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Association between maternal physiological and pathological factors and the risk of stillbirth and perinatal mortality

MERUYERT SHARIPOVA[1], GULYASH TANYSHEVA[1], KHALIDA SHARIPOVA[2], BOLOGAN ION[3] and AIZHAN SHAKHANOVA[4]

[1]Department of Obstetrics and Gynaecology, Semey Medical University, Semey 071400, Republic of Kazakhstan; [2]Department of Obstetrics and Gynaecology, Astana Medical University, Astana 010000, Republic of Kazakhstan; [3]Department of Obstetrics and Gynaecology, Nicolae Testemițanu State University of Medicine and Pharmacy, Chisinau MD-2004, Republic of Moldova; [4]Department of Internal Medicine and Rheumatology, Semey Medical University, Semey 071400, Republic of Kazakhstan

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Abstract. Females with fetuses which are considered small for gestational age (SGA) or a large for gestational age (LGA) require increased attention as regards the management of pregnancy, as they may have various pregnancy-related complications at birth. Stillbirths are the result of fetal growth retardation (FGR) and reduced fetal reserve from stress during labor and these fetuses often do not reach their optimal birth weight. The aim of the present study was to determine the association between fetal weight and maternal physiological and pathological characteristics. The present study was a retrospective study. In the present study, 6,547 individual charts and illness lists of pregnant women hospitalized for delivery in antenatal clinics and maternity hospitals were analyzed. The results revealed that maternal physiological and pathological characteristics were statistically higher in the group of newborns with SGA and LGA than the group of newborns with a normal weight. According to the ROC analysis, maternal age, weight and body mass index (BMI) were independently associated with the risk of prediction of SGA or LGA. It was found that the maternal BMI at the beginning of pregnancy could influence the birth weight of the newborns. The maternal age and BMI were independently associated with the risk of predicting of stillbirth or perinatal mortality. On the whole, these results indicate a high risk of stillbirth and perinatal mortality regardless of fetal weight in the study population. Therefore, it is necessary to prevent the risk of stillbirth and perinatal mortality in healthy newborns, as well as in small newborns who were born with a normal weight, but have FGR.

Correspondence to: Dr Meruyert Sharipova, Department of Obstetrics and Gynaecology, Semey Medical University, 103 Abay Kunanbayev St., Abay Region, Semey 071400, Republic of Kazakhstan
E-mail: meruert_sharipov@mail.ru

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Introduction

Quality antenatal monitoring of the newborn at birth and timely medical intervention reduce perinatal mortality (1). Perinatal mortality depends on the condition of the newborn at birth, timely observation during pregnancy and timely medical procedures (1). Perinatal mortality is common among fetuses born with a low birth weight for their gestational age, which can be caused by fetal growth retardation (FGR), even in preterm newborns (2). Fetuses with FGR do not reach to their intrauterine growth potential due to multiple risk factors, and such infants have a high risk of morbidity and mortality compared to healthy infants (3). Small for gestational age (SGA) is most often defined as a birth weight <2,500 g (4). A newborn which is considered large for gestational age (LGA) is most often defined to have a birth weight >4,000 g (5,6). Often, a fetus with FGR is considered to be one that weighs <10th percentile for gestational age; however, this does not take into account the individual growth potential of each fetus (7). FGR can be present in a fetus that weights >10th percentile, it also has not realized its growth potential. Conversely, constitutionally small, yet healthy fetuses can have an overdiagnosis of FGR (3). FGR is associated with adverse perinatal outcomes (8). Females with fetuses considered to be SGA and LGA require increased attention in the management of pregnancy, as they may have various pregnancy-related complications at birth. Timely and quality obstetric care is the main and important condition in the detection of pregnancy complications and reduces the risks of stillbirth and perinatal mortality up to 28 days of life (9). Children who were considered to be SGA and LGA at birth, have been observed as adults to have a higher risk of developing diabetes, cardiovascular disease, certain types of cancer, and a high risk of mortality from a variety of causes (10).

Stillbirths are the result of FGR and reduced fetal reserve from stress during labor and these fetuses often do not reach their optimal birth weight (11). Therefore, it is crucial to perform the timely early diagnosis of fetal FGR inn order to reduce the number of stillbirths (12). Fetal weight monitoring during pregnancy, taking into account the risks that were present at the beginning of the pregnancy and that may have

occurred during the pregnancy, can reduce the incidence of stillbirth and perinatal mortality (13,14). Maternal age and parity should be considered when estimating fetal weight, as well as other non-invasive methods of diagnosing the gestational age of the fetus (14). The early diagnosis of FGR can reduce the incidence of stillbirth and can allow for a reduction in morbidity in full-term newborns (15). Other studies have noted that newborns considered LGA were significantly less likely to be referred for pre-testing and missed early detection of fetal overgrowth (16,17). Maternal physiological factors, such as weight at the beginning of pregnancy, age and parity can influence the birth weight of the fetus and the risk of stillbirth and perinatal mortality. In addition, the presence of maternal pathological factors, such as hypertension, diabetes mellitus and pre-eclampsia may increase the risk of stillbirth and perinatal mortality. The present study investigated the effects of maternal physiological and pathological characteristics on fetal birth weight and on the risk of stillbirth and perinatal mortality.

Subjects and methods

Study population. The total number of charts analyzed was 9,580 individual charts and hospital records. Of these, 3,033 individual charts and hospital records were not included in the study as they had incomplete maternal and fetal data. The total of 6,457 the individual cards and hospital records of pregnant females hospitalized for delivery in women's consultations and maternity hospitals in Semey city and nearby settlements in Zyryanovsk city, Astana city, Aksu city, Almaty city, Atyrau city, in Kazakhstan between January 1, 2016 and December 31, 2021. The populations served in these counseling centers and maternity hospitals were of similar ethnic and social backgrounds and had similar standards of clinical management of pregnant women. The inclusion criteria were the following: Females who gave consent for the study were between the 22nd and 42nd weeks of gestation; i.e., they were term singleton pregnant females with the presence of ultrasound screening of the first trimester of pregnancy at 10-14 weeks. The exclusion criteria included females with multiple pregnancies, pregnancies complicated by neonatal chromosomal or structural anomalies of the fetus. The gestation period was calculated from the first day of the final menstrual period and corrected by the index of the coccygeal-parietal size at the first screening ultrasound according to the Clinical Protocol of the Ministry of Health of the Republic of Kazakhstan 'Management of physiological pregnancy' dated September 19, 2013. Individual charts and hospital charts for pregnant women standardized at the national level across the Kazakhstan. The Ethics Committee of Semey Medical University approved the research protocol (#2 of from 10/25/2018), according to the Declaration of Helsinki 1964. Informed consent was obtained from each patient in writing.

Data collection. Maternal demographic and clinical characteristics were recorded from individual pregnancy charts, including the maternal age, height, weight, body mass index (BMI) at the beginning of pregnancy, parity, presence of disease [a history of arterial hypertension (AH), diabetes mellitus (DM), pre-eclampsia, gestational hypertension (GH) and gestational DM (GDM) in the given pregnancy] and the neonatal characteristics of the newborn. BMI was defined as the weight (kg)/height in (m^2). Pre-term birth was defined as a birth between 22 and 37 full weeks of gestation.

Concentration measurements. Newborns that were born weighing up to 2,500 g were considered as newborns with a low birth weight. Newborns who were born weighing >4,000 g were considered as overweight newborns. Newborns born, but who succumbed before the period of 28 days were recorded as perinatal mortality. Females with a maternal BMI at the beginning of pregnancy up to and including 18.49 kg/m^2 was considered as underweight. Those with a BMI between 18.5 and 24.9 kg/m^2 was considered a normal weight. Those with a BMI between 25 and 29.9 kg/m^2 was considered as overweight, and those with a BMI >30 kg/m^2 was considered obese.

Statistical analysis. All statistical analyses were performed using IBM SPSS Statistics Version 26 (IBM Corp.) and the Stat Tech v. 3.0.9 program (developed by Stattech LLC). All variables were examined to determine whether they were normally distributed. Descriptive statistics included median (Q1-Q3) for non-normally distributed continuous variables. The results were compared between fetal weight groups and birth outcome groups. Non-parametric tests, such as the Kruskal-Wallis test were used for non-normally distributed for comparisons between three groups. The χ^2 test or Fisher's test were used for comparing differences in categorical variables between groups. The diagnostic significance of maternal physiological factors (age, parity and BMI) in predicting the birth of a small or large fetus and birth outcomes was assessed using receiver operating characteristic (ROC) analysis. All confidence intervals (CIs) were 95%. A value of P<0.05 was considered to indicate a statistically significant difference.

Results

Comparisons of the subjects and general information. The study population comprised 6,547 females aged from 18 to 47 years. The total number of newborns born with a normal weight was 5,253 newborns. A total of 566 newborns were born weighing <2,500 g, and 728 newborns weighed >4,000 g. The maternal demographic and neonatal characteristics of the study population between the fetal weight group groups are presented in Table I. Females with a newborn weighing <2,500 g and those with a newborn weighing >4,000 g were older in age than females who had newborns with a normal weight (P=0.0001; Table I). As the maternal age increased to >25 years, the risk of having a newborn weighing <2,500 g and a newborn weighing >4,000 g increased each year. Females aged 25-29 years gave birth to newborns weighing <2,500 g 1.19-fold more often, those aged 30-34 years gave birth to newborns weighing <2,500 g 1.44-fold more often, and females >35 years of age gave birth to newborns weighing <2,500 g 1.82-fold more often than those aged 20-24 years (Table I). Females aged 25-29 years gave birth to newborns weighing >4,000 g 1.64-fold more often, those aged 30-34 years gave birth to newborns weighing >4,000 g 1.74-fold more often, and females >35 years of age gave birth to newborns weighing >4,000 g 1.93-fold more often than those aged 20-24 years (Table I). Females <20 years of age gave birth to newborns weighing <2,500 g less often than those aged 20-25 years.

Table I. Maternal demographic and neonatal characteristics by fetal weight group (n=6,547).

Parameters	Fetal weight (g) <2,500 n=566	OR (95% CI)	2,500-4,000 n=5,253	>4,000 n=728	OR (95% CI)	P-value (χ^2 test)	P-values (Kruskal-Wallis test) <2,500 vs. 2,500-4,000 g	<2,500 vs. >4,000 g	2,500-4,000 vs. >4,000 g
Maternal age, years Me (Q_1-Q_3)	29 (25-33)		27 (24-32)	29 (25-33)			0.0001	0.9	0.0001
Maternal age in years, n (%)						0.0001			
<20	12 (0.18)	0.8 (0.44-1.5)	173 (2.64)	9 (0.14)	0.56 (0.28-1.12)				
20-24	122 (1.86)	1.0	1,444 (22.05)	134 (2.05)	1.0				
25-29	170 (2.6)	1.19 (0.94-1.52)	1,684 (25.72)	257 (3.92)	1.64 (1.32-2.52)				
30-34	146 (2.23)	1.44 (1.12-1.86)	1,197 (18.28)	193 (2.95)	1.74 (1.38-2.19)				
>35	116 (1.77)	1.82 (1.39-2.38)	755 (11.53)	135 (2.06)	1.93 (1.49-2.49)				
BMI, kg/м^2) Me (Q_1-Q_3)	23.44 (20.03-27.59)		22.58 (20.28-25.71)	24.98 (22.03-28.68)			0.004	0.0001	0.0001
BMI, n (%)						0.0001			
WD	65 (0.99)	1.57 (1.18-2.1)	467 (7.13)	29 (0.44)	0.59 (0.4-0.87)				
NW	286 (4.37)	1.0	3,236 (49.43)	340 (5.19)	1.0				
OW	125 (1.91)	1.29 (1.04-1.61)	1094 (16.71)	220 (3.36)	1.91 (1.59-2.3)				
Ob	90 (1.37)	2.23 (1.73-2.89)	456 (6.96)	139 (2.12)	2.9 (2.33-3.62)				
Parity, n (%)						0.0001			
0 births	203 (3.1)	1.0	1,774 (27.1)	174 (2.66)	1.0				
1st birth	168 (2.57)	0.81 (0.65-1.0)	1,821 (27.81)	230 (3.51)	1.29 (1.05-1.58)				
2 births	116 (1.77)	0.9 (0.71-1.15)	1,121 (17.12)	194 (2.35)	1.76 (1.42-2.19)				
≥3	79 (1.21)	1.29 (0.97-1.7)	537 (8.2)	130 (1.98)	4.47 (1.93-3.16)				
Sex, n (%)						0.0001			
Boy	293 (4.47)	1,1 (0.93-1.31)	2,591 (39.57)	452 (6.9)	1.68 (1.43-1.97)				
Girl	273 (4.17)	1.0	2,662 (40.66)	276 (4.21)	1.0				
Duration in days, Me (Q_1-Q_3)	235 (204-255)		279 (273-285)	285 (280-289)			0.0001	0.0001	0.0001
Premature birth, n (%)						0.0001			
No	116 (1.77)	-	5,100 (77.9)	727 (11.1)	-				
Yes	450 (6.87)	-	153 (2.34)	1 (0.01)	-				

Data for age, weight, height and BMI are presented as the median (Q_1-Q_3) and were analyzed using the Kruskal-Wallis test followed by Dunn's post hoc test. Categorical variables were analyzed using the Chi-squared test. BMI, body mass index; WD, weight deficit; NW, normal weight; OW, overweight; Ob, obesity. P-values <0.05 were considered to indicate statistically significant differences.

Table II. Maternal characteristics by extragenital diseases in fetal weight groups (n=6,547).

	Fetal weight (g)					
	<2,500		2,500-4,000	>4,000		
Parameters	n=566	OR (95% CI)	n=5,253	n=728	OR (95% CI)	P-value (χ^2 test or Fisher's test[a])
Hypertension						0.0001
No	521 (7.96)	1.0	5,141 (78.52)	717 (10.95)	1.0	
1st degree	36 (0.55)	4.61 (3.07-6.92)	77 (1.18)	9 (0.14)	0.84 (0.42-1.68)	
2 degrees	9 (0.14)	2.54 (1.21-5.31)	35 (0.53)	2 (0.03)	0.41 (0.1-1.7)	
Pre-eclampsia						0.0001
No	395 (6.03)	1.0	5,022 (76.71)	713 (10.89)	1.0	
1st degree	19 (0.29)	2.26 (1.37-3.72)	107 (1.63)	6 (0.09)	0.39 (0.17- 0.9)	
2 degrees	152 (2.32)	15.58 (12.04-20.18)	124 (1.89)	9 (0.14)	0.51 (0.26-1.01)	
Gestational hypertension						0.029
No	541 (8.26)	1.0	4,986 (76.16)	675 (10.31)	1.0	
Yes	25 (0.38)	0.86 (0.57-1.31)	267 (4.08)	53 (0.81)	1.47 (1.08-1.99)	
Diabetes mellitus						0.12[a]
No	565 (8.63)	-	5,242 (80.08)	723 (11.04)	-	
1 type	1 (0.01)	-	7 (0.11)	4 (0.06)	-	
2 type	0 (0)	-	4 (0.06)	1 (0.01)	-	
Gestational diabetes						0.0001
No	561 (8.57)	1.0	5,135 (78.43)	692 (10.57)	1.0	
Yes	5 (0.08)	0.39 (0.16-0.95)	118 (1.8)	36 (0.55)	2.26 (1.55-3.32)	

Data are presented as categorical variables and were analyzed using the Chi-squared test or Fisher's test. P-values <0.05 were considered to indicate statistically significant differences.

Females with a newborn weighing <2,500 g (P=0.004) and females with a newborn weighing >4,000 g had a significantly higher BMI (P=0.0001). A total of 561 females were underweight, 3,862 females had a healthy weight, 1,439 females were overweight and 685 females were obese P=0.0001 (Table I). As demonstrated in Table I, maternal underweight, overweight and obesity at the beginning of pregnancy increased the risk of having a newborn weighing <2,500 g by 1.57-, 1.29- and 2.23-fold, respectively. Maternal underweight was associated with a reduced risk of having a newborn weighing >4,000 g. In addition, maternal overweight and obesity at the beginning of the pregnancy increased the risk of having a newborn weighing >4,000 g by almost 2-fold (Table I).

While examining the effect of parity on fetal weight, it was demonstrated that newborns weighing <2,500 g were more often born to mothers who had a history of three or more births than mothers who had newborn weighing between 2,500-4,000 g and mothers who had newborns weighing >4,000 g. The risk of having a newborn weighing >4,000 g increased with each birth from 1.29- to 4.47-fold (Table I). In the present study sample, boys were born 1.1-fold more often with a weight <2,500 g and 1.68-fold more often with a weight >4,000 g compared to girls. Term fetuses were more likely to be born at term, and newborns weighing <2,500 g were more likely to be born prematurely (Table I).

The present study also examined the influence of maternal pathological factors, such as a history of AH and DM, preeclampsia, GH and GDM in a given pregnancy, on fetal weight at birth. The maternal characteristics by extragenital diseases of the study population between the fetal weight group groups are presented in Table II. A maternal history of AH increased the risk of having a newborn weighing <2,500 g. The birth of a newborn weighing >4,000 g was less common among females with AH and with preeclampsia (Table II). The risk of having a newborn weighing <2,500 g increased in females with preeclampsia, and this risk increased with the severity of preeclampsia (Table II). The presence of GH, on the contrary, increased the risk of having a newborn weighing >4,000 g by 1.47-fold and reduced the risk of having a newborn weighing <2,500 g (Table II). The presence of GDM in a given pregnancy increased the risk of having a newborn weighing >4,000 g by 2.26-fold. The presence of any type of maternal DM in the present study sample did not affect fetal weight at birth (Table II).

In the present study, birth outcomes were categorized into three groups as follows: Live birth, stillbirth and perinatal mortality up to 28 days of life. A total of 6,312 births were live births. Stillbirth accounted for 193 cases, and the mortality of a newborn up to 28 days of life accounted for 42 cases. The results of analyzes by birth outcome group are demonstrated in Tables III, IV and V. The mean maternal age by birth

Table III. Maternal demographic characteristics in birth outcome groups (n=6,547).

Parameters	Birth outcome					P-value (χ^2 test)	Live birth vs. stillbirth	Live birth vs. perinatal mortality	P-values (Kruskal-Wallis test) Stillbirth vs. perinatal mortality
	Live birth n (%)	Stillbirth n (%)	OR (95% CI)	Perinatal mortality n (%)	OR (95% CI)				
Maternal age, years; Me (Q_1-Q_3)	28 (24-32)	29 (25-33)		30 (25-34.25)			0.004	0.02	0.4
Maternal age in years, n (%)						0.01			
<20	186 (2.84)	8 (0.12)	1.98 (0.91-4.32)	0	-				
20-24	1,655 (25.28)	36 (0.55)	1.0	9 (0.14)	1.0				
25-29	2,046 (31.25)	57 (0.87)	1.28 (0.84-1.95)	8 (0.12)	0.72 (0.28-1.87)				
30-34	1,469 (22.44)	52 (0.79)	1.63 (1.06-2.5)	15 (0.23)	1.88 (0.82-4.3)				
>35	956 (14.61)	40 (0.61)	1.92 (1.22-3.04)	10 (0.15)	1.92 (0.78-4.75)				
BMI, kg/м^2) Me (Q_1-Q_3)	22.85 (20.41-26.15)	23.83 (20.31-27.59)		25.08 (21.29-29.98)			0.1	0.05	0.25
BMI, n (%)						0.01			
DW	539 (8.24)	17 (0.26)	1.15 (0.68-1.93)	5 (0.08)	2.17 (0.79-5.95)				
NW	3,743 (57.17)	103 (1.57)	1.0	16 (0.24)	1.0				
OW	1,383 (21.12)	45 (0.69)	1.18 (0.83-1.69)	11 (0.17)	1.86 (0.86-4.02)				
Ob	647 (9.88)	28 (0.43)	1.57 (1.03-2.41)	10 (0.15)	3.62 (1.63-8.0)				
Parity, n (%)						0.13			
0 births	2,071 (31.64)	61 (0.93)	-	19 (0.29)	-				
1st birth	2,149 (32.82)	59 (0.9)	-	11 (0.17)	-				
2 births	1,382 (21.11)	40 (0.61)	-	9 (0.14)	-				
≥3	710 (10.85)	33 (0.5)	-	3 (0.04)	-				

Data for age, weight, height and BMI are presented as the median (Q_1-Q_3) and were analyzed using the Kruskal-Wallis test followed by Dunn's post hoc test. Categorical variables were analyzed using the Chi-squared test. BMI, body mass index; WD, weight deficit; NW, normal weight; OW, overweight; Ob, obesity. P-values <0.05 were considered to indicate statistically significant differences.

Table IV. Maternal characteristics by extragenital diseases in birth outcome groups (n=6,547).

	Fetal weight (g)					
Parameters	Live birth, n (%)	Stillbirth, n (%)	OR (95% CI)	Perinatal death n (%)	OR (95% CI)	P-value (χ^2 test of Fisher's test[a])
Hypertension						0.0001[a]
No	6,160 (94.09)	184 (2.81)	1.0	35 (0.53)	1.0	
1st degree	106 (1.62)	9 (0.14)	2.84 (1.42-5.7)	7 (0.11)	11.62 (5.05-26.76)	
2 degrees	46 (0.7)	0	-	0	-	
Pre-eclampsia						0.0001[a]
No	5,951 (90.9)	159 (2.43)	1.0	20 (0.3)	1.0	
1st degree	123 (1.88)	6 (0.09)	1.83 (0.79-4.21)	3 (0.05)	7.26 (2.13-24.75)	
2 degrees	238 (3.63)	28 (0.43)	4.4 (2.89-6.72)	19 (0.29)	23.75 (12.51-45.1)	
Gestational hypertension						0.7
No	5,982 (91.37)	181 (2.76)	-	39 (0.6)	-	
Yes	330 (5.04)	12 (0.18)	-	3 (0.05)	-	
Diabetes mellitus						0.002[a]
No	6,299 (96.21)	189 (2.89)	1.0	42 (0.64)	1.0	
1 type	8 (0.12)	4 (0.06)	16.66 (4.97-55.82)	0	-	
2 type	5 (0.08)	0	-	0	-	
Gestational diabetes						0.04[a]
No	6,154 (94)	193 (2.95)	-	41 (0.63)	-	
Yes	158 (2.41)	0	-	1 (0.01)	-	

Categorical variables were analyzed using the Chi-squared test of Fisher's test. P-values <0.05 were considered to indicate statistically significant differences.

outcome differed significantly (Table III). The risk of stillbirth and perinatal mortality increased with age. The risk of stillbirth was almost 2-fold higher in females <20 years of age compared to females aged 20-25 years. This risk was highest in females >25 years of age. The risk of stillbirth was 1.28-fold higher in females aged 25-29 years, it was 1.63-fold higher in females aged 30-35 years and was 1.92-fold higher in females >35 years of age compared to females aged 20-25 years (Table III).

Higher mean BMI scores were observed in the perinatal mortality groups compared with live births (Table III). The risk of stillbirth increased in underweight, overweight and obese mothers by 1.15- to 1.57-fold. The risk of perinatal mortality was markedly higher in underweight and obese mothers (Table III). In the present study sample, parity did not affect fetal mortality.

As demonstrated in Table IV, the presence of a maternal history of AH and DM and the complication of this pregnancy with preeclampsia increased the risk of stillbirth and perinatal mortality in the present study sample. Perinatal mortality was particularly high in mothers with AH and preeclampsia. However, stillbirths were more common in mothers with type 1 DM. GH a given pregnancy did not influence fetal mortality in the present study sample (Table IV).

As demonstrated in Table V, stillbirth and perinatal mortality were more likely to be observed when the fetal weight was <2,500 g, which was expected. Premature birth often resulted in stillbirth and perinatal fetal mortality, since a premature fetus often cannot adapt to the external environment and may have various congenital anomalies. However, stillbirth and perinatal mortality also occur in full-term pregnancies, and the cause of mortality is sometimes unclear. Fetal sex was not found to influence fetal mortality in the present study.

ROC analysis. The present study also assessed the diagnostic significance of maternal physiological factors (age, parity and BMI) in predicting the birth of a small or large fetus using ROC curves (Fig. 1). The area of the ROC curve corresponding to the association between the prediction of small or large fetal weights and maternal age, maternal weight and maternal BMI was 0.43±0.009 (95% CI, 0.42-0.45; P=0.0001); 0.45±0.009 (95% CI, 0.45-0.47; P=0.0001) and 0.4±0.009 (95% CI, 0.39-0.42; P=0 .0001), respectively (Fig. 1). The age threshold was 20.5 years at the cut-off point. A higher risk of delivering a small or large fetus was predicted for females ≥20.5 years of age. The sensitivity and specificity of the method were 93.7 and 96.4%, respectively (Table VI). The threshold value of maternal parity at the cut-off point was 0.5. A high risk of having a small or large fetus was predicted during the first pregnancy, and this risk decreased with each birth. The sensitivity and specificity of the method were 66.2 and 70.9%, respectively. The threshold BMI value was 18.5 kg/m^2 at the cut-off point. A higher risk of having a small or large fetus was predicted for females with a BMI ≥18.5 kg/m^2. The sensitivity and specificity of the method were 91.1 and 92.7%, respectively (Fig. 1 and Table VI).

Table V. Neonatal characteristics in birth outcome groups (n=6,547).

Parameters	Birth outcome					P-value (χ^2 test or Fisher's test[a])	P-values (Kruskal-Wallis test)		
	Live birth. birth. n (%)	Stillbirth. n (%)	OR (95% CI)	Perinatal mortality. n (%)	OR (95% CI)		Live birth vs. stillbirth	Live birth vs. perinatal mortality	Stillbirth vs. perinatal mortality
Sex, n (%)						0.62			
Boy	3,209 (49.01)	104 (1.59)	-	23 (0.35)	-				
Girl	3,103 (47.4)	89 (1.36)	-	19 (0.29)	-				
Fetal weight (g), Me (Q_1-Q_3)	3,420 (3,090-3,750)	1,577 (758-2,750)		800 (595-962.5)			0.0001	0.0001	0.0001
Fetal weight (g)						0.0001[a]			
<2,500	389 (5.95)	137 (2.09)	-	40 (0.61)	-				
2,500-4,000	5201 (79.44)	50 (0.76)	-	2 (0.03)	-				
>4,000	722 (11.03)	6 (0.09)	0.86 (0.37-2.02)	0	-				
Duration in days, Me (Q_1-Q_3)	279 (272-285)	220 (188-265)		194 (184-205)			0.0001	0.0001	0.0001
Premature birth, n (%)						0.0001			
No	5,883(89.86)	58 (0.89)	-	2 (0.03)	-				
Yes	429 (6.55)	135 (2.06)	-	40 (0.61)	-				

Data for fetal weight and duration in days are presented as the median (Q_1-Q_3) and were analyzed using the Kruskal-Wallis test followed by Dunn's post hoc test. Categorical variables were analyzed using the Chi-squared test of Fisher's test. P-values <0.05 were considered to indicate statistically significant differences.

Table VI. Sensitivity and specificity of maternal demographic and neonatal characteristics in predicting the birth of a small or large fetus.

Parameters	Cut-off point	Crude		P-value
		Sensitivity (%)	Specificity (%)	
Predicting the birth of a small or large fetus				
Maternal age, years	20.5	93.7	96.4	0.0001
BMI (kg/m^2)	18.5	91.1	92.7	0.0001
Parity, n (%)	0.5	66.2	70.9	0.0001
Predicting stillbirth or perinatal mortality				
Maternal age, years	21.5	92.3	90.2	0.0001
BMI (kg/m^2)	18.5	90.6	91.4	0.0001

BMI, body mass index. P-values <0.05 were considered to indicate statistically significant differences.

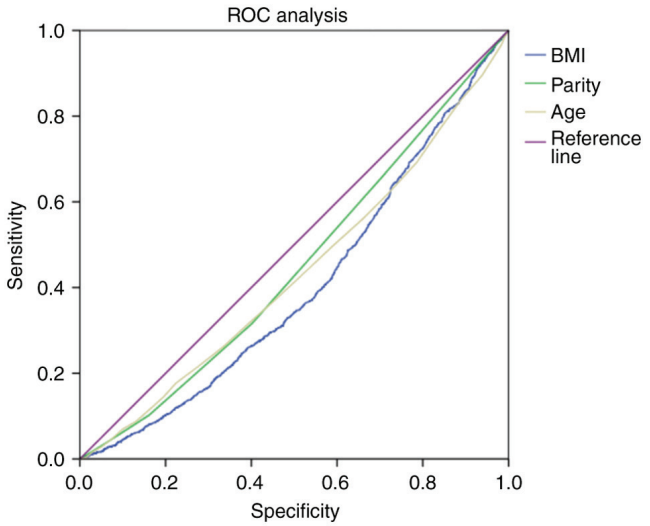

Figure 1. ROC analysis of the association between fetal weight and maternal age, parity and BMI. ROC, receiver operating characteristic; BMI, body mass index.

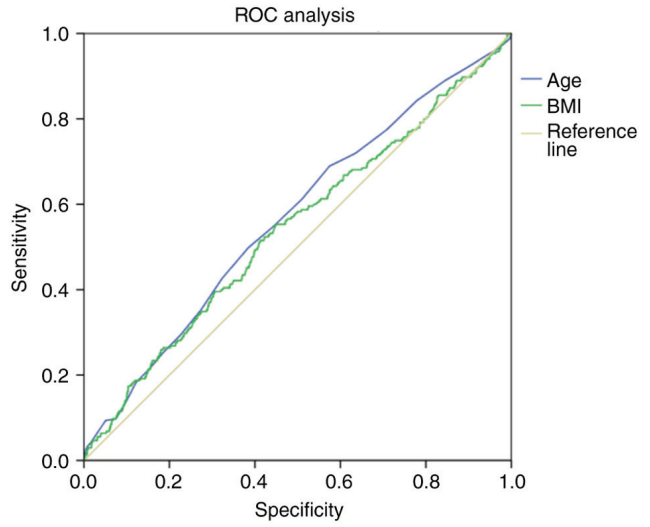

Figure 2. ROC-analysis of the association between fetal mortality and maternal age and BMI. ROC, receiver operating characteristic; BMI, body mass index.

The present study further assessed the diagnostic value of maternal physiological factors (age and BMI) in predicting stillbirth or perinatal mortality using ROC curves (Fig. 2). The area of the ROC curve corresponding to the association between the prognosis of fetal mortality and maternal age and maternal BMI was 0.57±0.019 (95% CI, 0.53-0.61; P=0.0001) and 0.54±0 .02 (95% CI, 0.5-0.58; P=0.025), respectively (Fig. 2). The age threshold was 21.5 years at the cut-off point (Table VI). A higher risk of stillbirth or perinatal mortality was predicted in females aged ≥21.5 years. The sensitivity and specificity of the method were 92.3 and 90.2%, respectively. The threshold BMI value is was 18.5 kg/m^2 at the cut-off point. A higher risk of stillbirth and perinatal mortality was predicted in females with a BMI ≥18.5 kg/m^2. The sensitivity and specificity of the method were 90.6 and 91.4%, respectively (Table VI).

Discussion

The present study aimed to investigate the association between fetal weight and maternal physiological and pathological characteristics. The results revealed that maternal physiological and pathological characteristics were statistically higher in the group of newborns considered SGA and LGA than the group of newborns with normal weight. According to the results fo the ROC analysis, maternal age, maternal weight and maternal BMI were independently associated with risk of prediction of SGA or LGA. In the present study, the maternal BMI at the beginning of pregnancy was found to influence the birth weight of the newborns. However, different studies have yielded varying results. In the study by Cnattingius *et al* (18), the opposite result was found for the association between maternal BMI and low fetal weight. The authors of that study claimed that obesity protected from fetuses with a low birth weight. However, they did not use individualized centiles. Perhaps the individual physiological characteristics of the mother were not taken into account (18). A newborn weighing 3,500 g would be considered normal for the general population and for a pregnant woman of normal weight. However, in a pregnant woman with a high BMI, a fetus weighing 3,500 g may be below the 10th percentile (19).

The maternal age and BMI were found to be independently associated with risk of predicting of stillbirth or perinatal mortality. In the present study, maternal weight at the beginning of pregnancy was found to be associated with the risk of perinatal mortality. Pregnant females who were underweight, overweight and obese at the beginning of pregnancy were at a higher risk of their newborns experiencing perinatal mortality. The study by Gardosi *et al* (19) analyzed the incidence of low birth weight fetuses in BMI groups using an adapted individual standard and found a directly proportional association between perinatal mortality and BMI. Defined by individual percentiles, fetuses with a low birth weight were more common in the group with a higher BMI, and also agreed well with the trend in perinatal mortality rates (19). According to the result of the unadapted standard, the incidence of fetuses with a low birth weight was high in thin pregnant women, and on the contrary, it was lower in women with a high BMI. This actually hides the fact that a fetus can be relatively small compared to its optimal weight. However, the adapted standard indicates that obese pregnant women may be at an increased risk of having a fetus with a low birth weight (19,20). Gardosi *et al* (19) argued that when maternal parity was taken into account, the adapted low birth weight fetal standard better reflected the risk of perinatal mortality, while the unadapted standard overestimated the frequency of fetuses with a low birth weight in females when parity was not taken into account, which did not reflect the increased mortality.

In the present study, the risk of stillbirth and perinatal mortality increased with age. Females with a newborn weighing <2,500 g and those with newborns weighting >4,000 g were older than females who had newborns with a normal weight. In other studies, fetal weight at birth was influenced by maternal age and parity (21). According to the French College of Obstetricians and Gynecologists, the development of FGR was influenced by a maternal age >35 years and parity (22). In a previous study in Slovenia, fetal weight at birth was found to be influenced by maternal height, maternal weight at early gestation, maternal age and parity, fetal sex and GDM (23).

In another study conducted in Iran, fetal birth weight was shown to be influenced by maternal height, maternal weight in early pregnancy, parity and the sex of the baby, as well as paternal height and weight (24). In that study, fetal birth weight was also shown to be influenced by rural residence, anemia, pre-existing and GDM and pre-eclampsia (24). Another study reported an association of fetal birth weight with maternal height, maternal weight at the beginning of pregnancy, parity, ethnicity, gestational age at delivery and fetal sex. Adverse pregnancy outcomes were associated with FGR regardless of gestational age at delivery (2). In a French study, fetal height and birth weight were influenced by gestational age, fetal sex, maternal height and weight at the beginning of pregnancy, parity and ethnicity (25).

In the INTERGROWTH and NICHD studies, fetal weight varied by fetal sex, maternal race and ethnicity (26,27). Studies in recent years have shown that the fetus loses between 10 and 30% of its body weight between the time of intrauterine death and the subsequent postnatal assessment. The majority of newborns who are stillborn may have had a normal weight prior to mortality and FGR may have appeared after birth. On the other hand, newborns who are stillborn with FGR who were born with a normal birth weight may be missed (27). In the present study sample, boys were born with a weight <2,500 g and with a weight >4,000 g compared to girls. Newborns weighing <2,500 g were more likely to be born prematurely. This was expected, since the pathological course of pregnancy could cause various pregnancy complications, both for the fetus and for the mother. The results obtained are similar to those of other studies. In their study, Pritchard *et al* found that female infants below the 10th percentile had no risk of stillbirth, hospitalization to the intensive care unit, low Apgar scores, and emergency caesarean section, but had increased risks associated with medical interventions for the induction of labor. In addition, newborn boys weighing below the 10th percentile had a high risk of perinatal mortality, to the intensive care unit hospitalization, Apgar scores <7 at 5 min and operative delivery (29). In another study, the authors reported that male fetuses weighed more than female fetuses, and that maternal height, early pregnancy weight, and maternal parity influenced fetal birth weight (26). Another study found that male infants considered to SGA were more likely to have a higher risk of stillbirth, perinatal mortality, admission to the intensive care unit, Apgar <7 at 5 min and emergency cesarean section compared to female infants (29). Other researchers suggest using fetal growth assessment standards adjusted for the variable fetal sex to identify male infants at increased risk of adverse outcomes, including stillbirth (25).

Maternal factors for the development of FGR include GDM, renal failure, autoimmune diseases, erythematous heart disease, cyanotic heart defects, hypertension, hyperglycemia or preeclampsia, antiphospholipid syndrome, use and abuse of psychoactive substances, multiple pregnancy, exposure to teratogens and infectious diseases (3). The present study confirmed the influence of maternal pathological factors, such as a history of AH and DM, preeclampsia, GH and GDM in a given pregnancy on fetal weight at birth. The maternal characteristics by extragenital diseases of the study population between the groups of fetal weight. A maternal history of AH increased the risk of having a newborn weighing <2,500 g. Females with AH and preeclampsia in were less likely to give birth to a newborn weighing >4,000 g. The risk of having a newborn weighing <2,500 g increased in females with preeclampsia during this pregnancy, and this risk increased with the severity of preeclampsia. During pre-eclampsia, there will be placental ischemia, which leads to uteroplacental hypoperfusion and increases the risk of stillbirth and perinatal death (30). In preeclampsia, placental lesions are common as a consequence of maternal hypoperfusion (31). In the case that preeclampsia begins early in pregnancy, it increases the likelihood of placental damage associated with hypoperfusion. Other authors have stated that pregnant women with pre-eclampsia in early pregnancy often had vascular lesions and placental hypoplasia, and by contrast, pregnant women with pre-eclampsia diagnosed at the end of the third trimester had placental hyperplasia (32).

In the present study, the presence of GH in this pregnancy increased the risk of having a newborn weighing >4,000 g and reduced the risk of having a newborn weighing <2,500 g. A Chinese-American study reported that the early onset of GH and preeclampsia was relatively more unfavorable for the fetus and increased the risk of FGR (33). Increased blood pressure

during pregnancy leads to endothelial dysfunction and reduced placental perfusion, this creates conditions for reduced fetal growth and a low birth weight (34).

In the present study, a significant association was found between females with GDM in a given pregnancy and the risk of having a newborn weighing >4,000 g. The presence of any type of diabetes in the mother in the present study sample did not affect fetal weight at birth. This result may be due to the fact that diabetes has long been a known factor, which leads to the birth of a newborn weighing >4,000 g; pregnancy management in such females is always carried out in collaboration with endocrinologists, and such females receive full observation, treatment and prophylaxis to prevent the influence of DM on the fetus. A previous study found that fetuses with FGR were more likely to be born to women with coronary heart disease, AH and insulin resistance (35). Assessing the risk of adverse perinatal outcomes in GDM, the authors of a previous cohort study reported that GDM was associated with an increased risk of preterm labor, an increased risk of stillborn fetuses and pre-eclampsia, fetal delivery with LGA (36). Fetuses with LGA are common in pregnant women with DM and GDM, as even moderate maternal hyperglycemia increases the rate of accelerated fetal growth (37).

The present study had certain limitations, which should be mentioned. Firstly, the present study had a retrospective design and the data collection was based on materials from the medical history and individual cards of pregnant females. The second limitation is that the diagnosis of FGR may have included newborns that are physiologically small and may have missed large fetuses that have not reached their physiological potential.

In conclusion, despite improvements in knowledge and the understanding of pathological conditions during pregnancy, there is still a high risk of stillbirth and perinatal mortality, regardless of fetal weight. Therefore, it is necessary to prevent the risk of stillbirth and perinatal mortality in healthy newborns, as well as in small newborns who were born with a normal weight, but have FGR. Thus, further studies which large sample sizes are required in the future to investigate the issue of fetal FGR.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MS, KS, BI and GT were major contributors to the study and made substantial contributions to the conception and design of the study. MS and AS performed the data collection and the statistical analyses of the data. MS and AS also participated in the writing the manuscript. MS and AS confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Semey Medical University, which approved the research protocol (Protocol # 2 of from 10/25/2018). Informed consent was obtained from each patient in writing.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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