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Original Article

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The Effect of Teamwork Training on Missed Nursing Care among NICU Nurses during the COVID-19 Pandemic

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ABSTRACT

Background: Missed nursing care can cause considerable problems in patients' treatment processes. One way to reduce it and patient safety is teamwork training for nurses. This study aimed to determine the effect of teamwork training on missed nursing care among the nurses in Neonatal Intensive Care Unit (NICU).

Methods: This quasi-experimental study was performed in 2021 (during the COVID-19 pandemic) on 20 nurses working in NICU. Teamwork training was done using the Team STEPPS method. The missed nursing care questionnaire was completed before, immediately and one month after the intervention.

Results: The mean score of missed nursing care decreased from 72.7 ± 4.78 before the intervention to 53.5 ± 6.81 immediately after that, and the difference was statistically significant ($P < 0.01$). The mean score of missed nursing care was 58.2 ± 5.51 one month after the intervention, which was significantly different from that immediately after the intervention ($P < 0.02$).

Conclusion: Teamwork training had a considerable impact on reducing missed nursing care during the COVID-19 pandemic in NICU. Also, too many processes related to admission and discharge is the most important factor that resulted in missed nursing care. We suggest that other tools be utilized to measure the amount of teamwork among nurses in the future. It is recommended to consider teamwork training courses for nurses as a necessary part of in-service training. Conducting teamwork training workshops for nursing students can provide them the knowledge necessary to use teamwork strategies and tools to meet those challenges.

Introduction

The neonatal period refers to the first 28 days of life and is important because most infant deaths in the first year of life occur in the neonatal period.[1] Neonatal mortality accounts for 45% of mortality in children under five[2], and late fetal and early infantile stage is the period of life that has the highest mortality rate compared to other age groups.[3] The neonatal nurse is the first person to identify the potential dangers and critical situations of the neonates and take action to eliminate them and not performing the nursing procedures correctly will have irreparable consequences.[4] Therefore, specialized nursing care plays an important role in the survival and health of infants.[3]

Nurses in NICUs face a variety of challenges that can lead to inadequate care and the emergence of numerous problems and difficult conditions for the growth and development of infants. Care challenges in NICUs can be divided into four categories of interactions (professional interactions, interactions with families, interactions with infants), care (routine care, understanding the need for developmental care, and the conflict between traditional and developmental care), NICU structure (non-compliance with physical and equipment standards, survival or mortality causes), nurses' competency (insufficient proficiency and inappropriate employment).[5] Sometimes nurses realize that it is impossible to fully provide the required nursing care and choose not to perform all the steps and aspects of a nursing care for various reasons, and this leads to a phenomenon called missed nursing care.[6]

Missed nursing care is any type of necessary patient care that is overlooked or significantly delayed. This index is operationally evaluated based on the number of times that nurses have not performed nursing services.[7] The concept of missed nursing care was first introduced by Kalisch in 2006, who in a qualitative study, identified nine important missed nursing care types including ambulation, turning, delayed or missed feedings, educating patients, discharge planning, emotional support, hygiene, intake and output documentation, and surveillance.[8] In NICUs, some degree of missed nursing care has been reported and evaluated. In a study on self-reporting of missed nursing care in NICUs, attention to daily rounds, evaluating the effects of medications 30-60 minutes after injection or according to the protocol, and feeding infants with hunger symptoms were identified as missed nursing care frequently reported by nurses. These nurses identified repeated interruptions in the provision of care for various reasons, the urgency of a patient's condition, an unexpected increase in the number of patients admitted to the ward, or critically ill patients as the main reasons for missed nursing care.[9] In a study in 2016, Tubbs-Cooley examined NICU wards in Magnet hospitals for differences in the amount of missed nursing care compared to non-Magnet hospitals, and concluded that there were missed nursing care in NICUs of Magnet hospitals, too, and they are no different from non-Magnet hospitals.[10] In a study in the NICUs of six hospitals in Nairobi, Gathara et al. reported that at least 80% of nursing care was provided to only 14% of neonates, with neonatal visits and non-assessments during phototherapy as the most missed nursing care.[11] Also, nurses in a study reported lack of sufficient time as the main cause of missed nursing care.[12]

Tubbs-Cooley and co-workers have reported a significant association between missed nursing care and patients' treatment processes. When nurses substitute oral feeding with gavage feeding for reasons not related to the newborn's clinical condition (no action is taken by nurses to start oral feeding at the appropriate time), it takes significantly more days for the infant to fully develop its oral feeding ability and subsequently be discharged from the NICU.[13] Other studies also found that missed nursing care reduces the overall quality of patient care, job satisfaction of the nurse[14,15], patient

satisfaction with the treatment process[15,16], increases the risk of unwanted complications[17], lost length of stay, and the possibility of readmission.[14]

In general, missed nursing care is one of the important indices of the quality of nursing care.[8] As a result, it is important to study the factors that affect it and improve nursing care. On the other hand, other studies have demonstrated the essential role of teamwork in reassuring patients of safety and quality of care.[18] According to a qualitative study, the conceptual analysis of teamwork in healthcare is a dynamic process consisting of two or more individuals with appropriate healthcare skills and backgrounds who share common health goals and seek to assess, plan, or evaluate patient care in a coordinated manner, both physically and mentally.[19] Effective teamwork in nursing makes a significant contribution to improving the quality of healthcare by reducing errors[20,21], missed nursing care[22], the time required to do procedures[23], improving communication between patients, families, and therapists.[24] In a study on Icelandic nurses, Bragadóttir et al. concluded that missed nursing care, in addition to being significantly associated with age, place of work and shortage of nursing staff, also had a significant inverse relationship with the amount of teamwork.[25] One study reported that 66% of nurses had a positive attitude towards teamwork, and this can help identify roles and responsibilities, creating transparency at work, and increasing the quality of nursing care.[26]

Considering the importance and impact of missed nursing care on patients' treatment outcomes and the scanty studies on the impact of teamwork on reducing missed nursing care, especially in NICUs in Iran, the present study aimed to determine the effect of teamwork training with team STEPPS method on missed nursing care and its related factors among NICU nurses during the COVID-19 pandemic.

Materials and Methods

This quasi-experimental study was conducted on 20 NICU nurses in the Bushehr Shohadaye Khalije Fars Hospital in 2021(during the COVID-19 pandemic). Due to the small size of statistical population, the census method sampling was used, and the questionnaire was distributed to the total statistical population before, immediately after, and one month after the intervention.

The inclusion criteria were having at least two months of work experience in the NICU, willingness to participate in the study, and not attending a teamwork training course in the last six months. The exclusion criteria were failure to answer the questionnaire items, working in auxiliary shifts at the NICU (very few working shifts and only when needed), and the end of the service period before the end of the study.

Data collection tool was a questionnaire to assess missed nursing care in the NICU and the questionnaire was answered based on the latest working shift of the nurse because in the last shift, nurses remember more accurately the missed nursing care compared to the previous shifts. The Missed Nursing Care Survey (MISSCARE Survey) in adult's wards was developed by Kalisch and Williams in 2009. It has three parts: Items on demographic characteristics and job satisfaction of nurses, items on the frequency of missed nursing care in the relevant wards (Section A) and items on the reasons for missed nursing care in the wards (Section B). Cronbach alpha values ranged from 0.64 to 0.86. Confirmatory factor analysis demonstrated a good fit of the data. Pearson correlation coefficient on a test-retest of the same subjects yielded a value of 0.87 on part A and 0.86 on part B.[27] In 2014, Tubbs-Cooley et al. modified the questionnaire according to the specific conditions and characteristics of the NICU. They retained the overall structure of the questionnaire but modified items in Section A according to the NICU's special care and added items to Section B based on feedback from NICU nurses.[9] To confirm the validity and reliability of the Persian version of the tool, Emami

et al. assessed the questionnaire by a qualitative review method by 20 nurses participating in two different health systems. The review continued until all participating nurses agreed on the content, meaning, and terms of the audit. The reliability of Section A and B was 87% and 86%, respectively. The questionnaire was also presented to ten professors of the School of Nursing and neonatologists, and after obtaining their comments, the validity of the questionnaire was checked again.[28]

In this study, the content of the training taken from the Team Strategies and Tools to Enhance Performance and Patient Safety (STEPPS) Team, resulted from more than two decades of research by the US to develop the best teamwork training system for medical staff.[29] Agency for Healthcare Research and Quality provides a set of flexible, evidence-based tools and strategies to improve patient safety and reduce missed nursing care through improving communication and other teamwork skills. Team STEPPS enhances teamwork skills in four main areas: leadership (ability to lead and coordinate team members, assign tasks, evaluate group performance, motivate subordinates, plan, organize and maintain a positive group environment); position control (tracking the performance of other team members to ensure that work goes on as expected and appropriate methods have been applied); mutual support (providing feedback and coaching to improve performance and assist a teammate in doing a task, when a mistake occurs, or completing the work of team members who have a high workload); and communication (start of the message by the sender, receipt and acceptance of the message by the recipient, and confirmation of the message by the original sender) (Table 1).[29]

The trainings were provided to the nurses by "train the trainer" technique, so that first the head nurse learned the necessary training in relation to teamwork using Team STEPPS method in two days in a thoroughly planned manner. Then he presented the trainings to the nurses for one month and in seven sessions, with the participation of the researcher, in the form of explaining and presenting the materials using PowerPoint™ and in combination with presenting different pre-designed scenarios and discussing them. For effective learning and in order to make enough time to discuss the topics, the number of participants in each session did not exceed 10 people, the length of the sessions was 1 hour and each topic was taught in two working shifts so that all nurses had the opportunity to attend the sessions. The purpose and content of each training session was as follows. MISSCARE survey was completed by nurses before, immediately after, and one month after the intervention. Table 1 shows the content of educational sessions for NICU nurses. This table was prepared based on MISSCARE Survey and modified the questionnaire by Tubbs-Cooley et al.[9] according to the specific conditions and characteristics of the NICU. Also, it was approved by four experts with PhD degree in healthcare services management.

The data were analyzed in SPSS software version 24. P value less than 0.05 was considered statistically significant. For qualitative variables, the chi-square test and Fisher's exact test were used, while for quantitative variables, paired t-test was used when the data were assumed to be normal, and Mann-Whitney non-parametric test was employed when the data did not follow a normal distribution.

All participants in the study were informed of the study objectives and signed a written informed consent form and were assured of the confidentiality of their personal information and the voluntary nature of participation.

Results

The mean age of nurses was 33.9 ± 6.36 years, the mean work experience was 95.3 ± 57.34 months, and the mean work experience in NICU was 53.7 ± 36.75 months. The maximum number of working shifts that nurses could have during a month was 24 shifts. Table 2 shows the results related to the demographic characteristics of nurses.

Table 1. The content of educational sessions for NICU nurses

Session	Purpose	Educational content
1	Introduction, acquaintance, and expression of purpose Introduction and review of teamwork	Familiarity with the staff and the initial practice of teamwork, training goals, training programs for future sessions, required training supplies, review of barriers to teamwork, introduction of Team STEPPS plan and how it was developed, the results of benefiting from effective teamwork skills and its characteristics.
2	Familiarity with the team structure and role of NICU nurses and other ward members in the neonatal care team	Defining the team, considering the infant and its family as a member of the care team, the responsibility of clinical teams towards infants and their families and how to communicate with them, the responsibility of the patient's family as members of the care team towards nurses, multi-team system for neonatal care, key members of the care team, teams designed for emergencies, coordinating teams, subordinate and support services, the role of hospital managers in the performance of care teams
3	Teaching how to communicate properly between NICU nurses	Explaining how communication affects team processes and outcomes of nursing care, defining a standard and effective communication, identifying challenges and shortcomings in communication between NICU nurses, learning the tools and strategies that can lead to communication improvement in NICU nursing teams
4	Leadership and crisis management training for NICU nurses	Teaching the extent and effect of leadership on team processes and outcomes of neonatal treatment, explaining the different types of team leadership, teaching activities that are effective in a successful team leadership, explaining the tools that should be used for team leadership in critical situations and the different scenarios in NICU
5	Training NICU nurses to effectively monitor and control situations	Explaining the extent and impact of effective nursing supervision on team processes and patient treatment outcomes, training STEP as a mental and reminiscent tool for NICU nurses to help effectively monitor critical situations and dominate the environment [including paying attention to the neonatal clinical condition, to team members, to the environment, and moving towards goals], continuous and very precise mindfulness training to monitor all neonatal changes, identifying barriers to NICU nurses for effective situational monitoring and awareness, creating a shared mental image of position monitoring and control among nurses.
6	Training NICU nurses to support each other	Explaining the extent and effect of mutual support of nurses on team processes and outcomes of neonatal treatment, teaching specific strategies to create and develop more mutual support among NICU nurses, determining specific tools to facilitate mutual support of nurses, explaining problem-solving strategies in the treatment setting
7	Summarizing the training provided in the previous six sessions and addressing nurses' problems	Nurses were asked to explain how and in what clinical context they use each of the tools and strategies learned in this training plan, and they were also given the opportunity to practice by creating simulated situations. Simultaneously with monitoring their performance, the observed problems were resolved.

Table 3 shows the mean missed nursing care. The mean missed nursing care was 72.7 ± 4.78 before the intervention, 53.5 ± 6.81 immediately after the intervention, and 58.2 ± 5.51 one month later (Table 3).

Based on the results of paired t-test (Table 4), there was a significant difference in the mean score of missed nursing care among the studied nurses between before the intervention and immediately after it (P = 0.01), and immediately after the intervention and one month later by t-test (P = 0.021).

Regarding the factors related to missed nursing care, the results showed that "large volume of activities related to admission and discharge" is the most important factor related to missed nursing care, so that the effect of this factor was considered "very important" by 95% of nurses before the intervention, 90% of them immediately after the training, and 80% of them a month later. Lack of time, lack of nursing staff, and large amount of information to be recorded were other important factors that for more than 70% of nurses before and after the intervention had a "very important" impact on the missed nursing care.

Table 2. Frequency distribution of demographic characteristics of the subjects

Variable	Component	N (%)	Variable	Component	N (%)
Mean number of shifts per month	16	1 (5)	Mean number of patients per shift	2	13 (65)
	20	6 (30)		3	7 (35)
	22	7 (35)		Total	20 (100)
	24	6 (30)			
	Total	20 (100)			
Type of working shifts	Morning	1 (5)	Last working shift (before intervention)	Morning	10 (50)
	Combined	19 (95)		Evening	4 (20)
	Total	20 (100)		Night	6 (30)
				Total	20 (100)
Number of patients in the last shift (before intervention)	2	11 (55)	Last working shift (immediate after intervention)	Morning	6 (30)
	3	8 (40)		Evening	7 (35)
	4	1 (5)		Night	7 (35)
	Total	20 (100)		Total	20 (100)
Number of patients in the last shift (immediate after the intervention)	2	6 (30)	Last working shift (one month after the intervention)	Morning	5 (25)
	3	13 (65)		Evening	6 (30)
	4	1 (5)		Night	9 (45)
	Total	20 (100)		Total	20 (100)
Number of patients in the last shift (one month after the intervention)	1	1 (5)			
	2	6 (30)			
	3	11 (55)			
	4	2 (10)			
	Total	20 (100)			

Table 3. Mean score of missed nursing care before, immediately and one month after the intervention

Group	Number	Mean ± SD
Before the intervention	20	72.7 ± 4.78
After the intervention	20	53.5 ± 6.81
One month after the intervention	20	58.2 ± 5.51

The findings of this study indicated that from the point of view of all nurses studied, lack of familiarity with equipment and procedures, lack of knowledge about job descriptions and lack of knowledge about the patient's need for care had no effect on missed nursing care.

Discussion

The findings of the present study showed that teamwork training for nurses can reduce missed nursing care. According to a study, missed nursing care has a significant and inverse relationship with the mean teamwork between nurses.[30] In the present study with purpose of determining the effect of teamwork training on missed nursing care among the nurses in Neonatal Intensive Care Unit (NICU), the researchers with complete awareness of this issue, tried to institutionalize "patient-centered" (and not nurse-centered) performance among NICU nurses.

It was well explained frequently during the trainings that although caring for patients in the ward was provided as case method, nurses should know that all members of the nursing team are responsible for all patients in one working shift and where necessary, they should prioritize work, interact and support other colleagues to provide complete patient care. Hajinabi et al. conducted a study aimed at determining the relationship between patient safety and teamwork among nurses and in a report consistent with the present study stated that teamwork and patient safety are directly related and increasing teamwork can reduce nursing errors.[31]

Table 4. Paired t-test results of the comparison of mean score of missed nursing care

Group	T statistic	Degrees of freedom	Significance level
Before the intervention - after the intervention	11.566	19	0.001
After the intervention - one month after the intervention	-2.523	19	0.021

Similar to the present study, Kalisch et al. taught teamwork with the "train the trainer" technique and suggested that teamwork has led to a reduction in missed nursing care. In their intervention, after designing different scenarios, they practically simulated them and practiced various group strategies by playing a role in different pre-designed situations. [32] Also, Kalisch designed the Nursing Teamwork Survey (NTS) tool to measure the amount of teamwork among nurses[33], and both he and other researchers used it to measure the amount of teamwork and its comparison with missed nursing care.[22,30,32,34] Regarding the factors related to missed nursing care, the results showed that from the point of view of NICU nurses, they were well acquainted with the equipment and procedures, considered all nursing care necessary to accelerate the process of healing newborns, and were well aware of their job descriptions. Therefore, these three components would not contribute to creating the ground for missed nursing care. From the nurses' point of view, the large volume of activities related to admission and discharge, lack of time to complete time-consuming care and lack of nursing staff can be very important reasons for missed nursing care as the nurses stated in the present study. Meanwhile the large volume of activities related to the admission and discharge of patients is the main factor for missed nursing care. In a study also stated exactly the same factors as the main reason for missed nursing care.[35] The present finding is also consistent with the results of some studies[7, 36-40], such that the importance of "nursing staff shortage" in causing missed nursing care did not reduce much even after providing teamwork training to nursing staff. This issue indicates the need for nursing managers in all decision-making levels to pay more attention to the lack of nursing staff, because otherwise it can have devastating effects on the treatment of patients and lead to more burnout of nurses.

Teamwork is a very important component that if nurses learn its skills and tools, their attitude towards the work environment and interaction with other colleagues will change and ultimately lead to improving the safety and treatment quality of patients. By teamwork training, nurses learn to direct patient care in critical situations, to support their colleagues when their workload increases or need help, to communicate clearly and securely with each other, constantly monitor ward conditions and ultimately share their understanding of patients' and ward condition with other colleagues.

Although in the present study, we tried to design diverse clinical scenarios and hold discussion about them to teach teamwork to nurses in a practical way, due to the lack of willingness of nurses in the study, simulation of different situations and role-playing by nurses was not conducted. Nonetheless, the researcher believes that practicing teamwork strategies and tools in the form of role-playing can lead to deeper and more stable learning in nurses.

Conclusion

Teamwork training had a considerable impact on reducing missed nursing care during the COVID-19 pandemic in NICU. Also, large volume of activities related to admission and discharge is the most important factor caused missed nursing care. We suggest that other tools be used to measure the amount of teamwork among nurses in the future. It is recommended to consider teamwork training courses for nurses as a necessary part of in-service training. By holding teamwork training workshops for nursing students, they can be provided with the knowledge needed to use teamwork strategies and tools to meet those challenge.

Conflict of Interest

The authors have no conflict of interest.

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Original Article

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Prevalence of Hypertrophic Cardiomyopathy in Neonates of Diabetic Mothers: A Six-month Follow-up Study

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Gestational diabetes

ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is known to be the most common cardiac disorder in fetuses of diabetic mothers, especially when diabetes is not controlled in pregnancy. This study aimed as to estimate the prevalence of HCM in neonates born to diabetic mothers and to evaluate therapeutic interventions with follow-up after six months. We also focused on the possible association of neonatal HCM with the maternal type of diabetes.

Methods: A cross-sectional study was conducted between October 2016, and September 2017, in the Cardiac Clinic of Yazd, a city in the center of Iran. The subjects were 150 neonates of mothers with diabetes. We determined HCM through fetal echocardiography before treatment and assessed the maternal and fetal factors. Finally, after a 6-month follow-up period, the data were analyzed statistically.

Results: According to the results, the prevalence of HCM in neonates of diabetic mothers was 14% ($P < 0.0001$). The results showed that there is a relationship between maternal uncontrolled diabetes and the incidence of HCM in the infant ($P < 0.0001$), but there is no relationship between the type of diabetes and the incidence of HCM. Our results also showed that propranolol was effective in improving HCM, and spontaneous recovery of HCM was low in infants.

Conclusion: We concluded that controlling maternal diabetes has the greatest effect on the prevention of HCM in neonates. Also, neonates of diabetic mothers need more heart tests and follow-ups. Therefore, more studies on the effects of maternal diabetes-induced HCM in neonates are needed.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most typical heritable cardiovascular disease described by left ventricular hypertrophy that is characterized by abnormal loading states, with cardiomyocyte hypertrophy and confusion, and raised cardiomyocyte fibrosis as key histopathological hallmarks.[1,2] These changes can cause heart failure and death. Cardiac difficulties owing to congenital heart deformity and ventricular hypertrophy are the main reasons for morbidity and mortality in fetuses and neonates of mothers with diabetes. The incidence of HCM varies widely, ranging from 10% and 71%.[3] Generally HCM has an incidence of 0.47/100,000 children and accounts for 42% of childhood cardiomyopathy. It represents a heterogeneous group of disorders with a diversity that is more apparent in childhood than at any other age.[4]

The connection between maternal diabetes and congenital abnormality is well documented.[5] The prevalence of diabetes in gestation has been rising in concordance with the worldwide epidemic of obesity. Not only is the prevalence of type I diabetes and type II diabetes rising in women of reproductive years, but even there is a surprising increase in the declared rates of gestational diabetes mellitus (GDM).[6,7] Also, maternal hyperglycemia is a critical risk factor for congenital heart disease (CHD).[8,9] The reason for this anomaly is usually unidentified, with 1% of all subjects associated with diabetes of pregnant mothers.[10,11] Some writers assert that fetal echocardiography should be advised to all pregnant women with diabetes.[12]

Fetal hyperinsulinemia in response to maternal hyperglycemia has been seen as the reason for HCM in neonates of diabetic mothers.[11] An expansion in the ventricular wall thickness may also be affected in the cardiovascular transformations seen in fetuses of mothers with diabetes, but septal hypertrophy is extensively investigated given the higher number of insulin receptors (IR) in the septum of the heart.[12] More suitable glycemic control of diabetic mothers is related to a lower occurrence of fetal heart disorder but not necessarily with lower fetal myocardial hypertrophy.[5] Diabetic HCM is usually a self-limiting issue with no significant clinical outcome and is not identified as a structural malformation of the heart. This temporary event usually regresses within the first few months of life.

Statistics display that 5.4% of Iranian women are diabetics, most of who are at the years of productivity.[13] Due to the increase of diabetes in pregnant mothers, the exact prevalence of hypertrophy in the babies of these mothers has not yet been determined. Therefore, we aimed to investigate the prevalence of HCM in fetuses of diabetic pregnant women before drug use with fetal echocardiography and evaluate therapeutic interventions with follow-up after six months.

Materials and Methods

This cross-sectional study was performed between October 2016, and September 2017, and 150 neonates of diabetic mothers were enrolled. After the approval of the Research Ethics Committee of Shahid Sadoughi University and obtaining written consent from all the parents of the infants, they were included in the study. Statistical analysis was performed on the data obtained from patients' files. The research included singleton fetuses of pregnant women identified with diabetes, without malformations and other disorders that could interfere with fetal growth. The identification of diabetes was established on the standards provided by the American Diabetes Association (ADA), that is, blood glucose (sugar) level. To assess hereditary heart problems in neonates, myocardial thickness, left ventricular myocardial performance index (LVMPI), ejection fraction (EF), shortening fraction and right ventricular myocardial performance index (RVMPI), and tricuspid flow and mitral E/A ratio were assessed in echocardiographic tests with Doppler.

Table 1. Prevalence of Hypertrophic Cardiomyopathy in Neonates of Mothers with Type I and II Diabetic

Variable		Number	Number (%) of HCM	P
Type of diabetes	Type I	43	7 (16.3)	0.392
	Type II	107	14 (13.0)	

Statistical analysis: All variables were descriptively investigated, with quantitative variables represented as means and standard deviations. Data were statistically analyzed utilizing the Statistical software (SPSP version 20). The analysis and frequency were calculated using the Fisher's exact testwith the 95% confidence interval (95%CI).

Results

In this cross-sectional study, 150 neonates born to a diabetic mother who had been referred to the Yazd Heart Clinic by a neonatologist were studied and followed up. All the neonates were full term and singleton. The following results were obtained. We categorized diabetic mothers by type of diabetes: 47 mothers had type I diabetes and 103 mothers had type II diabetes (Table 1). We only considered the type of diabetes in mothers and have insufficient information on mothers with GDM and pre-GDM.

Examination of maternal blood sugar and HBA1C in the first trimester of pregnancy showed that diabetes was controlled in 126 mothers (84%) and not controlled in 24 mothers (16%) (Table 2). Examination of neonatal echocardiography results at the first visit showed that 21 neonates (14%) had HCM. For clinical follow-up of the therapeutic effect on heart problems, propranolol was randomly administered (one in half) to neonates.

Relationship between maternal type of diabetes and the incidence of HCM in neonates: we examined the relationship between the type of diabetes and the incidence of HCM in neonates and the results showed that out of 43 neonates born to mothers with type I diabetes, 7 neonates (16.3%) had HCM, in other words, 33.3% of HCM patients were born to a mother with type I diabetes. Also from 107 neonates born to mothers with type II diabetes, 14 neonates (13.1%) had HCM, in other words, 66.7% of HCM patients were born to a mother with type II diabetes. These results were tested by Fisher's exact test and are not statistically significant by calculating P = 0.392, which means that in this study there is no relationship between the type of maternal diabetes and the incidence of HCM (Table 1).

Incidence of HCM in neonates of diabetic mothers based on controlled or uncontrolled diabetes: In our research, diabetes was controlled in 126 mothers (84%) and not controlled in 24 mothers (16%) (Table 2). All of the 21 neonates with HCM were born from mothers whose diabetes was uncontrolled (87.5%). Also, none of the 126 neonates from the diabetic mothers whose diabetes was controlled had HCM. In other words, 100% of HCM patients were born to mothers whose diabetes was not controlled. This result was tested by Fisher's exact test and is statistically significant by calculating P < 0.0001, which means that in this study there is a direct relationship between maternal uncontrolled diabetes and the incidence of HCM in the infant (Table 2).

Results of six-month follow-up: Among 21 neonates with HCM, 10 (47.6%) neonates were randomly selected and given propranolol for 6 months (Table 3).

Table2. Prevalence of Hypertrophic Cardiomyopathy in Neonates of Mothers with Controlled and Uncontrolled Diabetic

Controlled Diabetes	Number	Number (%) of HCM	P
No	24	21 (87.5)	< 0.0001
Yes	126	0 (0.0)	

Table 3. Six-month Follow-up After Birth for Neonates with Hypertrophic Cardiomyopathy with Prescription Propranolol

Prescription of propranolol in HCM (n = 21)	Number	Follow up after 6 months	Number (%)	P
Yes	10	Improving	10 (100)	< 0.0001
		Persistent	0 (0)	
No	11	Improving	3 (27.3)	< 0.0001
		Persistent	8 (72.7)	

Since the treatment of hereditary congenital malformations is more effective in infants, we performed drug intervention to increase the speed of hypertrophy treatment in 10 infants. In some symptomatic neonates, we had chosen propanol to decrease the course of spontaneous treatment of cardiomyopathy. According to previous studies, propanol does not have any specific side effects in low and standard doses. At the end of 6 months, after control echocardiography, it was found that all (100%) neonates with HCM who took propranolol had a full recovery. This result was tested by Fisher's exact test and was statistically significant by calculating $P < 0.0001$, which meant that in this study, propranolol consumption was effective in improving HCM. Our results also showed, out of 11 neonates (52.4%) with HCM who were not prescribed propranolol at the end of 6 months, 8 neonates (72.7%) still had HCM after echocardiography. This result was tested by Fisher's exact test and was significant by calculating $P < 0.0001$, which meant that in this study the rate of spontaneous improvement of HCM was low among neonates (Table 3).

Discussion

Prior investigations have demonstrated that maternal hyperglycemia may lead to HCM and heart diastolic action disability,[14] and described HCM related to diabetes during pregnancy. Distinct from sarcomeric HCM, neonatal HCM related to diabetes during gestation is self-limiting and in fact, tend to settle in weeks to months.[15] Previous reports demonstrate that maternal diabetes has teratogenic impacts on the development of the fetal cardiovascular system, with a reported risk of malformation in published investigations of 1.7-4.0%.[10]

Gestational diabetes is related to difficulties during pregnancy and raised the risk of type II diabetes subsequently in mothers.[16] Type II diabetes is an advanced disorder that positions important stress on patients and their families and creates a vicious cycle of metabolic disorders for future generations.[17] Despite advances in medical care supplied during gestation to diabetic mothers, the cardiovascular difficulties in their neonates are yet more recurring than in the neonates of the global population.[5] HCM is a well-recognized comorbidity in neonates of diabetic mothers and is ascribed to a compensating addition in fetal insulin secretion. Neonates with congenital hyperinsulinism have extreme antenatal and postnatal insulin secretion because of defects in pathways of insulin secretion (most typically the KATP channel). When at more developed gestational ages, fetal hyperinsulinemia following insufficient maternal glycemic control raises the expression of insulin receptors (IR) in cardiomyocytes, Insulin, an anabolic hormone, induces hypertrophy and hyperplasia of cardiomyocytes, followed by myocardial hypertrophy.[18-20]

HCM has been documented in some neonates with hyperinsulinism, but its expanse and risk factors for its expansion have not been assessed.[11] One Cohort study assessed the overall prevalence of hypertrophy in children. In a 10‐Year Medicaid Cohort in pediatrics, Nandi et al. achieved a prevalence rate for pediatric HCM of 1.2/1,000,000 and an annual incidence rate

of 1.3/100,000. In their cohort study, cardiac-related mortality was 2.9% and 70.0% of those who died were ≤ 13 months of age.[21] This suggests that in the general population, the prevalence of hypertrophy is very low. But in neonates of diabetic mothers, the incidence of hypertrophy is very high.

The results of this research demonstrate that diabetes in pregnant women plays a critical role in the prevalence of HCM. According to our results, the prevalence of HCM was 14% in neonates of diabetic mothers (P = 0.0001). The most similar result to this study was done by Akbariasbagh et al. in 2016. They assessed cardiovascular malformations in infants of diabetic mothers. According to their results, the prevalence of cardiovascular anomalies was significantly higher in infants of diabetic mothers and the prevalence of HCM was 9%.[13]

Other studies evaluating the prevalence of HCM in neonates of diabetic mothers reported a higher prevalence than our results. Muhammad et al. in Egypt estimated the frequency of cardiac complications in infants of diabetic mothers in NICU. They achieved the frequency of HCM was 30% in infants of diabetic mothers.[22] Palmieri et al. evaluated the prevalence of HCM in fetuses of mothers with gestational diabetes before beginning treatment. They showed the prevalence of HCM in fetuses of pregnant women with GDM before treatment was 54% (95%CI: 41.3-65.1%).[12] Roodpeyma et al., in 2013 evaluated cardiovascular disease in neonates of diabetic mothers. They also investigated possible associations between neonates' heart lesions and the type of maternal diabetes. They demonstrated a high prevalence of CHD in IDDM (type II) in their pediatric cardiology clinic and the prevalence of HCM was observed in 46.9% of cases. In their study neither the types of maternal diabetes nor the somatic results of newborns were associated with the happening of cardiovascular disease.[5]

While HCM in infants of diabetic mothers is reversible and often mild or asymptomatic, it can be harmful and lead to infant or fetal death. Most symptomatic neonates require only supportive care with supplemental oxygen, but β-adrenergic blockers such as propranolol may be essential to improve ventricular output.[11] In one study, Ostman-Smith showed in patients with heart failure due to HCM, side effects of beta-blockers are surprisingly rare, even at very high doses.[23] We used propanol therapy to increase the recovery rate of HCM. The recovery rate was 100%, but in the control group, the spontaneous recovery rate was 27%.

As a consequence, the efficiency of diagnostic methods (such as fetal echocardiography, before and after birth), providing particular attention to diabetic mothers, and requiring therapeutic and supportive care to symptomatic neonates appears very recommendable in such subjects.[13] We conclude that knowing the prevalence of HCM among newborns in diabetic mothers provides a good basis for accurately managing diabetes during pregnancy and early diagnosis and treatment of postpartum abnormalities, which may reduce the severity of HCM.

Conclusion

The prevalence of HCM in our study was 14%, which percentage is very high compared to the total prevalence of HCM. This suggests that the assessment of infants of diabetic mothers is very important. Regardless of the type of maternal diabetes, control of diabetes in pregnant women seems to be essential in preventing HCM in neonates. Early echocardiography in neonates is effective in diagnosing HCM. Therefore in all diabetic mothers, the echocardiography of their neonates should be done. In some symptomatic neonates, we had prescribed propanol to decrease the course of spontaneous treatment of cardiomyopathy due to the low rate of spontaneous recovery in neonates. This suggests that propranolol may be effective for the treatment of affected infants with HCM.

Conflict of Interest

The authors have no conflict of interest.

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Original Article

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Incidence and Risk Factors Related to Gestational Diabetes Mellitus among Women in Yazd: A Prospective Cohort Study

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ABSTRACT

Background: The incidence of Gestational diabetes mellitus (GDM) is increasing worldwide. The exact prevalence of GDM in Iran is unknown. This study aimed to identify the incidence of GDM and the risk factors based on a cohort study in Yazd.

Methods: This is a prospective cohort study involving 3110 pregnant women attending prenatal clinics in Yazd, Iran between 2015 and 2020. GDM was diagnosed using an Oral Glucose Tolerance Test (OGTT) for each participant at 24-28 weeks of gestation. Demographic information was collected at enrollment and during pregnancy. The multivariate logistic regression models were used to identify risk factors for GDM.

Results: The overall incidence of GDM was 10.93% in this study. The incidence of GDM in the first, second and third trimesters were 5.65, 2.25 and 3.11%, respectively. The mean age of mothers was calculated to be 28.64 ± 5.53 years. By logistic regression, significant factors associated with GDM were age, Preeclampsia, Pregnancy High blood pressure, history of diabetes mellitus (DM) and obesity.

Conclusion: In this population, the incidence of GDM was 10.93%, which was high. The significant risk factors for GDM were age, BMI, smoking, smoking exposure in the current pregnancy and history of GDM and DM. Also, GDM pregnancies have a higher risk of preeclampsia and gestational hypertension. Therefore, considering the high incidence of GDM in Yazd, general screening is highly recommended and more studies are needed in other parts of Yazd province.

Introduction

Gestational diabetes mellitus (GDM) is a global public health concern with potential consequences for the health of a mother and her offspring.[1] GDM is impaired glucose tolerance that first occurs or is diagnosed after pregnancy.[2] The prevalence of GDM is increasing year after year globally, particularly in low-income and developing countries.[2] Globally, the average estimate of GDM is between 6 and 13%. In the United States, recent estimates suggest that up to 9% of all pregnancies are complicated by GDM. In Central and South America, the recent overall prevalence of GDM has been estimated at 11%.[1] The prevalence of GDM reported in Europe varies considerably, occurring in more than 20% of pregnancies in certain populations.[3] A meta-analysis showed that the prevalence of GDM was 20.9% in Asia, and 14.8% in China.[4]

In Iran, in previous studies conducted in different regions, the prevalence of GDM was between 1-18%.[5] Moreover, this difference is related to race, lifestyle, and differences in data collection methods, non-random selection, and diagnostic criteria. In a review article conducted in 11 provinces of Iran (2009), the prevalence of GDM was reported in the range of 1.3 to 8.9%.[6]

GDM can cause maternal and neonatal complications such as premature rupture of membranes, preeclampsia, and preterm labor and increase the risk of long-term endocrine disorders.[2] GDM is also associated with an increased risk of perinatal morbidity including malformations, neonatal hypoglycemia, shoulder dystocia, and perinatal mortality.[1,7] Women who develop GDM have an elevated lifetime risk of type 2 diabetes mellitus. Currently, a series of studies have shown that women with GDM are also at risk of developing cardiovascular diseases (CVD).[8] However, limited information is available about genetic and environmental factors that are implicated in the progression from GDM to T2DM.[9] Generally risk factors for GDM include overweight and obesity, advanced maternal age, family history of diabetes, nonwhite race, previous unexplained stillbirth, hypertension, polycystic ovary syndrome (PCOS), and hyperlipidemia.[10] Obesity and a family history of diabetes have been consistently identified as major risk factors for GDM in previous studies.[1] Also, women who conceive at an older age are likely to have a higher body mass index (BMI).[4] In 2010, the IADPSG developed a consensus statement for a new strategy to diagnose GDM. The chosen cut-off point for glucose on a 75 g OGTT conveyed adverse outcomes of $\geq$ 1.75 compared with women with mean glucose levels at 24-28 weeks.[3]

GDM is the most common metabolic disorder in pregnancy, which is caused by insulin resistance and carries many risks for the mother and the fetus. Therefore, it is important to update its prevalence data in different geographical areas.[11] The exact estimate of the incidence of GDM in pregnant women in Yazd is still unknown. We aimed to calculate the incidence of GDM and report the critical risk factors for the development of GDM, in a cohort study on mothers in 5 centers, during 5 years in Yazd using IADPSG/WHO 2013 diagnostic criteria.

This study may determine the incidence, risk factors and pregnancy outcomes of delivery with GDM in Yazd, which is important for researchers to design more effective intervention measures such as diet, exercise and other early interventions. Understanding the incidence and risk factors in the region will help develop targeted interventions to reduce the adverse outcomes of GDM.

Materials and Methods

Data Collection: This study is a prospective cohort study using the Mother-Infant Study Cohort data. 3110 pregnant women participated in this study. The target population of the study included all pregnant women who participated in the Mother-Infant Study Cohort in Yazd. All pregnant women participating in this research have been

examined for GDM and its related causes. Exclusion criteria included type 1 and 2 diabetes and the use of drugs such as steroids affecting glucose metabolism.

To collect data, a comprehensive data collection form was used in the context of the required information and the investigated variables. The said form included the following information: history of diabetes in the first-degree family, history of pre-diabetes, history of GDM, mother's age, body mass index, body fat percentage, fasting blood sugar, triglycerides, cholesterol, alcohol consumption, smoking, history of previous high-risk pregnancy, history of stillbirth, history of miscarriage, urinary tract infection, history of hypertension, history of abnormality, systolic blood pressure, diastolic blood pressure, history of pre-eclampsia, history of macrosomia.

The diagnosis of GDM was made according to the latest national guidelines for screening and diagnosis of gestational diabetes. Women with GDM are identified through the glucose challenge test (GCT) by measuring 50 grams of glucose and blood sugar one hour later. So values less than 131 are negative and disease-free, but values equal to or higher than 130 are considered positive in this program. In the next step, if the GCT was positive, a 3-hour glucose tolerance test (OGTT) was requested for them. OGTT was performed after three days of a diet without carbohydrate restriction and in a fasting state, first, fasting blood Sugar (FBS) was recorded and then 100 grams of glucose was prescribed. Then the blood glucose level was measured at intervals of one, two, and three hours after consuming the glucose solution. Finally, the diagnosis was made based on the American Diabetes Association criteria ($Bs3h > 140, Bs2h \geq 150, Bs1h > 180, FBS > 95$). Diabetes should be proven in at least two glucose tests. In this way, if the result was positive in at least 2 glucose tests, the person was diagnosed with gestational diabetes. After collecting information, the data was analyzed using SPSS software version 19, and statistical tests of chi-square, independent t, analysis of variance, and logistic regression were used at a significance level of 1.15 α. ($P < 0.05$).

Results

Basic information: We used data from March 2016 and continue until February 2021. The study was approved by the Institutional Ethics Committee of Shahid Sadoughi University of Medical Sciences, and all participants signed written informed consent before testing. We confirmed that the research was performed following relevant clinical technical specifications.

The total number of people studied was 3110. Of the 3110 pregnant women, information on baseline characteristics was missing for a few mothers. Participants ranged in age from 15 to 45. The average age of mothers was calculated to be 28.64 ± 5.53 years. More than 50% of the studied people were between 26 and 35 years old. The distribution of pregnant women in the three age groups was 30.6, 57.3, and 12.1%, respectively. Out of those 1494 (48%), people had Higher education. The income of 2320 (78.3%) of the studied people was middle. Two thousand and three hundred twenty (78.3%) of participants belonged to the middle-income group. Most of the surveyed mothers 2427 (79.2%) were housewives. The demographic characteristic of pregnant women shows in Table 1.

Table 1. Baseline Sociodemographics Characteristics of the Studied Subjects

Variables	Frequency	Percent (%)
Age		
15-25	951	30.6
26-35	1783	57.3
36-45	376	12.1
Level of education		
Primary	516	16.6
High school	1100	35.4
Higher education	1494	48.0
Income		
Low	302	10.2
Middle	2320	78.3
High	342	11.5
Employment status		
Housewife	2427	79.2
Employed	637	20.8

Characteristics and history of the study population: Characteristics of pregnant women are shown in Table 2. The mean pre-pregnancy BMI was 26.6 kg/m2. In our population, 53.2% of pregnant women had BMI < 25 (underweight), and 30% had a normal BMI (25- 29.9). Only 16% had BMI > 30 and were overweight (Table 2). More than 60% of the investigated mothers had a history of pregnancy and 34.2% of these mothers had a history of parity (parity = 1). Also, 33.7% had no history of pregnancy and were experiencing their first pregnancy in this study. The frequency of history of GDM in pregnant women was 6.7%, which was close to the frequency of history of GDM in the family of pregnant women (10.6%). Pregnant women with GDM may be more likely to have a history of GDM. The frequency of the history of DM in pregnant women was low (3.7%), While the frequency of a history of diabetes in the families of pregnant women was high (46.2%). The history of pregnancy hypertension was 2.9% and 8% in participants and their families, respectively.

Table 2. Characteristics of the Study Population and Their Family

Variables	Frequency	Percent (%)
Participants		
BMI (kg/m2)		
25 < (underweight)	1656	53.6
25-29.9 (normal)	933	30.3
30 ≥ (overweight)	498	16.1
History of pregnancy		
Yes	2007	66.3
No	1021	33.7
Parity		
0	1021	33.7
1	1034	34.2
2	641	21.2
≤ 3	330	10.9
Preeclampsia		
Yes	42	1.4
No	2994	98.6
History of GDM		
Yes	205	6.7
No	2829	93.3
History of DM		
Yes	115	3.8
No	2917	96.2
History of gestational hypertension		
Yes	89	2.9
No	2940	97.1
High cholesterol		
Yes	78	2.6
No	2977	97.4
Urinary tract infection		
Yes	1325	43.7
No	1707	56.3
Smoking history		
Yes	6	0.2
No	3104	99.8
History of hookah use since three months before pregnancy		
Yes	126	4.1
No	2984	95.9
Exposure to cigarette smoke in recent pregnancy		
Yes	337	10.8
No	2773	89.2
Family		
History of GDM		
Yes	306	10.6
No	2573	89.4
History of DM		
Yes	1437	48.6
No	1521	51.4
History of gestational hypertension		
Yes	230	8
No	2650	92
History of miscarriage		
Yes	968	33.5
No	1922	66.5
History of recurrent miscarriages (≤ 2)		
Yes	335	11.3
No	2622	88.7
History of stillbirth		
Yes	259	9
No	2618	91
History Preterm Delivery		
Yes	325	11.3
No	2547	88.7
Treatment		
Diabetes Treated With Insulin	54	44
Diabetes Treated Without Insulin	69	56
Family history of diabetes treated with insulin	791	43.9
Family history of diabetes treated Without insulin	1012	56.1

The amount of history of miscarriage in

the family (mother and sister) was 31.1% and the history of recurrent miscarriages was 10.8%. Also, the history of premature birth in the family of pregnant women was 10.5 % (Table 3). In our study, almost all mothers (99.8%) were non-smokers and small percentages (0.02%) were smokers. However, 10.8% of pregnant women were exposed to cigarette smoke during their recent pregnancy (Table 2).

Incidence of GDM in first, second, and third trimesters: The study initially included 3110 patients, including 340 with GDM. The overall incidence of GDM in our population of Yazd pregnant women was 10.93% (95% CI: (9.85- 12.08)). Table 3 shows the incidence of GDM by trimesters in first, second, and third. The incidence of GDM in the first, second, and third trimesters were 5.65, 2.25 and 3.11%, respectively. In the first trimester, the risk of GDM in women was higher than in other months (95% CI: (4.78-6.42)). This shows that diagnosis in the first trimester is more valuable.

Table 3. The Incidence of GDM in Each Trimester of Pregnancy

	Frequency	Risk (CI)*
Overall	340	1093 (9.85-12.08)
The first trimester	173	5.65 (4.78-6.42)
The second trimester	70	2.25(1.75-2.83)
The third trimester	97	3.11(2.53-3.79)

* Per 100 people

Risk factors associated with GDM: Table 4 shows the results of multiple logistic regression analysis on associations between potential risk factors and GDM. Maternal and family risk factors for GDM development at enrolment are displayed in this Table. The most important risk factors in GDM among our population were analyzed, which include the following. Significant risk factors associated with GDM were age (P = 0.003, 95% CI (1.184-2.341)), BMI (P = ≤ 0.001, 95% CI (1.210- 2.124)), history of DM, history of GDM, Smoking exposure in the current pregnancy and smoking three months before pregnancy. Also, GDM pregnancies have a higher risk of preeclampsia (P = 0.008, 95% CI (1.340-7.277)) and gestational hypertension (P = 0.040). The incidence of GDM was strongly associated with a history of previous GDM (P ≤ 0.001, 95% CI: 1.543-3.584) and a history of DM (P ≤ 0.001, 95% CI: 3.408- 9.052).

There was no significant difference in the following risk factors, including education, income, number of parity, cystitis, history of gestational hypertension, high blood pressure, and previous pregnancy. There wasn't any significant relation between GDM with family risk factors such as a history of diabetes, history of stillbirth or history of miscarriage. Other non-significant risk factors include a history of familial recurrent miscarriage, gestational hypertension, GDM, preterm delivery, high blood pressure, DM, and gestational hypertension.

Discussion

GDM is a common health problem during pregnancy and is defined as intolerance of carbohydrate levels in women at the beginning or during pregnancy.[12,13] Women with GDM are more likely to suffer pregnancy complications, and the diagnosis is associated with both immediate and long-term adverse consequences for their offspring.[3] In pregnant women, the excess amounts of blood glucose are transferred to the fetus. This causes several disorders in neonates.[14] The prevalence of GDM has increased in recent decades in parallel with older age at the time of pregnancy and the western lifestyle, which is associated with economic prosperity.[4] GDM affects approximately 15.1% of women worldwide, which, if untreated, has severe consequences for maternal and neonatal outcomes. Gestational diabetes is managed with conventional medications like insulin and oral antidiabetics such as metformin, in addition to diet and exercise.[15]

This study estimated the prevalence of GDM in Yazd and determined the risk factors and consequences related to it (and outcomes).

Table 4. Risk Factors Associated with GDM by Multivariate Logistic Regression Models

Characteristics	Odds Ratio	95% CI	P
Age.cat	Ref.		0.005
Age.cat(1)	1.665	1.184-2.341	0.003
Age.cat(2)	2.059	1.286-3.296	0.003
BMI1.CAT	Ref		
BMI1.CAT(1)	1.603	1.210- 2.124	0.001
BMI1.CAT(2)	2.089	1.485-2.939	≤ 0.001
Education.cat	Ref		0.827
Education.cat(1)	1.090	0.740-1.605	0.663
Education.cat(2)	1.005	0.671- 1.505	0.981
Incom.cat	Ref		0.055
Incom.cat(1)	1.307	0.846- 2.019	0.228
Incom.cat(2)	0.789	0.429- 1.450	0.445
previous pregnancy	0.717	0.441- 1.166	0.180
Number of parity.cat	Ref		0.777
Number of parity.cat(1)	1.050	0.684- 1.612	0.823
Number of parity.cat(2)	1.149	0.754- 1.752	0.519
Preeclampsia	3.123	1.340- 7.277	0.008
History of GDM	2.352	1.543- 3.584	≤ 0.001
History of DM	5.554	3.408- 9.052	≤ 0.001
Gestational hypertension	0.334	0.117- 0.951	0.040
History gestational hypertension	1.059	0.402- 2.789	0.907
High Blood Pressure	2.381	0.899- 6.309	0.081
Cystitis	1.112	0.868- 1.426	0.400
Daily Smoking	4.760	0.729- 31.062	0.103
Smoking three months before pregnancy	1.953	1.155- 3.303	0.013
Smoking exposure in the current pregnancy	1.607	1.135- 2.276	0.008
Family			
Gestational hypertension	1.120	0.734- 1.710	0.599
History of GDM	1.388	0.965- 1.996	0.077
History of DM	1.212	0.939- 1.564	0.140
Miscarriage	1.045	0.797- 1.370	0.753
Recurrent miscarriage	1.409	0.977- 2.034	0.067
Still birth	1.120	0.741- 1.692	0.591
Preterm delivery	0.832	0.560- 1.237	0.364

In our study, the prevalence of GDM was 10.9%. When we compare our results with the prevalence of diabetes in the world and in Iran, we find that the prevalence of diabetes in Yazd was relatively high. The estimated prevalence of GDM in Yazd (10.93%) is similar to the estimate of the meta-analysis conducted in 2019. Behboudi-Gandevanis et al., in a meta-analysis estimated the worldwide prevalence of GDM. The pooled overall prevalence of GDM in the diagnostic threshold used in IADPSG criteria was 10.93% (95% CI 10.5-10.93%).[16]

In the following, we have given examples of the global prevalence of diabetes, the amount of which is different. In 2018, Stark S et al. estimated the prevalence of GDM in the United States to be 7.6%, with 19.7% of these women subsequently developing diabetes. They observed that women with a history of GDM, obesity and a family history of diabetes, should be closely monitored for blood sugar.[10] In 2018, Groof Z et al., evaluated the prevalence, risk factors, and fetal outcomes of GDM in Kuwait. They estimated that 12.6% of mothers had GDM in their last pregnancy. The prevalence of GDM increased with maternal age and pre-pregnancy BMI.[17] In Gloria et al., a study in Peru in 2018, the prevalence of GDM was approximately 16% of pregnant women. The most risk factors for the incidence of GDM

were associated with maternal obesity, family history of diabetes, and antepartum depression among Peruvian women.[1] Generally obesity and maternal age are the two most important factors independently affecting the risk of GDM.[4] Stacey et al., evaluated GDM and the risk of late stillbirth in England, UK. They concluded optimal screening and diagnosis of GDM reduces the higher risks of late stillbirth in women "at risk" of GDM and/or with elevated FPG.[18]

Our result was higher than the Iranian meta-analysis done in 2015 by Jafari Shabiri et al. They conducted a systematic review and meta-analysis to evaluate the prevalence and risk factors of GDM in Iran. Their results showed the prevalence of GDM was 3.41% and the highest and lowest prevalence rates were 18.6% and 1.3%, respectively.[19] Perham et al., evaluated the prevalence of GDM in Qom, Iran in 2018. They reported 20.76% of women had gestational diabetes. GDM was significantly associated with maternal age, BMI, history of GDM, a family history of type II diabetes in first-degree relatives, history of preterm labor, history of macrosomia and known hypothyroidism before pregnancy.[11] Vakili et al., evaluated the prevalence of GDM and Its risk factors in the city of Maybod, Yazd in 2013-2014. Their results showed that the prevalence of GDM in the mentioned group is 27.1 %, which is considered to be high in comparison with other parts of Iran.[5] In 2012 Vakili et al., evaluated the prevalence of GDM and its risk factors in Yazd. The prevalence of GDM in the present study was 12%.[20] A cross-sectional study was conducted in Yazd province from March 2008 to March 2011 by Rashidi et al. They used logistic regression was used to calculate the Odds Ratio at 95% Confidence Interval to estimate the independent association of different risk factors with GDM. Their results showed the overall prevalence of GDM was 3.3%.[21]

According to most studies overweight and obesity, gestational BMI, older age, having family history of T2DM/GDM, prepregnancy overweight, and prior history of giving stillbirth/miscarriage were associated with increased risk of GDM. In our study age, preeclampsia, pregnancy HBP, history of DM, BMI, exposure to secondhand smoke during the current pregnancy, and smoking three months before pregnancy, were correlated with an increased risk of GDM. We estimated the incidence of GDM in Yazd to be 10%, which is high. Considering that the incidence of GDM is high in Yazd, there is a need for more studies in this field. Considering the above risk factors, society can strengthen education for high-risk populations, determine effective prevention strategies, and develop and improve early intervention management models for diabetic patients. Also, Public health measures may be helpful to prevent excessive gestational weight gain. In general, timely diagnosis, treatment, intervention, and accurate control of blood glucose levels lead to improved outcomes for mother and baby.

Conclusion

Our study found that 10.93% of women in Yazd are affected by GDM. Advanced age, pregnancy HBP, history of diabetes mellitus, and BMI were independent risk factors for GDM. Moreover, because of GDM's high incidence in Yazd, general screening is strongly recommended and more studies are needed to be conducted in other parts of Yazd province. In order to better understand the importance and response to GDM in Yazd, there is a need to formulate national strategies, guidelines and policies by gaining empirical knowledge about the current situation. According to the recommendations, general screening is strongly recommended among Yazd women. Also, doctors should refer patients with diabetes to resources related to the risks of diabetes and request a diabetes test after delivery to reduce the burden of diabetes and its complications.

Conflict of Interest

The authors have no conflict of interest.

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The present study was approved by the Ethics Committee of Islamic Azad University/ Yazd Branch (IR.SSU.SPH.REC.1399.176).

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Original Article

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Positive Predictive Value of Screening Tests in the First and Second Trimester of Pregnancy in the Diagnosis of Trisomy 21, 18, and 13 Using Amniocentesis

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ABSTRACT

Background: The aim of this study is to analyze the positive predictive value (PPV) of trisomies 21, 18 and 13 at first and second trimester using amniocentesis for clinical practice.

Methods: : This is a descriptive cross-sectional study in which data were extracted from a cohort project of mother and infant conducted between March 2016 and February 2021 among 3110 pregnant women in Yazd city.

Results: Out of 3110 pregnant women, 84 mothers were at high risk in the screening tests of the first and second trimesters of pregnancy and therefore were candidates for amniocentesis. None of them were detected by the positive amniocentesis method. The mean age of mothers was 33.2 years. The causes of amniocentesis included old age (45.9%), positive results of Down syndrome screening (23%), high NT ultrasound (4.9%), and pathological results of anomaly scan sonography (3.8%).

Conclusion: In this study, the PPV was zero and the number of false positives in screening tests was 84 (100%). This may be because our population was normal and had no history of genetic abnormalities or other special conditions.

Introduction

The most common chromosomal abnormalities are trisomy 21, also referred to as Down's Syndrome (DS), trisomy 18, which is also known as Edwards' syndrome (ES), and trisomy 13.[1] The incidence of trisomy 21 increases with the age of the mother. Therefore, trisomy 21 screening and diagnosis for the fetus is an important subject for pregnant women over 35 years old and other high-risk mothers.[2]

First-trimester screening (FTS) is a valid screening method for major chromosomal aneuploidies.[3] FTS considers a combination of maternal age, Nuchal translucency (NT) Scan, and maternal serum. This maternal serum screening is done by a combination of two biochemical markers including serum free β-human chorionic gonadotrophin (free β-hCG) and pregnancy- associated plasma protein A (PAPP-A).[2] FTS is performed at 11 to 13 weeks of pregnancy; using ultrasound to scan the fetal neck for enlarged NT. Increased NT is associated with not only trisomy 21 but also with other chromosomal abnormalities.

Second-trimester screening with quadruple marker test or quad screen has been replaced by FTS due to earlier diagnosis of chromosomal abnormalities, higher detection rates, and use of increased NT as a marker of cardiac abnormalities and other structural defects.[4] The main objectives of the second trimester are as follows: To identify the relationship between quad test or second-trimester serum markers, consisting of alpha-fetoprotein (AFP), unconjugated estriol (uE3), free β-human chorionic gonadotrophin (β-hCG) and inhibin-A (IHA).[5,6] Ultrasound (USG) has become an important part of obstetrics and gynecology care for the health of the fetus and the diagnosis of prenatal abnormalities.[7]

Women at high risk may receive genetic counseling or more invasive testing.[2] Identification of any of these findings warrants further counseling and possible referral to a prenatal diagnostic center with the option of invasive testing for fetal karyotyping.[7]

Invasive prenatal diagnosis for fetal trisomy is usually based on high-risk mothers, abnormal FTS, abnormal ultrasound findings, or second-trimester abnormalities. However, data on the PPV of these screening modalities and the resulting incidence of termination of pregnancy (TOP) in case of a positive result are scattered.[8] Although sensitivity and specificity are important performance metrics, PPV and negative predictive value (NPV) become more clinically relevant after results have returned.[9] The PPV analysis showed that the more the number of indications is more; the PPV tends to be maximized.[10]

Invasive prenatal diagnosis tests obtain the sampling of fetal genetic material through amniocentesis or chorionic villus sampling (CVS).[11] The invasive procedures may still result in intrauterine infection or miscarriage. Therefore, the invasive prenatal diagnosis is not accepted by some pregnant women. Non-invasive prenatal screening (NIPS) is the alternative for these women.[11,12] Diagnosing the chromosomal abnormalities and fetal disorders in the early stages of pregnancy can prevent future adverse conditions for the infant and his/her family.[13]

We performed a retrospective cohort study and screened key maternal serum biomarkers in 3110 pregnant women with old age and other risk factors. Then we analyzed the PPV of trisomy 21, 18, and 13 in high risk pregnant women of Yazd. The PPV of first and second screening tests was not investigated in Yazd so in this study we aimed to evaluate the PPV of the first and second-trimester screening tests for identifying high-risk mothers and fetal chromosomal disorders in pregnant women. On the other hand, our aim was to investigate the reliability of maternal serum screening for high-risk pregnant women in the first and second trimesters of pregnancy.

Materials and Methods

This cross-sectional descriptive study was

conducted between 2016 and 2021 in Yazd city. The data were extracted from the mother and infant cohort study (MICS) in Yazd conducted by Shahid Sadougi University of Medical Sciences and registered in the relevant system. Data included demographic information, screening results, and maternal ultrasound. Then, the data were analyzed by descriptive statistics.

Research Methods: The data needed for the research was obtained from the information recorded in the Yazd mother and baby cohort system. In this cohort, the mothers were informed about the work process by experts in a briefing session. Each participant read and signed the informed consent form. They were examined by a gynecologist. Questionnaires of pregnant mothers were completed. Their blood samples were used for preliminary tests. The results of the tests requested by the specialist (including screening tests of the first and second trimesters of pregnancy for trisomy 21, 18 and 13) and ultrasound were recorded in the system. If any of the tests were positive (high-risk mother), the patient was recommended for amniocentesis by a specialist and the results were recorded in the system, and these results were used in this research.

Subjects: A total of 3110 pregnant women who were referred to participating hospitals after 12 weeks of pregnancy, participated in our cohort study. The inclusion criteria were: Gestational age more than 12 weeks, singleton pregnancy and participation in the Yazd cohort study. The exclusion criteria included: Mothers who were visited after the 20th week, non-Iranian women, and mothers who migrated to other cities.

Results

This study was carried out with the special purpose of positive predictive value of screening tests in the first or second trimester of pregnancy; that the amount of positive predictive value was zero and the number of false positive cases was 84. In this study, among the 3110 pregnant mothers who were examined in the cohort, 84 people underwent amniocentesis, and all of them had a negative amniocentesis (normal karyotype).

Patient characteristics: The maternal age ranged from 19 to 40 years of age with a median of 32.3, and 33 cases were older than 35 years. The average weight of the mothers was 64.74 with a minimum of 39 and a maximum of 92 kg, and their average height was 160.79 with a range of 146 to 175 cm. None of the mothers had diabetes and were non-smokers; one of the mothers had twins. None of the mothers had children with congenital anomalies or Down syndrome. The mean NT of mothers was 1.82 mm with a range of variation of 0.5 to 3.2. None of the mothers used assisted reproductive methods to conceive.

Frequency of mothers based on age: According to Table 1, from the total information of 75 pregnant mothers, the number of mothers with high-risk age was 33 (44%) and the number of mothers with low-risk age was 42 (56%). So half of the mothers in the age group were high risk and half of them were in the low risk group.

Number of pregnancies: According to Table 1, the information of 75 pregnant mothers is available. The number of first and second time mothers were 14 (18.7%) and 23 (30.7%), respectively. The number of third time mothers was 27 (36%). Nine participants (12%) were fourth time mothers, and 2 mothers (2.7%) became pregnant 5 times. Therefore, most of the mothers were in their third pregnancy, which is not a high number.

History of abortion: Of the total of 73 people whose information is available, the number of mothers who have not had a history of previous abortion was 55 (75.3%), the number of mothers who have had a history of 1 previous abortion was 13 (17.8%), the frequency of mothers who have had a history of 2 previous abortion was 4 (5.5%). The number of mothers who had a history of 4 previous abortions was 1.4%. Most mothers had a history of 1 abortion, which is not a large number (Table 1).

Table 1. Characteristics of Mothers (Age, Number of pregnancies and Previous Abortions)

Frequency of mothers based on age	Number of mothers	Percentage of mothers
Old age (≥ 35)	33	44
Young age (< 35)	42	56
Total	75	100
Number of pregnancies	Frequency of mothers	Percentage of mothers
1	14	18.7
2	23	30.7
3	27	36
4	9	12
5	2	2.7
Total	75	100
Number of previous abortions	Frequency of mothers	Percentage of mothers
0	55	75.3
1	13	17.8
2	4	5.5
3	1	1.4
Total	73	100

Causes of amniocentesis in mothers: According to Figure 1, the reason for amniocentesis of the mothers was as follows: 28 people (45.9%) due to old age, 14 people (23%) at high risk of Down syndrome in the screening test, and 7 people (11.5%) average risk of Down syndrome in screening test, 5 people (8.2%) simultaneously with risk of Down syndrome and old age, 3 people (5 %) NT measurement ≥ 3mm, 1 person (1.6%) high risk of trisomy 18 and 13 in the screening test, 1 person (1.6%) due to thalassemia minor of the mother, 1 person (1.6%) due to the swelling of the fetal kidney in the ultrasound and 1 person (1.6%) due to the short nasal bone of the fetus in the ultrasound scan. Amniocentesis was performed to diagnose genetic disorders. The reason for amniocentesis was not available in 22 cases. Therefore, the most common reason was related to old age and high risk of Down syndrome in the screenings.

Risk of trisomies in the screening of the first and second trimester screening: According to the table 2, among the people who have performed FTS *(First trimester screening)* screening, 11 people (24.4%) had high risk, 26 people (57.8%) had moderate risk, and 8 people (17.8%) had low risk of Down syndrome (trisomy 21). Some mothers at moderate risk of Down syndrome were referred for amniocentesis with a doctor's diagnosis, and others had amniocentesis for other reasons. For trisomy 18, one person (2.2) was at high risk, 3 (6.7) were at moderate risk, and 41 (1.91) were at low risk. For trisomy 13, one person (2.2%) had high risk, 4 people (8.9%) had moderate risk, and 40 people (88.9%) had low risk. Among the people who performed the quad test, 5 people (83.3%) were at high risk, 1 person (16.7%) was at moderate risk of Down syndrome. Among mothers who had the test and were available, none were at low risk.

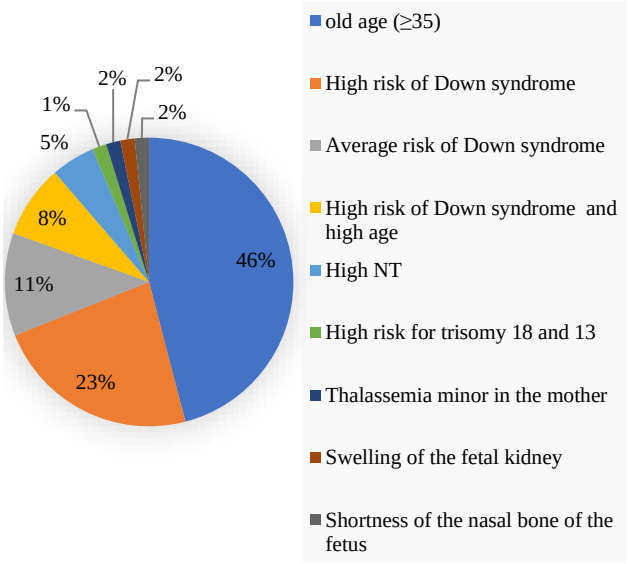

Figure 1. Causes of amniocentesis in mothers

Table 2. Prevalence of the Risk of Trisomies in the Screening of the First and Second Trimester

Screening risk		First combined test			Second combined test		
		T 21	T18	T13	T21	T18	T13
High risk (≥1.250)	N (%)	11 (24.4)	1 (2.2)	1 (2.2)	5 (83.3)	0	-
Moderate risk (1.250-1.1500)	N (%)	26 (57.8)	3 (6.7)	4 (8.9)	1 (16.7)	1 (16.7)	-
low risk (<1.2500)	N (%)	8 (17.8)	41 (91.1)	40 (88.9)	0 (0)	5 (83.3)	-
Total		45 (100)	45	45	6	6	-

For trisomy 18, one person (16.7) showed moderate risk and 5 people (83.3) showed low risk for this trisomy, and the high-risk number was zero. Therefore, the number of subjects with a high risk of trisomy was small.

FTS: According to Table 3, from the total of 55 mothers whose NT values are available, 4 cases (7.27% of mothers) had an NT value greater than 3 mm (high risk) and 52 cases (92.72%) were at low risk. More Mothers were in the low- risk group in terms of NT. As can be seen in Table 3, of the 46 subjects who had β-hCG and PAPP_A tests registered, the multiple of the median (MoM) value for high-risk hCG-β, i.e. more than 1.5, was observed in 24 subjects (52.17%), and MoM was less than 1.5 in 22 mothers (47.82%). The MoM value for PAPP_A ≤ 0.5 was considered high risk and seen in 17 mothers (36.95%). Twenty nine mothers (63.04%) had PAPP_A level more than 0.5. Therefore, according to β-hCG, about half of the mothers were in the high-risk group, and according to PAPP_A, most of the mothers were in the low-risk group.

QUAD TEST in second trimester screening: According to Table 4, quadruple data for AFP are available from 7 mothers, one mother (16%) had a minimum AFP MoM value of 0.53. The protein results of the other five mothers include values of 0.55, 0.56, 0.67, 0.78, and 0.81. One mother had a maximum MoM AFP value of 1.01. The mean AFP was 0.67 and all mothers had AFP MoM less than 2 and screened negative.

Table 3. NT Amount in NT Ultrasound and B-hCG and PAPP-A Values in FTS

Biomarker amount	Frequency	Percentage
NT amount		
NT < 3mm	51	92.72
NT ≥ 3mm	4	7.27
Total	55	100
β_hCG < 1.5	22	47.82
β_hCG ≥ 1.5	24	52.17
Total	46	100
PAPP_A ≤ 0.5	17	36.95
PAPP_A > 0.5	29	63.04
Total	46	100

According to Table 4, the average βhCG was 1.67. Five mothers had βhCG MoM below 2 and were negative in screening. One mother had a βhCG MoM of 3.55 and was at high risk. Also, the average uE3 MOM was 2 and the uE3 MOM of five mothers was normal and above 0.5 but one mother's uE3 MOM was 0.35 and at high risk. The average inh-A MOM was 2 and most mothers had normal levels of inh-A MOM, just one mother's inh-A MOM was more than two.

According to Table 5, the ultrasound information of 27 people was available. Those sonographic markers were normal for all of these people except for one person whose fetal nasal bone length was shorter than normal.

Table 4. The Amount of AFP, βhCG, uE3 and inh-A in the Quad Test of Mothers

Marker	Mean ± SD	Median	Maximum	Minimum	Number of mothers	Total
AFP	0.70 ± 0.17	0.67	1.01	0.53	7	100
βhCG	1.91 ± 0.83	1.67	3.55	1.21	6	100
uE3	0.80 ± 0.34	0.83	1.34	0.35	6	100
inh-A	1.58 ± 0.456	1.63	2.12	0.97	6	100

Table 5. Risk of aneuploidy depending on the soft marker detected on ultrasound

Soft marker	Number of mothers with normal markers	Number of mothers with abnormal markers
Nuchal fold thickness	27	0
Nasal bone length	26	1
Ventriculomegaly	27	0
Hyperechogenic bowel	27	0
Echogenic intracardiac	27	0
Choroid plexus cyst	27	0
Pyelectasis	27	0
Short femur & amp; humerus	27	0

Discussion

In the present study, we combined the data from 5 years of screening in the Yazd cohort study after the first and second prenatal screening policies by evaluating the PPV of different referral categories after invasive testing. Previous studies evaluating trisomy screening showed that the risks of T18 and T13 were small as part of a combination trial, but the combination trial nevertheless picked up more cases of T21.[8] According to previous studies, the probability of positive FTS is directly influenced by many factors, including maternal age and gestation. Amniocentesis is necessary for all FTS-positive mothers and will almost always detect chromosomal abnormalities.[14]

The results of our study on the causes of amniocentesis showed that the most common indications were older age, more than 35 years (46%), high risk of Down syndrome (23%) and average risk of Down syndrome (11.5%) in the screening test. The positive result of maternal serum screening, which accounts for more than half of the amniocentesis cases in our population (42%). In our study, the PPV for aneuploidies at karyotyping following amniocentesis after referral for abnormal screening findings was zero for all screening tests.

The most similar study to ours is Siljee and et al. They evaluated PPV for detection of trisomies 21, 18 and 13 and termination of pregnancy rates after referral for advanced maternal age. They showed that for referral from advanced maternal age (AMA), the PPV for T21 was 1.0% for amniocentesis and 1.8% for chorionic villus biopsy (CVB); for the combined test at a maternal age ≥ 36 years, these percentages were 4.9% and 12.5%, respectively and for maternal age < 36 years, 4.4% and 8.1%, respectively.[8]

According Li, et al., FTS is an effective means of screening for trisomy 21 in Southeast Asian populations. The PPV of FTS in detecting trisomies 21, 18 and 13 at 1:1,000 selected risk cut‐offs was 5.64%.[3] In another study that was performed in Iran by Heidari et al., predictive value of FTS markers for Down Syndrome (DS) in Iranian Pregnancies was evaluated. The PPV for PAPP-A, β-hCG, NT, and NB were 60.99%, 46.51%, 55%, and 100%, respectively. They concluded the novel decision-tree model base on serum markers revealed a better predictive value to achieve high sensitivity and specificity of first trimester DS screening in Iranian population.[15] Yassaee et al., in a comparative study evaluated amniocentesis following positive first trimester combined screening. Only 17.1% cases out of 70 (mothers with positive FTS) showed positive amniocentesis, which had a significant relationship with chromosomal abnormality. First trimester combined screening has very high accuracy (94.6%) in prediction of genetic abnormalities.[14] Abib et al. in Brazil evaluated first-trimester combined screening test for aneuploidies. The results of 2,748 patients were analyzed. The first trimester combined test achieved PPV of 6.91% and negative predictive value (NPV) of 99.76%. They concluded the combined test of

aneuploidy screening showed a detection rate inferior to those described in the literature for a higher FP rate.[16]

However according to Shirazi et al., the sensitivity of the first-trimester test was more than sensitivity of second- trimester screening but specificity of the second-trimester test more than sensitivity of first -trimester screening.[13] Ali Akbari et al., analyzed indications of amniocentesis and PPV of cytogenetic findings of chromosomal abnormalities. In their work the PPV analysis showed that the more the number of indications; the PPV tends to be maximized. Investigating indications and results of embryonic amniocentesis samples in the present study indicates the importance of genetic screening for the identification of chromosomal abnormalities in 5.5% of pregnant women.[10] Dar et al., said PPVs are more valuable to clinicians than detection rates. When the detection rate is close to 100% (as in the case for trisomy 21), it may provide a misleading view on noninvasive prenatal testing (NIPT) and suggest that it is actually a diagnostic test.[17]

Most studies evaluated PPV of non – invasive prenatal screening (NIPS) and few study assessed PPV of invasive prenatal screening such as amniocentesis. The studies evaluated PPV of NIPS reported range of 1 to 93 percent. Petersen AK et al. evaluated PPV estimates for cell-free NIPS from data of a large referral genetic diagnostic laboratory. Their results showed the PPV for trisomy 13, 18, and 21 were consistent with previous reports at 45%, 76%, and 84%, respectively.[12]

Neufeld-Kaiser et al., evaluated PPV of NIPS for fetal chromosome disorders. They reported the PPV for all conditions included in the screen was 77.4 % (95 % CI, 63.4-87.3).[9] Zhu and et al. evaluated efficiency of NIPS in pregnant women at advanced maternal age. Their results indicated the PPV of NIPS for detecting fetal trisomy 21 were 90.98. The PPV parameter for detecting fetal trisomy 18 was 67.92, and for detecting trisomy 13 was 27.78. The prevalence of fetal trisomy 21 increased exponentially with maternal age. The high-risk percentage incidence rate of fetal trisomy 21 was significantly higher in the pregnant women at 37 years old or above than that in pregnant women at 35 to 37 years old.[11] Meck et al., evaluated PPV of NIPS for Aneuploidy. They showed The PPV for NIPS were as follows: 93% for trisomy 21, 58% for trisomy 18, 45% for trisomy 13 and 23% for monosomy X.[18] Cell-free fetal DNA-based NIPS has been proven to be of high sensitivity and specificity for detecting common chromosomal aneuploidies (trisomies 21, 18 and 13), with low false positive and false negative rates. [11] It seems that NIPS had a higher sensitivity specificity and PPV than Invasive prenatal diagnosis, for detecting fetal trisomies 21, 18 and 13 in pregnant women.[11]

In this paper, we investigated the PPV of trisomies 21, 18, and 13 in mothers who referred to our cohort study after a combined first-trimester test or ultrasound and second-trimester findings, but we found that the PPV is very low and zero. Therefore, there is a need for more studies to analyze PPV and suggest improvements for clinical practice.

Conclusion

According to the results, the most common reason for introducing patients to amniocentesis was old age. The results of screening tests and various studies showed that the PPV of screening tests was very low and their false positive rate was very high. It is necessary to significantly decrease the number of unnecessary prenatal interventional diagnoses and improve the efficiency of prenatal screening.

Conflict of Interest

The authors have no conflict of interest.

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The present study was approved by the Ethics Committee of Islamic Azad University/ Yazd Branch (IR.IAU.YAZD.REC.1400.018).

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Review Article

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Genetic Association between ITPKC rs28493229 Polymorphism and Susceptibility to Kawasaki Disease: A Meta-Analysis

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ABSTRACT

Background: Studies investigating the association between ITPKC rs28493229 polymorphisms and Kawasaki disease (KD) risk found inconsistent data. Thus, we performed this meta-analysis to combine and analyze the available studies to get a precise estimation of the association.

Methods: Relevant studies identified in the PubMed, Web of Science, Scopus, and CNKI databases were used to perform a meta-analysis. Pooled odds ratios (OR) with a 95% confidence interval (95% CI) were calculated under fixed- and random-effects models to appraise the association.

Results: A total of eight case-control studies with 2,721 KD cases and 5,307 controls were selected. The results showed a statistically significant association between ITPKC rs28493229 polymorphism and an increased risk of KD under all five genetic models, i.e., allele (C vs. G: OR = 1.434, 95% CI 1.209-1.700, $P \leq 0.001$), homozygote (CC vs. GG: OR = 2.085, 95% CI 1.423-3.055, $P \leq 0.001$), heterozygote (CG vs. GG: OR = 1.530, 95% CI 1.359-1.722, $P \leq 0.001$), dominant (CC+CG vs. GG: OR = 1.490, 95% CI 1.229-1.806, $P \leq 0.001$), and recessive (CC vs. CG + GG: OR = 1.799, 95% CI 1.231-2.629, $P = 0.002$) in the overall population. When stratified by country, there was a significant association among Taiwanese.

Conclusion: Our meta-analysis results supported that the ITPKC rs28493229 polymorphism is strongly associated with susceptibility to KD.

Introduction

Kawasaki disease (KD; OMIM 300530) is an acute vasculitis of the medium- and small-sized arteries of childhood.[1-3] Population-based age adjusted-data showed that children under five years of age are mostly affected by KD with a male predominance. In the last decades, KD has been the Primary cause of acquired heart disease in children in East Asia, Europe, and North America.[1,4] It is noticeably more prevalent in Japan and other Asian countries (69-240 per 100.000) compared with Western countries (4-15 per 100.000) in children under the age of 5 years.[5-7] As the available data for specific diagnostic tests of KD are limited, the diagnosis is based on the presence of clinical criteria.[8,9] In 2004, American Heart Association (AHA) mounted diagnostic guidelines for the initial estimate, treatment in the acute phase, and long-term management of KD.[10] Standard treatment in acute KD consists of a single dose of high-dose intravenous immunoglobulin (IVIG) at 2 g/kg, preferably given within 10 days after the onset of fever.[11-13]

Although recent studies provide new insights into the mechanisms of immune activation in KD[14], the exact etiology of KD is still unknown. It is supposed that KD reflects an abnormal inflammatory response to one or more infectious agents or toxins in genetically predisposed people.[15] The prevalence of KD is increased in siblings with a history of KD or children with parental history of KD.[16] Inositol 1,4,5-trisphosphate (IP3) is a second messenger which transduces signals from cell surface receptors in T cells. Inositol 1,4,5-trisphosphate 3-kinase (ITPK) phosphorylates IP3 and serves as a negative regulator of the Ca^{2+} /nuclear factor of the activated T-cell signaling pathway.[17,18] Genome-wide association studies (GWAS) have emphasized the importance of functional variants in the *ITPKC* gene, which is a negative regulator of T-cell activation through the Ca2+/NFAT signaling pathway (Figure 1). Functional polymorphisms in the *ITPKC* gene may contribute to increased T cell activation, increased expression of cytokines, and immune hyper-reactivity in KD.[14,19,20]

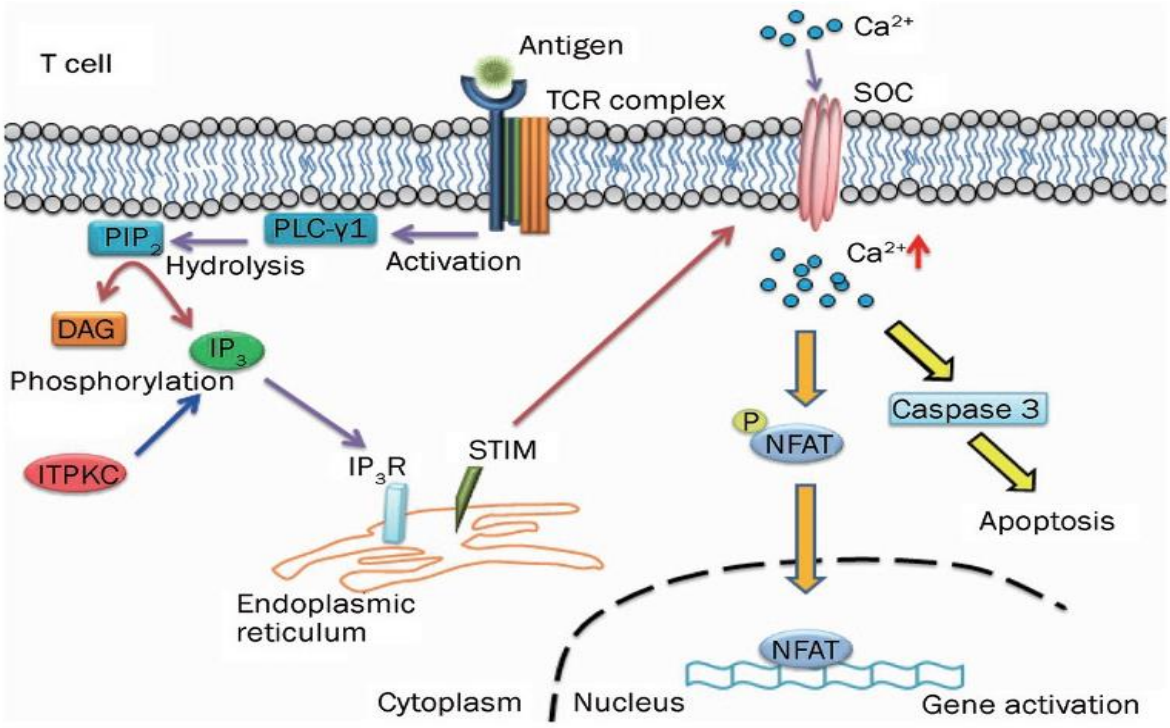

Figure 1. The ITPKC signaling pathways contribution to the susceptibility or clinical status of Kawasaki disease[20]

The C allele of the responsible SNP (rs28493229, C allele) alters the splicing efficiency of ITPKC intron 1 and then reduces the amount of mature ITPKC mRNA, which in turn results in increased signaling through the calcineurin/NFAT pathway and cell activation, and may contribute to immune hyperactivity in KD.[19]

The *ITPKC* gene, also recognized as MDR1, is located on chromosome 19q13.2. The *ITPKC* gene product is widely localized in the nucleus and cytoplasm and has both nuclear import and nuclear export activity. In 2008, Onouchi et al. provided new insights into the mechanisms of immune activation in Kawasaki disease and emphasizes the role of ITPKC rs28493229 polymorphism in the pathogenesis of KD.[14] However, some studies have shown no association between KD and polymorphism rs28493229 in ITPKC. For example, in 2018, Kim et al. reported that the ITPKC rs28493229 polymorphism has a protective effect against KD symptoms.[21] Thus, the association of the ITPKC rs28493229 polymorphism with KD risk is still ambiguous. Meta-analysis offers an opportunity to aggregate information from multiple studies, improving statistical power by increasing the sample size to exactly evaluate genetic polymorphisms outcomes on disease susceptibility. To assess the association between *ITPKC* rs28493229 polymorphism and the risk of KD, we performed a meta-analysis based on all eligible case-control studies published up to March 05, 2020.

Materials and Methods

Literate Search Strategy: Ethical approval was not required for this study, as it is a systematic review and meta-analysis. This work was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We have performed a comprehensive literature search on electronic databases including PubMed, EMBASE, Wed of Science, Elsevier, Google Scholar, Cochrane Library, SciELO, SID, WanFang, VIP, Chinese Biomedical Database (CBD), and Chinese National Knowledge Infrastructure (CNKI) to identify all relevant studies on the association between *ITPKC* rs28493229 polymorphism and Kawasaki disease risk up to March 05, 2020. Combinations of the following MeSH terms and keywords were used in the search: (“Kawasaki Disease” OR “KD” OR “Mucocutaneous Lymph Node Syndrome”) AND (‘’Inositol 1,4,5-trisphosphate 3-kinase C’’ OR ‘’ ITPKC’’ OR ‘’IP3KC’’ OR ‘’IP3-3KC’’) AND (‘’Gene’’ OR ‘’Single-Nucleotide Polymorphism” or “SNP” OR ‘’Polymorphism’’ OR ‘’Genotype’ OR ‘’Allele’’ OR ‘’Variation’’ OR ‘’Mutation’’). The search was limited to human studies published in English, Farsi, and Chinese language. We also reviewed the references list of relevant reviews and eligible publications to find other potential sources.

Inclusion Criteria: Studies meeting the following criteria were included: 1) studies with case-control or cohort design; 2) studies evaluated the association of *ITPKC* rs28493229 polymorphism and Kawasaki disease risk; 3) studies with available and sufficient data for calculating an odds ratio (OR) with 95% confidence interval (CI). The following exclusion criteria were also used: 1) animal studies or in vitro studies; 2) studies with sufficient data on genotype frequencies; 3) studies evaluated the association of other polymorphism of *ITPKC*; 4) linkage studies or family-based studies (including sibling, twins and trios-parents studies); 5) abstracts, case reports, commentaries, editorials, conference articles, reviews, proceedings and meta-analyses; and 6) duplicates or overlapping studies. If more than one study was published by the same author(s) using repeated or overlapped data, the studies with the largest sample size or the most recently published study were included in the meta-analysis.

Data Extraction: Two authors independently reviewed all eligible articles and extracted all necessary data according to

the inclusion criteria. For any discrepancies, a discussion was made to reach an agreement. If the two authors could not reach a consensus, then a third investigator was consulted to resolve the dispute and a final decision was made by the majority of the votes. For each eligible study, the following data were collected: first author name, year of publication, country of origin, ethnicity (Caucasian, Asian, African, Mixed populations), source of controls (hospital-based or population-based), genotyping methods, sample size, allele and genotype frequency of *ITPKC* rs28493229 polymorphism in cases and controls, Minor Allele Frequency (MAFs) and Hardy-Weinberg equilibrium (HWE) in healthy controls. In this meta-analysis different case-control groups or cohorts in one publication were considered independent studies.

Statistical Analysis: The strength of the association between *ITPKC rs28493229* polymorphism and KD risk was estimated by odds ratio (OR) with the corresponding 95% confidence intervals (CIs). The significance of pooled ORs was tested by Z-test, in which $P < 0.05$ was considered significant. The association of *ITPKC rs28493229* polymorphism was estimated under five genetic models, i.e., allele (C vs. G), homozygote (CC vs. GG), heterozygote (CG vs. GG), dominant (CC + CG vs. GG), and recessive (CC vs. CG + GG)**.** The chi-square test was used to evaluate the between-study heterogeneity. If $P < 0.10$, it was considered to have significant heterogeneity in statistics. Moreover, I^2 test to quantify the heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance ($I^2 < 25\%$, no heterogeneity; I^2 25-50%, moderate heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity).[22] When significant heterogeneity existed, we selected a random-effects model (the DerSimonian and Laird method) for statistics. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used. The Hardy-Weinberg equilibrium (HWE) of the controls was evaluated by Fisher exact test and a p-value less than 0.05 was considered significant disequilibrium (HWE-violating). Subgroup analyses by ethnicity, country, source of controls, and genotyping methods were performed to explore the potential sources of between-study heterogeneity in the meta-analysis. One-way sensitivity analysis, by which a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set for the pooled OR, was carried out to assess the stability of the results. Moreover, sensitivity analysis was done by excluding HWE-violating studies. Begg's funnel plots were generated to assess the potential influences of the publication bias on the results. An asymmetrical plot usually indicates the existence of publication bias.[23] Moreover, Egger's linear regression test which measures funnel plot asymmetry using a natural logarithm scale of OR was performed to evaluate the symmetry of the plot. All statistical tests were performed using CMA software. All P values in the meta-analysis were 2-sided, and P values less than 0.05 were considered significant.

Results

Characteristics of Selected Studies: The process of the literature search and selection is shown in figure 2. Initially, our search strategy yielded 101 possibly relevant articles. Twenty-nine studies were removed due to duplication, and 79 articles were removed because they were not case-control studies, human research, or without available data and previous meta-analyses. Finally, a total of eight case-control studies with 2,721 KD cases and 5,307 controls were included in the meta-analysis.[14,17,18,21,24-27] The characteristics of the included studies are summarized in table 1. KD cases in the studies ranged from 17 to 637 and selected studies were published between January 2008 and January 2018. In terms of ethnicity, seven studies were performed among Asians and one study was conducted among Caucasians.

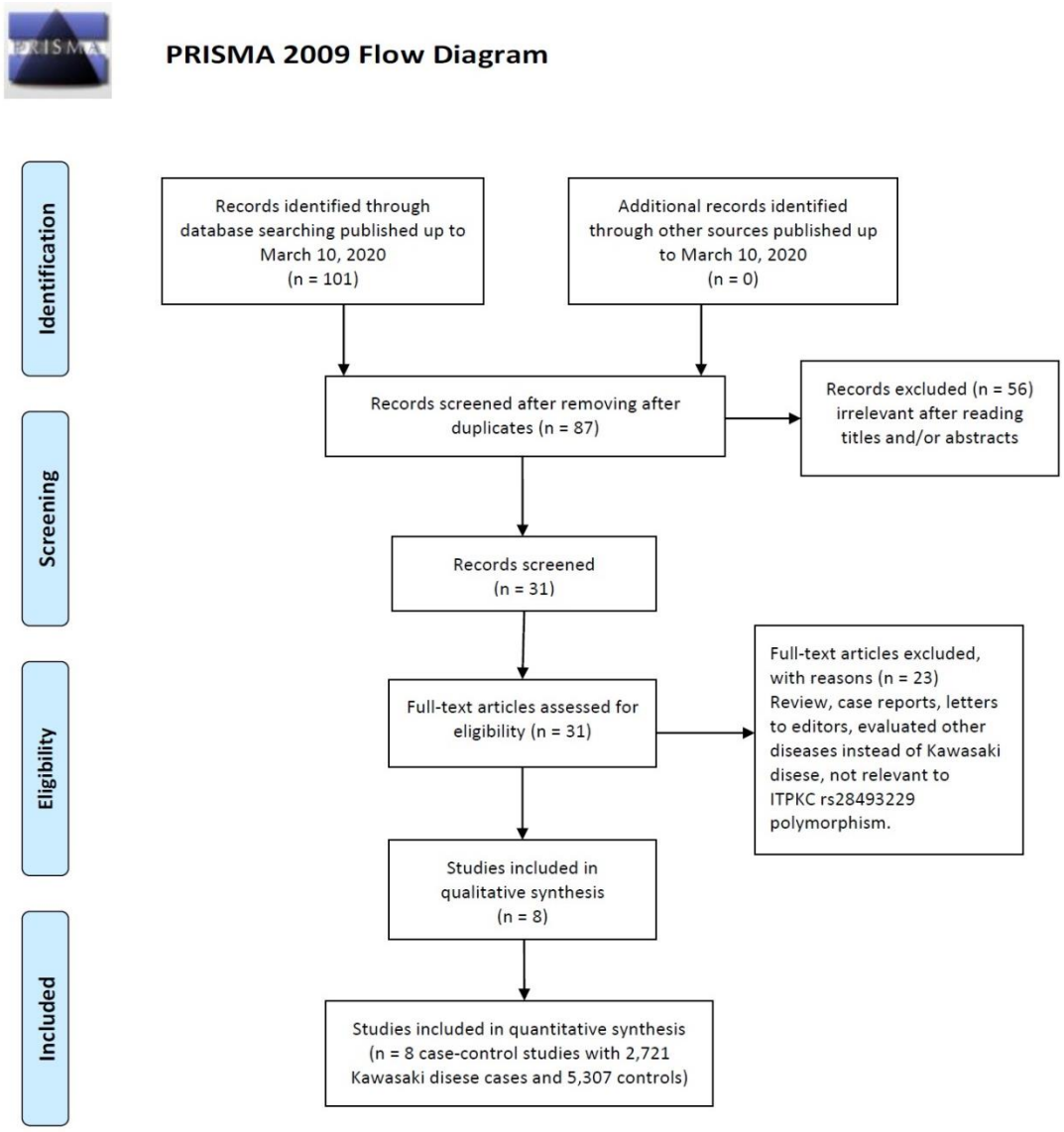

Figure 2. Flowchart of literature search and selection process

The studies have been carried out in Japan, Taiwan, China, South Korea, and Australia. As seen in table 1, three genotyping methods including TaqMan, sequencing, and RFLP-PCR were used to genotype the *ITPKC* rs28493229 polymorphism. The allele, genotype, and minor allele frequency (MAF) distributions for *ITPKC* rs28493229 polymorphism in KD cases and healthy controls were presented in table 1. Hardy-Weinberg equilibrium (HWE) was calculated for all eight publications and $P < 0.05$ was considered as a departure from HWE (Table 1).

Quantitative Data Synthesis: The summary results for the association between *ITPKC rs28493229* polymorphism and KD risk are shown in table 2. Overall, pooled data revealed a significant association between the *ITPKC rs28493229* polymorphism and an increased risk of KD under all five genetic models, i.e., allele (C vs. G: OR = 1.434, 95% CI 1.209-1.700, $P \leq 0.001$), homozygote (CC vs. GG: OR = 2.085, 95% CI 1.423-3.055, $P \leq 0.001$, Figure 2B), heterozygote (CG vs. GG: OR = 1.530, 95% CI 1.359-1.722, $P \leq 0.001$), dominant (CC+CG vs. GG: OR = 1.490, 95% CI 1.229-1.80 been carried out6, $P \leq 0.001$), and recessive (CC vs. CG+GG: OR = 1.799, 95% CI 1.231-2.629, $P = 0.002$) (Figure 3A-E).

Table 1. Characteristics of Studies Included in This Meta-Analysis

Author/Year	Country (Ethnicity)	SOC	Genotyping Methods	Case/Control	Cases					Controls					MAFs	HWE
					Genotypes			Allele		Genotypes			Allele			
					GG	GC	CC	G	C	GG	GC	CC	G	C		
Onouchi 2008	Asians	PB	TaqMan	637/1034	376	234	27	986	288	756	249	29	1761	307	0.148	0.126
Onouchi 2011	Japan(Asian)	PB	Sequencing	546/938	330	191	25	851	241	662	261	15	1585	291	0.155	0.059
Chi 2011	Taiwan(Asian)	NS	TaqMan	385/1158	323	61	1	707	63	1008	147	3	2163	153	0.066	0.327
Lin 2011	Taiwan(Asian)	NS	Sequencing	280/492	236	43	1	515	45	454	37	1	945	39	0.040	0.787
Kuo 2011	Taiwan(Asian)	PB	TaqMan	334/1131	282	50	2	614	54	981	142	8	2104	158	0.070	0.256
Peng 2012	China(Asian)	HB	PCR-RFLP	223/318	195	27	1	417	29	274	40	4	588	48	0.075	0.078
Natividad 2013	Australia(Caucasian)	HB	Sequencing	17/26	16	1	0	33	1	22	4	0	48	4	0.077	0.670
Kim 2018	Korea(Asian)	HB	TaqMan	299/210	231	64	4	526	72	178	32	0	388	32	0.076	0.232

SOC: source of control; PB: population-based; HB: hospital-based; NS: not stated; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium

Table 2. Summary Risk Estimates for Association of ITPKC rs28493229 Polymorphism with Kawasaki Disease Risk

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	C vs. G	Random	51.87	0.042	1.434	1.209-1.700	4.143	≤0.001	0.386	0.216
	CC vs. GG	Fixed	13.11	0.330	2.085	1.423-3.055	3.768	≤0.001	0.763	0.408
	CG vs. GG	Fixed	49.08	0.056	1.530	1.359-1.722	7.029	≤0.001	0.173	0.225
	CC+CG vs. GG	Random	54.33	0.032	1.490	1.229-1.806	4.061	≤0.001	0.173	0.193
	CC vs. CG+GG	Fixed	8.69	0.362	1.799	1.231-2.629	3.033	0.002	0.548	0.523
Taiwanese	C vs. G	Random	59.37	0.085	1.360	1.116-1.658	3.043	0.002	0.548	0.387
	CC vs. GG	Fixed	0.00	0.887	1.048	0.327-3.358	0.079	0.937	0.296	0.260
	CG vs. GG	Random	56.84	0.099	1.471	1.058-2.045	2.298	0.022	1.000	0.197
	CC+CG vs. GG	Random	58.89	0.088	1.407	1.142-1.734	3.203	0.001	1.000	0.191
	CC vs. CG+GG	Fixed	0.00	0.903	1.006	0.314-3.221	0.010	0.992	0.296	0.255
Source of Controls										
PB	C vs. G	Random	61.46	0.075	1.103	0.591-2.060	0.308	0.758	1.000	0.642
	CC vs. GG	Random	60.77	0.110	1.326	0.073-5.977	0.190	0.849	NA	NA
	CG vs. GG	Fixed	34.06	0.219	1.206	0.855-1.701	1.067	0.286	1.000	0.506
	CC+CG vs. GG	Random	51.97	0.125	1.133	0.634-2.024	0.422	0.673	1.000	0.587
	CC vs. CG+GG	Random	58.45	0.121	1.005	0.173-5.829	0.006	0.995	NA	NA
HB	C vs. G	Fixed	45.00	0.162	1.541	1.366-1.739	7.024	≤0.001	0.296	0.142
	CC vs. GG	Fixed	39.16	0.193	2.214	1.482-3.308	3.879	≤0.001	1.000	0.671
	CG vs. GG	Random	60.38	0.080	1.544	1.218-1.956	3.594	≤0.001	0.296	0.421
	CC+CG vs. GG	Random	59.82	0.083	1.578	1.256-1.982	3.913	≤0.001	0.296	0.280
	CC vs. CG+GG	Fixed	41.70	0.180	1.888	1.267-2.812	3.126	0.002	1.000	0.759

Table 2. Summary Risk Estimates for Association of ITPKC rs28493229 Polymorphism with Kawasaki Disease Risk (Continue)

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Genotyping Methods										
TaqMan	C vs. G	Fixed	42.31	0.158	1.493	1.308-1.705	5.928	≤0.001	0.734	0.441
	CC vs. GG	Fixed	0.00	0.596	1.751	1.073-2.857	2.243	0.025	0.734	0.897
	CG vs. GG	Random	50.90	0.106	1.500	1.190-1.891	3.435	0.001	0.734	0.295
	CC+CG vs. GG	Random	55.38	0.081	1.505	1.185-1.912	3.354	0.001	0.734	0.357
	CC vs. CG+GG	Fixed	0.00	0.661	1.476	0.908-2.400	1.571	0.116	0.734	0.942
Sequencing	C vs. G	Fixed	40.66	0.185	1.606	1.349-1.911	5.337	≤0.001	1.000	0.833
	CC vs. GG	Fixed	0.00	0.704	3.248	1.719-6.136	3.629	≤0.001	NA	NA
	CG vs. GG	Random	52.74	0.120	1.641	1.053-2.557	2.189	0.029	1.000	0.308
	CC+CG vs. GG	Fixed	44.85	0.163	1.656	1.357-2.021	4.967	≤0.001	1.000	0.807
	CC vs. CG+GG	Fixed	0.00	0.722	2.874	1.528-5.408	3.274	0.001	NA	NA

PB: population-based; HB: hospital-based; NA: Not Applicable

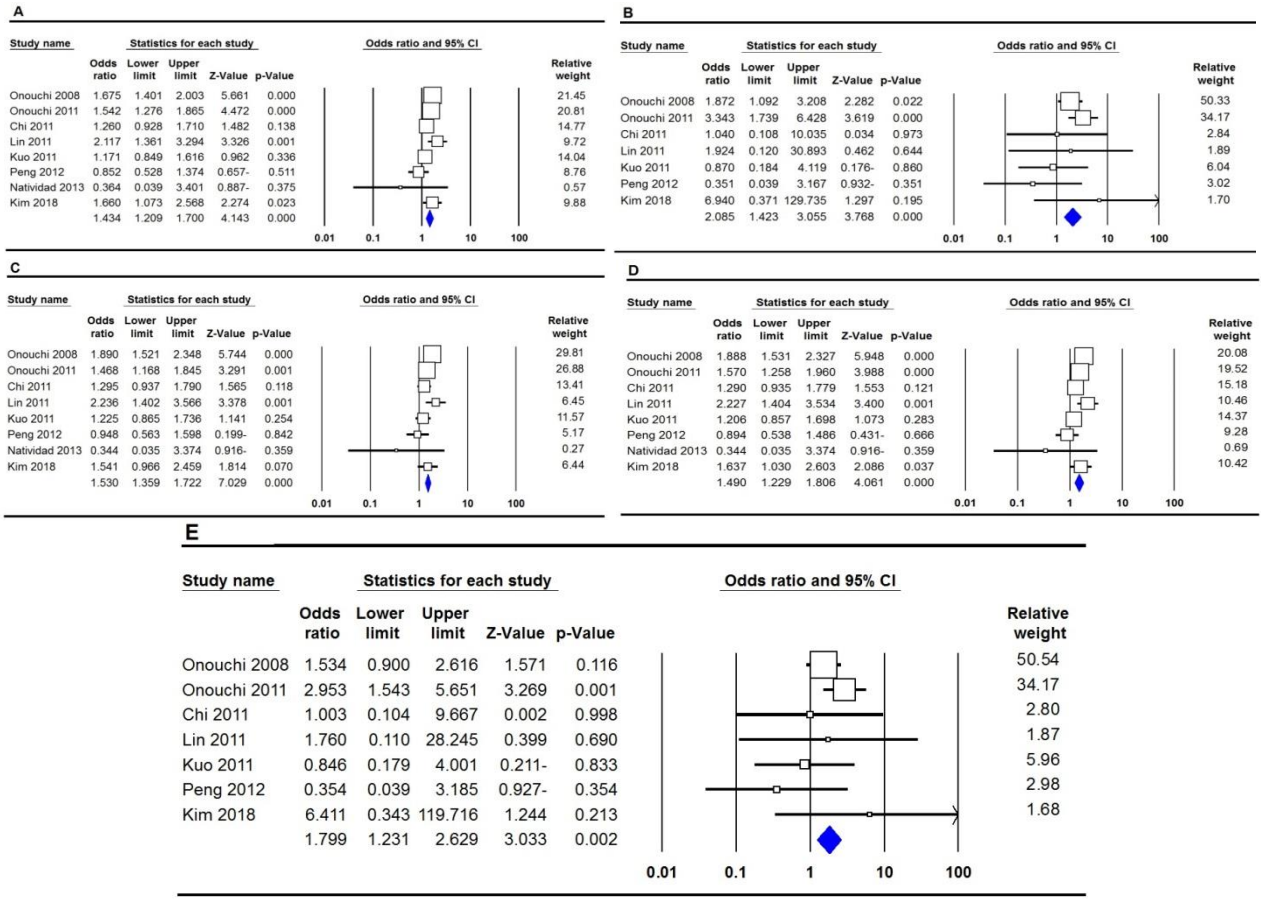

Figure 3. Forest plot for association of ITPKC rs28493229 polymorphism with risk of KD in the overall population. A: allele model (C vs. G); B: homozygote model (CC vs. GG); C: heterozygote model (CG vs. GG); D: dominant model (CC+CG vs. GG); and E: recessive model (CC vs. CG+GG)

Moreover, we performed subgroup analysis based on country of origin and ethnicity. Because of insufficient data, we did not analyze the association between *ITPKC rs28493229* polymorphism and KD risk in Caucasians. We analyzed the association between *ITPKC rs28493229* polymorphism and KD risk in Asians, and a significant association was observed under all five genetic models. Moreover, there was a significant association among Taiwanese under three genetic models, i.e., allele (C vs. G: OR = 1.360, 95% CI 1.116-1.658, P = 0.002), heterozygote (CG vs. GG: OR = 1.471, 95% CI 1.058-2.045, P = 0.022), and dominant (CC+CG vs. GG: OR = 1.470, 95% CI 1.142-1.734, P = 0.001). In the subgroup analysis regarding the source of controls, an increased risk of KD was found in the hospital-based subgroup under all five genetic models, but not in the population-based subgroup. Furthermore, these data were further stratified by genotyping methods, a significant association between the *ITPKC rs28493229* polymorphism and KD risk was observed in TaqMan and sequencing subgroup, in agreement with the overall data.

Between-Study Heterogeneity: There was no considerable heterogeneity detected between studies included in the analysis. The I^2 value under two models, i.e., allele (C vs. G: I^2 = 51.87; P_H = 0.042) and dominant (CC + CG vs. GG: I^2 = 54.33; P_H = 0.032) was greater than 50%, indicating that the included studies show heterogeneity. Therefore, we have performed subgroup analyses by ethnicity, country, source of controls, and genotyping methods to explain the potential source of heterogeneity. As shown in

table 2, when subgroup analyses were performed, the between-study heterogeneity did not change considerably, indicating these factors might not be the major source of heterogeneity in this meta-analysis.

Sensitivity Analysis: Sensitivity analysis was performed to test the influence of individual studies on the stability of the overall ORs by omitting one study at a time. The omission of any single study did not significantly affect the pooled ORs or 95% CIs, suggesting the meta-analysis results may be reliable.

Publication Bias: Begg's and Egger's linear regression tests were used to assess the potential publication bias for the association between *ITPKC rs28493229* polymorphism and KD risk in the overall meta-analysis. Table 2 lists the publication bias assessment method with its respective P-value for each test. The shapes of the funnel plots did not show any evidence of publication bias in the overall population, as shown in figure 4. Moreover, Egger's test did not find any publication bias under all five genetic models, i.e., allele (C vs. G: P_{Beggs} = 0.386; P_{Eggers} = 0.216), homozygote (CC vs. GG: P_{Beggs} = 0.763; P_{Eggers} = 0.408), heterozygote (CG vs. GG: P_{Beggs} = 0.173; P_{Eggers} = 0.225), dominant (CC + CG vs. GG: P_{Beggs} = 0.173; P_{Eggers} = 0.193), and recessive (CC vs. CG+GG: P_{Beggs} = 0.548; P_{Eggers} = 0.523), suggesting no evidence of publication bias.

Discussion

To date, only a meta-analysis has been performed to evaluate the *ITPKC* rs28493229 polymorphism and KD risk in the global population in 2012.[28] Therefore, it is necessary to perform an updated meta-analysis to evaluate the *ITPKC* rs28493229 polymorphism and KD risk based on previous and newly published eligible case-control studies. In the current study, we systematically reviewed and meta-analyzed the relationship between *ITPKC* rs28493229 polymorphism and KD risk. The results of this meta-analysis revealed a strong association between the *ITPKC* rs28493229 polymorphism and an increased risk of KD under all five genetic models.

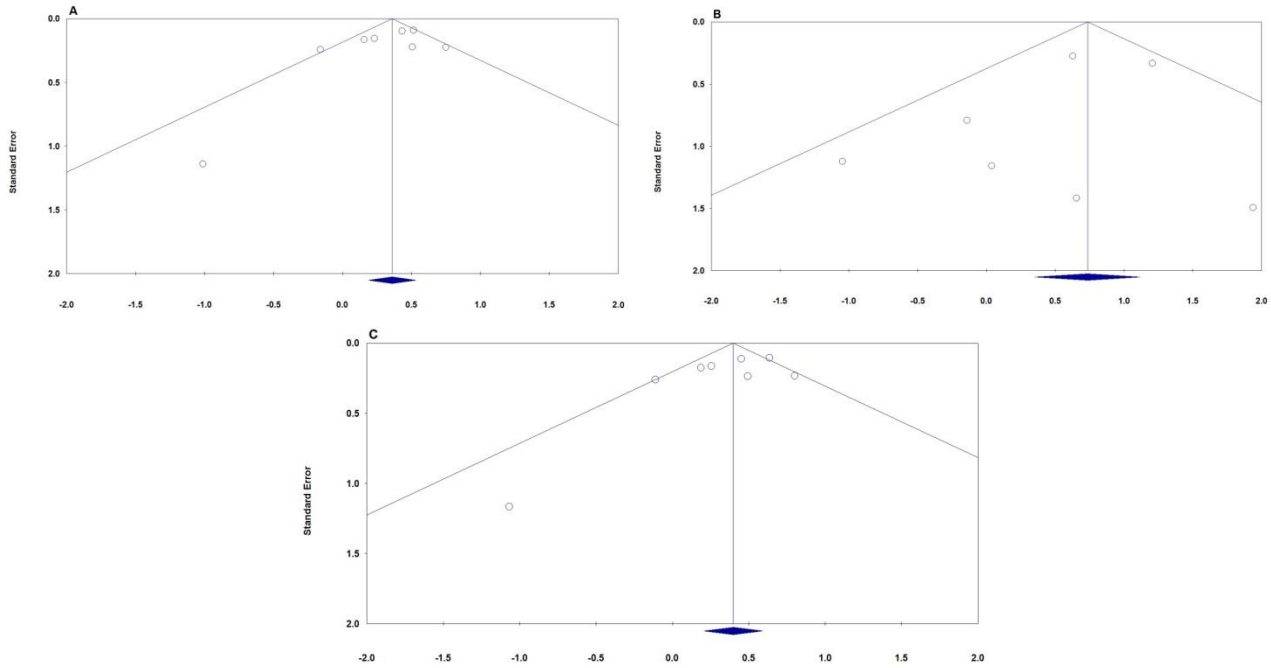

Figure 4. The funnel plots of publication bias for association of the ITPKC rs28493229 polymorphism with risk of KD in the overall population. A: allele model (C vs. G); B: homozygote model (CC vs. GG); and C: dominant model (CC+CG vs. GG)

Our pooled data strongly support the *ITPKC* rs28493229 polymorphism role in the development of pediatric KD. In 2008, Onouchi et al., found that the *ITPKC* rs28493229 polymorphism was significantly associated with increased susceptibility to KD and an increased risk of coronary artery lesions in US and Japanese children.[14] Two years later, another case-control study performed by Chi et al. evaluated the association among 385 unrelated Taiwanese pediatric patients with KD (222 male and 163 female). The results of this study did not reveal a significant association between *ITPKC* rs28493229 polymorphism and KD risk KD or CALs in Taiwanese children.[17] Khor et al., in a large case-control GWAS in 2,173 KD patients and 9,383 healthy controls evaluated the association of this locus with KD risk. Their results confirmed the previous findings of a genetic association in the region of the *ITPKC* gene.[29] In 2018, Kim et al. in the most recently published study revealed a significant association between the *ITPKC* rs28493229 polymorphism and an increased risk of KD in Korean children.[21] In 2012, Lou et al., in a meta-analysis based on seven case-control studies with 3,821 cases, and 12,802 controls evaluated the relationship of *ITPKC* rs28493229 polymorphism with KD risk under the allele genetic model. Their results showed a significant association between the C allele of rs28493229 polymorphism and an increased risk of KD (OR = 1.53, 95% CI = 1.34-1.74, P < 0.001).[28] However, their polled data remains an open field, because their data reliability and the number of included studies were smaller than that needed to receive a reliable conclusion. Moreover, they evaluated the association only under the allele genetic model, and subgroup analyses were also not conducted.

Between-study heterogeneity is to be expected in a meta-analysis. The clinical variation, study design, ethnicity, sample size, source of controls, genotyping method, and HWE are among the major causes of heterogeneity.[30-34] In the current meta-analysis, we perceived that significant heterogeneity was found in two genetic models. After subgroup analyses by ethnicity, the heterogeneity still existed with a slight reduction. Meanwhile, other available variables including publication year, sample size, and genotyping method could not be considered as the source of the heterogeneity, suggesting the existence of other unknown factors influencing the heterogeneity among included studies.

Similar to other meta-analyses, there were several limitations in the current study. First of all, we only searched the literature issued in English and Chinese. Thus, potentially relevant papers published in other languages may not be identified, which might introduce potential selection bias. Second, the majority of the included studies in this meta-analysis were conducted on Asians which may introduce ethnicity bias, and further studies should perform on Caucasians and Africans. Third, because of the limited study number in subgroup analysis, the power used to detect the association between *ITPKC rs28493229* polymorphism and KD risk may not be strong enough. Fourth, there was a significant heterogeneity under the allele and dominant genetic models in the overall population, which could be because the analysis included few studies in the analysis or due to insufficient data that limited further subgroup analysis. So, more relevant case-control studies are required to be performed and then included in the meta-analysis to get more reliable and scientific data. Finally, this meta-analysis exclusively concentrated on the association between *ITPKC rs28493229* polymorphism and KD risk without considering gene-gene or gene-environment interactions. Therefore, to comprehensively demonstrate the etiology of KD, it is extremely required to study the combined interaction of the related genes.

Conclusion

In summary, our pooled data revealed that the *ITPKC rs28493229* was significantly

associated with susceptibility to childhood KD. The results of this meta-analysis may improve our understanding of the role of *ITPKC rs28493229* polymorphism in the etiology of KD, and aid in the diagnosis of high-risk patients with KD. Because of the limitations mentioned above in the meta-analysis, larger and well-designed studies in different ethnicities are needed to confirm our data.

Conflict of Interest

The authors have no conflict of interest.

Acknowledgments

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Case Report

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A Case Report of Neurocutaneous Melanosis with Associated Dandy-Walker Complex

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ABSTRACT

Background: Neurocutaneous melanosis (NCM) and Dandy-Walker malformation (DWM) are two forms of rare congenital neurodysplasia. NCM is a rare dysmorphogenesis characterized by single or multiple giants pigmented cutaneous nevi and the involvement of benign and/or malignant melanocytic tumors of the leptomeninges. DWM is a rare congenital malformation of the brain. Cystic enlargement of the fourth ventricle is its characteristic that communicates with an enlarged posterior fossa, cerebellar dysgenesis, high tentorial insertion, and hydrocephalus. However, these two conditions are rare, and NCM associated with DWC is even more unusual.

Case Report: Here, we report a male newborn with macrocephaly and multiple pigmented nevi over his whole body with regular borders and normal weight, height, and spine. He was finally diagnosed as NCM in association with DWC.

Conclusion: After diagnosing NCM in association with DWC, appropriate follow-up is recommended; however, there is no particular treatment to prevent the malignant change.

Introduction

Studies have demonstrated significant associations between congenital abnormalities of the skin and the central nervous system.[1] A rare congenital neurocutaneous syndrome, named neurocutaneous melanosis (NCM), is characterized by large or multiple pigmented nevi in combination with leptomeningeal melanosis or Melanoma.[2-4] Cutaneous lesions are usually diagnosed at birth - though more may appear later- but neurological

manifestations emerge as the pressure gradient between the cerebrospinal fluid and venous pressure decreases.[5,6] The condition presents in the form of Dandy-Walker malformation (DWM), including the growth of the posterior fossa, high-set tentorium, underdevelopment (small size and abnormal position) of the middle part of the cerebellum (cerebellar vermis), and cystic dilation of the fourth ventricle that is communicating with the posterior fossa and also hydrocephalus.[3] Although shunt placement and chemotherapy may result in temporary alleviation, the prognosis of the association of NCM and DWM is still inferior, and affected children usually die earlier than age four years.[4,5] Here, we present a rare case of NCM in association with DWC.

Case Report

The case is a male newborn in Shahid Sadoughi Hospital with multiple pigmented skin patches. He was a product of a non-consanguineous marriage with an uneventful delivery. There was no family history of a similar condition. In physical examination, he had a macrocephaly and multiple pigmented nevi over his whole body with an average size of 20-50 mm and regular borders (Figure 1).

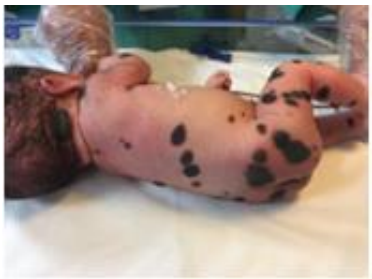

Figure1. Multiple congenital melanocytic nevi

His weight, height, and spine were normal. Routine laboratory investigations at admission to the neonatal intensive care unit showed normal values for his age. Computerized tomography (CT) showed bi-compartmental hydrocephalus with enlargement of the posterior fossa and vermian hypoplasia, suggesting a DWM. There was no evidence of space-occupying lesions and no calcifications or hemorrhages (Figure 2).

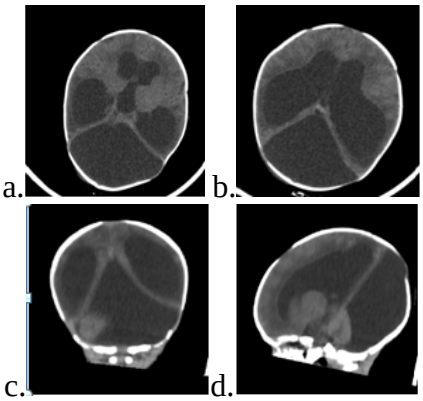

Figure2. Computed tomography demonstrates the hydrocephalus and hypoplasia of cerebellum and enlarged fourth ventricle: a,b: hydrocephalus, c,d: hypoplasia of cerebellum, d: enlarged fourth ventricle

Discussion

NCM is a rare congenital disorder characterized by excessive proliferation of melanin-producing cells in both the skin and leptomeninges. To our knowledge, nearly 300 cases of this non-heritable syndrome are reported in the literature[4] and 10% were associated with DWM.[4,5] The criteria for this lesion were as follows; 1) giant nevus (greater than 20 cm in adults and lesions that are approximately 9 cm in diameter on the head or 6 cm on the body in infants), 2) multiple nevi (greater than or equal to 3 lesions), 3) no evidence of cutaneous Melanoma, except in cases where meningeal lesions are histologically benign, 4) no evidence of meningeal Melanoma except in cases where the cutaneous lesions are benign.[1,7] According to the above criteria, our case was compatible with the diagnosis of neurocutaneous melanosis. Neurocutaneous melanosis may be associated with syndromes such as Sturge-Weber or von Recklinghausen's disease. Associations were also reported with the Dandy-Walker complex, spinal lipoma, and arachnoid cyst.[6,7] The association of DWM with NCM has an inferior prognosis.[8] In all reported cases, the patients showed rapid neurological deterioration and death by four years of age. These two abnormalities show a

phenotypic marker for more profound melanotic infiltration of the leptomeninges, increasing the risk of malignant transformation.[5] An insult to the development of the cerebellar hemisphere and the fourth ventricle may result in the Dandy-Walker complex. The fourth ventricle-cisterna Magna cyst may be formed due to any failure of incorporation between the choroid plexus and the roof of the fourth ventricle or the delayed opening of the foramen Magendie. The meningeal cells influence cerebellar development. In NCM, the development of both the cerebellum and the fourth ventricle may be disrupted because of the melanin-containing abnormal leptomeninges.[8,9]

Conclusion

In this report, we presented a case of NCM with DWM. The association of NCM with DWM is increasingly recognized, and it carries an inferior prognosis.

Conflict of Interest

The authors have no conflict of interest.

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Case Report

http://wjpn.ssu.ac.ir

Turner Syndrome and Beta Thalassemia Major: A Rare Association

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ABSTRACT

Background: Turner syndrome (TS) is the most common genetic disorder affecting only females. The criteria for diagnosis include the complete or partial absence of the second sex (x) chromosome (with or without cell line mosaicism) plus short stature and primary ovarian failure with or without the presence of other phenotypic TS features. The genotype in TS, as tested in peripheral blood, is most commonly 45xo. β-thalassemia major or transfusion-dependent thalassemia refers to severe β-thalassemia that requires early transfusion therapy. The association between Turner syndrome and thalassemia major is rare, which may result from transcription factor gene mutation.

Case Report: We report a girl with thalassemia major who was treated by recurring monthly transfusions since the age of six months. Short stature, triangular face, low set ear, hypertelorism, webbed neck, lordosis and genu valgum were observed in the examination. The patient was diagnosed with Turner syndrome, and her karyotype also was defined as 45xo.

Conclusion: In the case of Turner syndrome and β-thalassemia major association, a mutation in the transcription factor gene is proposed, which can be confirmed by genetic testing.

Introduction

Turner syndrome (TS) is caused by complete or partial monosomy of the x chromosome.[1] About half the patients with TS have a 45xo chromosome complement.[2,3] Turner syndrome occurs in 1 of 2000 to 4000 live female births.[4,5] It is also defined by a combination of phenotypic features. Small size for gestational age, webbed neck, protruding ears, and lymphedema of the hands and feet are the clinical signs of Turner syndrome. However,

many infants are phenotypically normal. Older children and adults have short stature and show variable dysmorphic features. Structural renal anomalies (60%) and congenital heart defects (40%) are common features of TS. Bicuspid aortic valves and coarctation of the aorta are the most common heart defects. Following gonads' replacement by fibrous streaks, primary amenorrhea and lack of secondary sex characteristics happen.[6] Chromosome analysis must be considered routinely in short females. Ultrasonography of the heart, kidneys, and ovaries is recommended after the diagnosis is established. Plasma levels of gonadotropins, particularly follicle-stimulating hormone (FSH), are markedly increased by 10-11 years of age.[7]

To detect autoimmune thyroiditis, thyroid function tests should be checked regularly. Measuring tissue transglutaminase immunoglobulin A antibodies, Turner syndrome females should be screened for celiac disease. Initial testing should be done around age four and repeated every 2-5 years.[7]

Treatment with recombinant human growth hormone increases height velocity in children with Turner syndrome. Replacement therapy with estrogens is indicated at 12-13 years.[7]

On the other hand, thalassemia represents a group of genetic disorders of globin-chain production resulting from an imbalance between α-globin and β-globin chain production.[8,9] β-thalassemia syndromes originate from a genetic deficiency in the synthesis of beta-globin chains. There are more than 200 different mutations leading to absent or decreased globin production. Inadequate β-globin gene production leading to decreased levels of normal hemoglobin (HbA) and unbalanced α and β-globin chain production leading to ineffective erythropoiesis are two related features that contribute to the sequelae of β-thalassemia syndromes.[3]

If not treated, children with homozygous β-thalassemia usually become symptomatic from progressive anemia during the 2nd 6 mo of life. Chronic transfusion therapy dramatically improves the quality of life and reduces the complications of severe thalassemia.

Transfusion induces hemosiderosis, which becomes the major clinical intricacy of transfusion-dependent thalassemia.[3]

Case Report

A four-year and seven-month-old girl with thalassemia major who was treated by recurring monthly transfusion since the age of six months had been referred to the endocrine clinic. Her parents were consanguineous. In the examination, triangular face, low set ear, hypertelorism, webbed neck, lordosis, and genu valgum were observed. Her weight and height were measured as 11kg (< 5%) and 91cm (< 5%, SDS = -3.5), respectively. The patient was diagnosed with Turner syndrome, and her karyotype was also defined as 45xo. Her kidney sonography, echocardiography, and thyroid were normal. The patient's laboratory tests for celiac disease were also negative. In the patient's follow-up examinations at ten years of age, her growth velocity was low, and the results of her paraclinical tests were as follows:

Table1. The Results of Paraclinical Test

Paraclinical tests of the patient		
LH		3.7 U/L
FSH		29.5 U/L
Estradiol		< 5 pg/ml
BMD	Lumbar spine	-3.1
	Femur	-3.5

Discussion

Turner syndrome (TS) is a rare chromosomal disorder affecting females and is characterized by short stature and lack of sexual development at puberty. Patients with TS have an abnormal karyotype involving the X chromosome.[10] Many patients with Turner syndrome are identifiable at birth because of a characteristic edema of the dorsum of the hands and feet. Low birth weight and reduced birth length are common. Characteristic appearance in childhood includes webbing of the neck, a low posterior hairline, a small mandible, prominent ears, epicanthal folds,

high arched palate, a barrel chest, widely spaced nipples, cubitus valgus and hyperconvex fingernails. The diagnosis is often first suspected at puberty when breast development fails. Short stature, the cardinal finding in all females with Turner syndrome, may be present with little in the way of other clinical manifestations.[11]

Our patient's karyotype was 45xo, and ultrasonography of the heart and kidneys was normal. The results of her thyroid and celiac disease were also normal. In follow-up at ten years, growth velocity was low and primary hypogonadism was diagnosed according to laboratory test results.

Thalassemia is a group of disorders resulting from an inherited abnormality of production of the globin moiety of hemoglobin. Thalassemia syndromes are characterized by varying degrees of ineffective hematopoiesis and increased hemolysis.[12]

Turner syndrome and thalassemia major association are rare, which may result from transcription factor gene mutation. Our patient was not investigated for genetic tests due to the high cost.

Conclusion

In the case of Turner syndrome and beta-thalassemia significant association, a mutation in the transcription factor gene is proposed, which can be confirmed by genetic testing.

Conflict of Interest

The authors have no conflict of interest.

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Case Series
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Glycogen Storage Disease Type Ia, Different Clinical Manifestations and Outcome: A Case Series

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ABSTRACT

Background: Conversion of glucose-6-phosphate to glucose is the final step in both glycogenolysis and gluconeogenesis. In glycogen storage disease type Ia (GSD type Ia), decreased activity of the enzyme glucose-6-phosphatase leads to an increased concentration of glucose-6-phosphate within the hepatocytes and shunting into alternative pathway with the following consequences: hyperlactatemia, hyperuricemia and hypertriglyceridemia. Patients develop hypoglycemia within 3 to 4 hours after a meal.

Case Report: We reported four patients with GSD type Ia with different clinical manifestations such as hypoglycemia, hepatomegaly, lactic acidosis, hyperchylomicronemia, and hyperuricemia and also described their prognosis.

Conclusion: Previously, many children with GSD Ia died in infancy or early childhood. Recurrent severe hypoglycemia can cause brain damage, but the prognosis has improved dramatically with early diagnosis and long term maintenance of optimal metabolic control.

Introduction

Glycogen storage disease type I (GSD I) is an autosomal recessive disorder due to the absence or deficiency of glucose-6-phosphatase activity in the liver, kidney and intestinal mucosa. It has two subtypes: type Ia, in which glucose-6-phosphatase is the defective enzyme and type Ib, in which the defective enzyme is a translocase that transports glucose-6-phosphate across the microsomal membrane. Deficiency of the enzymes in both type Ia and Ib cause inadequate hepatic conversion of glucose-6-phosphate to glucose through

normal glycogenolysis and gluconeogenesis, leading to fasting hypoglycemia.[1,2]

The genes for glucose-6-phosphatase and translocase are located on chromosomes 17q21 and 11q23, respectively. Common pathogenic variants have been identified.

Clinical manifestation: Patients with GSD type Ia may present in the neonatal period with hypoglycemia and lactic acidosis but more often present at 3-4 months of age with hepatomegaly, hypoglycemic seizures, or both.[1] Affected children often have a doll-like face with fat cheeks, relatively thin extremities, short stature and a protuberant abdomen, which could be a consequence of massive hepatomegaly.[1] The kidneys are also enlarged, whereas the spleen and heart are not involved.[1]

Hypoglycemia and lactic acidosis, hyperuricemia and hyperlipidemia are the biochemical characteristics of GSD type Ia. Hypoglycemia and lactic acidosis can develop after a short fast. Despite marked hepatomegaly, the liver transaminase levels are usually normal or only slightly elevated. Easy bruising and epistaxis are common and are associated with a prolonged bleeding time as a result of impaired platelet aggregation and adhesion. The plasma may be milky in appearance due to strikingly elevated triglyceride levels. Cholesterol and phospholipids are also elevated, but are less prominent.

There is an increased risk of pancreatitis secondary to the lipid abnormalities. In the 2nd or 3rd decade of life, some patients with GSD type Ia develop hepatic adenomas that can hemorrhage and turn malignant in some cases.

Renal diseases are another late complication and most patients with GSD type Ia > 20 yr of age have proteinuria. Many also have hypertension, renal stones, nephrocalcinosis and altered creatinine clearance.

Diagnosis: The clinical presentation and laboratory findings of hypoglycemia, lactic acidosis, hyperuricemia and hyperlipidemia lead to a suspected diagnosis of GSD type Ia. Gene-based variant analysis by single gene sequencing or gene panels provides a non-invasive way to diagnose most patients with GSD types Ia and Ib.[3]

Treatment: Treatment focuses on maintaining normal blood glucose levels and is achieved by continuous nasogastric (NG) infusion of glucose or oral administration of uncooked cornstarch.

Medium-chain triglyceride (MCT) supplementation improves metabolic control, leading to improved growth in children. Since fructose and galactose cannot be converted directly to glucose in GSD type Ia, these sugars should be restricted in the diet.[4]

Dietary therapy improves hyperuricemia, hyperlipidemia and renal function. The control of hyperuricemia can be further augmented by the use of allopurinol. Hyperlipidemia can be reduced with lipid-lowering drugs such as HMG-CoA reductase inhibitors and fibrate. Citrate supplements can be beneficial for patients with hypocitraturia by preventing or ameliorating nephrocalcinosis and the development of urinary calculi.

Prognosis: Previously, GSD type Ia was associated with high mortality at a young age, and even for those who survived, the prognosis was guarded. Inadequate metabolic control during childhood can lead to long-term complications during adulthood. Clinical outcomes have improved dramatically with early diagnosis and effective treatment. However, serious complications such as renal disease and the formation of hepatic adenomas with a potential risk for malignant transformation persist.[5]

Case report

Case 1: A 3.5-month-old infant boy was admitted to our center due to poor feeding, lethargy, frequent vomiting, respiratory distress and generalized tonic-clonic seizure following a respiratory infection. The patient had a history of hospitalization on the first day of birth due to apnea, cyanosis and hypoglycemia (BS = 10mg/dl) for six days.

The patient's parents were consanguineous. There was a history of GSD type Ia in the patient's paternal family (case 2). He had hepatomegaly in the examination (Table 1).

Table 1. Case 1: Laboratory Test Results

pH = 7.32	HCO3 = 4.2 mg/dl	Pco2 = 8
Lactate > 100 mg/dl	BS = 12 mg/dl	TG = 541 mg/dl
Cholesterol = 178 mg/dl	Uric acid = 7.3 mg/dl	SGPT = 103 mg/dl
SGOT = 321 mg/dl	AlKP = 1544 mg/dl	Urine ketone +

The patient was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. Phenobarbital was prescribed to the patient under the supervision of a neurologist. After correcting the acidosis, the patient was treated with frequent lactose-free formula feeds every 1.5-3h and MCT.oil. OMEGA-3 was also prescribed due to hyperlipidemia. The patient was also treated with oral bicarbonate after discharge. The diagnosis of GSD type Ia was confirmed in the genetic study. In the follow-up, the patient had a history of repeated hospitalizations with the same symptoms as above, which decreased after starting raw corn starch from six months, and now at the age of 4.5 years, he is metabolically controlled with the above treatments and is doing very well.

Case 2: A 9-year-old boy was admitted to our center due to lethargy, vomiting and respiratory distress. The patient had a history of frequent hypoglycemia and metabolic acidosis following fasting since birth. She was fed via gastrostomy feeding tube insertion. Huge hepatomegaly was observed in the examination. The patient had a liver biopsy and the result was reported to be macrovesicular steatosis. His parents were consanguineous (Table 2).

The patient was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. After correcting the acidosis, according to the nutritionist's opinion, the patient was given a limited galactose, fructose and sorbitol diet that was included raw corn starch and MCT.oil. Allopurinol was prescribed due to high uric acid. Genetic study of this patient confirmed GSD type Ia. In follow-up, the patient had frequent epistaxis and hematuria due to kidney stones, which were broken down by ultrasonic lithotripsy. The patient also had short stature and delayed puberty. At the age of 15, he is now relatively controlled metabolically with the above treatments.

Case 3: A 4.5-month-old infant boy who was hospitalized since two months due to abdominal distension. He had a medical history of being hospitalized in two days due to hypoglycemia and 3.5 months due to COVID-19. He had huge hepatomegaly in the examination. He was born to consanguineous parents (Table 3).

The patient had melena during hospitalization. He was treated with omega-3, MCT.oil and lactose-free formula every 1.5-3 hours. In the follow-up, the patient's triglyceride remained around 1300 mg/dl. GSD type Ia was confirmed in the genetic study and raw corn starch was started after 6 months of age. At the age of 2 years, the patient was admitted in our center with lethargy and respiratory distress due to a respiratory viral infection, the results of the tests are in Table 4.

He was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. He is now relatively metabolically controlled, but the patient's TG is still above 1000.

Table 2. Case 2: Laboratory Test Results

pH = 7.21	HCO3 = 6.4 mg/dl	Pco2 = 16
BS = 25 mg/dl	Uric acid = 10.9 mg/dl	Lactate = 59 mg/dl
TG = 200 mg/dl	Cholesterol = 140 mg/dl	SGOT = 24 mg/dl
SGPT = 18 mg/dl	AlKP = 391 mg/dl	Urine ketone +2

Table 3. Case 3: Laboratory Test Results (The Blood Sample Was Milky)

pH = 7.39	HCO3 = 19.4 mg/dl	Pco2 = 32
TG = 15130 mg/dl	Cholesterol = 966 mg/dl	BS = 55 mg/dl

Table 4. Case 3: Results of Laboratory Test at the Age of 2 Years

pH =7.03	HCO3 = 6.3 mg/dl	Pco2 = 24
BS = 32 mg/dl	TG = 1814 mg/dl	Cholesterol = 235 mg/dl
Uric acid = 11 mg/dl	SGOT = 264 mg/dl	SGPT = 311 mg/dl

Case 4: A 12-year-7-month-old girl was admitted to our center due to hypoglycemia and respiratory distress following a respiratory viral infection. The patient had a history of frequent hypoglycemia and metabolic acidosis since the age of 4 months and was treated with raw corn starch after being diagnosed with GSD type Ia. (Genetic testing has not been done for the patient). In the examination, the patient had huge hepatomegaly, thin limbs and delayed puberty. Her laboratory data is presented in Table 5.

She was treated with serum DW 10% at a rate of 1.5 times the maintenance fluid and intravenous bicarbonate. After correcting the acidosis, according to the nutritionist's opinion, the patient was given a limited galactose, fructose and sorbitol diet which was contained raw corn starch, MCT.oil, oMega-3 and oral bicarbonate.

Discussion

GSD type Ia is caused by glucose 6-phosphatase deficiency. The incidence of GSD type Ia is approximately 1 in 100,000 births.[6,7] Patients have impaired production of glucose from both glycogenolysis and gluconeogenesis which leads to develop hypoglycemia within 3 to 4 hours after a meal. Lactic acid, uric acid, cholesterol and triglycerides are characteristically elevated. GSD type Ia is occasionally diagnosed when hepatomegaly and a protuberant abdomen are discovered during a routine physical examination. Symptomatic hypoglycemia develops when the interval between feedings increases or when illness disrupts normal feeding. Hypoglycemia is not often recognized. The disorder is discovered when the child presents with tachypnea (from lactic acidosis), seizures, lethargy, developmental delay, or failure to thrive.[8]

Conclusion

Intensive dietary treatment with improved metabolic control has led to reduced morbidity and mortality and improved quality of life. Long-term cerebral function is normal if hypoglycemic damage is prevented. Most patients can lead fairly normal lives, but patients may develop complications of different organ systems.[4,7]

Conflict of Interest

The authors have no conflict of interest.

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Table 5. Case 4: Laboratory Test Results

pH = 7.19	HCO3 = 6.9 mg/dl	Pco2 = 18
BS = 22 mg/dl	Uric acid = 6.7 mg/dl	Lactate = 122 mg/dl
TG = 703 mg/dl	Cholesterol = 229 mg/dl	SGOT = 313 mg/dl
SGPT = 178 mg/dl	Urine ketone +	

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