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Original Research Article

Relation of Raised HbA1C Level with Congenital Deformity of Fetus Detected by Anomaly Scan in 2nd Trimester of Pregnancy in Diabetic Mother

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Abstract

Background: Pregnant women with pre-existing diabetes face an elevated risk of congenital anomalies in their offspring. However, research on the pattern of congenital anomalies and its correlation with blood sugar control in pre-gestational diabetic mothers is limited, especially in our country's context. This study investigated the association between elevated HbA1c levels and congenital anomalies in diabetes-related pregnancies. ***Objective:*** To assess whether raised HbA1c levels were linked to an increased incidence of congenitally deformed fetal outcomes in pregnancies affected by diabetes. ***Method:*** This cross-sectional study was conducted from August 2018 to September 2019 at the Department of Obstetrics and Gynaecology, DMCH. Women with pre-gestational diabetes were sequentially enrolled if they provided informed consent. Data, including HbA1c levels and anomaly scans, were collected at 18-24 weeks of gestation. Participants were divided into two groups based on HbA1c levels: Group-1 (elevated HbA1c) and Group-2 (normal HbA1c). Statistical analysis was performed using SPSS 22, with significance at $p<0.05$. ***Result:*** The mean ages of Group 1 and Group 2 were 31.60±2.89 & 30.51±2.99 (SD) years. Both groups were similar concerning age, residence, education, occupation, economic status, and BMI ($p>0.05$ in all factors). Mean HbA1C (%) of Group-1 and Group-2 were 8.57±2.22 & 6.18±0.20 ($p<0.001$), respectively. Congenital anomalies were more frequent in Group 1 (15.6 vs 2.2; $p<0.05$), and it is associated with high blood sugar levels ($p<0.001$) and with a previous history of anomalous babies in preceding pregnancies. ***Conclusion:*** Elevated HbA1c levels are associated with an increased incidence of congenital anomalies in pregnancies complicated by diabetes. This underscores the importance of strict glycemic control in pregnant women with pre-gestational diabetes to mitigate the risk of adverse fetal outcomes. Further, population-based studies are desired to validate these findings and inform clinical management strategies.

Keywords: Pre-gestational diabetes, HbA1c, Congenital anomalies, Glycemic control, Fetal outcomes.

INTRODUCTION

Diabetes has emerged as a global health concern, posing significant challenges due to its impact on mortality, disability, and economic burden [1]. The prevalence of diabetes in Asia has witnessed a notable surge, with varying incidence rates in pregnancy, reaching up to 10% depending on population samples and diagnostic criteria [2]. Gestational diabetes, a specific form of complicating pregnancy, has seen a marked increase, affecting approximately 16.9% of pregnancies globally, with the highest prevalence in Southeast Asia at 25%. Pregnancy introduces unique

metabolic demands, necessitating physiological changes, especially in glucose metabolism, to support both maternal and fetal requirements [3].

Role of HbA1c and Hyperglycemia in Congenital Anomalies

Mean HbA1c levels serve as reliable indicators of overall glycemic control during pregnancy, correlating closely with meal-related glucose measurements [4]. Hyperglycemia during the critical first trimester, coinciding with organogenesis, poses a heightened risk of congenital malformations, with an incidence as high as 8% in uncontrolled diabetic pregnancies, two to three times that of the general population [5]. Contrary to earlier beliefs, a negative correlation exists between severe hypoglycemia in the first trimester and the incidence of congenital malformations [6]. Animal experiments suggest the involvement of factors like maternal ketonemia, fetal zinc depletion, and inhibited somatomedin action in the etiology of malformations due to maternal diabetes [7].

Mechanism of Diabetic Embryopathy

Diabetic embryopathy primarily targets the yolk sac, with suggested mechanisms involving diminished phosphoinositide or arachidonic acid turnover. Prostaglandin deficiency adversely affects embryogenesis and membrane function, facilitating high glucose influx into cells and generating free radicals, causing morphological damage and embryonic lipid peroxidation. Prostanoid deficiency at a crucial fetal development stage contributes to embryonic malformations, creating a multifactorial origin for the high incidence of malformations in newborns of diabetic mothers [8].

Association of Elevated HbA1c with Adverse Pregnancy Outcomes

Elevated HbA1c is associated with increased risks of adverse pregnancy outcomes, including abortion, stillbirth, and congenital abnormalities [9]. Despite a broad range of acceptable A1C values around conception, up to 10 standard deviations above the reference level, studies suggest a positive association between even slightly raised A1C levels and an increased risk of major congenital abnormalities [10]. Establishing an A1C threshold below which further reduction doesn't improve fetal prognosis remains a critical research gap.

Importance of Screening and Management

Universal screening for abnormal glucose tolerance during the first and second trimesters is crucial for early detection and effective management. Aggressive treatment of mild carbohydrate intolerance in pregnancy has shown a correlation with decreased infant perinatal mortality and morbidity rates. The incidence of fetal structural defects due to maternal pregestational diabetes is significantly higher than in non-diabetic pregnancies, emphasizing the need for vigilant monitoring and management [11].

The escalating prevalence of diabetes in pregnancy, particularly in Asia, demands a comprehensive understanding of its implications on maternal and fetal health. Monitoring HbA1c levels, managing glycemic control, and elucidating the mechanisms behind diabetic embryopathy are crucial for preventing congenital anomalies and adverse pregnancy outcomes. Universal screening and effective management strategies are imperative for mitigating the risks associated with diabetes during pregnancy.

OBJECTIVES

General Objective

- To find out the association of raised HbA1c with congenitally deformed fetal outcome in pregnancy with diabetes

Specific Objective

- To detect the HbA1c level in patients with diabetes in 2nd trimester of pregnancy
- To detect fetal congenital anomaly by ultrasonogram at 18-20 weeks in pre-gestational diabetic patients with both high levels of HbA1c and normal HbA1c level
- To compare the rate of congenital anomaly between the high HbA1c level group and the normal HbA1c level group

MATERIALS AND METHODS

Study Design

This cross-sectional comparative study was conducted at the Department of Obstetrics and Gynaecology, DMCH, from August 2018 to September 2019. The study included 45 patients in each group attending the obstetric outpatient department. Eligible women who provided informed consent were consecutively enrolled and followed up with HbA1c and ultrasound profiles at 18-20 weeks to identify fetal congenital anomalies. Sample collection utilized purposive sampling techniques to represent the study population comprehensively.

Inclusion Criteria

- Pre-gestational diabetes (either has the previous document of her diagnosis or under anti-diabetic treatment starting before pregnancy) in 2nd trimester of pregnancy
- Age >18 and up to 35 years
- Provided informed consent

Exclusion Criteria

- Age more than 35 years
- Gestational diabetes mellitus
- Pregnancy with a congenital malformed baby without DM (such as TORCH infection positive, taking teratogenic or cytotoxic drugs, and exposure to radiation, which are the risk factors for congenital malfunction)
- Positive Smoking history

- Pregestational diabetes at 1st & 3rd trimester of pregnancy

Data Collection

The data collection was a one-year-two-month cross-sectional comparative study conducted at the DMCH outpatient department from August 2018 to September 2019; ethical clearance was obtained. Diabetic pregnant women attending the second trimester, precisely at 18-24 weeks, were assessed by the attending doctor and the principal investigator. After diagnosis confirmation, patients were informed about the study's aims, objectives, and procedures. Written informed consent, aligning with the Helsinki Declaration, was obtained. Subjects were purposively enrolled and categorized into Group 1 (HbA1c >6.5%) and Group 2 (HbA1c <6.5%). TORCH antibody screening and anomaly scans were performed, and the investigator collected data through interviews and examination. Congenital anomalies were recorded from anomaly scan reports, and respondents' socio-demographic profiles were documented to analyze the association between HbA1c levels and fetal outcomes comprehensively.

Data Analysis

Statistical analyses were performed using the window-based computer software Statistical Packages for Social Sciences (SPSS-22). The data collected from the study population were entered into a Microsoft Excel 2021 spreadsheet. A thorough assessment ensured data completeness, accuracy, and consistency before analysis. Exploratory data analysis included summarizing categorical variables through frequency tables and continuous variables using mean, median, percentiles, and standard deviation measures. Associations were determined using chi-squared tests and student t-tests when applicable. A significance level of $p<0.05$ was considered for statistical significance in each analysis. The results were effectively presented in tables, figures, and diagrams for comprehensive interpretation.

Ethical Consideration

The ethical approval of this study was paramount, with measures in place to minimize physical, psychological, social, and legal risks throughout all stages. Stringent safety protocols were followed, restricting data access to research personnel only. Ethical clearance was obtained from the DMCH authority, aligning with the Helsinki Declaration's principles. Patients were fully informed of the study's design and their right to withdraw consent at any time. Written consent was obtained from each participant voluntarily. Confidentiality was strictly maintained, with data anonymized during the presentation. Data analysis was conducted only on subjects completing the study with valid informed consent. As procedures were noninvasive, there were no safety concerns for patients or researchers. Additionally, there was no conflict of interest, and the study posed no additional burden on patients or service providers, aligning with routine hospital practices.

RESULTS

In this study, pregnant mothers who had pregestational diabetes were screened. The study population was sorted using measurement of HbA1C level at 2nd trimester of pregnancy. Those with HbA1C ≥ 6.5% were Group 1, and those with HbA1C < 6.5% were Group 2. A total of 45 cases and an equal number of Group 2 were included, adding up to a total sample of 90 participants.

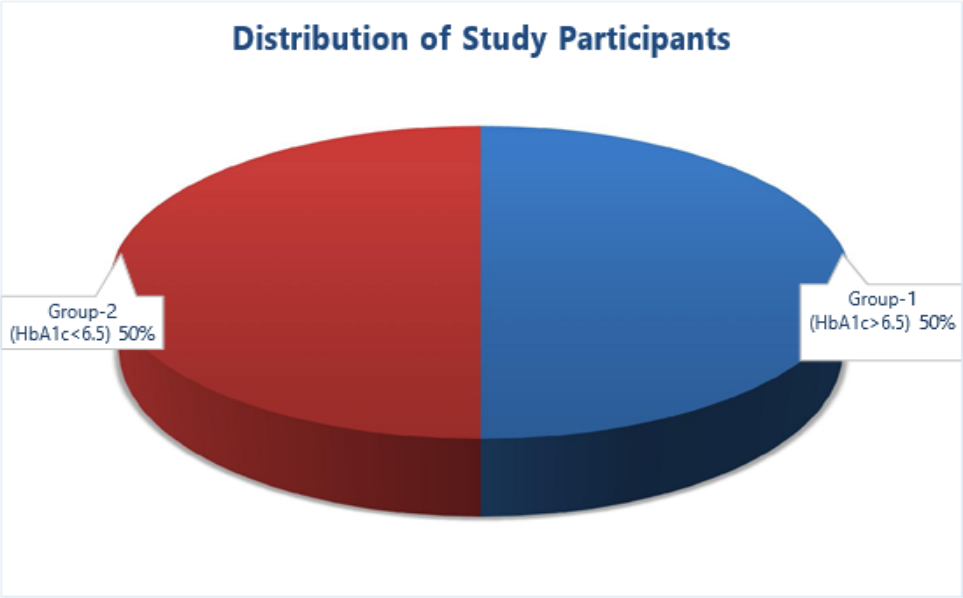

Figure 1: Distribution of study participants (n=90)

Table 1: Age distribution of study population (n=90)

Age (years)	Group-1 (n=45)	Group-2 (n=45)	Total (n=90)	p-value
18 – 25	1 (2.2%)	3 (6.7%)	4 (4.4%)	
26 – 30	10 (22.2%)	13 (28.9%)	23 (25.6%)	0.409
31 – 35	34 (75.6%)	29 (64.4%)	63 (70%)	
Mean±SD	31.60±2.89	30.51±2.99	31.06±2.98	0.083

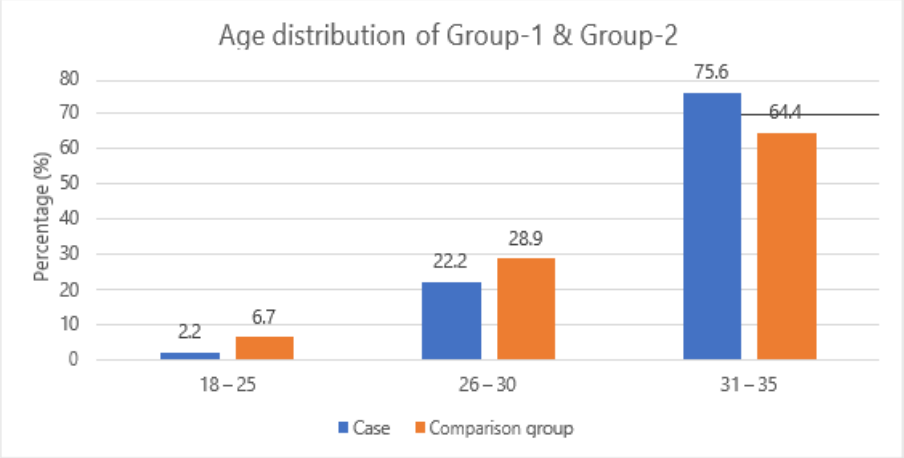

Figure 2: Age distribution of Group-1-Group-2

The mean age of all study subjects was 31.06±2.98 years. The mean age of Group-1s was 31.60±2.89, and that of Group-2 was 30.51±2.99 years. The difference was not statistically significant (p>0.05). Most participants were aged 31 – 35 years (70%). Distribution was similar across groups (p>0.05).

Table 2: Demographic and Clinical Characteristics of Study Population (n=90)

Characteristic	Group-1 (n=45)	Group-2 (n=45)	Total (n=90)	p-value
Residence				
Rural	16 (35.6%)	18 (40.0%)	34 (37.8%)	0.664
Urban	29 (64.4%)	27 (60.0%)	56 (62.2%)	
Educational Qualification				
Primary	7 (15.6%)	8 (17.8%)	15 (16.7%)	0.885
Secondary	18 (40.0%)	19 (42.2%)	37 (41.1%)	
Higher Secondary	11 (24.4%)	8 (17.8%)	19 (21.11%)	
Graduation	6 (13.3%)	5 (11.1%)	11 (12.2%)	
Illiterate	3 (6.7%)	5 (11.1%)	8 (8.9%)	
Occupation				
Housewife	33 (73.3%)	32 (71.1%)	65 (72.2%)	0.919
Government Service	6 (13.3%)	8 (17.8%)	14 (15.6%)	
Private Service	3 (6.7%)	2 (4.4%)	5 (5.6%)	
Others	3 (6.7%)	3 (6.7%)	6 (6.7%)	
Economic Status				
Good	14 (31.1%)	8 (17.8%)	22 (24.4%)	0.315
Average	27 (60.0%)	31 (68.9%)	58 (64.4%)	
Poor	4 (8.9%)	6 (13.3%)	10 (11.1%)	
BMI				
Normal (18.5 – 24.9)	12 (26.7%)	19 (42.2%)	31 (34.4%)	0.219
Overweight (25 – 29.9)	30 (66.7%)	25 (55.6%)	55 (61.1%)	
Obese (≥ 30)	3 (6.7%)	1 (2.2%)	4 (4.4%)	
History of ANC				
Regular	34 (75.6%)	29 (64.4%)	63 (70.0%)	0.503
Irregular	6 (13.3%)	8 (17.8%)	14 (15.6%)	
None	5 (11.1%)	8 (17.8%)	13 (14.4%)	
History of Congenital Anomaly Baby				
Present	3 (6.7%)	2 (4.4%)	5 (5.6%)	0.645
Absent	42 (93.3%)	43 (95.6%)	85 (94.4%)	

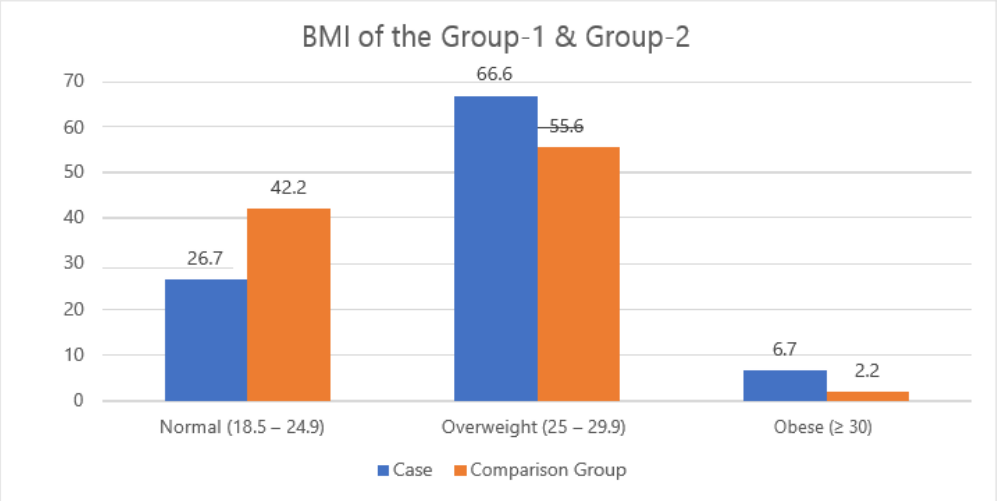

Figure 3: BMI of the Group-1-Group-2

The characteristics of the study population (n=90) were analyzed based on various factors. Most participants were from urban areas (62.2%), with a comparable distribution across groups (p=0.664). Educational qualifications varied, with secondary education being the most common (41.1%). Homemakers constituted the majority of occupations (72.2%), showing a similar distribution between groups (p=0.919). The economic status was predominantly average (64.4%), with no significant difference between groups (p=0.315). Most participants had an overweight BMI (61.1%), while 34.4% had a normal BMI. Regular antenatal care was prevalent (70%), and a history of congenital anomaly babies was present in 5.6% of cases. These demographic characteristics provide insights into the diversity of the study population, laying the groundwork for further analysis of their impact on pregnancy outcomes.

Table 3: Glycemic Profile of Study Population at 2nd Trimester of Pregnancy (n=90)

Glycemic Profile	Group-1 (n=45) Mean±SD	Group-2 (n=45) Mean±SD	p-value
HbA1C (%)	8.57±2.22	6.18±0.20	<0.001
FBS (mmol/l)	8.60±1.18	6.76±0.10	<0.001
2HABF (mmol/l)	12.91±2.08	10.90±0.06	<0.001

The glycemic profiles of Group-1 (n=45) and Group-2 (n=45) reveal significant differences in key parameters. Group-1, with higher HbA1C levels (8.57±2.22%), also exhibited elevated FBS (8.60±1.18 mmol/l) and 2HABF (12.91±2.08 mmol/l) compared to Group-2 (HbA1C: 6.18±0.20%, FBS: 6.76±0.10 mmol/l, 2HABF: 10.90±0.06 mmol/l) (p<0.001 for all). These findings underscore the impact of glycemic control on pregnancy outcomes, emphasizing the importance of managing blood glucose levels in diabetic pregnancies.

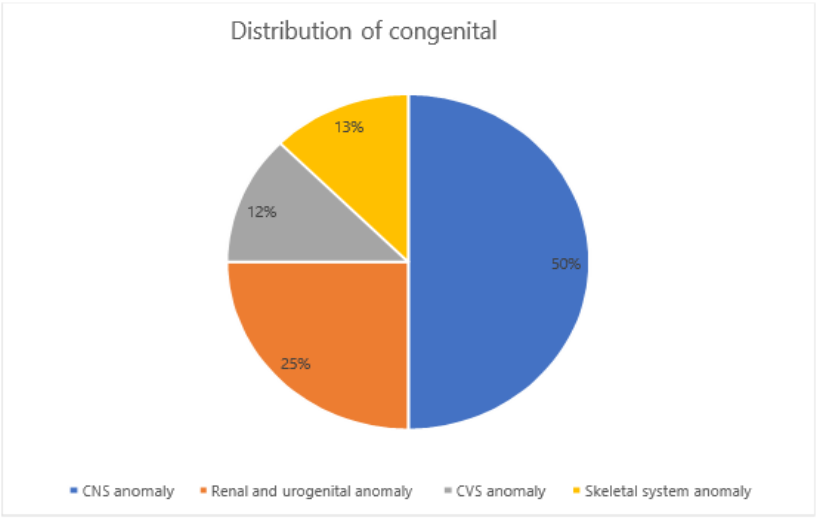

Figure 4: Type of congenital anomaly detected on the scan

The distribution of congenital anomalies detected on scans among the study population (n=8). The most prevalent anomalies involve the Central Nervous System (CNS), with 50% of cases including anencephaly and hydrocephalus. Other identified anomalies include renal and urogenital anomalies (25%), cardiovascular system (CVS) anomalies (12.5%), and skeletal system anomalies (12.5%). This information emphasizes the diverse impact of maternal diabetes on fetal development, underscoring the importance of monitoring and managing glycemic control during pregnancy.

DISCUSSION

This comprehensive study, encompassing 90 pregnant women with a history of diabetes, delves into various dimensions of diabetes during pregnancy, including demographic characteristics, BMI distribution, congenital anomalies, and the impact of glycemic control on fetal outcomes. By thoroughly analyzing these factors, we aim to unravel the intricate interplay between diabetes and pregnancy outcomes, providing valuable insights for clinical practice and interventions geared toward enhancing maternal and fetal health.

The mean age of the participants in this study aligns with prior research, indicating a prevalent age range of 31-35 years, corresponding to a higher incidence of diabetes in this age group. This underscores the significance of age as a risk factor for diabetes in pregnancy and emphasizes the necessity for targeted interventions among women in this age bracket to mitigate associated risks [12].

Demographic characteristics such as urban residence, educational level, and socioeconomic status play a pivotal role in the prevalence and management of diabetes in pregnancy. Most participants in this study were urban housewives with an average socioeconomic status, reflecting patterns observed in similar studies. Urbanization and higher educational attainment have been associated with an increased risk of diabetes, highlighting the need for tailored interventions and healthcare strategies targeting these populations. In this study, 62.2% were from urban areas, and 41.1% had up to a secondary level of education [13].

Body Mass Index (BMI) distribution among the participants revealed a significant proportion with overweight status (25-29.9), consistent with findings from other investigations. The association between diabetes in pregnancy and higher BMI underscores the importance of weight management and lifestyle modifications in mitigating the risks associated with gestational diabetes. Healthcare providers should prioritize counseling on healthy eating habits and physical activity to promote optimal maternal and fetal health outcomes. In this study, 61.1% of the patients had a BMI between 25-29.9 (overweight) [14-16].

Anomaly ultrasound scans revealed a noteworthy incidence of congenital anomalies among the study participants. Group-1, characterized by higher HbA1C levels, exhibited a substantially elevated rate of anomalies compared to Group-2, emphasizing the critical role of glycemic control in reducing the risk of congenital anomalies. These findings are consistent with previous research highlighting the correlation between poor glycemic control and adverse pregnancy outcomes, including congenital anomalies. The recurrence of anomalies among mothers with a history of congenitally abnormal babies underscores the importance of preconception counseling and close monitoring during subsequent pregnancies. In this study, 8.9% of the participants had fetuses with congenital anomalies, with 15.6% in Group-1 and 2.2% in Group-2. Thus, diabetic mothers with high HbA1c levels had a sevenfold higher risk of having fetuses with congenital anomalies [17, 18].

The study's focus on HbA1C levels is pivotal, with Group-1 exhibiting significantly higher mean HbA1C values than Group-2. This association underscores the importance of glycemic control in reducing the risk of adverse pregnancy outcomes. Studies have consistently demonstrated that poor glycemic control is associated with an increased risk of congenital anomalies and other adverse pregnancy outcomes. Healthcare providers should prioritize glycemic control through lifestyle modifications, medication management, and regular monitoring to optimize maternal and fetal health outcomes. In this study, the mean HbA1C value of Group-1 was 8.57±2.22, and that of Group-2 was 6.18±0.20. The difference in mean HbA1C levels between mothers of fetuses with congenital anomalies and those with normal fetuses was statistically significant ($p<0.001$). Additionally, the differences in FBS and 2HABF glucose levels between these two groups were also statistically highly significant ($p<0.001$) [19,20].

Analyzing the types of congenital anomalies observed among the study participants provides valuable insights into the spectrum of abnormalities associated with diabetes in pregnancy. This study's predominant central nervous system (CNS) anomalies differ from the cardiovascular system anomalies reported in some studies. However, the variation in findings across studies underscores the complex nature of anomalies associated with pregestational diabetes. Future research should focus on elucidating the underlying mechanisms contributing to specific anomalies to inform targeted interventions and management strategies. In this study, 50% of the congenital anomaly fetuses had CNS anomalies, 25% had renal and urogenital system anomalies, 12.5% had cardiovascular anomalies, and 12.5% had skeletal urogenital anomalies [21, 22].

Despite its contributions, this study has several limitations that warrant consideration. Its hospital-based nature and relatively small sample size limit the

generalizability of the findings. Future research should aim to replicate these findings in larger, more diverse cohorts to enhance the robustness and applicability of the results. Further investigation is needed to elucidate the molecular mechanisms underlying the observed associations between diabetes in pregnancy and adverse outcomes. By addressing these limitations, future research can contribute to a more comprehensive understanding of the complex interplay between diabetes and pregnancy outcomes and inform targeted interventions to improve maternal and fetal health.

Although this study has provided valuable insights into the relationship between diabetes in pregnancy and adverse outcomes, further research is desired to validate and expand upon these findings. Healthcare providers should leverage these insights to develop personalized care plans that prioritize glycemic control, lifestyle modifications, and close monitoring for pregnant women with diabetes, thereby optimizing maternal and fetal health outcomes. The imperative role of cancelation through tailored interventions is underscored, and the findings indicate a need for a multifaceted approach to address the complex web of factors influencing pregnancy outcomes in the context of diabetes.

CONCLUSION

In a study, elevated HbA1C levels in mothers with diabetes mellitus are linked to a higher risk of congenital anomalies in their offspring, particularly in cases with a history of anomalous babies. However, caution is desired due to study limitations such as a small sample size and single-center confinement. Central nervous system anomalies were most prevalent among the anomalies observed, emphasizing the need for targeted interventions to mitigate these risks.

Recommendation

- Further population-based study is recommended to finalize the result
- Diabetes mothers should be cautious with sugar control before and during the pregnancy
- Fetal ECHO should be included to diagnose the CVS anomaly
- Proper antenatal care should be sought

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