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The influence of advanced age and obesity on pregnancy course and outcome in patients with diabetes mellitus

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Abstract

Introduction: Older women are at greater risk of suffering from a series of comorbidities such as obesity, diabetes, and hypertension that could negatively affect pregnancy course and outcomes. This study aims to investigate the impact of maternal age and pre-pregnancy body mass index (BMI) on pregnancy outcomes of women with diabetes mellitus (DM).

Material and methods: The study included 323 diabetic pregnant women. All complications throughout pregnancy and the early neonatal period were noted. The women were divided into groups according to age decade and BMI.

Results: 84.8% of women reported pregnancy complications, with a higher prevalence in obese women (p = 0.003). However, most children had a good outcome with few early neonatal complications (36.85%). Old and obese women with DM often showed complications, and their newborns had higher birth weight (p = 0.003) and more neonatal complications (p = 0.041). Maternal BMI (p = 0.016; OR = 1.064), but not age (p = 0.801), was found to be a significant predictor of pregnancy complications.

Conclusions: Pregnant women with DM should be considered as high-risk patients. Advanced age and increased BMI prior to pregnancy are risk factors for pregnancy complications. Maternal obesity is the most important predictor of pregnancy complications in women with DM. Pregnancy outcome can be good for both mothers and children with a timely and adequate approach.

Key words: age, BMI, diabetes mellitus, pregnancy, complications, outcome.

Introduction

Current socioeconomic trends and improved achievements of assisted reproduction in the past couple of decades have resulted in women having children at a later age. However, delayed reproduction can cause significant pregnancy complications. Older women are more likely to have different comorbid conditions such as obesity, diabetes, and hypertension that could negatively impact pregnancy course and outcome [1]. Moreover, it was proven that even healthy women of advanced age have increased pregnancy complication rates. While it is documented in numerous studies that a maternal age of 35 years or more is generally associated with both adverse maternal and neonatal pregnancy outcomes, data on how age influences pregnancy outcomes in the setting of comorbidity are limited [2]. Obesity presents a significant public health problem in many parts of the world. Current investigations found that almost 40% of the world's population is overweight and 13% are obese [3–5]. Visceral fat increases insulin resistance potentiating development of the metabolic syndrome and diabetes mellitus. This is specifically important during pregnancy because it is well known that gestational diabetes mellitus (GDM) can be a risk factor for different adverse pregnancy outcomes [6].

Pre-existing diabetes in pregnancy (pregestational) refers to type 1 and type 2 diabetes identified before pregnancy. Severe maternal complications of pregnancy might develop in poorly controlled patients, comprising preeclampsia-eclampsia, myocardial infarction, isch-

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aemic stroke, sepsis, venous thromboembolism, and even fatal outcome [7]. Nephropathy and proliferative retinopathy can progress during pregnancy and contribute to poorer pregnancy and birth outcomes. Levels of glycosylated haemoglobin (A_{1c}) above 7% in the first trimester are associated with poorer birth outcomes. The teratogenic effects of hyperglycaemia may be aggravated by obesity, improper nutrition, smoking, and alcohol use. Foetal complications include major congenital malformations, most commonly related to the cardiovascular system [8]. Adverse pregnancy outcomes also comprise macrosomia and shoulder dystocia with vaginal delivery, neonatal hypoxic-ischaemic encephalopathy, and even neonatal mortality. Neonates of poorly controlled diabetic patients have higher frequency of respiratory distress, polycythaemia, hypoglycaemia, hypocalcaemia, and hyperbilirubinaemia. Both the increasing frequency of type 1 and type 2 diabetes and advanced maternal age at conception can further increase the risk of adverse maternal and neonatal outcomes. Thus, it is thought that a combination of overweight/obesity and diabetes mellitus (DM) could have a multiplicative or additive effect and amplify the risk of maternal and foetal complications in pregnancy, delivery, and the neonatal period. However, although 50–70% of diabetic women are overweight/obese, data on pregnancy complications and outcomes in these patients are still insufficient and conflicting [9].

Therefore, the study aimed to investigate the impact of advanced age and obesity on pregnancy outcomes in women with diabetes mellitus.

Material and methods

The study included all pregnant women with DM who were followed up and delivered in our clinic during a 6-year period (1 January 2012 – 31 December 2017), and it was approved by the local Ethics Committee. We excluded all first-trimester miscarriages from the study. The main inclusion criterion for our study was having diabetes mellitus. The diagnosis of DM was based on World Health Organization diabetes diagnostic criteria (fasting plasma glucose level ≥ 7.0 mmol/L and/or plasma glucose ≥ 10 mmol/L one hour after a 75-g oral glucose load and/or glycated haemoglobin HbA_{1c} ≥ 48 mmol/mol) [10–12].

According to DM type, all women were separated into 4 groups: DM insulin dependent, DM without insulin therapy, GDM with or without the need for insulin therapy. In the case of gestational DM, the gestational week (GW) at the time of diagnosis was registered. According to protocols of obstetric surveillance in our institution all pregnant women are screened for GDM at 24–28 weeks of pregnancy. In the case of significant disturbance of serum glycaemic levels DM is diagnosed even before 24th GW. We also noted if the investigated women had an endocrinological or special gynaecological consultation prior to or during pregnancy regarding their DM and potential risks in pregnancy.

During the first examination in pregnancy, general and obstetric medical history data such as age, nationality, family history of DM, gravidity (number of previous term vaginal deliveries, caesarean section – CS, planned or urgent, spontaneous miscarriages, intentional pregnancy abortions, previous neonatal death), and the presence of comorbidities (chronic hypertension – HTA, other illnesses such as endocrinological, pulmonary, neurological, etc.) as well as all DM complications (retinopathy, neuropathy, nephropathy, etc.) were determined for all patients.

Based on the patient's height and weight the body mass index (BMI) was calculated according to standard formula. Pre-pregnancy BMI was classified in a standard manner (normal weight: BMI 18.5 to 25; overweight; BMI 25.1 to 30; obesity class I: BMI 30.1 to 35; severe obesity class II BMI 35.1 to 40; very severe obesity class III BMI 40.1 to 45; morbid obesity class IV: BMI ≥ 45.1). For the purpose of this study, class I and II, and III and IV obesity were assessed together. Moreover, the patients were also divided into 2 groups regarding obesity (no vs. yes BMI ≥ 30.1) and assessed accordingly [10, 11].

Patients were also divided into 4 groups according to age decades (≤ 25 years; 25.1 to 35 years; 35.1 to 45 years; ≥ 45.1 years). In addition, based on the usual age of 35 years after which mothers are considered to be of advanced age, the examined women were categorized as younger and older (≥ 35.1) [1].

Moreover, we proposed 3 levels of pregnancy risk regarding mother's age and BMI (low if both parameters were not increased – young and not obese; intermediate if one parameter was increased – old or obese; high if both parameters were increased – old and obese).

Women were closely monitored throughout pregnancy with regular monthly check-ups that included laboratory testing (blood count, biochemical analyses with glucose level determination both fasting and after meals, urine sampling, microbiological analyses, cardiotocography – CTG, gynaecological and ultrasound examination with measurement of foetal biometry and placental thickness, Doppler blood flow of umbilical and medial cerebral artery, and biophysical profile evaluation). We noted all pregnancy complications such as hypertension/preeclampsia, antepartum bleeding, contractions, violation of uteroplacental blood flow (VUPB) on Doppler; violation of fetoplacental blood flow on Doppler, amniotic fluid volume disturbances according to amniotic fluid index (AFI) (oligoamnion or hydramnion), premature preterm rupture of membranes, pathologic nonreactive CTG that was an indication for urgent CS, foetal anomalies, etc. In the case of impending preterm birth women were treated with corticosteroids to enhance maturation of foetal lungs.

At the end of pregnancy, we recorded the delivery type (spontaneous or induced vaginal delivery, planned or urgent CS) and time (GW). For every child their birth weight was measured and Apgar score in first and fifth minute was determined. We also noted the child's sex (male/female).

In the early neonatal period, while still hospitalized (approximately for 3 days after birth if there were no complications), all complications were registered, such as neonatal hypoglycaemia, jaundice, congenital hypothyreosis, necrotizing enterocolitis, pulmonary HTA, pulmonary problems, neonatal strength problems, need for neonatal oxygenation, intubation, or resuscitation, convulsions, sepsis, small or large anomalies, etc. The child's weight at discharge was also noted. Moreover, any sign of postpartum hypertension in mothers was recorded.

Finally, all data collected throughout pregnancy as well as pregnancy outcomes were analysed by methods of descriptive and analytical statistics using the IBM SPSS 20 software for Windows. The significance of differences between categories of assessed parameters of mothers and children before and after delivery according to age and BMI categories was examined by Kruskal-Wallis χ^2 test. Correlations of investigated parameters with patients' age and BMI were tested using Spearman correlation. Binary logistic regression equations (adjusted for DM type and having pre-existing comorbidities) were used to investigate the impact of patients' age and BMI on pregnancy and neonatal complications.

Results

The study included 323 pregnant women with diagnosed DM who on average were 34.26 ±6.56 years of age. The mean BMI of investigated women was 34.01 ±7.85. There were significantly fewer low-risk (25.7%) than intermediate-risk (40.9%) and high-risk (33.4% old and obese mothers) pregnancies (p = 0.004). Women had between one and eleven previous pregnancies, but in most cases one previous term delivery. The most common type of DM in our sample was GDM that was not treated with insulin (61.9%). Most women did not have DM-related complications, but more than 75% had some other comorbidity.

Descriptive parameters of investigated women and children according to age and BMI groups are presented in Table 1. Differences in frequency of examined maternal and foetal parameters according to patients' age and BMI are presented in Tables 2, 3.

Some types of maternal complications throughout pregnancy were registered in 84.8% of cases, while complications were multiple in 50.8% of pregnancies. Nevertheless, both pregnancy and neonatal complications were noted in a similar number of low-, intermediate-, and high-risk pregnancies (pregnancy 83.33%, 84.09%, 85.95%, p = 0.647; neonatal 32.53%, 41.67%, 34.26%, p = 0.319, respectively). Moreover, most children had good pregnancy outcome with a mean ±SD Apgar score of 7.52 ±1.13 in the first and 8.61 ±0.92 in the fifth minute after birth. Significantly fewer children had early neonatal complications (overall 36.85%).

Table 1. Descriptive parameters of investigated women and children according to age and body mass index groups

	Age (years)				*p*-value	BMI				*p*-value
	Younger		Older (≥ 35.1)			Not obese		Obese (≥ 30.1)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Patients age	28.92	3.53	40.05	3.42	–	32.77	6.26	36.62	6.34	0.001
BMI before PREG	31.75	6.96	36.43	8.04	0.001	29.10	3.60	41.75	6.36	–
Gravidity	1.26	1.46	3.13	2.28	0.001	2.00	2.03	2.41	2.22	0.002
GW at diagnosis	23.29	12.57	25.94	8.43	0.028	23.41	12.36	26.37	7.58	0.001
Max glycaemia	6.81	4.82	5.97	1.55	0.039	6.56	4.43	6.15	1.87	0.001
SBP before PREG	124.95	18.36	130.59	15.86	0.021	123.62	16.25	133.16	17.54	0.001
DBP before PREG	82.14	12.35	85.87	9.68	0.019	81.53	11.07	87.21	10.82	0.001
SBP PREG	131.56	19.79	138.64	20.75	0.011	131.79	22.39	139.09	17.06	0.009
DBP PREG	85.61	11.88	89.61	11.17	0.012	85.08	12.05	90.73	10.43	0.001
Placenta thick	38.23	7.87	37.65	7.76	0.535	37.21	7.12	39.15	8.71	0.001
AFI	38.84	58.01	60.12	75.93	0.016	44.22	59.52	56.22	78.86	0.307
GW at birth	37.53	2.51	37.44	2.64	0.747	37.33	2.72	37.74	2.29	0.120
Baby birth weight [kg]	3.57	8.07	3.69	9.48	0.190	3.47	8.84	3.88	8.14	0.001
Discharge weight [kg]	3.44	5.61	3.66	6.59	0.008	3.41	6.02	3.76	5.89	0.001
Apgar 1 min	7.57	1.06	7.47	1.20	0.426	7.55	1.11	7.47	1.17	0.982
Apgar 5 min	8.64	0.91	8.55	0.95	0.364	8.62	0.96	8.57	0.86	0.976

AFI – amniotic fluid volume index, BMI – body mass index, DBP – diastolic blood pressure, GW – gestational week, PREG – pregnancy, SBP – systolic blood pressure

Table 2. Differences in frequency of examined maternal and foetal parameters according to age

Patients age [years]		≤ 25	25.1–35	35.1–45	≥ 45.1	KW χ^2	*p*	Young	Older	KW χ^2	*p*
Obesity BMI	No	16	67	31	1	21.552	0.001	83	32	17.457	0.001
	Yes	10	90	100	8			100	108		
DM type	INS	9	18	1	0	4.207	0.240	27	1	0.688	0.407
	No INS	0	13	17	0			13	17		
	G INS	4	24	33	4			28	37		
	G no INS	13	102	80	5			115	85		
Retinopathy	No	15	124	125	9	**31.431**	**0.001**	139	134	**30.601**	**0.001**
	Yes	11	33	6	0			44	6		
Nephropathy	No	15	121	123	9	**28.449**	**0.001**	136	132	**29.610**	**0.001**
	Yes	11	36	8	0			47	8		
Neuropathy	No	17	131	123	9	**18.877**	**0.001**	148	132	**17.105**	**0.001**
	Yes	9	26	8	0			35	8		
Chronic HTA	No	21	123	98	5	2.953	0.399	144	103	2.101	0.147
	Yes	5	34	33	4			39	37		
HTA after pregnancy	No	17	115	86	3	7.375	0.061	132	89	2.847	0.092
	Yes	9	42	45	6			51	51		
Other comorbidity	No	6	37	33	2	0.141	0.987	43	35	0.446	0.504
	Yes	20	120	98	7			140	105		
DM in family	No	22	134	116	7	1.296	0.730	156	123	0.131	0.718
	Yes	4	23	15	2			27	17		
Pregnancy complication number	No	3	19	26	1	6.112	0.106	22	27	2.228	0.136
	One	4	61	43	2			65	45		
	Multi	19	77	62	6			96	68		
Pregnancy complication	No	3	19	26	1	3.745	0.290	22	27	3.242	0.072
	Yes	23	138	105	8			161	113		
Uteroplacental flow violation	No	20	123	90	5	5.085	0.166	143	95	**4.314**	**0.038**
	Yes	6	34	41	4			40	45		
Fetoplacental flow violation	No	21	133	105	5	5.284	0.152	154	110	0.598	0.439
	Yes	5	24	26	4			29	30		
Preeclampsia	No	23	133	113	9	1.820	0.611	156	122	0.262	0.609
	Yes	3	24	18	0			27	18		
Bleeding antepartum	No	26	152	126	9	1.345	0.718	178	135	0.017	0.897
	Yes	0	5	5	0			5	5		

Table 2. Cont.

Patients age [years]		≤ 25	25.1–35	35.1–45	≥ 45.1	KW χ^2	*p*	Young	Older	KW χ^2	*p*
Rupture of membranes	No	22	140	114	8	0.605	0.895	162	122	0.009	0.923
	Yes	4	17	17	1			21	18		
Irregular amniotic fluid	No	18	143	117	8	**10.604**	**0.014**	161	125	0.007	0.932
	Yes	8	14	14	1			22	15		
Vaginal delivery	No	17	135	111	7	7.264	0.064	152	118	0.029	0.865
	Yes	9	22	20	2			31	22		
Caesarean section	No	23	140	117	5	9.510	0.023	163	122	0.007	0.935
	Yes	3	17	14	4			20	18		
Term birth	Preterm	8	26	29	1	3.884	0.274	34	30	0.404	0.525
	In term	18	131	102	8			149	110		
Neonatal resuscitation	No	23	135	115	6	3.299	0.348	158	121	0.470	0.493
	Yes	3	22	16	3			25	19		
Neonatal intubation	No	23	141	116	8	0.132	0.988	164	124	0.005	0.942
	Yes	3	16	15	1			19	16		
Neonatal convulsions	No	26	156	131	9	1.057	0.787	182	140	0.923	0.337
	Yes	0	1	0	0			1	0		
Small anomalies	No	24	149	128	9	2.761	0.430	173	137	3.357	0.067
	Yes	2	8	3	0			10	3		
Large anomalies	No	26	155	129	8	5.869	0.118	181	137	0.293	0.588
	Yes	0	2	2	1			2	3		
Pulmonary problems	No	26	146	124	8	2.489	0.477	172	132	0.279	0.597
	Yes	0	11	7	1			11	8		
Neonatal jaundice	No	25	152	127	9	0.340	0.952	177	136	0.263	0.608
	Yes	1	5	4	0			6	4		
Strength problems	No	25	146	129	8	5.723	0.126	171	137	**4.921**	**0.027**
	Yes	1	11	2	1			12	3		
Other complications	No	22	132	112	6	2.245	0.523	154	118	0.021	0.885
	Yes	4	25	19	3			29	22		
Neonatal complications number	No	17	99	83	5	0.451	0.930	116	88	0.209	0.647
	One	2	26	23	1			28	24		
	Multi	7	32	25	3			39	28		
Has neonatal complications	No	17	99	83	5	0.281	0.964	116	88	0.065	0.799
	Yes	9	58	48	4			67	52		

BMI – body mass index, DM – diabetes mellitus, G – gestational, HTA – hypertension, INS – insulin
Bold – significant

Table 3. Differences in frequency of examined maternal and foetal parameters according to body mass index

Patients BMI		**≤ 25**	**25.1 to 30**	**30.1 to 40**	**≥ 40.1**	χ^2	***p***	**Normal**	**Obese**	χ^2	***p***
Age	Young	28	51	79	10	**22.226**	**0.001**	79	89	**18.848**	**0.001**
	Older	8	28	101	18			36	119		
DM type	INS	6	17	5	0	3.971	0.265	23	5	0.953	0.329
	No INS	0	4	20	6			4	26		
	G INS	5	8	42	10			13	52		
	G no INS	25	50	113	12			75	125		
Retinopathy	No	24	58	166	25	**24.784**	**0.001**	82	191	**20.476**	**0.001**
	Yes	12	21	14	3			33	17		
Nephropathy	No	23	53	165	27	**36.492**	**0.001**	76	192	**30.787**	**0.001**
	Yes	13	26	15	1			39	16		
Neuropathy	No	27	59	168	26	**21.870**	**0.001**	86	194	**18.014**	**0.001**
	Yes	9	20	12	2			29	14		
Chronic HTA	No	33	69	133	12	**27.971**	**0.001**	102	145	**24.983**	**0.001**
	Yes	3	10	47	16			13	63		
HTA after pregnancy	No	30	60	117	14	**11.115**	**0.011**	90	131	**25.370**	**0.001**
	Yes	6	19	63	14			25	77		
Other comorbidity	No	11	21	41	5	1.846	0.605	32	46	2.718	0.099
	Yes	25	58	139	23			83	162		
DM in family	No	33	71	148	27	6.701	0.082	104	175	0.003	0.993
	Yes	3	8	32	1			11	33		
Pregnancy complication number	No	8	11	28	2	6.096	0.107	19	30	**8.696**	**0.003**
	One	12	27	65	6			39	71		
	Multi	16	41	87	20			57	107		
Pregnancy complication	No	8	11	28	2	2.900	0.407	19	30	3.595	0.058
	Yes	28	68	152	26			96	178		
Uteroplacental flow violation	No	27	63	133	15	7.352	0.061	90	148	**5.563**	**0.018**
	Yes	9	16	47	13			25	60		
Fetoplacental flow violation	No	28	59	152	25	4.948	0.176	87	177	0.060	0.806
	Yes	8	20	28	3			28	31		
Preeclampsia	No	32	65	159	22	3.258	0.354	97	181	0.217	0.641
	Yes	4	14	21	6			18	27		
Bleeding antepartum	No	35	78	172	28	2.871	0.412	113	200	1.967	0.161
	Yes	1	1	8	0			2	8		

Table 3. Cont.

Patients BMI		≤ 25	25.1 to 30	30.1 to 40	≥ 40.1	χ^2	*p*	Normal	Obese	χ^2	*p*
Rupture of membranes	No	33	69	155	27	2.956	0.398	102	182	0.446	0.504
	Yes	3	10	25	1			13	26		
Irregular amniotic fluid	No	29	71	161	25	2.554	0.466	100	186	0.223	0.637
	Yes	7	8	19	3			15	22		
Vaginal delivery	No	20	49	118	24	7.018	0.071	69	142	**10.227**	**0.001**
	Yes	16	30	62	4			46	66		
Caesarean Section	No	32	72	157	24	1.003	0.801	104	181	1.360	0.244
	Yes	4	7	23	4			11	27		
Term birth	Preterm	10	22	28	4	7.240	0.065	32	32	**7.215**	**0.006**
	In term	26	57	152	24			83	176		
Neonatal resuscitation	No	32	69	154	24	0.368	0.947	101	178	0.104	0.747
	Yes	4	10	26	4			14	30		
Neonatal intubation	No	33	71	161	23	1.712	0.634	104	184	1.607	0.205
	Yes	3	8	19	5			11	24		
Neonatal convulsions	No	36	79	179	28	0.794	0.851	115	207	0.631	0.427
	Yes	0	0	1	0			0	1		
Small anomalies	No	32	77	175	26	6.545	0.088	109	201	0.001	0.986
	Yes	4	2	5	2			6	7		
Large anomalies	No	36	77	177	28	1.520	0.678	113	205	0.746	0.388
	Yes	0	2	3	0			2	3		
Pulmonary problems	No	36	76	166	26	4.106	0.250	112	192	0.637	0.425
	Yes	0	3	14	2			3	16		
Neonatal jaundice	No	33	79	173	28	7.065	0.070	112	201	0.328	0.567
	Yes	3	0	7	0			3	7		
Strength problems	No	35	76	170	27	0.819	0.845	111	197	1.416	0.234
	Yes	1	3	10	1			4	11		
Other complications	No	29	68	150	25	1.211	0.750	97	175	0.053	0.818
	Yes	7	11	30	3			18	33		
Neonatal complications number	No	21	52	114	17	0.946	0.814	73	131	0.001	0.993
	One	5	13	28	6			18	34		
	Multi	10	14	38	5			24	43		
Has neonatal complications	No	21	52	114	17	0.673	0.879	73	131	0.050	0.823
	Yes	15	27	66	11			42	77		

BMI – body mass index, DM – diabetes mellitus, G – gestational, HTA – hypertension, INS – insulin
Bold – significant

Patient's BMI was correlated with patient's age (p = 0.001), having chronic HTA (p = 0.001), as well as HTA after pregnancy (p = 0.001), gravidity and the number of previous CS (p = 0.001), placental thickness (p = 0.002), VUPB (p = 0.010), presence of hydramnion (p = 0.005), delivery by CS (p = 0.008), weight of the child upon birth and at discharge (p = 0.001), as well as the number of pregnancy complications (p = 0.013). On the other hand, it was negatively associated with having DM-related complications (p = 0.001), need for foetal lung maturation therapy (p = 0.009), and vaginal delivery (p = 0.002).

Older patient's age was associated with higher BMI (p = 0.001), higher blood pressure before (p = 0.020) and during pregnancy (p = 0.004), having more DM-related complications (p = 0.001), higher gravidity (p = 0.001), higher AFI (p = 0.005), greater weight of the child upon birth and at discharge (p = 0.001), fewer small anomalies of the foetus (p = 0.019), and fewer registered strength problems of the neonate (p = 0.043).

Women with DM who were both old and obese (high-risk pregnancy group) more often had retinopathy (p = 0.001), nephropathy (p = 0.001), neuropathy (p = 0.001), increased fasting glucose levels (p = 0.025), HTA (p = 0.007), and hypertension after pregnancy (p = 0.018) compared to women with low or intermediate risk. These patients were also more often multigravidas (p = 0.001) mostly consulted for risk prior to pregnancy. Diabetes mellitus was diagnosed in earlier GW (p = 0.001) in women from this high-risk group. In addition, old and obese women had thicker placentas (p = 0.044), while their children had different neonatal complications (p = 0.041) and greater weight (p = 0.003) than children of women with low or intermediate pregnancy risk. On the other hand, no significant differences were noticed between the 3 investigated groups of pregnancy risk (low, intermediate, and high risk) regarding patients' comorbidities (p = 0.644), family history of DM (p = 0.334), GW of delivery (p = 0.352), Apgar score of the child (p = 0.298), and all other investigated maternal pregnancy and early neonatal complications ($p \geq 0.05$).

Based on the performed logistic regression, we obtained a significant model of relationship between pre-pregnancy BMI with pregnancy complications (B = 1.721; Wald = 123.158; R^2 Nagelkerke = 0.054; classification = 84.8%; χ^2 = 10.245; p = 0.017). It was proven that higher BMI can increase the risk for pregnancy complications in women with DM (p = 0.016; OR = 1.064).

Conversely, maternal age was not a significant predictor of pregnancy complications (χ^2 = 1.006; p = 0.801). No other significant models for prediction of neonatal complications were obtained ($p \geq 0.05$).

Discussion

Diabetes mellitus is considered to be one of the most important independent risk factors for most adverse perinatal outcomes, including major foetal malformations and stillbirth [7, 8, 13]. Obese women are more insulin resistant than normal weight women. Therefore, risk of developing GDM is significantly higher in obese pregnant women [14]. Out of a dozen risk factors for gestational DM, the most significant are advanced age, being overweight prior to or during pregnancy, diabetes in the family, and GDM in a previous pregnancy. The prevalence of obesity has revently been increasing dramatically worldwide. It is estimated that up to 40% of women in reproductive age and pregnant women worldwide have increased BMI, and obesity is a confirmed risk factor for GDM development [15, 16].

The severe consequences of increased maternal adiposity along with hyperglycaemia in early pregnancy are well documented. According to literature data, high maternal BMI (both overweight and obesity) during pregnancy is positively associated with more frequent occurrence of different antenatal, intrapartum, postpartum, and neonatal complications. The most usual antenatal complications are recurrent miscarriages [3, 6]. Compared with mothers with normal BMI, in obese mothers during pregnancy morbidities such as hypertensive disorders and preeclampsia, thromboembolic disorders, macrosomia, malformations, infectious morbidity, preterm delivery, delivery by CS, postpartum haemorrhage, and even stillbirth were reported with significantly higher prevalence [17]. When population-attributable risk was taken into consideration in some investigations, it was concluded that if women maintained normal BMI during the pre-pregnancy or early pregnancy period, 14–35% fewer women developed gestational diabetes and hypertensive disorders in pregnancy [18]. Infants of overweight and obese mothers are often either macrosomic or have low birth weight, low Apgar score, and neonatal hypoglycaemia and require prolonged hospital admissions [14, 19]. Furthermore, intrapartum care of vaginal and operative deliveries as well as anaesthetic and operative interventions in obese women demand extra care and costs. Besides, maternal obesity was also found to have long-term negative effects on offspring's risk for developing metabolic disease [9, 20]. The growing epidemic of maternal overweight/obesity accounted for almost two million deaths in 2010 worldwide. However, there are still discrepancies between literature data, mostly in the classification of BMI and its cut-off levels and adjustments for confounders [18]. Some studies do not confirm correlation of obesity with adverse pregnancy outcomes that occur rarely, such as chorioamnionitis and neonatal death, which contribute more to inadequate early induction and preterm rupture of membranes. Therefore, there is still a need to investigate more thoroughly BMI-related risks for better antenatal care [19, 20].

Pregnancies occurring in women of advanced age show a rising trend over the last few decades, both

in developed and developing countries due to extended education, seeking career opportunities, contraception use and successful assisted reproductive techniques as infertility treatment [21–24]. Currently the most widely accepted cut-off for advanced maternal age is 35 years, although lately it is getting higher, up to the age of 40 years. However, there is no doubt that the risk of maternal and foetal complications increases steadily with advancing maternal age. A recently published study confirmed the link between a steady and continuous increase in age with the incidence of various complications in pregnancy like pre-eclampsia, gestational diabetes, prematurity, and CS rate. This increase is significantly higher after the age of 35 years [25]. Moreover, it was confirmed that advanced maternal age is a risk factor for both negative obstetric outcomes and for child morbidity up to 5 years of age [26].

Women over 35 years old, compared with their younger counterparts, have higher risk of different pregnancy complications. One explanation is based on the fact that older women are also more likely to have pre-existing comorbidities that could deteriorate during pregnancy and negatively impact pregnancy outcome [1]. Older women are known to have higher risk of developing gestational diabetes than women in their twenties or thirties. The incidence of GDM increases linearly with maternal age, reaching a plateau at around the age of 40 years, even after adjusting for confounding factors associated with decreased insulin sensitivity, such as ethnicity and obesity. This association still needs to be thoroughly investigated, but the aetiology could be based on progressive vascular endothelial damage in older age [27].

Numerous studies have investigated the influence of older maternal age on adverse pregnancy outcomes, including preeclampsia, gestational hypertension, GDM, preterm birth, placenta praevia, placental abruption, delivery of small or large for gestational age neonates, and elective or emergency Caesarean section. Moreover, both miscarriage and perinatal death (antepartum and intrapartum stillbirth as well as early neonatal death) have been registered more often in pregnancies of women over 35 years old [2, 28–29].

Nevertheless, the literature data show contradictory results. After adjusting for other maternal characteristics, advanced maternal age was found to positively correlate with miscarriage, development of preeclampsia, and GDM as well as delivery by Caesarean section, but not stillbirth, spontaneous preterm delivery, and gestational hypertension. Consequently, further research is still needed to better understand age-related pregnancy complications [19, 30].

As far as we know, our study is the first to investigate the association between maternal BMI and age, as well as their interaction in women with DM with a wide range of potential adverse obstetric outcomes. In our sample around 85% of women had pregnancy complications, but the overall outcome of investigated pregnancies was good for both mothers and children. This finding could be explained by the fact that all women were regularly checked-up throughout pregnancy and promptly and adequately treated according to their conditions. We found that complications of DM such as retinopathy, nephropathy, neuropathy, as well as HTA occurred more often in older and obese patients. Women from this high-risk pregnancy group also developed hypertension after pregnancy more often. Moreover, children of old and obese women had higher birth weight and more neonatal complications compared to children of women with low or intermediate pregnancy risk. However, only maternal BMI and not age was found to be a significant predictor of pregnancy complications. No precise predictors of early neonatal complications were identified in this study.

Conclusions

Pregnant women with DM should be considered as high-risk patients due to their elevated rate of pregnancy complications. Increased maternal BMI was confirmed as the most important predictor of pregnancy complications in women with DM. Nevertheless, both pregnancy and neonatal complications were noted in a similar number of low-, intermediate-, and high-risk pregnancies according to patients' age and BMI. These findings imply that with timely and adequate treatment pregnancy outcomes can be good for both mothers and children.

Disclosure

The authors report no conflict of interest.

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