
	Assisted birth	49 (64.5)	395 (56.6)	0.187		
	Prematurity	5 (6.6)	47 (6.7)	0.959		
	GA < 35th week	3 (3.9)	13 (1.9)	0.225		
Newborn infant	Birth weight (g)	2467 (± 372)	3254 (± 503)	**< 0.001**	0.624 (0.335 - 2.813)	
	Need for resuscitation	2 (2.6)	20 (2.9)	0.906		
	NICU	4 (5.3)	44 (6.3)	0.719		
	RDS	2 (2.6)	14 (2.0)	0.717		
	Hypoglycaemia	3 (3.9)	26 (3.7)	0.925		
	Combined	13 (17.1)	126 (18.1)	0.838		
	Birth defect	6 (7.9)	52 (7.4)	0.889		
	Major birth defect	2 (33.3)	26 (50)	0.439		

OR: odds ratio; $_a$OR: adjusted odds ratio
BMI: body mass index; IUFD: intra-uterine foetal death; GA: gestational age; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome

had been identified in the mother (screening for vaginal infections and urine culture). Neonatal deaths were only found in group 2 patients, including the two aforementioned babies and an infant suffering from hypoxic-ischaemic encephalopathy with the need for hypothermia. One case of IUFD at the 28th week of pregnancy occurred over this period of time, due to an umbilical cord accident.

Maternal reclassification was only available in 527 / 774 (68%) patients and only one major defect – unilateral renal agenesis - was found in a pregnant mother with abnormal glucose metabolism. In total, 40 pregnant mothers have been found with permanent abnormal glucose metabolism (7.9% of those included in the study). These abnormalities were mainly found in the group of mothers having given birth to SGA and LGA newborn infants and in those in group 2 presenting with hypoglycaemia.

Globally, infants of diabetic mothers (IDM) born between 2008 and 2010 showed lower morbidity, lower prematurity, lower prevalence of respiratory distress syndrome (RDS) and lower rate of AS <7 at 5 minutes when compared to the remaining newborn infants born at the MBB over the same period (shown in Table 5 and based on DRG codes), leading to a lower number of admissions to the NICU. Instead, a significantly higher rate of brachial plexus palsy has been found in IDM. A similar pattern was found in group 2 patients (2011 - 2013) even though showing a non-significant association, except regarding Erb's palsy, which had no expression in IDM, while a significant difference has been found regarding the incidence of birth defects.

DISCUSSION

Some differences between both groups of newborn infants can be explained by the change of approach to GDM, mainly over the most recent years, with the new approach allowing for an earlier diagnosis, due to the relevance of fasting glucose, to a lower-threshold for initiating an insulin therapy and to a more careful approach to newborn infants with hyperbilirubinaemia.[9,28]

BW and its relationship with GA is crucial for the assessment of newborn infants and is often used to estimate the risk of perinatal morbidity and mortality. Lubchenco growth charts[29] were published in 1963 and have been widely used in IDM; however, it is well known that these are currently non-adapted to the Portuguese population: newborn infants are not divided by gender and foetal macrosomia is overvalued.[30] Olsen growth curves[27] have been used in the Portuguese national DRG record, they have been more recently population-based and the analysis of multi-ethnic groups has been included, with newborn infants divided by gender. The classification of newborn infants according with intra-uterine growth is crucial in the population of IDM, in whom foetal macrosomia and/or LGA newborn infants and their association with perinatal and neonatal morbidity is its greatest paradigm.[16,17,20,31]

Foetal growth of an IDM has been extensively studied. Non-modifiable and modifiable factors have an influence on its expression. Genetics has been included among non-modifiable factors (even though it is known that its expression can also be changed in the long-term), in addition to gender, parity, maternal age and height; maternal weight and BMI, weight gain during pregnancy, maternal diet and

Table 5 – Comparison of mortality in IDM and in remaining newborn infants born at the MBB (DRG)

	2008 - 2010				2011 - 2013			
	IDM	MBB*			IDM	MBB*		
Number	421	8874	*p*	OR	353	7563	*p*	OR
Caesarean birth	129 (30.6)	2409 (27.1)	0.156		128 (36.3)	2068 (27.3)	< 0.001	1.512 (1.210 - 1.889)
Prematurity	23 (5.5)	895 (10.1)	0.002	0.515 (0.336 - 0.789)	29 (8.2)	776 (10.3)	0.124	
NICU	26 (6.2)	797 (9.0)	0.048	0.667 (0.446 - 0.999)	22 (6.2)	690 (9.1)	0.063	
Apgar < 7 at 5 minutes	1 (0.2)	54 (0.6)	0.332		1 (0.3)	85 (1.1)	0.136	
RDS	5 (1.2)	398 (4.5)	0.001	0.256 (0.105 - 0.622)	11 (3.1)	216 (2.9)	0.775	
Hypoglycaemia	6 (1.4)	77 (0.89)	NA		23 (6.5)	41 (0.81)	NA	
Hyperbilirubinaemia	46 (10.9)	626 (7.1)	0.003	1.616 (1.177 - 2.219)	45 (12.9)	1043 (13.8)	0.649	
Clavicular fracture	1 (0.2)	17 (0.2)	0.834		1 (0.3)	22 (0.3)	0.979	
Erb's palsy	7 (1.7)	9 (0.17)	< 0.001	16.655 (6.172 - 44.940)	0	10 (0.1)	0.494	
Birth defects	21 (5.0)	446 (5.0)	0.972		37 (10.5)	257 (3.4)	< 0.001	3.33 (2.317 - 4.785)

* Newborn infants from non-diabetic mothers; N/A: not available

IDM: infant from diabetic mother; MBB: Maternidade Bissaya Barreto; DRG: diagnosis-related groups; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; OR: odds ratio

physical activity have been included as modifiable factors, among others.[32] Pre-gestational BMI has consistently been considered as the most crucial independent factor for foetal macrosomia and also seems to be independent from maternal metabolic control.[32,33]

The impact of most recent diagnostic criteria of GDM in maternal and neonatal health, as well as a decreased prevalence of LGA newborn infants and increased prevalence of SGA have been analysed at different national meetings of the *Sociedade Portuguesa de Diabetologia*. Pre-gestational BMI, poor maternal weight gain during pregnancy, particularly in pregnant mothers with BMI < 25 kg/m^2 (underweight and normal weight) and the presence of gestational hypertension have also been described.[15,34] A decreased prevalence of LGA infants was also found, which has been associated with an increased prevalence of SGA infants that became more prevalent. Maternal obesity, a history of GDM, foetal macrosomia and multiparity were found to be among those most significantly associated with these changes, unlike maternal poor weight gain during pregnancy and the presence of obstetric complications such as hypertension that were significantly associated with SGA newborn infants. LGA infants and neonatal macrosomia involved an increased risk of labour-related perinatal complications.[2,17,22] LGA infants are associated with a higher need for insulin therapy and caesarean births and non-associated with an increased neonatal morbidity. An accurate maternal metabolic and nutritional control can reduce the incidence of macrosomia / LGA.[3,17]An individual medical approach to pregnant mothers with GDM (insulin therapy in association with diet and exercise) together with foetal ultrasound assessment are crucial for foetal growth control.

A good metabolic control is generally associated with a decreased prevalence of hypoglycaemia and this would be expected to happen mainly in LGA and SGA newborn infants,[35] which was not found in this study.

An approximately 24% rate of hypoglycaemia has been described in IDM by different studies,[36] as it is well known that its incidence depends on the diagnostic criteria that were used. Even though capillary glucose determination is less reliable, mainly with high haematocrit and lower glucose level, it is frequently used in newborn infants, as small blood samples are needed and allowing for a quick diagnosis and action.[37]

Hypoglycaemia in IDM has been associated with maternal obesity, with acidosis at birth, with SGA newborn infants and with the need for insulin during pregnancy and/ or with intra-partum hyperglycaemia.[38] In this study, it has been mainly associated with an earlier diagnosis and with concomitant morbidity (gestational hypertension). Intra-partum metabolic control has not been analysed in this study and foetal hyperinsulinism has been one most frequently studied; however, there is a group of newborn infants with no foetal hyperinsulinism showing a response to maternal intra-partum hyperglycaemia with an excessive production of insulin leading to hypoglycaemia over the first hours of life.[3,39] There is an accurate monitoring approach to these pregnant mothers during delivery and this has not been significantly modified over the study period.

Pre-gestational diabetes is associated with a high risk for birth defects,[4] higher than the risk found in women with poor glycaemic control[4] which has remained unchanged despite the approaches aimed at controlling blood glucose at embryogenesis.[17,20,21,40,41] A 2 to 3% prevalence rate of birth defects has been found in general population[17,40,42,43] and was slightly higher (1.3 times) in IDM.[21,44] There is mainly an increased risk in mothers with GDM who turned out to present with type-2 diabetes mellitus.[4,20,42] A surprisingly increased prevalence of birth defects has been found in this study, which seems related to an early diagnosis (17.2% before the 10th week of pregnancy) and necessarily with the metabolic control throughout this particularly sensitive period of pregnancy. However, we cannot establish that this increased prevalence is associated with the change in diagnostic criteria. Birth defects found in this study were those usually described in IDM[21,40,41] and a small expression has been found regarding the defects of the nervous system. These are easily identifiable in pregnancy and pregnant mothers may opt for medical assisted termination of pregnancy before an established diagnosis of GDM has been reached.

Around 10% of newborn infants are admitted to the NICU at the MBB, higher than the rate found in IDM (6%). Despite of an increased morbidity, most infants have been monitored close to their mothers.

The optimization of prenatal care, aimed at an improved maternal morbidity, a reduction in foetal macrosomia leading to a reduction of peripartum complications with dreadful consequences for newborn infants has been the core of medical literature on perinatal care of pregnant mothers with GDM.

Hypoglycaemia, GA at diagnosis (mainly when before the 10th week) and abnormal fasting glucose were mostly associated with morbidity and the need for insulin therapy (mainly when initiated before the 10th week of pregnancy) were mostly associated with the presence of birth defects. These factors were both associated with GDM diagnosed over the first trimester of pregnancy (screening with fasting glucose) and with an early initiated insulin therapy, aimed at an adequate metabolic control.

No significant increase in the number of reclassified pregnant mothers with diabetes or pre-diabetes has been found and the result was only available regarding only 68% of the mothers. There has been an effort towards providing pregnant mothers with an earlier diagnosis of GDM (first trimester) but, unlike what would be expected, a lower number of women with a permanent abnormality of glucose metabolism has been found, when compared to the global sample. The result of clinical reclassification is only available for a low percentage of Portuguese mothers and this is a national concern.[15]

CONCLUSION

An increased number of patients with neonatal hypoglycaemia, SGA newborn infants and birth defects have been found upon the implementation of a new medical approach to GDM diagnosis and treatment. Pre-gestational maternal characteristics (BMI), earlier GDM diagnosis, accurate metabolic control, 'over-adherence' to dietary recommendations (lower weight gain during pregnancy) and probably infant metabolic status at embryogenesis were the main factors explaining for this change.

Healthcare approaches to all women and mostly to those presenting with significant neonatal morbidity, in addition to a joint action with the monitoring team of diabetic pregnant mothers seem crucial.

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HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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REFERENCES

1. Watson D, Rowan J, Neale L, Battin M. Admissions to neonatal intensive care unit following pregnancies complicated by gestational or type 2 diabetes. Aust N Z J Obstet Gynaecol. 2003;43:429–32.
2. Mitanchez D, Burguet A, Simeoni U. Infants born to mothers with gestational diabetes mellitus: Mild neonatal effects, a long-term threat to global health. J Pediatr. 2014;164:445–50.
3. NICE. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. 2015. [consultado 2016 jul 12]. Disponível em: https://www.nice.org.uk/guidance/ng3.
4. Dailey TL, Coustan DR. Diabetes in pregnancy. Neoreviews. 2010;11:e619–26.
5. Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2010;23:199–203.
6. Yogev Y, Metzger BE, Hod M. Establishing diagnosis of gestational diabetes mellitus: Impact of the hyperglycemia and adverse pregnancy outcome study. Semin Fetal Neonatal Med. 2009;14:94–100.
7. Simões A, Robalo R, Gomes G, Aleixo F. Diabetes gestacional nos anos 2000 e 2010: retrato de uma sociedade. Rev Port Endocrinol Diabetes Metab. 2013;8:21.
8. Tieu J, McPhee AJ, Crowther CA, Middleton P. Screening and subsequent management for gestational diabetes for improving maternal and infant health. Cochrane Database Syst Rev. 2014;2:CD007222.
9. Sociedade Portuguesa de Endocrinologia Diabetes e Metabolismo, Sociedade Portuguesa de Diabetologia, Sociedade Portuguesa de Obstetrícia e Medicina Materno-Fetal, Seção de Neonatologia da Sociedade Portuguesa de Pediatria. Relatório de Consenso sobre Diabetes e Gravidez. Lisboa: SPEDM, SPD, SPOMMF, SPP; 2011.
10. Ramos G, Moore T. Endocrine disorders in pregnancy. In: Gleason G, Devaskar S, editors. Avery's disease of the newborn. 9th ed. Philadelphia: Elsevier / Saunders; 2012. p. 75–87.
11. Stewart Z, Murphy H. Gestational diabetes. Medicine. 2014;43:44.
12. Metzger BE, Persson B, Lowe LP, Dyer AR, Cruickshank JK, Deerochanawong C, et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. Pediatrics. 2010;126:e1545–52.
13. Reece EA, Moore T. The diagnostic criteria for gestational diabetes: To change or not to change? Am J Obstet Gynecol. 2013;208:255–9.
14. Visser GH, De Valk HW. Is the evidence strong enough to change the diagnostic criteria for gestational diabetes now? Am J Obstet Gynecol. 2013;208:260–4.
15. Massa AC, Rangel R, Cardoso M, Campos A. Diabetes gestacional e o impacto do actual rastreio. Acta Med Port. 2015;28:29–34.
16. Reece EA, Leguizamón G, Wiznitzer A. Gestational diabetes: the need for a common ground. Lancet. 2009;373:1789–97.
17. Ramos GA, Hanley AA, Aguayo J, Warshak CR, Kim JH, Moore TR. Neonatal chemical hypoglycemia in newborns from pregnancies complicated by type 2 and gestational diabetes mellitus - the importance of neonatal ponderal index. J Matern Fetal Neonatal Med. 2012;25:267–71.
18. Hunt KF, Whitelaw BC, Gayle C. Gestational diabetes. Obstet Gynaecol Reprod Med. 2015;24:238–44.
19. Fong A, Serra A, Gabby L, Wing D, Berkowitz K. Hemoglobin A1c as an early predictor of gestational diabetes in obese patients: a subgroup analysis. Am J Obstet Gynecol. 2014;210:S137.
20. Langer O. Pregnancy complicated by diabetes mellitus. In: Martin R, Fanaroff A, Walsh M, editors. Neonatal-perinatal medicine. 9th ed. St Louis: Elsevier; 2011. p. 291.
21. Ogata ES. Problems of the infant of the diabetic mother. Neoreviews. 2010;11:e627–31.
22. Vandorsten JP, Dodson WC, Espeland MA, Grobman WA, Guise JM, Mercer BM, et al. NIH consensus development conference: diagnosing gestational diabetes mellitus. NIH Consens State Sci Statements. 2013;29:1–31.
23. Hartling L, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U . S . preventive of medical applications of research. Ann Intern Med. 2013;159:123-9.
24. Correia LG, Boavida JM, Almeida JPF de, Cardoso SM, Dores J, Duarte JS, et al. Diabetes: Factos e Números 2013 − Relatório Anual do Observatório Nacional da Diabetes. Lisboa: Sociedade Portuguesa de Diabetologia; 2013.
25. Brás L, Figueiredo L, Fonseca F. The influence of obesity and gestational weight gain on the newborn weight in a group of women with gestational diabetes. Rev Port Endocrinol Diabetes e Metab. 2013;8:70–6.
26. Institute of Medicine. Weight gain during pregnancy. Inst Med Natl Acad. 2009:1–2.
27. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics. 2010;125:e214–24.
28. Vaz A, Taborda A. Hiperbilirrubinémia - protocolo de actuação da MBB. Coimbra: Maternidade Bissaya Barreto; 2010.
29. Lubchenco LO, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics. 1966;37:403–8.
30. Cunha M, Marques A, Carreiro H, Machado M do C. Percentis do peso de nascimento para a idade gestacional, numa população de recém-

nascidos. Acta Pediátr Port. 2007;38:187–93.
31. Kim SY, Sharma AJ, Sappenfield W, Wilson HG, Salihu HM. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestational-age births. Obstet Gynecol. 2014;123:737–44.
32. Henriksen T. The macrosomic fetus: a challenge in current obstetrics. Acta Obstet Gynecol Scand. 2008;87:134–45.
33. Brás L, Figueiredo L, Fonseca F. The influence of obesity and gestational weight gain on the newborn weight in a group of women with gestational diabetes. Rev Port Endocrinol Diabetes Metab. 2013;8:70–6.
34. Almeida M, Amaral N, Dores J. Diabetes gestacional e o peso ao nascimento – o paradigma invertido? Rev Port Diabetes. 2015;10:3–10.
35. Persson B. Neonatal glucose metabolism in offspring of mothers with varying degrees of hyperglycemia during pregnancy. Semin Fetal Neonatal Med. 2009;14:106–10.
36. Menato G, Bo S, Signorile A, Gallo ML, Cotrino I, Poala CB, et al. Current management gestational diabetes mellitus. Expert Rev Obstet Gynecol. 2008;3:73–91.
37. Flores-le Roux JA, Sagarra E, Benaiges D, Hernandez-Rivas E, Chillaron JJ, Puig de Dou J, et al. A prospective evaluation of neonatal hypoglycaemia in infants of women with gestational diabetes mellitus. Diabetes Res Clin Pract. 2012;97:217–22.
38. Rozance PJ. Update on neonatal hypoglycemia. Curr Opin Endocrinol Diabetes Obes. 2014;21:45–50.
39. Cowett RM. Neonatal care of the infant of the diabetic mother. Neoreviews. 2002;3:e190–6.
40. Nizard J, Ville Y. The fetus of a diabetic mother: Sonographic evaluation. Semin Fetal Neonatal Med. 2009;14:101–5.
41. Nold JL, Georgieff MK. Infants of diabetic mothers. Pediatric Clinics of North America. 2004;51:619-37.
42. Teramo K. Diabetic pregnancy and fetal consequences. Neoreviews. 2014;15:e83–90.
43. Barthell J, Georgieff M. Infants of diabetic mothers. In: Buonocore G, Bracci RW, editors. Neonatology, a practical approach to neonatal diseases. 1st ed. Milan: Springer-Verlag; 2012. p. 379.
44. Lepercq J, Timsit J. Diabètes préalables à la grossesse: complications périnatales. Arch Pediatr. 2005;12:763–5.