Scientific Research Publishing

Open Journal of Pediatrics, 2025, 15(2), 150-176
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

The Impact of Gestational Diabetes Mellitus on Neurodevelopmental Outcomes in Infants

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How to cite this paper: Mkwambe, M.C., Deng, Y.P. and Zhao, D.C. (2025) The Impact of Gestational Diabetes Mellitus on Neurodevelopmental Outcomes in Infants. *Open Journal of Pediatrics*, **15**, 150-176.
https://doi.org/10.4236/ojped.2025.152015

Received: January 26, 2025
Accepted: March 4, 2025
Published: March 7, 2025

Abstract

Background: Gestational diabetes mellitus (GDM), a condition characterized by high blood sugar levels during pregnancy, is increasingly prevalent globally. While resolving after delivery, GDM can have lasting implications for the developing fetus, particularly regarding neurodevelopmental outcomes. This impact is garnering significant attention within the medical community, driving research into the underlying mechanisms and potential interventions. We aimed to investigate the prevalence and impact of gestational diabetes mellitus (GDM) on neurodevelopmental outcomes in infants. **Methods:** This retrospective cohort study was conducted using data collected from 2018 to 2022 at Zhongnan Hospital of Wuhan University. A total of 1430 mothers with gestational diabetes mellitus (GDM) and 1430 infants, aged 0 to 12 months, were included in the study. The inclusion criteria were as follows: mothers with a confirmed diagnosis of gestational diabetes mellitus and no history of pre-gestational diabetes mellitus, and infants aged 0 to 12 months born to these mothers with GDM. **Results:** A total of 1430 infants were included in the study, of which 832 (58.18%) were male and 598 (41.82%) were female. The prevalence of gestational diabetes mellitus (GDM) was 68.65%. The results of the Denver II Developmental Screening Test (DDST) were as follows: 1370 infants (95.80%) had normal development, 8 infants (0.56%) had abnormal development, 44 infants (3.10%) had suspicious development, and 8 infants (0.56%) were unable to be assessed. Factors associated with a higher likelihood of abnormal findings on the DDST included being a primiparous mother ($p < 0.001$), having a normal head circumference ($p = 0.002$), being under 6 months old ($p = 0.043$), and having a normal anterior fontanelle ($p < 0.001$). Regarding mental responses, infants with normal head circumference or microcephaly had poorer mental responses compared to those with macrocephaly ($p < 0.001$). Additionally, infants with lower birth weights (1 - 1.5 kg, 1.5 - 2.5 kg, and 2.5 - 4 kg) and a normal anterior fontanelle exhibited abnormal mental

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responses (all $p < 0.001$). No statistically significant differences in mental response were found based on gender, maternal age, gestational age, delivery method, or birth length ($p > 0.05$). **Conclusion:** The findings from this study underscore the significant impact of gestational diabetes mellitus on neurodevelopmental outcomes in exposed infants to GDM. Infants born to mothers with GDM showed varied neurodevelopmental and mental response impairments, with certain levels being more susceptible.

Keywords

Gestational Diabetes Mellitus, Infants, Mental Response, Neurodevelopmental Outcomes, Denver II Developmental Screening Test

1. Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications of pregnancy, with global prevalence rates ranging between 5% and 15% depending on diagnostic criteria and population characteristics. GDM is characterized by glucose intolerance with onset or first recognition during pregnancy and is associated with both short- and long-term risks for mothers and their offspring [1]. Gestational diabetes mellitus (GDM) has emerged as a significant public health concern, particularly in regions like China, where rapid urbanization, lifestyle changes, and increasing obesity rates have led to a rise in the prevalence of this condition. In China, the prevalence of GDM has been reported to range from 5.4% to 18.8%, depending on the region and the population studied [2]. The high variability in the reported prevalence can be attributed to differences in diagnostic criteria, ethnic variations, and regional disparities in healthcare access. In urban areas, where lifestyle factors such as poor diet and reduced physical activity are more prevalent, the incidence tends to be higher, while rural areas exhibit a relatively lower prevalence. However, as urbanization progresses, it is expected that the prevalence in rural areas will continue to rise [3]. GDM poses unique complications for both maternal and infant health. For mothers, GDM increases the risk of developing type 2 diabetes and cardiovascular diseases later in life [4]. For infants, GDM has been linked to a range of adverse neurodevelopmental outcomes. These include an increased risk of preterm birth, low birth weight, and neurological disorders [5]. Furthermore, recent studies suggest that infants born to mothers with GDM may be at heightened risk for neurodevelopmental delays, such as cognitive impairment, attention deficits, and emotional difficulties [6]. Despite these known risks, the specific neurodevelopmental outcomes associated with GDM in the Chinese population remain understudied.

Hyperglycemia may disrupt placental function, alter nutrient and oxygen delivery, and expose the developing brain to high levels of insulin and glucose, which are neurotoxic in excess [7]. Additionally, maternal metabolic dysregulation in GDM may induce abnormal patterns of neuronal differentiation and synaptogen-

esis, potentially impairing cognitive and motor functions [8].

Emerging evidence suggests an association between GDM and increased risks of neurodevelopmental disorders, including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). For instance, a meta-analysis by Xiang *et al.* reported a significant increase in ASD risk among children born to mothers with untreated GDM [9].

Studies also suggest potential associations with lower cognitive performance and impaired language skills in infancy and early childhood [10] [11]. These findings may be influenced by maternal factors such as obesity, advanced age, and comorbidities, which are often present in women with GDM.

Several studies emphasize the importance of gestational timing and treatment interventions in moderating outcomes. Early-onset GDM and poor glycemic control are particularly associated with worse neurodevelopmental trajectories [12] [13].

On the other hand, effective GDM management, including dietary modifications, insulin therapy, and glucose monitoring, has been shown to mitigate risks to neurodevelopmental health [14].

Birth weight and gestational age also play critical roles in determining the neurodevelopmental impact of GDM. Infants born large for gestational age (LGA) or small for gestational age (SGA) may experience additional vulnerabilities due to altered growth trajectories and metabolic imbalances [15]-[18]. Furthermore, preterm delivery, often associated with poorly controlled GDM, compounds the risk of neurodevelopmental impairments, including cerebral palsy and cognitive delays [19].

Understanding the pathways through which GDM influences neurodevelopment remains a priority for researchers. Recent advancements in neuroimaging, epigenetic profiling, and longitudinal cohort studies have provided new insights but also underscore the complexity of these interactions [20] [21].

Chronic hyperinsulinemia in fetuses of GDM mothers can promote neuroinflammation and insulin resistance in the brain, affecting learning and memory [22] [23]. Compromised placental function in GDM pregnancies limits oxygen and nutrient transfer, impairing brain development [24] [25].

Interdisciplinary approaches that integrate maternal health, placental biology, and pediatric neurodevelopment are essential to unraveling these complexities. Early detection and management of GDM are critical to mitigating adverse outcomes. Interventions such as dietary modifications, physical activity, and insulin therapy can improve glycemic control and reduce risks [26] [27]. Breastfeeding has also been shown to positively influence cognitive development in infants of GDM mothers [28].

Despite mounting evidence linking GDM to neurodevelopmental outcomes, gaps remain in understanding the specific pathways involved and the interaction of genetic and environmental factors [29] [30].

The findings from studies have been somewhat inconsistent with some reporting

significant associations while others found no significant effects. However, overall, the majority of studies suggest that maternal GDM may have a detrimental impact on neurodevelopmental outcomes in infants [31].

This study hypothesizes that infants born to mothers with gestational diabetes mellitus (GDM) exhibit poorer neurodevelopmental outcomes, including cognitive delays, and motor skill impairments, compared to infants born to mothers without GDM. Furthermore, the severity of GDM (e.g., gestational age, delivery methods, parity, maternal age) and infants' factors (anterior fontanelle status, birth weight, birth length, weight level results, head circumference results) will be associated with the degree of neurodevelopmental impairment in the offspring. Continued research is critical to identifying modifiable risk factors and developing targeted interventions to improve maternal and child health outcomes.

Therefore, in this study, we aimed to find the impact of gestational diabetes mellitus that exists during pregnancy on infants' neurodevelopmental outcomes.

2. Methods

2.1. Study Design and Population

This was a retrospective single tertiary hospital-based cohort study at Zhongnan Hospital of Wuhan University, from 2018 to 2022, in two departments: Pediatric and Obstetrics & Gynecology. All Infants exposed to gestational diabetes mellitus and their gestational diabetic mothers were recruited in the study under the following inclusion and exclusion criteria:

a) Infants, Inclusion criteria: Infants aged from 0 - 12 months; Infants born to mothers with a confirmed diagnosis of gestational diabetes mellitus; Infants with available medical records and neurodevelopmental assessment scores; Infants whose mothers did not use any medications or substances known to affect neurodevelopment during pregnancy; Infants whose mothers received consistent prenatal care throughout their pregnancy; Infants born to mothers who did not have any other significant medical conditions or complications during pregnancy.

Exclusion Criteria: Infants with a known genetic or congenital abnormality that could independently affect neurodevelopment; Infants with a history of significant neonatal complications that could impact neurodevelopment; Infants with incomplete or unavailable medical records and neurodevelopmental assessments; Infants with a history of significant medical conditions or complications during the prenatal or postnatal period may confound the relationship between maternal gestational diabetes and neurodevelopmental outcomes; infants born to mothers with pre-existing diabetes; Infants born to mothers who used medications or substances known to affect neurodevelopment during pregnancy.

b) Gestational Diabetic mothers, Inclusion Criteria: Mothers with a confirmed diagnosis of gestational diabetes during pregnancy; Mothers who received prenatal care and regular monitoring for gestational diabetes; Mothers who delivered a live-born infant; Mothers who did not have any significant medical conditions or complications during pregnancy, apart from gestational diabetes; Mothers who

did not use medications or substances known to affect neurodevelopment during pregnancy. **Exclusion Criteria:** Mothers with pre-existing diabetes (type 1 or type 2) prior to pregnancy; Mothers with other significant medical conditions or comorbidities that could independently impact neurodevelopment; Mothers who used medications or substances known to affect neurodevelopment during pregnancy; Mothers with a history of significant mental health disorders; Mothers with incomplete or unavailable medical records. Figure 1 provides details regarding inclusions and exclusion criteria of the study participants.

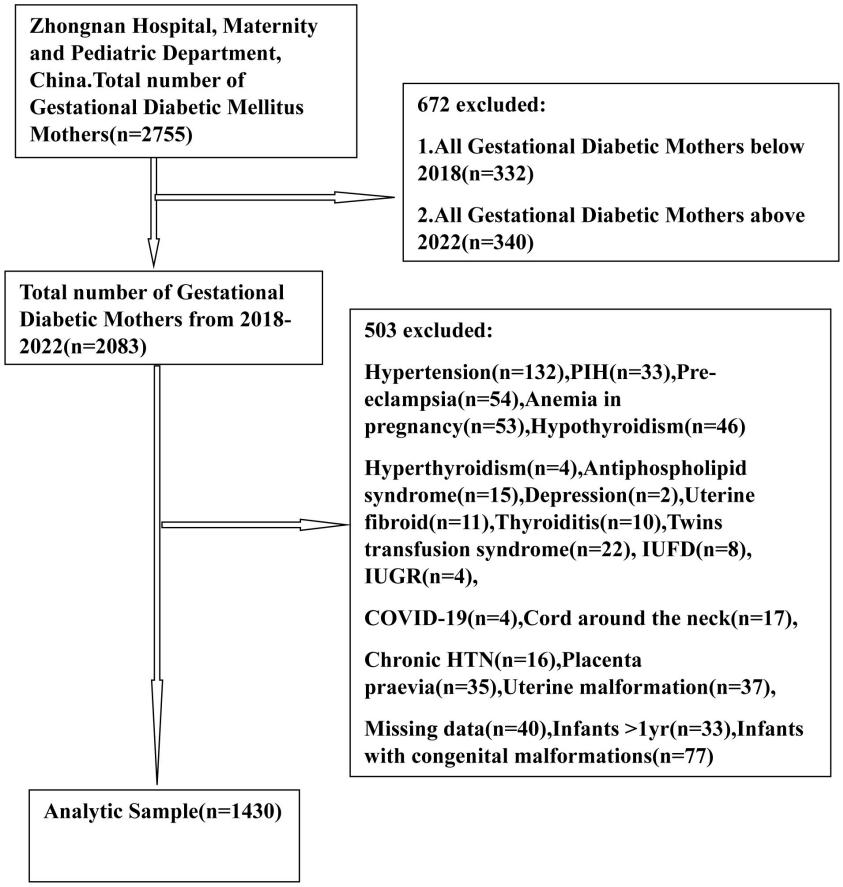

Figure 1. Flow chart; showing the detailed procedure for the inclusion or exclusion selection of study participants.

Clinical data assessment: Neurodevelopmental outcome and mental evaluation results were obtained from the record of the assessment of infants using the Denver II Developmental Screening Test (DDST-II). The Denver II Developmental Screening Test (DDST-2) is used to screen children's development from the age of 0 month to 6 years. It consists of 125 items, and the development of a child is measured based on these 125 items. The test usually takes 10-20 minutes to perform. Each test item is scored as pass, fail, refused or no opportunity. In the Denver II Developmental Screening Test for infants, the categories of normal, abnormal, suspicious, and unable to judge were used to assess a child's development

across four domains: personal-social, fine motor-adaptive, language, and gross motor skills.

Ethics consideration

Ethical approval was sought from Ethics Committee of Zhongnan Hospital of Wuhan University with a number (Kelun 2022042K) and exempted from signing the informed consent form.

2.2. Statistical Analysis

SPSS version 27 was used for statistical analysis. The independent samples t-test was used to compare the means of normally distributed data between the two groups, while the Mann-Whitney test was employed for continuous data that were not normally distributed. The chi-square test was used to assess the association between gestational diabetes mellitus and neurodevelopmental outcomes in infants. Results were indicated statistically significant for the p-value less than 0.05.

3. Results

The prevalence of Gestational diabetes mellitus for gestational diabetic mothers was 68.65%. In a total of 1430 infants born from Gestational Diabetic Mothers, male infants accounted for 832 (58.18%) and female infants 598 (41.82%). (**Figure 2**). The largest proportion of infants' assessments was at younger ages, occurring at 1 month, followed by 3, 2, 6, 0 and 4 months, representing 406 (28.38%), 191 (13.36%), 151 (10.56%), 131 (9.16%), 120 (8.39%) and 105 (7.34%) respectively. In contrast, the lowest numbers of Infants were at ages 5, 7, 8,9,10, 11 and 12 months, accounting for 94 (6.57%), 34 (2.38%), 55 (3.85%), 37 (2.59%), 30 (2.10), 28 (1.96), 48 (3.36) respectively. A larger proportion of infants were found with a normal birth weight of between 2.5 to 4 kg, accounting 929 infants (65.00%). The proportion of ELBW, VLBW, LBW and Macrosomia were 15 (1.00%), 83 (5.80%), 363 (25.40%), and 40 (2.80%) respectively. The proportion of Infants who had normal head circumference results were 1156 (81.00%), followed by Infants with small head which accounted for 250 (17.50%). Infants with larger heads were found to be 21 (1.50%) (**Table 1**). Infants with normal anterior fontanelles, accounted for 1362 (95.24%) of the study population. However, out of 1430, Infants with closed and not closed anterior fontanelles, accounted for 29 (2.03%) and 29 (2.03%) respectively. Our study revealed 2 (0.14%) and 8 (0.56%) Infants with enlarged and sunken anterior fontanelles with substantial impact on neurodevelopmental outcomes. The proportion of Infants' birth length AGA was 992 (69.40%), followed by Infants' birth length SGA, which accounted for 403 (28.20%). However, there were significant number of Infants' birth length with LGA, which accounted for 35 (2.40%). Infants with weight level below Middle and Above Middle were 226 (15.80%) and 172 (12.00%) respectively. The proportion of Infants with Infants with Average positive weight level and Average negative Weight Level were 445 (31.10%) and 355 (24.80%). However, Infants with low Weight level accounted for 232 (16.20%) (**Table 1**). Out of total 1430, the proportion of infants

delivered by SVD accounted for 465 (32.50%). Proportion of infants delivered C.D accounted for 959 (67.10%). Infants delivered by F.D accounted for 6 (0.40%). The majority of the 1430 mothers in the study had a gestational age falling between 37 - 42 weeks, totaling 832 mothers (58.20%). The proportion of mothers at gestation age of 32 - 36 weeks accounted for 443 (31.00%). The proportion of at gestational age of <32weeks accounted for 155 (10.80%). The majority of mothers fell within the age range of 25 to 34 years, comprising 1137 individuals (79.51%) out of the total 1430 mothers. However, there were 265 mothers (18.53%) who were considered to have advanced maternal age, being above 35 years old (Table 1).

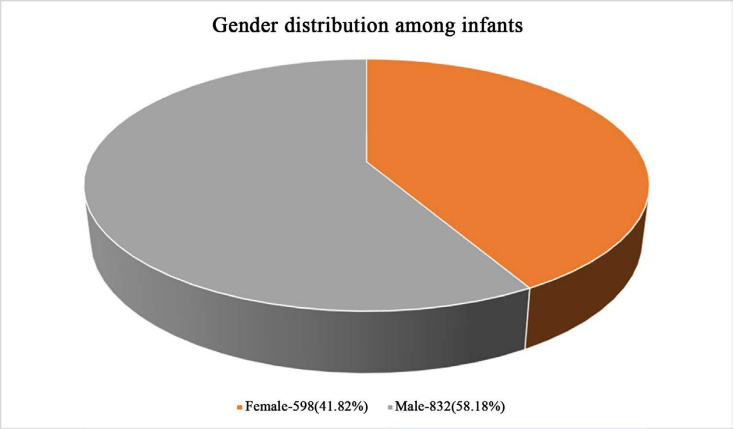

Figure 2. Distribution of gender in infants.

Table 1. Descriptive features.

Gestational age (weeks)	Normal range	n, %
1. Preterm birth		
a) Very preterm	<32	155(10.80)
b) Moderate to late preterm	32 - 36	443(31.00)
2. Term birth	37 - 42	832(58.20)
3. Post-term	>42	
Total		**1430**
Infants birth weight(kg)		**n (%)**
ELBW <1.0		15(1.00)
VLBW (1.0 - 1.5)		83(5.80)
LBW (1.5 - 2.5)		363(25.40)
NBW (2.5 - 4)		929(65.00)
Macrosomia > 4		40(2.80)
Total		**1430**
Maternal age(years)		**n, %**
20 - 24		28(1.96)
25 - 34		1137(79.51)
≥35		265(18.53)
Total		1430
Delivery method		**n, %**
Spontaneous vaginal delivery (S.V.D)		465(32.50)
Caesarean delivery (C.D)		959(67.10)

Continued

Forceps delivery (F.D)	6(0.40)
Total	1430
Number of times for visit	**n, %**
1	400(27.97)
2	307(21.47)
3	239(16.71)
4	233(16.29)
5	100(6.99)
6	73(5.10)
7	30(2.10)
8	22(1.54)
9	24(1.68)
10	2(0.14)
Head circumference results	**n, %**
Normal	1159(81.00)
Macrocephaly	21(1.50)
Microcephaly	250(17.50)
Total	1430
Anterior fontanelle results	**n, %**
Normal	1362(95.24)
Enlarged	2(0.14)
Sunken	8(0.56)
Closed	29(2.03)
Not closed	29(2.03)
Birth length results	**n, %**
AGA	992(69.40)
SGA	403(28.20)
LGA	35(2.40)
Total	1430
Weight level results	**n, %**
Below middle (below average)	226(15.80)
Above middle (above average)	172(12.00)
Average positive (within normal range)	445(31.10)
Average negative (within normal range)	355(24.80)
Low (below average)	232(16.20)
Total	1430

3.1. Denver Developmental Screening Results

Regarding developmental assessment, of the 1430 subjects, 1370 (95.80%) showed normal results, 8 (0.56%) had abnormal results, 44 (3.08%) were categorized as suspicious, and 8 (0.56%) had results that were unable to be judged based on DDST findings. Table 2 presents the DDST results across all four domains.

Table 2. Denver developmental screening test results (n = 1430).

DDST-II	Normal (n, %)	Abnormal (n, %)	Suspicious (n, %)	Unable to judge (n, %)
Total score	1370(95.80)	8(0.56)	44(3.08)	8(0.56)

Continued

Test results on domains	Pass (n, %)	Fail (n, %)	Refusal (n, %)	No opportunity (n, %)
Personal-social skills	1120(78.32)	256(17.90)	44(3.08)	10(0.70)
Fine mor skills	866(60.56)	465(32.52)	88(6.15)	11(0.07)
Gross motor skills	1000(69.93)	393(27.48)	26(1.82)	11(0.07)
Language skills	1237(86.50)	136(9.51)	50(3.50)	7(0.49)

DDST: Denver Developmental Screening Test.

There was no statistically significant difference in the probability of abnormal, suspicious, or unable to judge findings between male and female infants ($p = 0.163$). Similarly, no significant association was found between abnormal findings and maternal age ($p = 0.193$) or gestational age ($p = 0.566$). Delivery methods (spontaneous vaginal delivery, cesarean delivery, and forceps delivery) also showed no significant association ($p = 0.702$). However, there was a significant association with parity, where primiparous mothers had a higher likelihood of neurodevelopmental impairments in their infants' DDST results compared to multiparous mothers ($p < 0.001$). Infants with normal head size and microcephaly showed significantly more abnormal DDST results ($p = 0.002$). The probability of abnormal DDST findings was highest in infants younger than six months, especially around three months of age ($p < 0.001$). Regarding anterior fontanelle status, infants with normal, sunken, closed, or not closed fontanelles showed significantly more abnormal DDST results than those with enlarged anterior fontanelles ($p < 0.001$). Birth length ($p = 0.492$), birth weight ($p = 0.081$), and weight level ($p = 0.394$) showed no significant effect on abnormal DDST findings. Table 3 summarizes the statistical relationships between maternal and infant variables and the overall DDST results.

Table 3. (a) Association of maternal and infants' factors with the neurodevelopmental outcomes. (b) Continuation of Association of maternal and infants' factors with the neurodevelopmental outcomes.

(a)					
	Denver developmental screening test results				
Gender	**Normal** (n, %)	**Abnormal** (n, %)	**Suspicious** (n, %)	**Unable to judge** (n, %)	**P-value**
Female	570(41.60)	4(50.00)	23(52.30)	1(12.50)	**0.163**
Male	800(58.40)	4(50.00)	21(47.70)	7(87.50)	
Total	1370	8	44	8	
Maternal age (years)					
20 - 24	26(1.90)		1(2.30)	1(12.50)	
25 - 34	1086(79.30)	8(100%)	38(86.40)	5(62.50)	**0.193**
35 and >35	258(18.80)		5(11.40%)	2(25.00)	
Total	1370	8	44	8	
Gestational age (weeks)					
<32	145(10.60)	2(25.00)	7(15.91)	1(12.50)	**0.566**

Continued

32 - 36	449(31.30)	1(12.50)	10(22.73)	3(37.50)	
37 - 42	796(58.10)	5(62.50)	27(61.36)	4(50.00)	
Total	1370	8	44	8	
Delivery method					
S.V. D	439(32.00)	4(50.00)	19(43.18)	3(37.50)	
C.D	925(67.50)	4(50.00)	25(56.82)	5(62.50)	**0.702**
F. D	6(0.50)				
Total	1370	8	44	8	
Parity					
Para 1	778(56.80)	5(62.50)	30(68.20)	4(50.00)	
Para 2	296(21.60)	1(12.50)	9(20.50)	3(37.50)	**<0.001**
Para 3	184(13.40)	1(12.50)	4(9.10)		
Para 4	65(4.70)	1(12.50)			
Para 5	27(2.00)				
Para 6	8(0.60)		1(2.20)		
Para 7	9(0.70)				
Para 8	1(0.10)			1(12.50)	
Para 9	1(0.10)				
Para 10	1(0.10)				
Total	1370	8	44	8	
Head circumference results					
Normal	1108(80.88)	5(62.50)	38(88.37)	8(100)	**0.002**
Macrocephaly	18(1.31)	1(12.50)	1(2.33)		
Microcephaly	244((17.81)	2(25.00)	4(9.30)		
Total	1370	8	44	8	
Infants' age (months)					
0	116(8.47)		1(2.27)	3(37.50)	
1	394(28.76)	3(37.50)	7(15.91)	2(25.00)	
2	143(10.44)	1(12.50)	7(15.91)		
3	188(13.72)		2(4.55)	1(12.50)	**0.043**
4	104(7.59)		1(2.27)		
5	87(6.35)	1(12.50)	6(13.64)		
6	121(8.83)	2(25.00)	7(15.91)	1(12.50)	
7	31(2.26)		3(6.82)		
8	50(3.65)		4(9.09)	1(12.50)	
9	34(2.48)		3(6.82)		
10	29(2.12)	1(12.50)			
11	26(1.90)		2(4.55)		
12	47(3.43)		1(2.27)		
Total	1370	8	44	8	
Anterior fontanelle results					
Normal	1313(96.40)	7(0.51)	36(2.64%)	6(0.44)	
Enlarged	2(100)				
Sunken	1(12.50)		2(25.00)	1(12.50)	**<0.001**
Closed	5(17.24)	1(3.45)	2(6.90)		
Not closed	24(82.76)		4(13.79)	1(3.45)	
Total	1370	8	44	8	

Continued

Weight level results					
Above middle	216(15.80)	1(12.50)	8(18.20)	1(12.50)	
Average positive	428(31.20)	2(25.00)	11(25.00)	4(50.00)	
Average negative	337(24.60)	3(37.50)	15(34.10)		**0.394**
Below middle	161(11.80)	2(25.00)	7(15.90)	2(25.00)	
Low	228(16.60)		3(6.80)	1(12.50)	
Total	1370	8	44	8	

(b)

Denver developmental screening test results

Birth length	**Normal**	**Abnormal**	**Suspicious**	**Unable to judge**	**P-value**
AGA	955(69.70%)	5(62.50%)	27(61.36%)	5(62.50%)	
SGA	382(27.88%)	3(37.50%)	16(36.36%)	2(25.00%)	**0.492**
LGA	33(2.41%)	0	1(2.27%)	1(12.50%)	
Total	1370	8	44	8	
Birth weight					
ELBW	14(1.02%)	1(12.50%)			
VLBW	78(5.69%)	1(12.50%)	4(9.09%)		
LBW	347(25.33%)	1(12.50%)	13(29.55%)	2(25.00%)	**0.081**
NBW	894(65.26%)	4(50.00%)	26(59.09%)	5(62.50%	
Macrosomia/big baby	37(2.70%)	1(12.50%)	1(2.27%)	1(12.50%)	
Total	1370	8	44	8	
Weight level results					
Above middle	216(15.80)	1(12.50)	8(18.20)	1(12.50)	
Average positive	428(31.20)	2(25.00)	11(25.00)	4(50.00)	
Average negative	337(24.60)	3(37.50)	15(34.10)		**0.394**
Below middle	161(11.80)	2(25.00)	7(15.90)	2(25.00)	
Low	228(16.60)		3(6.80)	1(12.50)	
Total	1370	8	44	8	

3.2. The Relationship between Maternal and Infant Characteristics and Mental Responses

The overall mental responses of infants were categorized as follows: 124 (8.70%) showed normal responses, 208 (14.50%) had good responses, 841 (58.80%) had acceptable responses, and 64 (4.50%) had poor responses. On the other hand, a significant number of infants exhibited abnormal behaviors, including annoying noise (64, 4.50%), incessant annoying noise (30, 2.10%), crying and arguing (2, 0.10%), incessant crying and arguing (154, 10.80%), crying and making noise (5, 0.30%), and others (2, 0.10%). Table 4 presents a summary of these mental responses.

There was a significant association between poor mental responses and infants with birth weights ranging from 1 - 1.5 kg, 1.5 - 2.5 kg, and 2.5 - 4 kg ($p < 0.001$). Infants with normal or microcephalic head circumferences also showed a statistically significant association with poor mental responses ($p < 0.001$). Infants with low weight levels had poorer responses compared to those in the Above Middle, Average Positive, Average Negative, and Below Middle weight categories, with a significant association ($p < 0.001$). Regarding the anterior fontanelle, infants with a

normal anterior fontanelle had poor mental responses with a statistically significant association ($p < 0.001$). However, no statistically significant associations were found between gender ($p = 0.354$), maternal age ($p = 0.362$), gestational age ($p = 0.663$), birth length ($p = 0.978$), or delivery methods ($p = 0.616$) and general mental responses in infants. Table 5 provides a summary of the statistical relationships between maternal and infant factors and general mental responses in infants.

Table 4. Mental response in infants. (n = 1430).

Factor	n, %
Acceptable	841(58.80)
Good	208(14.50)
Normal	124(8.70)
Poor	58(4.50)
Annoying noise	30 (2.10)
Annoying noise incessantly	2(0.10)
Cry and argue	154(10.80)
Cry and argue incessantly	5(0.30)
Crying and making noise	2(0.10)

Table 5. (a) Association between Infants' birth features and Mental response outcomes. (b) Continuation of association between Maternal and Infants Factors with Infants' Mental response.

(a)						
	Birth weight (kg)					
Mental response	<1(n, %)	1 - 1.5(n, %)	1.5 - 2.5(n, %)	2.5 - 4 (n, %)	>4(n, %)	P-value
Acceptable	7(46.70)	38(45.80)	219(60.30)	553(59.50)	24(60.0)	
Good	2(13.30)	13(15.70)	53(14.60)	137(14.70)	3(7.50)	<0.001
Normal	1(6.70)	10(12.0)	35(9.60)	77(8.30)	1(2.50)	
Poor		8(9.60)	12(3.30)	42(4.50)	2(5.00)	
Annoying noise	1(6.70)		7(1.90)	21(2.30)	1(2.50)	
Annoying noise incessantly	1(6.70)		1(0.30)			
Cry and argue	3(20.0%)	12(14.50)	34(9.40)	96(10.30)	9(22.500)	
Cry and argue incessantly		2(2.40)	1(0.30)	2(0.20)		
Crying and making noise			1(0.30)	1(0.10)		
Total	15	83	363	929	40	
Head circumference results						
Mental response	Normal (n, %)	Macrocephaly (n, %)	Microcephaly (n, %)			
Acceptable	650(56.10)	9(42.90)	182(72.80)			
Good	198(17.10)	6(28.60)	4(1.60)			
Normal	106(9.10)		18(7.20)			
Poor	39(3.40)	1(4.80)	24(9.60)			<0.001
Annoying noise	25(2.20)	1(4.80)	4(1.60)			

Continued

Annoying noise incessantly	**1(0.10)**	**1(4.80)**				
Cry and argue	135(11.60)	3(14.30)	16(6.40)			
Cry and argue incessantly	3(0.30)		2(0.80)			
Crying and making noise	2(0.20%)					
Total	1159	21	250			
			Weight level results			
Mental response	Above middle (n, %)	Average positive (n, %)	Average negative (n, %)	Below middle (n, %)	Low (n, %)	
Acceptable	117(51.80)	228(51.20)	228(64.20)	110(64.00)	158(68.10)	
Good	62(27.40)	90(20.20)	38(10.70)	9(5.20)	9(3.90)	<0.001
Normal	16(7.10)	41(9.20)	31(8.70)	18(10.50)	18(7.80)	
Poor	3(1.30)	11(2.50)	13(3.70)	11(6.40)	26(11.20)	
Annoying noise	4(1.80)	14(3.10)	6(1.70)	3(1.70)	3(1.30)	
Annoying noise incessantly		1(0.20)	1(0.30)			
Cry and argue	23(10.20)	58(13.00)	37(10.40)	19(11.0)	17(7.30)	
Cry and argue incessantly	1(0.40)	1(0.20)	1(0.30)	1(0.60)	1(0.40)	
Crying and making noise		1(0.20)		1(0.60)		
Total	226	445	355	172	232	
			Anterior fontanelle results			
Mental response	Normal (n, %)	Enlarged (n, %)	Sunken (n, %)	Closed (n, %)	Not closed (n, %)	
Acceptable	821(60.30)	2(100)	3(37.50)	8(27.60)	7(24.10)	
Good	184(13.50)		4(50.00)	9(31.00)	11(37.90)	
Normal	120(8.80)			2(6.90)	2(6.90)	
Poor	63(4.60)		1(12.50)			
Annoying noise	27(2.00)			3(10.30)		
Annoying noise incessantly	1(0.10)			1(3.40)		<0.001
Cry and argue	139(10.20)			6(20.70)	9(31.00)	
Cry and argue incessantly	5(0.40)					
Crying and making noise	2(0.10)					
Total	1362	2	8	29	29	
			(b)			
			Maternal age (years)			
Mental response	20 - 24(n, %)	25 - 34(n, %)	35 and above (n, %)	**P-value**		
Acceptable	16(57.10)	672(59.10)	153(57.70)			

Continued

Good	**2(7.10)**	**167(14.70)**	**39(14.70)**	
Normal	4(14.30)	101(8.90)	19(7.20)	**0.362**
Poor		55(4.40)	9(3.00)	
Annoying noise	1(3.60)	18(1.60)	11(4.20)	
Annoying noise incessantly		2(0.20%)		
Cry and argue	5(17.90)	115(10.10)	34(12.80)	
Cry and argue incessantly		5(0.40)		
Crying and making noise		2(0.20)		
Total	28	1137	265	
		Gender		
Mental response	Female (n, %)	Male (n, %)		
Acceptable	364(60.90)	477(57.30)		
Good	80(13.40)	128(15.40)		
Normal	55(9.20)	69(8.30)		**0.354**
Poor	28(4.70)	36(4.30)		
Annoying noise	13(2.20)	17(2.00)		
Annoying noise inces-santly	1(0.20)	1(0.20)		
Cry and argue	54(9.00)	100(12.00)		
Cry and argue incessantly	1(0.20)	4(0.50)		
Crying and making noise	2(0.30)			
Total	598	832		
			Gestational age (weeks)	
Mental response	< 32(n, %)	32 - 36(n, %)	37 - 42(n, %)	
Acceptable	81(52.30)	269(60.70)	491(59.00)	
Good	23(14.80)	66(14.90)	119(14.30)	
Normal	14(9.00)	35(7.90)	75(9.00)	**0.663**
Poor	9(5.80)	16(3.60)	36(4.30)	
Annoying noise	4(2.60)	10(2.30)	16(1.90)	
Annoying noise incessantly	1(0.60)		1(0.10)	
Cry and argue	21(13.50)	42(9.50)	91(10.90)	
Cry and argue incessantly	2(1.30)	1(0.20)	2(0.20)	
Crying and making noise		1(0.20)	1(0.10)	

Continued

Total	**155**	**443**	**832**	
			Birth length	
Mental response	AGA (n, %)	SGA (n, %)	LGA (n, %)	
Acceptable	581(58.60)	239(59.30)	21(60.00)	
Good	147(14.80)	55(13.60)	6(17.10)	
Normal	90(9.10)	31(7.70)	3(8.60)	**0.978**
Poor	42(4.20)	21(5.20)	1(2.90)	
Annoying noise	23(2.30)	6(1.50)	1(2.90)	
Annoying noise incessantly	1(0.10)	1(0.20)		
Cry and argue	105(10.60)	46(11.40)	3(8.60)	
Cry and argue incessantly	2(0.20)	3(0.70)		
Crying and making noise	1(0.10)	1(0.20)		
Total	992	403	35	
			Delivery method	
Mental response	Spontaneous vaginal delivery	Caesarean section	Forceps delivery	
Acceptable	258(55.50)	578(60.30)	5(83.30)	
Good	70(15.10)	138(14.40)		
Normal	43(9.20)	81(8.40)		
Poor	25(5.40)	38(4.00)	1(16.70)	**0.616**
Annoying noise	8(1.70)	22(2.30)		
Annoying noise incessantly	2(0.40)			
Cry and argue	56(12.00)	98(10.20)		
Cry and argue incessantly	2(0.40)	3(0.30)		
Crying and making noise	1(0.20)	1(0.10)		
Total	465	959	6	

4. Discussion

4.1. Prevalence of Gestational Diabetes Mellitus

The present study found that gestational diabetes mellitus (GDM) has a significant impact on both the neurodevelopmental and mental development of infants. In our sample, 68.65% of the participants were affected by GDM. These findings on the prevalence of GDM differ from those reported in previous studies. Binbin Yin *et al.* reported that the prevalence of gestational diabetes mellitus (GDM) after the COVID-19 pandemic changed to 21.46%, 19.81%, and 18.48% in the years 2019, 2020, and 2021, respectively [32]. Wei *et al.* in the retrospective study which in-

cluded 3211 singletons of mothers with GDM at the Shanghai First Maternity and Infant Hospital between January 2017 and December 2019 found that the prevalence of GDM was 7% [33]. However, Chenghan Gao *et al*. found an incidence of GDM in mainland China at 14.8% [34]. The prevalence of gestational diabetes mellitus (GDM) has been consistently rising over the past few decades and is expected to keep increasing [35]. In China, the risk factors for gestational diabetes mellitus (GDM) include advanced maternal age, being overweight or obese before pregnancy, excessive weight gain during pregnancy, certain dietary habits, smoking, exposure to secondhand smoke, higher parity, a previous history of GDM, a history of fetal macrosomia, polycystic ovarian syndrome, a family history of diabetes, lower levels of education, and limited health knowledge [35]. Globally, Behboudi-Gandevani *et al*. found that the overall pooled prevalence of gestational diabetes mellitus (GDM), regardless of screening thresholds, was 4.4%. However, when the diagnostic thresholds based on IADPSG criteria were applied, the pooled prevalence rose to 10.6%. A similar pattern was observed, with significant regional variation in GDM prevalence. East Asia had the highest prevalence at 11.4%, while Australia had the lowest at 3.6%, regardless of the screening criteria used [36]. In Switzerland, a retrospective cohort study showed a notable increase in the prevalence of gestational diabetes mellitus (GDM) when the IADPSG criteria were applied. The prevalence rose from 3.3% using a 2-step screening approach to 11.8% with a 1-step screening method [37]. Early identification of high-risk individuals is essential, as it enables the implementation of preventive measures that can help reduce the incidence of gestational diabetes mellitus (GDM) and improve perinatal outcomes. In China, prioritizing prevention and intervention for GDM is critical. Effective strategies for managing and preventing GDM include lifestyle changes such as improving diet and increasing physical activity. The GDM One-day Care Clinic, established in 2011, has become a successful model for managing GDM. It offers patient education on the basics of GDM, dietary modifications, exercise plans, weight control, and blood glucose monitoring. This model has been widely adopted in hospitals and maternal and child health centers throughout China [35].

4.2. The Effect of Gestational Diabetes Mellitus on the Neurodevelopmental Outcomes of Infants

In this study, the overall DDST II results showed 1370 (95.80%) normal, 8 (0.60%) abnormal, 44 (3.10%) suspicious, and 8 (0.60%) unable to judge. Our results differed from those of Seyhan *et al*., who, in their study of 1000 subjects, reported that 741 (74.1%) had normal findings, 140 (14%) were considered at risk, and 119 (11.9%) had abnormal findings based on the DDST results [38]. Likewise, in their study, Meltem *et al*. found that the DDST-II results for Turkish children indicated that 82.1% had normal findings, 10.7% had questionable results, and 7.1% were categorized as abnormal [39]. In contrast, the study by Ibrahim *et al*. found that 134 subjects (38.5%) had normal results, 136 subjects (39%) had abnormal results,

and 78 subjects (22.4%) had questionable results on the DDST [40].

Gender showed no statistically significant association with neurodevelopmental outcomes. Similarly, a study by Ozkan *et al.* reported no differences between genders concerning DDST results for children aged 3 to 60 months [41]. While it is widely recognized that developmental disorders are more common in males, our study differed from Seyhan *et al.*'s study, which found that males were more likely to have suspicious and abnormal DDST findings compared to females [38]. Similarly, Xiang *et al.* discovered that male infants born to mothers with gestational diabetes were at a higher risk for certain neurodevelopmental issues, such as cognitive delays and behavioral problems, compared to female infants. This study suggests that gender differences may influence the neurodevelopmental outcomes of infants born to mothers with gestational diabetes [9].

Infants with normal anterior fontanelles showed suspicion, abnormal findings, and an inability to judge neurodevelopmental outcomes compared to those with abnormal anterior fontanelles. Our study aligns with previous research, which suggests that despite having normal anterior fontanelles, these infants may still raise concerns for potential neurodevelopmental issues due to underlying metabolic and environmental factors linked to gestational diabetes. Infants born to mothers with gestational diabetes are exposed to maternal hyperglycemia during crucial periods of fetal development, which can have lasting effects on neurodevelopment, regardless of the status of the anterior fontanelle. Additionally, subtle neurodevelopmental delays may not always be evident right away and may require long-term monitoring to detect cognitive, motor, or behavioral delays that might not be apparent during early assessments. Furthermore, the impact of gestational diabetes on neurodevelopment can vary among infants, and those with normal anterior fontanelles may still be at risk for developmental challenges due to individual genetic factors, environmental influences, and the severity of maternal diabetes [42]-[44].

Infants born at a gestational age between 32 and 42 weeks showed a higher number of abnormal and suspicious neurodevelopmental outcomes. A similar study found that neurodevelopmental impairments were most common at 32 weeks (the earliest gestational age), gradually decreased until 41 weeks, and were also more prevalent at 37 - 38 weeks (early term) compared to 39 - 40 weeks [45]. However, in their study, Hadden DR *et al.* found that early-onset gestational diabetes may have a greater impact on fetal growth and neurodevelopment than late-onset gestational diabetes [46]. Similarly, Ju Hyun Jin *et al.* in their study found that, while the highest rates of morbidities were observed in children born at the earliest gestational ages, those born moderate-to-late preterm also faced significantly more adverse neurodevelopmental outcomes compared to full-term children [47].

The mode of delivery (spontaneous vaginal, cesarean, or forceps delivery) showed no differences in neurodevelopmental outcomes in infants. Our results align with a previous study by Hanne Trap Wolf *et al.*, which found that the mode of delivery was not linked to neurodevelopmental impairments at 2 years of age [48]. Similarly, Yi-Ya Huang *et al.* used propensity scores and unit policies but

were unable to establish a statistically significant association between the mode of delivery and neurodevelopmental outcomes at 2 years of corrected age in perceivable singleton infants [49]. Moreover, Seyhan *et al.* in their study found no significant effect on DDST results regarding mode of delivery [38]. A possible explanation for this observation is that neurodevelopmental outcomes might not appear right away and could need long-term monitoring to properly evaluate.

Infants born from gestational Primiparous mothers showed greater neurodevelopmental impairments compared to multiparous. This could be because first-time mothers often experience longer labor and higher rates of instrumental deliveries (like forceps or vacuum), which may lead to birth trauma and subsequent neurodevelopmental challenges. Additionally, first-time parents tend to experience more stress and anxiety, which can adversely affect infant care and early development. However, Abubakar *et al.* suggested that with each additional pregnancy, the risk of negative developmental outcomes in later-born children increases [50].

Infants with normal head size and microcephaly exhibited more significant neurodevelopmental impairments compared to those with macrocephaly. A similar study found that a smaller head circumference was linked to lower cognitive scores during follow-up [51]. Similarly, Guellec I *et al.* in their longitudinal study that followed very preterm infants and found that head circumference at birth was strongly correlated with neurodevelopmental outcomes. Infants with smaller head circumference had higher rates of cognitive and motor delays [52]. Our study reinforces the importance of early head circumference as a predictor of neurodevelopmental outcomes. Moreover, careful monitoring of fetal growth—including head circumference measurements—can help identify infants born from gestational diabetic mothers who are at risk for later cognitive and motor impairments, allowing for early interventions and neurodevelopmental support.

Neurodevelopmental impairments were found to be statistically significant at a very early age, particularly before six months. A similar study by Bersain *et al.* indicated that neurodevelopmental outcomes were impacted as early as 3½ months in infants born to mothers with GDM. This suggests that more stringent diabetes control measures during pregnancy may be necessary to ensure the best neurodevelopmental outcomes. However, previous studies have reported that as preschool children get older, there tends to be an increase in abnormal developmental performance on the DDST [38] [53].

In terms of mental response, there were no differences observed based on the infants' gender. However, previous studies have indicated that female infants generally exhibit more advanced emotional regulation and social skills than males. Girls tend to engage more in social interactions and demonstrate higher levels of empathy, but they are also more likely to develop anxiety and depression later in life [54] [55]. However, Maenner *et al.* found that male infants are approximately four times more likely to be diagnosed with ASD than females. Male infants are at a greater risk for neurodevelopmental disorders like autism spectrum disorder (ASD) and ADHD, which can influence mental evaluation outcomes [56]. On the

other hand, Tamis-LeMonda *et al.* emphasized that parents tend to interact with boys and girls in distinct ways, which can influence their developmental paths and later evaluations [57]. This suggests that the relationship between gender and parenting styles can impact mental evaluation outcomes. Additionally, these findings highlight that gender differences in mental evaluations are shaped by a mix of biological, cognitive, social, and environmental factors.

Infants with microcephaly showed significantly better and worse mental outcomes in mental response compared to those with macrocephaly. Ornoy *et al.* reported that these children are more prone to exhibiting symptoms of ADHD and emotional challenges, regardless of their head circumference at birth [58]. But one study has linked larger head circumference with better emotional regulation and fewer behavioral issues, but these advantages don't seem to last into later childhood, indicating a complex relationship between prenatal growth patterns and postnatal outcomes [59]. Therefore, these findings suggest that while a larger head circumference in infants born to gestational diabetic mothers may offer some early mental benefits, the overall mental risk remains high due to the intricate interaction between prenatal metabolic conditions and postnatal environmental factors.

The mode of delivery showed no differences in mental response. Similar studies have found no statistically significant differences in mental outcomes between infants born via cesarean section and those born vaginally to mothers with GDM [60] [61]. However, Huang *et al.* found that children born via cesarean section to mothers with GDM were more likely to show behavioral problems and emotional difficulties than those born vaginally [62]. This link may be influenced by factors like changes in gut microbiota due to cesarean delivery, which can affect brain development and behavior.

Infants with a normal anterior fontanelle were found to have mental impairments compared to those with enlarged, small, closed, or open anterior fontanelles. A similar study by Kumar, M., & Dewan, P., reported that the size of the anterior fontanelle can vary significantly in healthy infants, and deviations from the typical size are more likely to signal potential issues rather than the normal size itself causing impairments [63]. This suggests that neurodevelopmental anomalies in infants with normal fontanelles could be linked to other underlying conditions that may not be immediately visible through fontanelle size alone.

Infants with Average positive and Average negative weight levels showed a higher likelihood of neurodevelopmental concerns compared to those with Above Middle, Below Middle, and Low weight levels. Our findings align with Taveras *et al.*, who found that infants with an average positive weight level experience rapid weight gain in the first six months, which is linked to a higher risk of obesity in later childhood and may affect cognitive and behavioral development [64]. Whilst, Belsky *et al.* found that higher birth weight was associated with better initial cognitive performance, but rapid postnatal weight gain was linked to higher risks of behavioral problems [65]. Infants with weight above the middle range typically do not show a high rate of suspicious neurodevelopmental outcomes unless there are

underlying health issues. Overweight infants might face metabolic challenges that could indirectly affect development.

Gestational age showed no significant difference for mental response in infants. However previous studies [66] [67], reported that, while full-term infants (37 - 42 weeks) of gestational diabetic mothers showed generally better outcomes than preterm infants, they still had a higher likelihood of poor mental outcomes compared to infants of non-diabetic mothers. Infants born late preterm and early term had higher rates of ADHD and other behavioral problems compared to those born at 39 - 42 weeks.

Infants with birthweights 1 - 1.5 kg, 1.5 - 2.5 kg and 2.5 - 4 kg showed significant poor mental outcomes compared to infants at birthweight <1 kg and >4 kg. Our study was consistent with previous studies, whereby, The EPIPAGE-2 study found that VLBW infants born to gestational diabetic mothers had higher rates of cognitive and behavioral problems at 5 years of age compared to infants with normal birth weights [68]. But, our study, differed from a study by Crume *et al*., who found that macrosomic infants had higher rates of metabolic syndrome, which was associated with lower cognitive function and increased behavioral problems in early childhood [69].

Infants with an AGA birth length demonstrated poorer mental outcomes compared to those with SGA or LGA birth lengths. One possible explanation for this finding in our study is that AGA infants may still experience unrecognized perinatal complications or less-than-ideal postnatal environments, both of which could negatively impact their neurodevelopment. Previous research indicates that factors such as socio-economic status, parental education, and the quality of postnatal care play a significant role in child development outcomes. For example, AGA infants might be more vulnerable to the negative effects of inadequate postnatal care and lower socio-economic conditions, whereas SGA or LGA infants may benefit from more focused interventions [70]. Another possible explanation is that some AGA infants may be at the lower end of the AGA spectrum, closer to the 10th percentile. These infants might experience less-than-ideal intrauterine growth, which isn't severe enough to be classified as SGA but could still influence their neurodevelopment. This mild form of growth restriction might be enough to affect cognitive outcomes, even if it doesn't meet the criteria for an SGA classification. One study found that SGA infants, who generally have shorter birth lengths, were more likely to have lower IQ scores at the age of 5 compared to those with birth lengths appropriate for their gestational age (AGA). Specifically, SGA infants experienced a notable decline in IQ and had a higher risk of scoring below 85. On the other hand, LGA infants did not exhibit significant differences in neurodevelopmental outcomes when compared to AGA infants [71].

Infants with low birth weights demonstrated notably poorer mental outcomes. A similar study by Chuhao Xi *et al.* found that low birth weight infants are generally at a higher risk for negative mental evaluation results [72]. This increased risk is often linked to factors such as undernutrition, health complications during the

prenatal and early postnatal periods, and less favorable growth environments. As a result, these infants are more likely to experience developmental delays and cognitive impairments compared to those with higher birth weights.

5. Conclusion

Gestational diabetes mellitus (GDM) has been steadily increasing in prevalence over recent decades and is expected to continue rising. This trend highlights the growing significance of GDM as a public health issue in China. Infants born to mothers with GDM exhibited a range of neurodevelopmental challenges and cognitive impairments, with some groups being more susceptible. While this study offers essential insights, it acknowledges several limitations. As a retrospective study, some critical data were unavailable to researchers. Therefore, our study did not include an analysis of the impact of maternal glycemic control, and infant glycemic control, with the concurrent neurodevelopmental outcomes. Additionally, the study population was demographically homogenous, which may limit the generalizability of the findings. Examining these factors could also provide an understanding of the effects of GDM on infants' neurodevelopmental outcomes. Future research needs to cover a wide geographical area and analyze maternal and infant glycemic control with the inclusion of therapies to expand upon these findings.

Authors' Contributions

The authors Maiko Charles Mkwambe, Youping Deng and Dongchi Zhao had full access to all the data and take responsibility of the integrity of the data and accuracy of the data analysis.

Concept and Design: Maiko Charles Mkwambe and Youping Deng.

Acquisition, analysis and interpretation of data: Maiko Charles Mkwambe.

Drafting of the Manuscript: Maiko Charles Mkwambe and Youping Deng.

Manuscript Review with critical Intellectual Contents: All authors.

Administrative, technical and material support: Youping Deng and Dongchi Zhao.

Supportive Supervision: Youping Deng and Dongchi Zhao.

Acknowledgements

We would like to express our sincere Gratitude to the Hospital Ethical Committee of Zhongnan Hospital of Wuhan University, for giving us permission to conduct our study. We would also like to extend our heartfelt appreciations to the Hospital General Practitioners of departments of Pediatrics and Obstetrics & Gynecology for their invaluable continuous support during data collection.

Ethics Consideration

This study was approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Kelun 2022042K) and exempted from signing the informed consent form.

Availability of Data and Materials

Data used to support the findings of this study are included in the article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

GDM	Gestational Diabetes Mellitus
DDST-II	Denver II Developmental Screening Test
NICU	Neonatal intensive care unit
BMI	Body Mass Index
WHO	Worl Health Organization
OGTT	Oral glucose tolerance test
OGCT	Oral glucose challenge test
aEVs	adipocyte-derived extracellular vesicles
HELLP syndrome	Hemolysis, elevated, liver enzymes, low platelet count syndrome
FPG	fasting plasma glucose
ADA	American Diabetes Association
IOM	Institute of Medicine
ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ADHD	Attention-deficit/hyperactivity disorder
VIM	Variability independent of the mean
LGA	Large-for-gestational-age
SGA	Small for gestational age
AGA	Appropriate for gestational age
PCOS	Polycystic ovarian syndrome
GCT	Glucose challenge test
HAPO study	Hyperglycemia and Adverse Pregnancy Outcomes study
ACOG	American College of Obstetricians and Gynecologists
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IDF	International Diabetes Federation
HI	Hyperinsulinism
IMGDs	intrauterine growth and development issues
BW	birth weight
IUFD	intrauterine fetal death
HTN	hypertension
COVID-19	Corona virus disease 2019
IUGR	Intrauterine growth restriction
ELBW	Extremely low birth weight
VLBW	Very low birth weight
LBW	Low birth weight
NBW	Normal birth weight
HBW	High birth weight
S.V.D	Spontaneous Vaginal Delivery
C.D	Caesarean Delivery
F.D	Forceps Delivery