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Gestational Diabetes Mellitus in Tajikistan: Prevalence and Management

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is currently the most common medical complication of pregnancy worldwide. The prevalence of undiagnosed hyperglycemia and even overt diabetes in women of reproductive age is increasing. No data are available on the prevalence of GDM in Tajikistan. This study evaluated the prevalence of GDM and the obstetric and neonatal outcomes of pregnancies in an urban and a rural setting of Tajikistan.

Methods: Cross-sectional study conducted among pregnant women presented to the the Reproductive Health Centers in Dushanbe and Qurghonteppa between December 2015 and May 2018. Pregnant women were included in the study during the 1st trimester of pregnancy. The collection of data was carried out according to a specially structured questionnaire, where data on visits were recorded. Between weeks 24 and weeks 28 of gestation an oral glucose tolerance test (OGTT) with 75 g of glucose was performed. GDM was diagnosed if any one of the venous plasma glucose values was met or exceeded (fasting $\geq$ 5.1 mmol/L; at 60 min $\geq$ 10.0 mmol/L and at 120 min $\geq$ 8.5-11.0 mmol/L). Obstetric and neonatal otcomes were recorded after delivery. H-Kruskal-Wallis, Mann-Whitney U and Chi-square tests were used.

Results: Of 2643 women (age 25.3±5.3 years, BMI 23.8±4.3 kg/m^2), 92.2% underwent an OGTT and of these 29.7% had elevated fasting plasma glucose values (mostly minimally elevated), while 2.8% had elevated 60 min and/or 120 min values. The overall prevalence of GDM was 32.4%. Age (p=0.001), weight (p=0.001), BMI (p=0.002) and parity (p=0.012) were associated with GDM. The obstetric and neonatal outcome of women with only elevated fasting glucose levels was not different from women with normal glucose levels. Women with abnormal blood glucose concentration after 60 min and/or 120 min had a significantly higher rate of complications, threatening miscarriage, infection of urinary tract and emergency Cesarean section while affected newborns had lower birth weight, lower APGAR and lower 30 min glucose levels.

Discussion: The study determined for the first time the prevalence of GDM in Tajikistan both in urban and rural areas. Most cases of GDM were diagnosed on the basis of slightly elevated fasting glucose level, which was not associated with adverse obstetric or neonatal outcomes, while women and neonates from women with elevated 60 min or 120 min values had significantly more complications. These findings are in agreement with recent studies from Denmark and the USA, showing

that very mild forms of GDM (identified by slightly elevated fasting glucose levels) are not associated with an adverse outcome.

Conclusion: Although the formal prevalence of GDM is high in Tajikistan, the applicability of the one step OGTT for the screening and diagnosis of GDM must be questioned, as most of the identified women have a normal pregnancy outcome. At the same time this strategy puts the burden of receiving a diagnosis of GDM on individual women and the burden of treating many more women on the health care system. A two-step screening or a one step screening in women with risk factors for GDM maybe a better strategy in a setting were the prevalence of « severe » GDM is low.

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III. ABBREVIATIONS

DM	–	Diabetes mellitus
GDM	–	Gestational diabetes mellitus
T1D	–	Type 1 diabetes mellitus
T2D	–	Type 2 diabetes mellitus
OGTT	–	Oral glucose tolerance test
BMI	–	Body mass index
IR	–	Insulin resistance
PL	–	Placental lactogen
ADA	–	American Diabetes Association
AT	–	Antibodies
FPC	–	Fetoplacental complex
AMP	–	Adenosine monophosphate
VSM	–	Vascular syncytial membrane
BM	–	Basal membrane
BP	–	Blood pressure
SBP	–	Systolic blood pressure
DBP	–	Diastolic blood pressure
NO	–	Nitric oxide
CS	–	Cessarian section
RDS	–	Respiratory distress syndrome
ATSMU	–	Avicenna Tajik State Medical University
USA	–	United States of America
UAE	–	United Arab Emirates
RF	–	Russian Federation
RT	–	Republic of Tajikistan
UK	–	United Kingdom
CA	–	Central Asia
Igf2	–	Insulin like growth factor
SIR	–	Substrate of insulin receptor
GAD	–	Glutamic acid decarboxylase
GLUT	–	Glucose transporter

GRADE	–	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	–	Glycated haemoglobin (A1c)
HAPO	–	Hyperglycemia and Adverse Pregnancy Outcomes
HLA	–	Human leukocyte antigen
IAA	–	Insulin autoantibody
ICA	–	Islet cells antibody of pancreas
IADPSG	–	International Association of Diabetes and Pregnancy Study Groups
IDF	–	International Diabetes Federation
MODY	–	Maturity onset diabetes of the young
TNF –α	–	Tumor necrosis factor –α
UCP-1	–	Uncoupling protein-1
FVPL	–	Fasting venous plasma level
GCT	–	Glucose challenge test
VPGL	–	Venous plasma glucose level
DIPSI	–	Diabetes In Pregnancy Study group of India
FIGO	–	International Federation of Gynecology and Obstetrics
NIH	–	US National Institutes of Health
WHO	–	World Health Organization

1. INTRODUCTION

1.1. Definition and epidemiology of gestational diabetes mellitus

Diabetes mellitus (DM) is a chronic condition that occurs when the pancreas produces insufficient insulin or when the body's insulin is not used efficiently.

According to recent classification of DM, distinguish type 1 diabetes (T1D), which is caused by the loss of beta cells, resulting in absolute insufficiency, type 2 diabetes (T2D) is caused by a violation of insulin action and/or insulin secretion. Specific types linked to genetic problems, as well as diseases that harm the pancreas, such as growth hormone and glucocorticoids overproduction, and gestational diabetes mellitus (GDM) in pregnant women [1].

Table 1.1 : Classificationf of Diabetes Mellitus according to American Diabetes Association [1]

I.	Type 1 diabetes – destruction of β-cells, associated with absolute insulin deficiency
	A. Mediated by auto-immune processes
	B. Idiopathic
II.	Type 2 diabetes - insulin resistence with relative insulin deficiency and/or defect of insulin secretion associated with insulin resistance
III.	Other Specific types of diabetes :
	A. Genetic defects of beta-cell function
	B. Genetic defects of insulin effect
	C. Diseases of the exocrine pancreas
	D. Endocrinopathies
	E. Drug – induced
	F. Infections
	G. Rare forms of auto-immune mediated diabetes
	H. Other genetic syndromes associated with diabetes
IV.	Gestational diabetes

Among the various types of extragenital pathology in terms of prevalence, direct and indirect impact on maternal, perinatal morbidity and mortality, GDM remains the most actual public health problem worldwide [2-7].

GDM is a type of DM characterized by hyperglycemia, first diagnosed during pregnancy [8], usually occurring in the second or third trimester of pregnancy [9].

According to the world literature, the prevalence of GDM ranges from 2.0 to 37.0% of the total number of pregnancies [4, 6, 7, 10]. In turn, it largely depends on the research methods used to detect hyperglycemia (one-step or two-step oral glucose tolerance test (OGTT)), threshold diagnostic criteria, characteristics of the studied population, prevalence of T2D in certain ethnic groups, age of mother, body mass index (BMI), socioeconomic status and race of women [6, 7, 10-13]. At the same time, according to other authors, the GDM epidemic is associated with an increase in urbanization, decrease in area and access to green landscapes, decrease in physical activity, change in diet and exposure to unfavorable environmental factors [14-17]. L. Kanguru et al. (2014), argue that the prevalence of GDM varies among countries, in general, the frequency of GDM in the world is 14% of all pregnancies and is increasing with the obesity epidemic [18].

According to other authors, the proportion of GDM varies widely from the studied population: for example, in the countries of the Middle East, such as the United Arab Emirates (UAE), it is 20.6%, Qatar – 16.3%, Bahrain – 13.5% and Saudi Arabia – 12.5% [19], in Australia – 9.5% and United States of America (USA) GDM effects 4.8% of all pregnancies [20].

According to the International Diabetes Federation (IDF, 2017), vast majority (88%) of hyperglycemia in pregnancy occurs in developing countries, where access to maternal and child health services is often limited [4].

The lowest incidence of GDM was found in the African Region – 10.4%, which is probably due to lower urbanization, malnutrition, lower obesity and higher rates of infectious diseases [4], while the highest in Southeast Asia – 24.8%, which may be directly related to the largest population (about 60% of the world's population) in the Asian continent [4, 21].

The prevalence of GDM in high-income countries ranges from 0.6% to 27.5%, while in low- and middle-income countries - from 0.4% to 24.3% [18]. Scientists have recorded that in the Russian Federation (RF) GDM complicates the course of pregnancy in 2-4% of cases [22-24], in Turkmenistan – 6.3% [25], in China - from 9.3 to 18.9% [26], in India, the prevalence of GDM ranges from 1 to 18% [27].

In the Republic of Tajikistan (RT), the referral rate of DM is growing steadily: if in 2000 it was 166.0 per 100.000 population, then in 2012 it reached 321.8 per 100.000 population [5]. In addition, the government-approved DM prevention program for 2006-2010 which has been implemented in the country. Within the framework of this program, the Law "On medical and social protection of citizens with diabetes mellitus" was adopted, and the Government Decree No. 130 of April 03, 2012 was developed and approved by the "National program for the prevention, diagnosis and treatment of diabetes mellitus in the Republic of Tajikistan for 2012-2017 years". Consequently, on the basis of the specified program, guidelines were developed for drawing up

clinical protocols in women with DM [28]. Simultaneously, in a study conducted in 2012 in Tajikistan, 1000 pregnant women with risk factors were examined, in whom a glucose tolerance test was conducted. As a result of the study, 162 (16.2%) patients were diagnosed with GDM [5]. It should be noted that the diagnostic criteria for the diagnosis of GDM in the above study used the recommendations proposed by the American Diabetes Association (ADA), in which threshold values of plasma glucose concentration were developed for ethnic varieties of the US population [29].

The prevalence of hyperglycemia during pregnancy as a percentage of total pregnancies increases rapidly with age and is highest among women over 45 years of age (45.4%), although the number of pregnancies in this age group is significantly lower [30]. Due to the higher fertility rate among young women, almost half (48.9%) of all cases of hyperglycemia in pregnancy (10.4 million) are in the age group of women under 30 years [4].

According to a study by P. Damm et al. (2016), 50% of women diagnosed with GDM, in the future from 5 to 10 years develop T2D [16], according to the observations of other authors, the development of cardiovascular diseases and metabolic syndrome were also noted [31-33]. According to the literature, in 20-50% of cases in women with GDM history, its re-development noted during the next pregnancy [22, 23]. At the same time, among all women giving birth 16–20 years after childbirth, overt diabetes mellitus occurs in 25–50% cases [34].

1.2. Etiology and pathogenesis of gestational diabetes mellitus

Pregnancy causes physiological insulin resistance (IR), which is a substantial risk factor for glucose metabolism abnormalities, which can lead to DM of any type, including GDM [35, 36].

Physiological IR is caused by the production of a number of hormones, in particular, placental lactogen (PL), estrogen, progesterone, increased cortisol production due to tissue effect disorders and increased insulin breakdown with activation of placental insulinase. Any violation in one of the above links can lead to the development of pathological IR, accompanied by the subsequent development of hyperglycemia [37, 38].

According to T.A. Buchanan et al (2012), pregnancy complicated by GDM is characterized by an inability of the Langerhans β cells of the pancreas to produce enough insulin to maintain normal maternal glycemia [39]. According to J. Xu et al. (2014), GDM occurs when the insulin produced in the mother's body cannot compensate for the state of decreased insulin sensitivity that occurs during pregnancy [40]. According to the results of the authors of experimental studies, a significant role in the development of GDM is attributed to genetic changes, such as mutation of

genes MODY, substrate of insulin receptor SIR-1, glycogen synthetase, hormone-sensitive lipase, β-adrenergic receptors, uncoupling protein UCP-1, HLA class II - DRB1, DQA1, and DQB, which lead to β-cell death, pancreatic islets of Langerhans, or protein molecular defects leading to decreased membrane concentration and activity of intracellular glucose transporters GLUT-4 in muscle tissue [19, 41-43]. In addition, scientists associate the development of diabetes with the presence of antibodies (AT) in glutamic acid decarboxylase (GAD), insulin (IAA) and islets cells antibodies of Langerhans (ICA) as predictors of the development of T1D in women with GDM [44, 45].

To date, the exact mechanism of the development of GDM is not fully understood. However, the opinions of scientists agree that the blood glucose level in women with a normal pregnancy in the first 3 months decreases by 0.5-1.0 mmol/L, this occurs as a result of increased volatile movement of amino acids through the feto-placental complex (FPC) that contribute to the suppression of the gluconeogenetic process [46].

Also, under the influence of estrogens, glucose passes passively from mother to fetus, this leads to the launch of compensatory processes for regulating glucose concentration in the mother's body due to hypertrophy and hyperplasia of β-cells of islets of Langerhans, this leads to an increase production of insulin. In the second trimester, there is an increase in the activity of the hormonal function of the placenta, which leads to an increase in prolactin and progesterone, which contribute to a decrease in insulin levels. As a result of prolactin's substantial lipolytic impact, the amount of free fatty acids increases, leading to a decrease in the insulin sensitivity of peripheral target organs. As a result, the processes of glucose utilization by insulin-sensitive cells are suppressed and IR is increased [47]. Thus, physiological changes that occur during pregnancy can be accompanied by a violation of compensatory processes, which contributes to an increase in insulin production in response to IR with the onset of GDM [48, 49].

The maternal factors in the development of IR and inflammation in GDM include disorders in the metabolism of adipose tissue. In later stages of pregnancy, it is the main source of inflammatory mediators - adipocytokines, including leptin, tumor necrosis factor –α (TNF –α), interleukin-6 (IL-6), adiponectin, resistin, visfatiniapelin [50-53]. TNF-α, a proinflammatory cytokine, is involved in the development of IR during pregnancy as well as T2D later in life. In late pregnancy, TNF-α has an inverse correlation with insulin sensitivity. Consequently, the neutralization of TNF-α molecule in the second half of pregnancy accompanied by an improvement in the state of insulin sensitivity in pregnant women [40]. Leptin is an anti-inflammatory hormone that plays an important function in energy metabolism [54, 55]. On the other hand, adiponectin is one of the anti-

inflammatory factors that have a positive effect on insulin sensitivity during pregnancy. It promotes glucose uptake into skeletal muscle by activating adenosine monophosphate (AMP) kinase [40].

Thus in pregnant women with GDM, an increase in TNF-α, leptin and a decrease in adiponectin implies an imbalance between pro- and anti-inflammatory cytokines produced by adipose tissue in the second half of pregnancy, that can contribute to the development of impaired glucose homeostasis [40].

Many researchers agree that hormones released by the placenta play a key role in the development of GDM. So, during pregnancy, with an increase in gestational age, namely between 20 and 24 weeks, size of the placenta begins to increase and the level of hormones, including estrogen, progesterone, cortisol and PL increases, leading to an increase in IR. After delivery, the placenta's hormone release ceases, and GDM passes, indicating the importance of placental hormones in the development of GDM [56, 57]. So, according to the results of the study by K.C. Kamana et al (2015), an increase in PL promotes lipolysis in a woman's body, while the level of free fatty acids increases, which provide energy needs in the mother's body, thereby preserving sugar and amino acids for the fetus. Thus, an increase in the level of free fatty acids has a direct competing effect on the penetration of glucose through insulin into cells. Therefore, PL is a potential insulin antagonist during pregnancy [56].

1.3. Role of mother-placenta-fetus system in the development of gestational diabetes

The placenta is a complex organ that transports nutrients, microelements, water, gases, and metabolic products during pregnancy. It also participates in the production of different hormones that control the transfer of substances from the mother to the baby and promote metabolic adaptations in the mother's body depending on the stages of pregnancy. These functions are provided by the anatomical and functional features of the placental barrier [58-60].

At the same time, the placental barrier is represented by the vascular syncytial membrane (VSM), consisting of a continuous layer of syncytiotrophoblast with the presence of multiple apical microvilli covering the maternal surface of the endothelial layer with an underlying basement membrane (BM) facing the fetal capillaries and between them there is a villous connective tissue [61]. Approximately 5-10% surface of the syncytiotrophoblast consists of epithelial plates, and 90% is occupied by microvilli [62]. There are also special sites through which various metabolites are transported to the fetus. In these areas, syncytiotrophoblast is very thin, there are no cytoplasmic organelles, basal plates of the trophoblast, and endothelium of fetoplacental vessels as a single complex. This structure makes it possible to reduce thickness of

diffusion surface between maternal and fetal circulation [62, 63]. Invasion of the trophoblast into decidua leads to the remodeling of the spiral uterine arteries into low resistance vessels. Due to the lack of innervation of blood vessels in the fetoplacental complex, their tone depends on the production of local vascular signaling molecules such as eicosanides, endothelin-1 and nitric oxide (NO). Any violation of this process leads to a limited flow of maternal blood into the intervillous space. [63]. Thus, one of the most important functions of the VSM is to maintain the optimal exchange area of nutrients and microelements between fetus and mother surfaces. An increase in thickness of the VSM and decrease in the exchange area expose fetus to a significant risk, leading to its hypoxia [64].

The placental anatomical structure prevents direct contact between both mother's and fetus's blood, highlighting the importance of carrier proteins, electrochemical gradients, and diffusion paths for metabolism all over the placental barrier. On surface of the placenta are carrier proteins for glucose, lactate, amino acids and fatty acids located. The transport of these substances depends on the concentration gradient between blood flow of mother and fetus [65].

A literature review showed that transport of substances through the placenta has a direct relationship with growth and weight of the placenta, morphology, namely, with the area of exchange and tissue thickness, presence of nutrient transporters, uterine and fetal-placental blood circulation [66, 67]. Placental growth and development, including size, morphology, and number of carriers, are regulated by built-in genes, like the insulin like growth factor (Igf2-H) complex. The activity of these genes differs depending on their number. Excessive presence of alleles of the paternal Igf2-H gene in comparison with the maternal leads to an increase in the size of placenta, as well as fetus [68].

The weight of the placenta is an important determinant of fetal weight and development. Literature data report that fetal and placental weights in healthy pregnancies are positively correlated at the end of pregnancy. If the placenta does not reach an adequate size and weight corresponding to the gestational age, it cannot ensure the full development of the fetus [8, 67]. So, J.M. Wallace et al. (2012), in their study, revealed an association of the placenta with the presence of a heavier mass and unfavorable neonatal outcomes, such as fetal hypoxia and macrosomia [8].

The placenta develops continuously throughout pregnancy, including periods of branched angiogenesis, unbranched angiogenesis, trophoblast differentiation, and syncytium production [69]. Unfavorable intrauterine conditions, such as hyperglycemia and hypoxia, cause morphofunctional alterations in the placenta, causing the influence of placental hormones on the fetus to be altered, resulting in poor postnatal outcomes [27, 70]. The period of disturbance

associated with morphological changes in development of decisive importance in determining the consequences of functional disorders of the placenta, as well as in programming the fetus [71, 72].

Morphological and functional disorders of the placenta develop in GDM pregnancies, which have a negative consequence on the fetus' growth and development [73]. Meanwhile, the impact of GDM on placental anatomy is unknown; however, a number of studies have linked the onset of morphological changes in the placenta to a decrease in maternal surface vascular permeability, fetal surface thrombosis, an imbalance of vasoactive signaling substances, and an increase in oxidative processes [74-77]. When glucose metabolism is impaired in early pregnancy, structural changes in the placenta are observed, while when GDM is detected in late pregnancy, functional disorders of the placenta, inflammatory reactions and oxidative stress are observed to a greater extent, which lead to chronic fetal hypoxia. Simultaneously, the hyperglycemic environment of early pregnancy promotes the activation of placental compensatory-adaptive mechanisms, such as the buffering of extra maternal sugar or a rise in vascular resistance, which can limit baby growth. Excessive fetal growth may occur if the mother's exposure to the diabetic environment, including hyperglycemia, hyperinsulinemia, and dyslipidemia, exceeds the placental capabilities to ensure compensatory-adaptive reactions [78]. It should be underlined that hyperglycemia and hypoxia are two significant contributors in the pathophysiology of GDM problems. Hyperglycemia leads to multiple mechanisms, including leukostasis, vasoconstriction, and anti-inflammatory responses, all contribute to hypoxia and oxidative stress in the placenta [79, 80].

Placenta of women with GDM in the anamnesis have immaturity of villi, fibrinoid necrosis of villi, angiomatosis, and increased angiogenesis [81]. According to the results of the study by E. Taricco (2009), in the second half of pregnancy, pronounced angiogenesis processes and vascularization occur in the villi of the placenta [76]. Under the action of hyperglycemic conditions, both processes may stop or not end. Consequently, this is accompanied by an underdevelopment of villi or a violation in the branching of villi, which are adaptive in nature to the intrauterine conditions that have arisen, which occurs at the onset of the development of diabetes. The results of the study by G. Daskalakis (2008) indicate that in the presence of GDM, metabolic disorders of intrauterine conditions affect the development of the fetus by changing gene expression on the epigenetic mechanism of sensitive cells that lead to the development of diabetes in adulthood [82]. Other gene expression studies claim that GDM disrupts trophoblast cell function by activating genes involved in immunological responses, fetal organ growth and development, cell death regulation, inflammatory responses, and endothelium rearrangement. All together leads to a state of chronic systemic inflammation of the placenta, followed by chronic fetal hypoxia [83, 84]. U.

Hiden et al. (2012) found that, in general, placentas from pregnancies with GDM are more often large, but the shape, area, location of the umbilical cord and the number of terminal villi in these placentas do not differ from placentas of pregnancies without GDM. At the same time, in placentas with the presence of GDM, an increase in the syncytiotrophoblastic surface occurs, as well as hypervascularization of the villi, which contribute to an increase in the fetal-placental endothelial surface [85]. According to some researchers, an increase in both Wharton's jelly and vascular lumen are the cause of the increase in umbilical cord diameter in GDM compared to normal pregnancy [86-88].

The production of glucose in the fetus during intrauterine life is low, therefore the fetus is fully reliant on the concentration of glucose in the mother's body. Because glucose can pass the placental barrier, fetuses from moms with hyperglycemia will certainly grow in gestation at higher glucose levels than normal [72]. The transport of glucose from mother to the fetus occurs due to the concentration gradient and group of protein transporters of glucose isoforms (GLUT) [89]. Thus, A. Peker et al. (2018), in their study showed no differences in transplacental glucose transfer in placentas burdened with GDM and normal pregnancy with established glucose concentration gradients and confirmed the data of other authors [90-92]. With regard to prolonged exposure to high concentrations of glucose in the prenatal period, generally accepted explanation for the effect on the fetus throughout pregnancy is the Pedersen hypothesis (1952) [51, 93]. According to this theory, glycemic control problems in the mother's body cause an increase in glucose concentration in the blood serum. Consequently, glucose from the mother's body crosses the placental barrier, while insulin does not. As a result, in the second trimester, fetal pancreas reacts to the resulting hyperglycemia by producing insulin at an autonomous level. The combination of hyperinsulinemia and hyperglycemia contributes to an increase in protein and fat production, leading to fetal macrosomia.

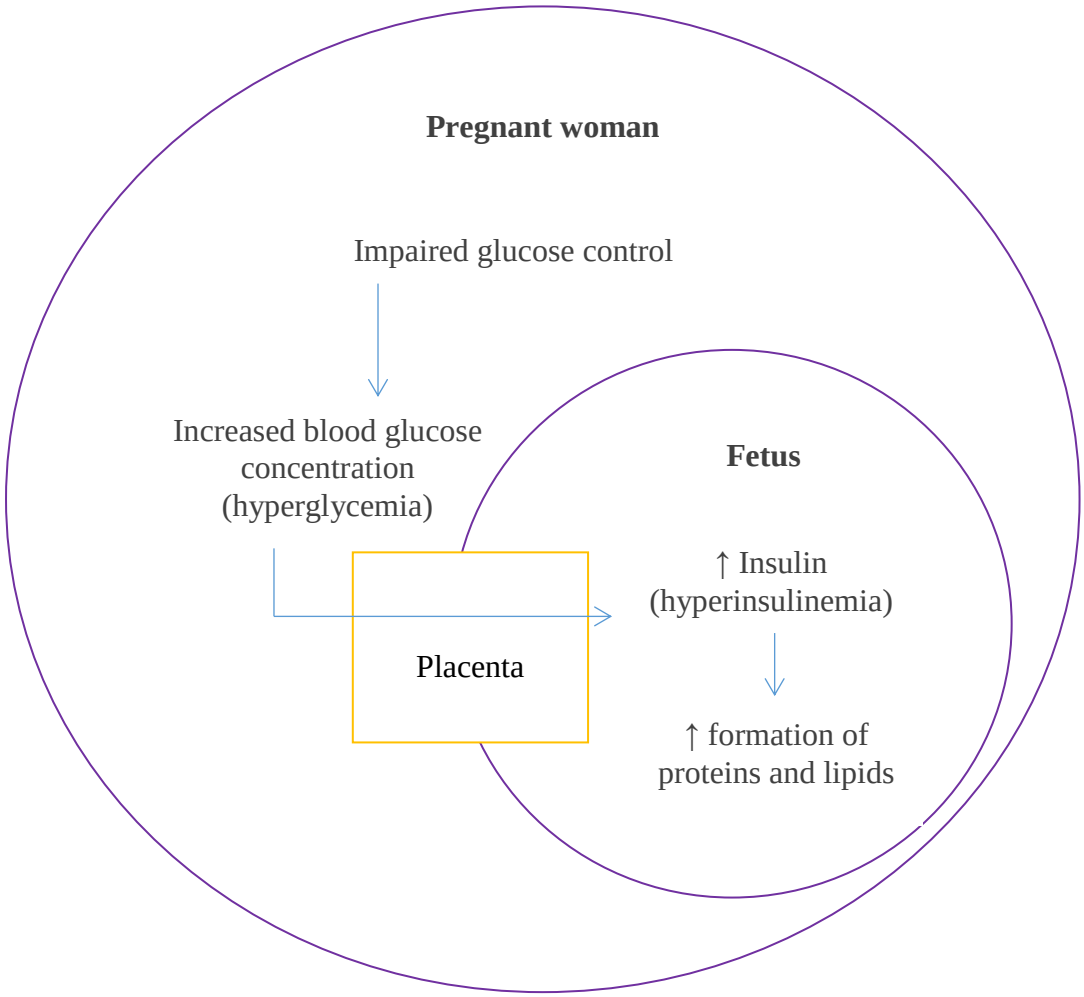

Figure 1.1: Modified Pederson's hypothesis reflecting the effects of hyperglycemia both in mother and fetus [51].

1.4. Maternal and perinatal complications in gestational diabetes mellitus

Despite the advances in obstetric diabetology, overall incidence of pregnancy complications and morbidity in newborns with GDM does not decrease below 80% [94]. The course of pregnancy with GDM is complicated by the threat of termination of pregnancy from 30 to 50% of cases [22], gestosis - from 25 to 65% [95], polyhydramnios - from 20 to 60%, placental insufficiency with the formation of severe forms, deterioration of the condition both of pregnant women and fetus, which requires early delivery, with a subsequent increase in the number of premature births [96]. The frequency of abdominal delivery in pregnant women with GDM ranges from 28.8 to 46.6% [97]. Among neonatal complications in GDM, a high frequency is attributed to shoulder dystocia - from 2.8 to 5.6%, clavicle fracture - from 6 to 19%, Erb's paralysis - from 2.4 to 7.8%, severe asphyxia - from 1.4 up to 5.3%, while cerebrovascular accident of traumatic origin is about 20% of cases [98]. At the same time, a team of scientists in the study of

hyperglycemia and adverse pregnancy outcomes (HAPO) among 25505 pregnant women from nine countries of the world, revealed a correlation between the development of hyperglycemia in mother with weight of newborn over 90th percentile, level of C-peptide in serum blood taken from the umbilical cord more than 90th percentile, presence of cessarean section (CS) and neonatal hypoglycemia. In addition, a direct relationship was found between development of hyperglycemia and presence of such secondary complications as: premature birth, trauma during childbirth with damage to the brachial plexus, intensive management of neonatal period, an increase in concentration of bilirubin in the blood, and presence of preeclampsia [99].

According to the results of many studies, among early maternal complications, hypertensive disorders during pregnancy, childbirth by CS and low frequency of breastfeeding predominate [39, 100]. Whereas, among the long-term consequences that arise both in mother and child are the development of obesity, T2D, cardiovascular pathologies and other chronic metabolic problems that occur throughout life [101, 102].

Frequent perinatal complications in GDM are birth of a large baby, neonatal hypoglycemia, hyperbilirubinemia, shoulder dystocia, and a higher percentage of adipose tissue in newborns than in newborns without GDM [103]. The development of perinatal pathology and death in newborns with GDM is greatly influenced by formation of disorders that occur during intrauterine development of fetus and functional changes in FPC [104-106].

P. Jamurzek et al. (2015), in their study found that in overweight or obese pregnant women with GDM, pregnancy was most often associated with unfavourable perinatal complications, such as big baby, birth trauma, neonatal hypoglycemia and respiratory distress syndrome (RDS) [81]. A literature review has shown that the development of a large fetus is linked to increased fetal nutrient intake, hyperglycemia, hyperleptinemia, hyperinsulinemia, dyslipidemia, decreased adiponectin, and pro-inflammatory cytokines in the mother, all of which cause functional and anatomical disorders in the placenta, disrupting macronutrient transport to the fetus [107-113]. Thus, K.C. Kamana et al. (2015), in their study, recorded that about 15–45% of newborns from mothers with GDM are born with a weight of 4000 g or more [56]. Gestational age at delivery, mother's BMI before pregnancy, weight gain during pregnancy, height, maternal hypertension play a significant role in the birth of children with a large mass. In a comparative analysis, obese women had twice the risk of having large fetuses than women of normal weight. Also, newborns with macrosomia after birth were found to have higher rate of severe hypoglycemia - five times, an increase in the development of jaundice - two times compared with newborns from mothers without GDM [56].

Among perinatal outcomes in pregnant women with GDM in the RT, proportion of macrosomia in the country was 42,5%, fetal asphyxia – 11,5%, cerebrovascular violation of traumatic genesis - 37.9% [114].

1.5. Diagnosis and treatment of gestational diabetes mellitus

The reason for the late diagnosis of GDM in many pregnant women is that there are no clinical manifestations of pathology, and the level of glucose in the blood may be within normal ranges. Therefore, in some cases, GDM is detected after childbirth when phenotypic signs of diabetic fetopathy are observed in the newborn, or it may be completely vague. According to the results of the some studies in 50-60% of pregnant women with GDM, pathology can be determined with a large delay of 4-20 weeks [94].

The first method for diagnosing GDM use of 3-hour OGTT with 100g of glucose was developed by J. O'Sullivan et al. (1964) [115], where test criteria were based on the likelihood of mother developing diabetes in the future and an increased risk of perinatal complications. According to the diagnostic method of J. O'Sullivan et al., study material was whole venous blood with threshold values of fasting glucose ≥4.9 mmol/L, 1 hour after glucose load ≥9.1 mmol/L, after 2 hours - ≥ 7.9 mmol/L and after 3 hours - ≥6.9 mmol/L, according to the results of which it was possible to estimate development of DM in 29% of women after 7-8 years [115].

A further revision of the diagnostic criteria by J. O'Sullivan et al. was carried out by the scientists Carpenter and Coustan (1982) [116]. Their modification consisted in use of venous blood plasma and slightly reduced threshold diagnostic criteria for glucose concentration: fasting ≥5.3 mmol/L, after 1 hour ≥10.0 mmol/L, after 2 hours ≥8.6 mmol/L and after 3 hours ≥7.8 mmol/L [116].

In 1999, World Health Organization (WHO) experts proposed use of 2-hour OGTT using 75g glucose. According to the WHO criteria, it was necessary to carry out OGTT in the morning after 8-14 hours of overnight fast and to measure the sugar concentration 2 hours after load, the threshold glucose thresholds for the GDM diagnosis in fasting condition were ≥7.0 mmol/L and after 2 hours ≥7.8 mmol/L.

WHO criteria did not have levels of evidence and relied solely on expert opinion and consensus. Consequently, the International Association of Diabetes and Pregnancy Groups (IADPSG) established to collaborate between different national and international communities to study diabetes in pregnancy [117]. The basis for the development of the IADPSG diagnostic studies was the five-year, blind, randomized study of HAPO, which examined over 25.505 pregnant women from various ethnic groups; OGTT was performed with 75 g of glucose at 24-32

weeks of gestation [99]. According to the results of this study, a number of scientists from the USA, RF, Japan, Germany, Israel etc., came to the conclusion that GDM is a significant problem leading to an increase in the number of adverse pregnancy complications both in mother and baby, therefore, screening, diagnosis and treatment of GDM is cost-effective for the country as a whole [118-120].

The ADA has developed diagnostic criteria for the setting of GDM [29], covering the ethnic varieties of a given population. Thus, use of a one-step 2h OGTT using 75 g of glucose criteria for the diagnosis are fasting glucose level of ≥ 5.3 mmol/L, after 1 hour ≥ 10.0 mmol/L and after 2 hours ≥ 8.6 mmol/L.

Simultaneously, the WHO's diagnostic criteria for hyperglycemia during pregnancy, which were suggested in 1999, lacked evidence, needed to be revised, and were a prerequisite for the formulation of new clinical guidelines for the management of pregnant women in this situation. So the recommendations were revised in 2013 by a working group created to study systematic reviews on the methodology for the assessment, development and quality of recommendation levels, (Grading of Recommendations Assessment, Development and Evaluation, GRADE), in cohorts of women with hyperglycemia during pregnancy, who were at an increased risk of getting problems during pregnancy, such as preeclampsia and delivering with a large infant [121]. Based on the results of this work, a guide was developed new diagnostic criteria for the threshold values of fasting glucose concentration ≥5.1-6.9 mmol/L, after 1 hour ≥10.0 mmol/L and after 2 hours ≥8.5-11.0 mmol/L.

Table 1.2: Evolution of glucose thresholds for the diagnosis of gestational diabetes mellitus

Management	**Fasting mmol/L**	**Glucose load in grams (OGTT)**	**After 1 hour mmol/L**	**After 2 hours mmol/L**	**After 3 hours mmol/L**
J. O'Sullivan et al.	≥ 4,9*	100 g	≥ 9,1*	≥ 7,9*	≥ 6,9*
Carpenter and Coustan	≥ 5,3**	100 g	≥ 10,0**	≥ 8,6**	≥ 7,8**
WHO, 1999	≥ 7,0**	75 g	-	≥ 7,8**	-
IADPSG	≥ 5,1**	75 g	≥ 10,0**	≥ 8,5**	-
ADA	≥ 5,3**	75 g	≥ 10,0**	≥ 8,6**	-
WHO, 2013	≥ 5,1-6,9**	75 g	≥ 10,0**	≥ 8,5-11,0**	-

* The material of the study was whole venous blood

** The study material was venous blood plasma

It should be noted that for many years, development of universal methods for screening and diagnosing GDM, manifest diabetes, which would facilitate the coverage of all pregnant women and timely prevention, treatment of GDM and its complications remains an urgent task. In a number of countries: Russia, USA, United Kingdom (UK), Canada, etc., a one-step two-hour OGTT is performed using 75 g of glucose, and at least one value of the venous plasma glucose level out of three, which would be equal to or higher than the threshold, is sufficient to establish the diagnosis of GDM [122]. However, if abnormal values were obtained for the first time and there are no symptoms of hyperglycemia, then the preliminary assessment of overt diabetes during pregnancy should be validated with fasting venous plasma glucose or glycated hemoglobin (HbA1c ≥6.5%) using standardized tests [122, 123].

Table 1.3: Threshold values of venous plasma glucose, HbA1c for the diagnosis of GDM and overt diabetes during pregnancy

Venous plasma glucose	**mmol/L**
Diagnosing GDM	
Fasting	≥ 5,1 – 6,9
After 1 hour*	≥ 10,0
After 2 hours*	≥ 8,5 -11,0
Manifest (newly diagnosed) diabetes mellitus	
Fasting	≥ 7,0
After 2 hours*	≥ 11,1
HbA1C	≥ 6,5%
Venous plasma glucose regardless of the time of day and food intake in the presence of symptoms of hyperglycemia	≥ 11,1

* OGTT with 75 g glucose

Based on the foregoing, more study is needed to establish the efficiency of new tactics in developing nations, as well as the cost-effectiveness of new screening and diagnosis strategies for GDM.

It is important to note that GDM is becoming more common, and most patients with a family history of GDM have T1D or T2D. There is also a global increase in GDM and T2D in parallel with obesity. According to the 2018 ADA guidelines, pre-conception should be considered an integral part of primary care for patients of all reproductive ages. Counseling includes family planning, effective contraception, prevention of adverse pregnancies, awareness of complications

that may arise from inadequate glycemic control and the risk of congenital anomalies [124]. According to the literature review, the initial stage in the complex of measures for the prevention and treatment of GDM, in order to control hyperglycemia in the mother includes lifestyle changes, including diet therapy, increased physical activity and a program to control weight gain. In case of insufficient effectiveness of these measures, drug therapy is used [125]. One of the risk factors for the development of GDM is obesity. Thus, in a study conducted by S.B. Koivusalo et al. (2016), found a positive relationship in reducing the incidence of the risk of developing GDM in obese women before pregnancy by changing their lifestyle, including the use of diet therapy and increased physical activity even before pregnancy [126]. If it is impossible to control hyperglycemia, despite 2 weeks of treatment with diet therapy and increased physical activity during pregnancy, drug therapy should be started [12]. Insulin or oral antidiabetic agents such as metformin and glyburidine have been shown to be the drugs of choice in the treatment of GDM [124, 127]. Insulin treatment is selected individually, at the same time, it requires a clear planning of doses and timing of use. Also, the dose of insulin can differ depending on the patient's blood glucose concentration, body weight, ethnic and demographic characteristics [128]. When treating GDM with metformin, the risk of having children with signs of prematurity increases, but there is a decrease in the risk of hypoglycemia in newborns and weight gain in women compare to insulin therapy. When glyburidine used in drug therapy, there is a high incidence of the risk of hypoglycemia in newborns, as well as the birth of children weighing more than 4000 g compared with insulin and metformin therapies [129]. It should be noted that there is no consensus on the use of antidiabetic drugs among the existing practice guidelines. Clinicians should choose optimal treatment strategy, taking into account the risk of complications when choosing a particular medication [130].

2. RATIONALE AND OBJECTIVES

Tajikistan, one of the countries of the former Soviet Union, declared independence on September 9, 1991. Tajikistan is a landlocked country in Central Asia (CA) that shares borders with Uzbekistan to the west, Kyrgyzstan to the north, China to the east, and Afghanistan to the south.

Figure 2.1: Map of Tajikistan indicating boundaries.

Source: https://www.maps-of-the-world.ru/asia/tajikistan

Most of Tajikistan's territory covered with mountains, with high Pamir ranges in the south and valleys in the west. The majority of people lives in the north and southwest valleys. The roads are frequently unreachable in the winter. The climate varies significantly depending on the altitude, characterized by very hot summers in the valleys, while in winter the temperature in the highlands drops below zero. The development of the country after the declaration of independence hampered by the civil war, disruptions in international trade, as well as the location in a politically unstable region.

The initial years of independence were marked by widespread deterioration in the population's health, owing to the rise of infectious and non-communicable diseases, as well as the difficulty of access to health care, particularly among the poor [131]. Due to deteriorating access to quality food and iodized salt, the prevalence of diseases caused by micronutrient deficiencies (iron deficiency anemia, iodine deficiency disorders, vitamin A deficiency) has grown, particularly among vulnerable sectors of the population [131]. The main causes of malnutrition were an unbalanced diet derived from animal fats and high rates of illnesses leading to diarrhea, especially in the summer [131]. Food shortages in some homes, particularly in rural and mountainous locations, as well as inadequate dietary habits for women of reproductive age, pregnant women, newborns, and early children, all contribute to poor nutrition [131]. Infant and maternal mortality estimates in Tajikistan vary greatly depending on the source and methodology used to calculate them [131]. Maternal health also remains a major concern [131]. Maternal mortality in Tajikistan, according to UNICEF, is due to poor antenatal care, insufficient birth management, and transportation issues, particularly in rural areas. [132].

Medical services are available at all levels of government: republican, regional, district, and rural. Primary care is offered in rural areas at health posts, rural polyclinics, and rural hospitals. Polyclinics / family medicine centers, district-level hospitals, specialist hospitals (regional or city), and more complex services in national hospitals provide primary and secondary health care in urban regions.

Tajikistan has young population. In 2007, 38.3% of the population was under the age of 15, down from 43.2 percent in 1990 [133]. Tajikistan is a country with a high birth tradition. In the 80s, the number of children in the family reached 10-12. Despite a drop from 5.1 in 1990 to 3.3 in 2007, the fertility rate remains strong, with an annual population growth rate of 1.5 percent in 2007 [133]. The average age at first marriage for a woman increased from 21.5 in 1989 to 23 in 2005 [134].

After the civil war of 1991-93, the country adopted a family planning program and, with the support of the President of the country, WHO and other international organizations, managed to reduce the birth rate to 25%, but nevertheless, the demographic indicators in the republic are not comforting [135]. In 2017, maternal mortality decreased to 24.1 per 100,000 live births (Data from WHO and Republic Medical Center under Ministry of Health and Social Protection) [136]. Extragenital pathology took the leading place in the structure of the causes of maternal mortality [137]. With the exception of Turkmenistan and Uzbekistan, there is no information on the prevalence of GDM in Central Asia.

As a result, the current study's goal was to determine the prevalence of GDM in two different settings in Tajikistan (urban and rural).

Secondary goals include two distinctions in Tajikistan's rural and urban locations, GDM risk factors, and maternal and neonatal outcomes.

One of the largest leading educational scientific and practical centers in the country is the Avicenna Tajik State Medical University (ATSMU), located in the city of Dushanbe. At the first meetings of scientists with representatives of the Medical Clinic in Munich and rector of ATSMU discussed issues related to the problems of gestational diabetes in Tajikistan, where it turned out that scientific research is required to identify the prevalence in the region, the results of which will further have a positive impact on the country's healthcare system.

Thus, in May 2015, a research project on gestational diabetes was developed between the Medical Clinic at the Ludwig Maximillian University in Munich and the Department of Obstetrics and Gynecology №1 of the ATSMU.

Research Centers for conducting research were selected seven Reproductive Health Centers located in Dushanbe (urban setting) and Reproductive Health Center and Department of Pathology of Pregnant Women of the Regional Clinical Hospital in the city of Qurghonteppa, Khatlon Region (rural setting), in which normally pregnant woman contact according to the registration address and receive antenatal care services. For delivery Reserach Centres were delivery department of the City Medical Center № 1 named after Karim Akhmedov (urban setting) and delivery department of the Regional Clinical Hospital in the city of Qurghonteppa (rural setting).

Before starting main study pilot study was conducted. As the pilot phase of the study progressed, some shortcomings were identified, among which the use of sucrose instead of glucose for OGTT, and use of inappropriate tubes for collecting and transporting blood to the laboratory without taking into account the climatic conditions in the study area, where the temperature reaches 45-50 ° C in summer. Consequently, above limitations were eliminated during the main study.

Figure 2.2: Map of Tajikistan indicating study area (Dushanbe and Qurghonteppa). Source:https://www.researchgate.net/figure/Map-over-Tajikistan-wwwmapscom

The key questions of the reseach were: (1) What is the prevalence of GDM in Tajikistan? (2) What are the primary risk factors for GDM, as well as obstetric and neonatal outcomes, in both urban and rural areas of the country? (3) What are the main steps needed on the management of GDM problem in Tajikistan?

3. METHODS

3.1. Object and scope of research

In accordance with the goals and objectives of this research work, we studied 2438 pregnant women out of 2643 who were observed in the Reproductive Health Centers in Dushanbe and were admitted to the delivery department of the City Medical Center № 1 named after Karim Akhmedov (urban setting), as well as the Reproductive Health Center and the Department of Pathology of Pregnant Women of the Regional Clinical Hospital in the city of Qurghonteppa (renamed to Bokhtar), Khatlon Region (rural setting), and admitted to the delivery section of the Regional Clinical Hospital in the city of Qurghonteppa during the period 2015-2018. The listed centers are clinical bases of the Department of Obstetrics and Gynecology № 1 ATSMU.

The key inclusion criteria were:

- Pregnancy before 28 weeks of gestation;
- Written and verbal inform consent.

The key exclusion criteria were:

- Known diabetes mellitus type 1 or type 2;
- Acute inflamatory diseases;
- Active malignancy;
- Uncontrolled thyroid diseases or other endocrine diseases.

The study took into account such parameters as age, weight and height indicators, blood pressure, gravidy, parity, family and medical anamnesis, complications of previous pregnancy and childbirth, perinatal outcomes and complications of the postpartum period. In addition, in newborns were studied anthropometric parameters, the state at birth, assessed by Apgar scale at the 1st, 5th, 10th and 30th minutes after birth, measurement of glucose consentration of a newborn in 30 minutes after birth, the presence of embryophetopathy, the development of neurological disorders, perinatal morbidity and mortality.

The diagnosis of "Gestational diabetes mellitus" based on OGTT results.

Pregnant women at the antenatal level were observed and examined according to the National Standards [138]. In addition, ultrasound examination of the fetus for the purpose of screening for the detection of embryophetopathy was carried out at 18-20 weeks, 28-32 weeks and 36-40 weeks; dopplerometry of fetal blood flow - at 28-32 weeks of pregnancy. General and biochemical blood tests were performed at 24-28 weeks of pregnancy.

Dynamic observation of the pregnant women began from the 1st trimester of pregnancy. The collection of primary data was carried out according to a specially developed questionnaire (Appendix 1), where data on three visits were entered (Appendix 2).

Visit № 1 consisted in assessing inclusion and exclusion criterias, collection of data on medical and family histories, study of the health status of women and their obstetric and gynecological histories, general clinical and obstetric research, laboratory diagnostic research, consultation by specialists, if necessary.

Visit №2 covered 24-28 weeks of pregnancy, the date of which was set at the first visit. At this stage, a gravidogram was compiled, OGTT, laboratory diagnostic studies, ultrasound fetometry, and Doppler blood flow assessment in the mother-placenta-fetus system were performed.

Visit №3 admission of a pregnant woman to childbirth, assessment of obstetric and perinatal outcomes. Labor management pregnant women was carried out in accordance with National Standards [139].

3.2. Research methods

3.2.1. Anthropometry

The measurement of the weight of women was carried out using a floor-standing medical mechanical balance of the lever mechanism RP-150 MG at all visits. The margin of error was ± 1.0-2.0 kg. The height of the women was measured at the first visit using a wall-mounted height meter for adults. BMI calculated using Quetelet's formula:

$$\textbf{BMI = body mass in kg/ (height in m)}^2$$

Subjects divided into groups depending on BMI based on the WHO classification (1997)

Table 3.1 : Classification of the degree of obesity by BMI

BMI (kg/m^2)	**Degree**
Less 18,49	Underweight
18,50 – 24,99	Normal body weight
25,00 – 29,99	Overweight
30,00 – 34,99	Obesity I degree
35,00 – 39,99	Obesity II degree
40,0 and more	Obesity III degree

Blood pressure was measured using mechanical blood pressure monitors, consisting of a shoulder cuff, a bulb (air blower), a stethoscope, and a manometer with a possible error of ± 3 mm Hg.

3.2.2. Clinical and anamnestic method

In study participants collected a general and obstetric-gynecological histories, pernicious habits, past and concomitant diseases, menstrual function, family and reproductive histories, complications of both previous and current pregnancy data.

3.2.3. Oral glucose tolerance test

Test preceded by an overnight fast for 8-14 hours, if necessary, participant could drink water. After taking sample of blood in fasting condition, the pregnant woman drank 75g of glucose dissolved in 250-300 ml of boiled water for no more than 5 minutes. During the test, active physical activity was not allowed. After 60 minutes and 120 minutes after postprandial load, repeated samples taken.

Determination of blood glucose level was carried out on the device Photocolorimeter KFK, with spectral range of wavelengths 315 – 980 nm, optical density measurement range 0 – 2, basic absolute error of temperature measurement, no more 0.3%, indication of measurement results and operating wavelength, microammeter M1792, dimensions 435 x 355 x 330 mm.

Diagnosis criteria for GDM were the threshold values of plasma glucose concentration proposed in the recommendations of the IADPSG, also confirmed by the WHO [140] as follows: fasting ≥ 5.1-6.9 mmol/L; after 1h of glucose load ≥ 10.0 mmol/L and after 2h of glucose load ≥ 8.5-11.0 mmol/L.

To establish the diagnosis of GDM, at least one value of the venous plasma glucose level out of three, which would be equal to or higher than the threshold was sufficient.

3.2.4. Measurement of glucose consentration of a newborn in 30 minutes

In newborns, at the 30th minute after birth carried out a bedside assessment of the level of glucose in the capillary blood by using glucometers StatStrip Xpress-i Glucose (Nova biomedical, USA) and Accu-Chek Performa (Roche, Germany).

3.3. Statistical analysis

Statistical analysis performed using the SPSS Statistics 23 software package (IBM, USA). The test of the hypothesis about the belonging of the distribution was carried out according to the

agreement criteria of the Kolmogorov-Smirnov and Shapiro-Wilk laws. The normal distribution hypothesis was rejected when the data differed significantly from the Gaussian normal distribution curve. The mean values and their standard deviation (M ±SD) were calculated for continuous variables and the proportion for categorical variables. Analysis of variance for independent absolute values was performed using ANOVA (H - Kruskal-Wallis test) for multiple comparisons and Mann-Whitney U-test for paired comparisons. Comparisons of qualitative indicators were carried out using a contingency table according to the $\chi 2$ criterion for the compared quantities over 10, according to the $\chi 2$ criterion with Yates' correction for the compared quantities over 5 and according to Fisher's exact criterion for the compared quantities less than 5. The null hypothesis of all methods of analysis of variance was rejected at $p < 0.05$.

3.4. Ethical considerations

This study conducted with respect for the participants according to the clinical protocol, the ethical principles derived from the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for Good Clinical Practice. Ethical approval obtained from Medical Ethics Committee (MEC) Ministry Health and Social Protection of the Republic Tajikistan. In addition, before data collection, the participants and their relatives were informed about the study's goal, technique, and expected outcomes. Informed consent was also collected from participants in the form of written and verbal consent, as well as from their relatives if necessary. Furthermore, all of the information gathered from the patients was kept private.

This study is registered on www.clinicaltrials.gov (Identifier: NCT02436551).

4. RESULTS

4.1. Prevalence of GDM in Tajikistan

In the period from December 2015 to May 2018, a cross-sectional study was carried out, where about 4000 pregnant women were recruited who applied to the Reproductive Health Centers in Dushanbe and to the Department of Pathology of Pregnant Women of the Maternity Department of the City Medical Center №1 named after K. Akhmedov (urban setting), and Reproductive Health Center and the Department of Pathology of Pregnant Women of the Regional Clinical Hospital in the city of Qurghonteppa, Khatlon Region (rural setting).

Informed consent was given by 2643 pregnant women who were recruited for the study. Of these, 205 (7.8%) were excluded from the study for reasons of non-compliance with the key inclusion or exclusion criteria (n=1 Diabetes mellitus type 1; n=9 Diabetes mellitus type 2), refusal to perform OGTT and/or not completing OGTT (n=65), glucose level <2.5 mmol/L (n=7), dropped out of observation until admission to childbirth (n=20), implausible gestational age (n=65) and twin pregnancies (n=38). 2438 (100%) women at gestational weeks from 24 to 28 weeks, in order to establish GDM, underwent one-step standard OGTT using 75 g of anhydrous glucose.

Of the surveyed contingent, after OGTT, 791 (32.4%) pregnant women were diagnosed with GDM, while 1647 (67.6%) without GDM. Among diagnosed pregnant women with GDM, fasting blood sugar value above the threshold level observed in 723 (29.7%) women, and in 68 (2.8%) women – elevation of blood sugar value above the threshold level in 60 and/or 120 minutes.

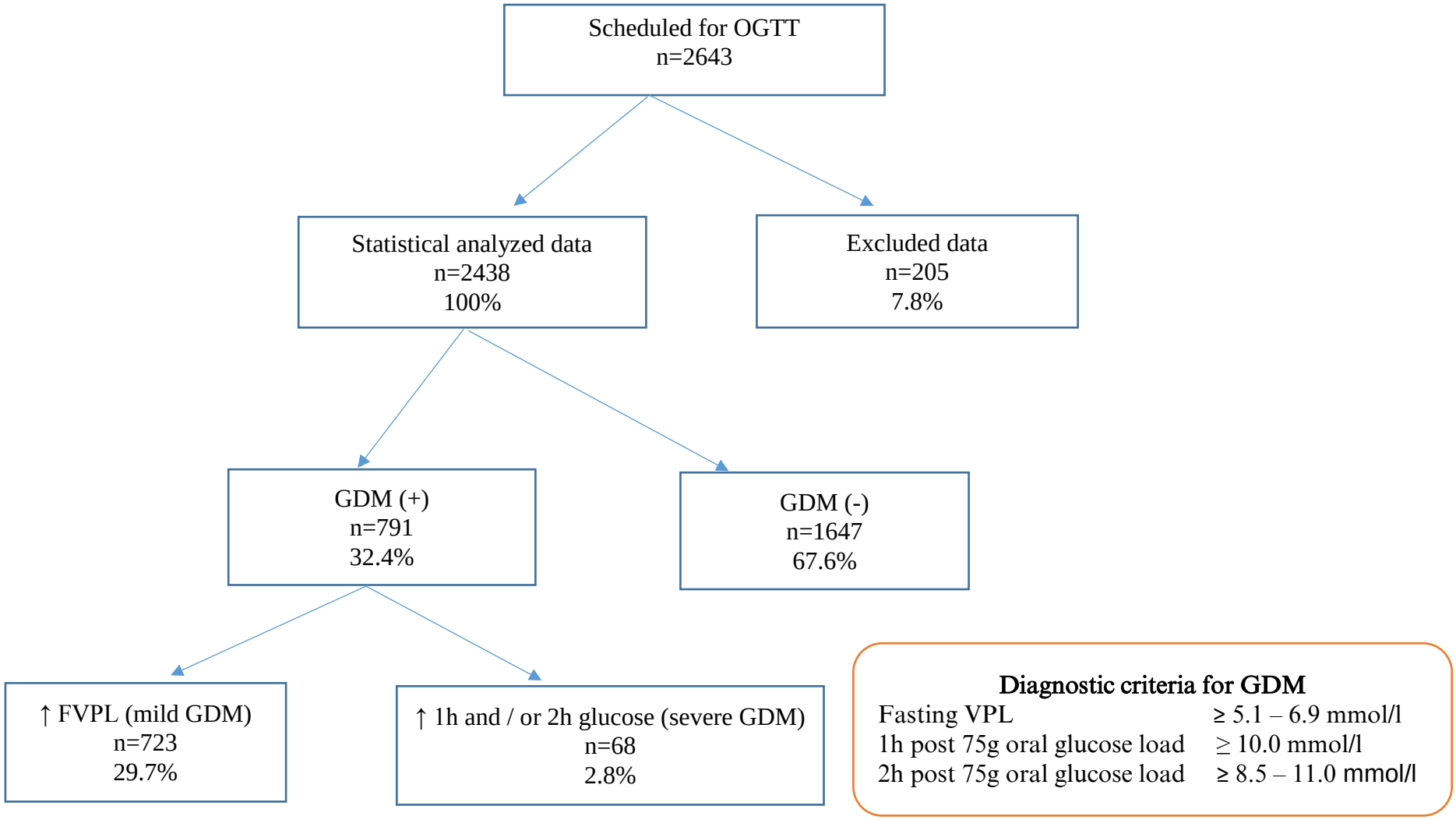

Figure 4.1: Flow diagram of the study

In the studied population at the time of the survey, the mean age of pregnant women 24.8 ±5.1 years. In general, the proportion of pregnant women aged 20-29 years (69.4%) prevailed, compared with women aged less than 20 years (12.8%) and 30 years and older (17.8%).

The mean weight of the surveyed contingent 59.6 ±11.1 kg. The proportion of pregnant women under 50 kg was 20.2%, while those over 50 kg accounted for 79.8% of the surveyed.

The mean height in the studied population 159.5 ±5.9 cm. According to the findings, the biggest percentage of pregnant women resided in the 151-160 cm group (54.3%), the smallest - >170 cm (2.9%), while pregnant women with a height of 161-170 cm was 35.9%, and ≤150 cm - 6.9%.

Analysis of distribution of pregnant women by BMI, showed predominance of pregnant women with a normal body weight of 64.5%, while the proportion of pregnant women with underweight was 7.1%, overweight - 21.2% and obese - 7.2 %.

In analysis of blood pressure (BP) indicators in the studied population the mean systolic (SBP) and diastolic (DBP) BP 100.6 ±10.1 and 63.6 ±7.4 mm of Hg, respectively. Mean arterial pressure 75.9 ±7.8 mm of Hg.

The pregnant women with parity 1 was 33.3%, with parity 2 - 28.3%, with parity 3 - 22.0% and with parity ≥4 - 16.4%.

According to the results of OGTT in the subjects, the mean fasting blood glucose 4.9 ±0.6 mmol/L, after 1 hour glucose load - 5.8 ±0.7 mmol/L and after 2 hours glucose load - 6.0 ±0.9 mmol/L.

At the time of OGTT, the mean gestational age 26.3 ±2.6 weeks of gestation.

In reproductive anamnesis, proportion of complications from previous pregnacies was 34.6%.

During the collection of anamnesis, pregnant women more often indicated the presence of diabetes mellitus (DM) and arterial hypertension (AH) in the family, in particular in their parents or husband's parents, as well as aunts and uncles on both sides. The analysis revealed that 10.2% of pregnant women have a relative with diabetes, and 19.4% have arterial hypertension.

The propostion of kinship marriage in the study population was 14.8%.

Table 4.1: Baseline maternal characteristics of the study population (N=2438)

Parameters	**n (%)**	**Mean ±SD**	**Median**	**25q – 75q**
Age (years)		24.8 ±5.1	24	21 – 28
<20	312 (12.8)			
20-24	1019 (41.8)			
25-29	674 (27.6)			
≥30	433 (17.8)			
Weight (kg)		59.6 ±11.1	58	52 – 65
≤40	25 (1.0)			
41 – 50	468 (19.2)			
51 – 60	1011 (41.5)			
>60	934 (38.3)			
Height (cm)		159.5 ±5.9	160	156 – 164
≤150	168 (6.9)			
151-160	1324 (54.3)			
161-170	876 (35.9)			
>170	70 (2.9)			
BMI (kg/m^2)		23.4 ±4.1	22.8	20.6 – 25.4
<18.5	172 (7.1)			
18.5 – 24.9	1572 (64.5)			
25.0 – 29.9	518 (21.2)			
≥30	176 (7.2)			
SBP (mm of Hg)		100.6 ±10.1	100	90 – 100
<120	2249 (92.2)			
120-139	163 (6.7)			
≥140	26 (1.1)			
DBP (mm of Hg)		63.6 ±7.4	60	60 – 70
<60	59 (2.4)			
60-89	2349 (96.3)			
≥90	30 (1.2)			
Mean arterial pressure (*mm of Hg*)		75.9 ±7.8	73.3	70.0-80.0
Parity				
1	812 (33.3)			
2	691 (28.3)			
3	536 (22.0)			
4	268 (11.0)			
5	97 (4.0)			
6	24 (1.0)			
7	6 (0.2)			
8	4 (0.2)			
Plasma glucose (mmol/l)				
Fasting		4.9 ±0.6	5.0	4.5 – 5.2
1 hour		5.8 ±0.7	5.8	5.3 – 6.2
2 hour		6.0 ±0.9	5.9	5.3 – 6.4
Gestational weeks at time of OGTT		26.3 ±2.6	26	24 – 28
Previous pregnancy complications	844 (34.6)			
Family history of diabetes	248 (10.2)			
Family history of hypertension	474 (19.4)			
Consanguimity	361 (14.8)			

Data presented as n (%) or as Mean ± Standard Deviation, Median, Interquartile range (Q1-Q3).

Interpretation of data on obstetric outcomes showed that in 91.1% cases used vaginal mode of delivery, planned CS performed in 2.9% of the subjects, and emergency CS in 5.9%. In three cases (0.1%), vacuum extraction used. Labor induction noted in 4.2% of cases.

Analysis of neonatal parameters showed that the mean gestational age of newborns during childbirth was 39.1 ±2.5 weeks of pregnancy. Preterm delivery observed in 9.3% of cases. Prolonged delivery in the surveyed contingent noted in 21.8% of cases.

The mean weight of newborns in the studied population 3225.2 ±618.3 grams. When studying the distribution of the weight of newborns, the largest proportion was the group of newborns weighing 3001-4000 grams (62.0%). The proportion of newborns with a weight of under 3000 g was 32.4%, while those with a weight of ≥4001 g- 5.6%.

The mean height of newborns in the studied population 50.7 ±3.8 cm. The highest proportion was in the group of 51-55 cm (58.3%), the lowest – in the group of ≥56 cm, 2.3%. The mean head circumference in the examined newborns 34.2 ±2.2 cm.

The mean of newborns on the Apgar scale at 5 minutes 7.9 ±0.8 points.

The mean blood sugar level at 30 minutes after birth in newborns 3.4 ± 0.7 mmol/L. Cluster analysis revealed that the proportion of newborns with a sugar level of 2.6-3.0 mmol/L - 23.7%, 3.1-3.5 mmol/L - 33.8%, 3.6-4.0 mmol/L - 24.4%, ≥4.1 mmol/L - 11.8% and with hypoglycemia - 6.3%.

Table 4.2: Baseline obstetric and newborn outcomes of the study population (N=2438)

	n (%)	Mean ±SD	Median	25q – 75q
Obstetrical outcomes				
Vaginal delivery	2221 (91.1)			
Planned cesarean section	71 (2.9)			
Emergency cesarean section	143 (5.9)			
Vacuum extraction	3 (0.1)			
Induction of delivery	103 (4.2)			
Newborn characteristics				
Gestational age at time of delivery		39.1 ±2.5	40	39 – 40
≤28	33 (1.4)			
29 – 36	192 (7.9)			
37 – 40	1681 (68.9)			
>40	532 (21.8)			
Birth weight (g)	2437 (99.9)	3225.2 ±618.3	3200	3000 – 3600
≤1000	39 (1.6)			
1001 – 2000	66 (2.7)			
2001 – 3000	685 (28.1)			
3001 – 4000	1512 (62.0)			
4001 – 5000	131 (5.4)			
≥5001	4 (0.2)			
Height (cm)	2435 (99.9)	50.7 ±3.8	51	50 – 53
≤45	135 (5.5)			
46 – 50	824 (33.8)			
51 – 55	1420 (58.3)			
≥56	56 (2.3)			
Head circumference (cm)	2418 (99.2)	34.2 ±2.2	34	34 – 35
Neonatal outcomes				
5-min APGAR (points)	2360 (96.8)	7.9 ±0.8	8	8 - 8
30-min glucose (mmol/l)	1949 (79.9)	3.4 ±0.7	3.3	3.0 – 3.7
≤2.5	122 (6.3)			
2.6 – 3.0	462 (23.7)			
3.1 – 3.5	658 (33.8)			
3.6 – 4.0	476 (24.4)			
≥4.1	231 (11.8)			

Data presented as n (%) or as Mean ± Standard Deviation, Median, Interquartile range (Q1-Q3).

4.2. Prevalence of GDM in urban and rural Tajikistan

1737 pregnant women in an urban setting gave their informed agreement to participate in the study. Of these, 127 (7.3%) were excluded from the study for reasons of non-compliance with the key inclusion or exclusion criteria (n=2 Diabetes mellitus type 2), refusal to perform OGTT and/or not completing OGTT (n=49), dropped out of observation until admission to childbirth (n=20), implausible gestational age (n=38) and twin pregnancies (n=18). To establish GDM, 1610 (100%) women between 24-28 weeks of pregnancy did a one-step conventional OGTT with 75 g of anhydrous glucose.

Of the surveyed contingent, after OGTT, 609 (37.8%) pregnant women diagnosed with GDM, while 1001 (62.2%) - without GDM.

906 pregnant women in rural areas gave their informed consent to participate in the study. Of these, 78 (8.6%) were excluded from the study for reasons of non-compliance with the key inclusion or exclusion criteria (n=1 Diabetes mellitus type 1; n=7 Diabetes mellitus type 2), refusal to perform OGTT and/or not completing OGTT (n=16), glucose level <2.5 mmol/L (n=7), implausible gestational age (n=27) and twin pregnancies (n=20). To establish GDM, 828 (100%) pregnant women between 24-28 weeks of pregnancy conducted a one-step OGTT with 75 g of anhydrous glucose.

Of the surveyed contingent, after OGTT, 182 (22.0%) pregnant women diagnosed with GDM, while 646 (78.0%) - without GDM.

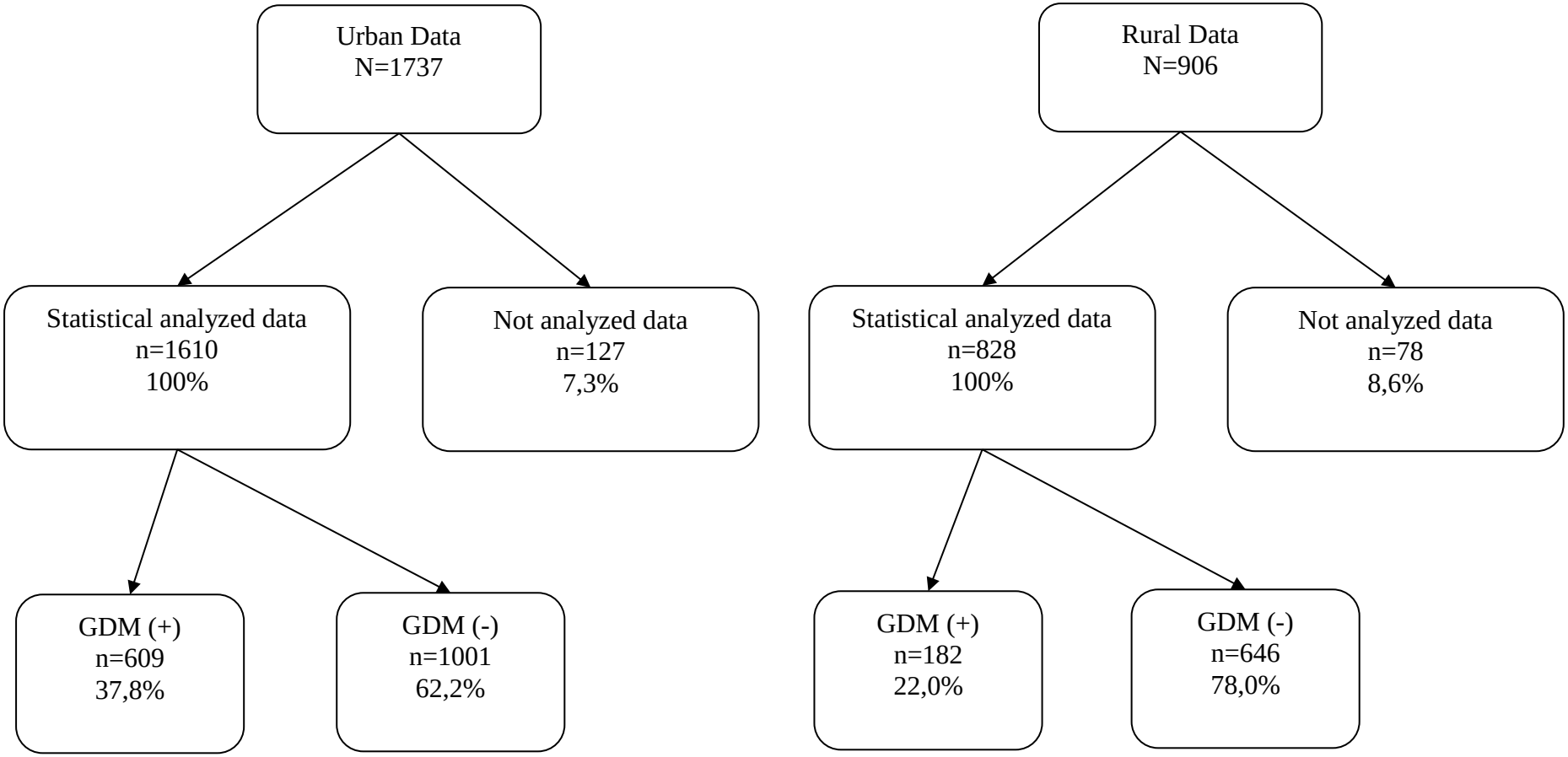

Figure 4.2: Prevalence of GDM in urban and rural Tajikistan

The average age of urbant pregnant mothers in the study population was 25.02 ±5.0 years. The proportion of pregnant women aged 20-24 years (41.0%) prevailed, compared with women aged 25-29 years (28.8%). In urban area the proportion of women with ≥30 years (18.7%) observed more compare to <20 years (11.5%),

The mean weight in the study population 60.27 ±11.1 kg. The proportion of pregnant women over 60 kg (40.9%) prevailed compare to .under 50 kg (17.1%).

The mean height 159.08 ±5.6 cm. The largest proportion of pregnant women was in the 151-160 cm group (59.8%), every third pregnant woman in urban setting had height between 161-170 (31.1%).

Analysis of distribution of pregnant women by BMI, showed a predominance of pregnant women with a normal body weight of 64.0%, while the proportion of pregnant women with underweight was 4.7%, overweight - 23.1% and obese - 8.3%.

The BP parameters in the studied population, showed the mean SBP and DBP 100.21 ±8.57 and 63.0 ±6.26 mm of Hg, respectively.

When analyzing the parity, the pregnant women with parity 1 was 32.1%, with parity 2 - 28.4%, with parity 3 - 21.7%, with parity ≥4 - 17.8%.

According to the results of OGTT in the subjects, the mean fasting blood glucose value was 4.97 ±0.6 mmol/L, 1 hour after glucose load - 5.79 ±0.7 mmol/L, and 2 hours after glucose load - 5.63 ±0.6 mmol/L.

The mean gestational age was 26.32 ±2.7 weeks of gestation, at the time of OGTT.

According to the data of family anamnesis, 7.8% of pregnant women have a relative with DM, and 11.7% - AH.

Table 4.3: Baseline maternal characteristics of the study participants in urban setting (N = 1610)

Parameters	**n (%)**	**Mean ±SD**	**Median**	**25q – 75q**
Age (years)		25.02 ±5.0	24	21 – 28
<20	185 (11.5)			
20-24	660 (41.0)			
25-29	464 (28.8)			
≥30	301 (18.7)			
Weight (kg)		60.27 ±11.1	58	53 – 66
≤40	7 (0.4)			
41 – 50	269 (16.7)			
51 – 60	676 (42.0)			
>60	658 (40.9)			
Height (cm)		159.08 ±5.6	159	155 – 163
≤150	106 (6.6)			
151-160	962 (59.8)			
161-170	501 (31.1)			
>170	41 (2.5)			
BMI (kg/m^2)		23.79 ±4.0	23.0	21.0 – 25.8
<18.5	75 (4.7)			
18.5 – 24.9	1030 (64.0)			
25.0 – 29.9	372 (23.1)			
≥30	133 (8.3)			
SBP (mm of Hg)		100.21 ±8.57	100	90 – 100
<120	1505 (93.5)			
120-139	103 (6.4)			
≥140	2 (0.1)			
DBP (mm of Hg)		63.0 ±6.26	60	60 – 60
<60	27 (1.7)			
60-89	1579 (98.1)			
≥90	4 (0.2)			
Parity				
1	517 (32.1)			
2	457 (28.4)			
3	349 (21.7)			
4	190 (11.8)			
5	74 (4.6)			
6	16 (1.0)			
7	3 (0.2)			
8	4 (0.2)			
Plasma glucose (mmol/l)				
Fasting		4.97 ±0.6	5.0	4.6 – 5.4
1 hour		5.79 ±0.7	5.8	5.4 – 6.3
2 hour		5.63 ±0.6	5.6	5.2 – 6.1
Gestational weeks at time of OGTT		26.32 ±2.7	26	24 – 28
Family history of diabetes	125 (7.8)			
Family history of hypertension	189 (11.7)			

Data presented as n (%) or as Mean ± Standard Deviation, Median, Interquartile range (Q1-Q3).

Analysis of obstetric outcomes showed, that in 92.5% used vaginal mode of delivery, planned CS performed in 4.4% of the subjects, and emergency CS in 3.0%. In one case (0.1%) was used vacuum extraction. Labor induction noted in 1.4% of cases.

Analysis of neonatal parameters showed that the mean gestational age of newborns during childbirth 39.43 ±1.9 weeks of pregnancy. Preterm delivery observed in 6.6% of cases. Prolonged delivery in the surveyed contingent noted in 19.3% of cases.

The mean weight of newborns in the studied population 3244.87 ±525.9 grams. The largest proportion was the group of newborns weighing 3001-4000 grams (63.3%). The proportion of newborns with a weight of under 3000 g was 31.8%, while those with a weight of ≥4001 g - 4.9%.

The mean height of newborns in the studied population 50.88 ±2.8 cm. The highest proportion of newborns in the group of 51-55 cm (57.1%), the lowest – in the group of ≥56 cm, 1.6%. The mean head circumference in the examined newborns 34.48 ±1.4 cm.

The mean of newborns on the Apgar scale at 5 minutes 7.89 ±0.6 points.

The mean blood sugar concentration at 30 minutes after birth in newborns 3.42 ±0.6 mmol/L. Cluster analysis revealed that the proportion of newborns with a sugar level of 2.6 - 3.0 mmol/L was 24.6%, 3.1-3.5 mmol/L - 38.5%, 3.6-4.0 mmol/L - 26.2%, ≥4.1 mmol/L - 8.7% and with hypoglycemia - 2.0%.

Table 4.4: Baseline obstetric and newborn outcomes of the study participants in urban setting (N=1610)

	n (%)	Mean ±SD	Median	25q – 75q
Obstetrical outcomes				
Mode of delivery				
Vaginal delivery	1490 (92.5)			
Planned cesarean section	71 (4.4)			
Emergency cesarean section	48 (3.0)			
Vacuum extraction	1 (0.1)			
Induction of delivery	23 (1.4)			
Newborn characteristics				
Gestational age at time of delivery		39.43 ±1.9	40	39 – 40
≤28	6 (0.4)			
29 – 36	100 (6.2)			
37 – 40	1193 (74.1)			
>40	311 (19.3)			
Birth weight (g)		3244.87 ±525.9	3200	3000 -3530
≤1000	9 (0.6)			
1001 – 2000	29 (1.8)			
2001 – 3000	474 (29.4)			
3001 – 4000	1019 (63.3)			
4001 – 5000	76 (4.7)			
≥5001	3 (0.2)			
Height (cm)		50.88 ±2.8	51	50 – 52
≤45	68 (4.2)			
46 – 50	597 (37.1)			
51 – 55	919 (57.1)			
≥56	26 (1.6)			
Head circumference (cm)	1609 (99.9)	34.48 ±1.4	35	34 – 35
Neonatal outcomes				
5-min APGAR (points)	1587 (98.6)	7.89 ±0.6	8	8 - 8
30-min glucose (mmol/l)	1567 (97.3)	3.42 ±0.6	3.3	3.0 – 3.7
≤2.5	31 (2.0)			
2.6 – 3.0	386 (24.6)			
3.1 – 3.5	603 (38.5)			
3.6 – 4.0	410 (26.2)			
≥4.1	137 (8.7)			

Data presented as n (%) or as Mean ± Standard Deviation, Median, Interquartile range (Q1-Q3).

In rural study population, the mean age of pregnant women 24.37 ±5.0 years. The proportion of pregnant women aged 20-24 years (43.4%) prevailed, compared with women aged 25-29 years (25.4%). In rural area the proportion of women with 30 years and older (15.9%) observed almost equally to the group of women with age less than 20 years (15.3%),

The mean weight in the study population 58.25 ±11.0 kg. The proportion of pregnant women over 60 kg (33.3%) prevailed compare to .under 50 kg (26,2%).

The mean height 160.33 ±6.3 cm. Almost equally proportion of pregnant women distributed in the 151-160 cm (43.7%) and 161-170 cm (45.3%) groups, whereas group with height ≤150 cm consist 7.5% and >170 cm - 3.5%.

In BMI analysis, observed a predominance of pregnant women with a normal body weight of 65.5%. The proportion of pregnant women with underweight 11.7% prevaleged over overweight - 5.2%.

The BP parameters showed mean SBP and DBP were 101.33 ±12.5 and 64.65 ±9.0 mm of Hg, respectively.

When analyzing the parity, the pregnant women with parity 1 was 35.6%, with parity 2 - 28.3%, with parity 3 - 22.6%, with parity 4 and more - 13.6%.

According to the results of OGTT in the subjects, the mean fasting blood glucose level 4.82 ±0.6 mmol/L, 1 hour after glucose load - 5.79 ±0.9 mmol/L, and 2 hours after glucose load - 6.68 ±1.1 mmol/L.

The mean gestational age at the time of OGTT was 26.2 ±2.4 weeks of gestation.

According to the data of family anamnesis, analysis revealed that 14.9% of pregnant women have a relative with diabetes, and 34.4% have arterial hypertension.

Table 4.5: Baseline maternal characteristics of the study participants in rural setting (N = 828)

	n (%)	Mean ±SD	Median	25q – 75q
Age (years)		24.37 ±5.0	23	20 – 27
<20	127 (15.3)			
20-24	359 (43.4)			
25-29	210 (25.4)			
≥30	132 (15.9)			
Weight (kg)		58.25 ±11.0	56	50 – 64
≤40	18 (2.2)			
41 – 50	199 (24.0)			
51 – 60	335 (40.5)			
>60	276 (33.3)			
Height (cm)		160.33 ±6.3	160	156 – 165
≤150	62 (7.5)			
151-160	362 (43.7)			
161-170	375 (45.3)			
>170	29 (3.5)			
BMI (kg/m^2)		22.64 ±4.0	22.0	19.8 – 24.7
<18.5	97 (11.7)			
18.5 – 24.9	542 (65.5)			
25.0 – 29.9	146 (17.6)			
≥30	43 (5.2)			
SBP (mm of Hg)		101.33 ±12.5	100	90 – 110
<120	744 (89.9)			
120-139	60 (7.2)			
≥140	24 (2.9)			
DBP (mm of Hg)		64.65 ±9.0	60	60 – 70
<60	32 (3.9)			
60-89	770 (93.0)			
≥90	26 (3.1)			
Parity				
1	295 (35.6)			
2	234 (28.3)			
3	187 (22.6)			
4	78 (9.4)			
5	23 (2.8)			
6	8 (1.0)			
7	3 (0.4)			
Plasma glucose (mmol/l)				
Fasting		4.82 ±0.6	5.0	4.4 – 5.0
1 hour		5.79 ±0.9	5.8	5.125 – 6.0
2 hour		6.68 ±1.1	6.6	6.0 – 7.0
Gestational weeks at time of OGTT		26.2 ±2.4	26	25 - 28
Family history of diabetes	123 (14.9)			
Family history of hypertension	285 (34.4)			

Data presented as n (%) or as Mean ± Standard Deviation, Median, Interquartile range (Q1-Q3).

Analysis of obstetric outcomes showed, that in 88.3% used vaginal mode of delivery, emergency CS in 11.5%. In two cases (0.2%) used vacuum extraction. Labor induction noted in 9.7% of cases.

Analysis of neonatal parameters showed that the mean gestational age of newborns during childbirth 38.62 ±3.3 weeks of pregnancy. Preterm delivery observed in 14.4% of cases. Prolonged delivery in the surveyed contingent noted in 26.7% of cases.

The mean weight of newborns in the studied population 3186.9±765.8 grams. The largest proportion was the group of newborns weighing 3001-4000 grams (59.64%). The proportion of newborns with a weight of under 3000 g was 33.6%, while those with a weight of ≥4001 g - 6.8%.

The mean height of newborns in the studied population 50.47±5.4 cm. The highest proportion of newborns in the group of 51-55 cm (60.7%), the lowest – in the group of ≥56 cm, 3.6%. The mean head circumference in the examined newborns 33.52±3.1 cm.

The mean of newborns on the Apgar scale at 5 minutes 7.89 ±1.0 points.

The mean blood sugar concentration at 30 minutes after birth in newborns 3.23 ±1.2 mmol/L. Cluster analysis revealed that the proportion of newborns with a sugar level of 2.6-3.0 mmol/L was 19.9%, 3.1-3.5 mmol/L - 14.4%, 3.6-4.0 mmol/L - 17.3%, ≥4.1 mmol/L - 24.6% and with hypoglycemia - 23.8%.

Table 4.6: Baseline obstetric and newborn outcomes of the study participants in rural setting (N=828)

	n (%)	Mean ±SD	Median	25q – 75q
Obstetrical outcomes				
Mode of delivery				
Vaginal delivery	731 (88.3)			
Emergency cesarean section	95 (11.5)			
Vacuum extraction	2 (0.2)			
Induction of delivery	80 (9.7)			
Newborn characteristics				
Gestational age at time of delivery		38.62 ±3.3	39	38 - 41
≤28	27 (3.3)			
29 – 36	92 (11.1)			
37 – 40	488 (58.9)			
>40	221 (26.7)			
Birth weight (g)	827 (99.9)	3186.9 ±765.8	3300	2900 - 3600
≤1000	30 (3.6)			
1001 – 2000	37 (4.5)			
2001 – 3000	211 (25.5)			
3001 – 4000	493 (59.6)			
4001 – 5000	55 (6.7)			
≥5001	1 (0.1)			
Height (cm)	825 (99.6)	50.47 ±5.4	52	50 – 53
≤45	67 (8.1)			
46 – 50	227 (27.5)			
51 – 55	501 (60.7)			
≥56	30 (3.6)			
Head circumference (cm)	809 (97.7)	33.52 ±3.1	34	33 – 35
Neonatal outcomes				
5-min APGAR (points)	773 (93.4)	7.89 ±1.0	8	8 - 8
30-min glucose (mmol/l)	382 (46.1)	3.23 ±1.2	3.2	2.6 – 4.0
≤2.5	91 (23.8)			
2.6 – 3.0	76 (19.9)			
3.1 – 3.5	55 (14.4)			
3.6 – 4.0	66 (17.3)			
≥4.1	94 (24.6)			

Data presented as n (%) or as Mean ± Standard Deviation, Median, Interquartile range (Q1-Q3).

Comparative analysis of maternal parameters showed that women in rural areas younger 24.37 ±5.0 compare to women in the urban area 25.02 ±5.0 (p=0.001). The weight of women in the urban setting prevailed 60.27 ±11.1 kg compare to the rural area 58.25 ±11.0 kg (p<0.001). Mean height significantly higher in rural women 160.3 ± 6.3 cm as compare to the urban 159.08 ± 5.6 cm (p<0.001).

BMI significantly higher in the group of women from urban setting 23.797 ±4.1 compare with rural setting 22.645 ±4.0 (p <0.001). In terms of BP, DBP significantly higher in group of subjects from rural area 64.65 ±9.0 mm of Hg compare with the urban area 63.0 ±6.3 mm of Hg (p <0.001).

In a comparative analysis of the parity parameter, no statistically significant differences found, with the exception of prevalence of women from the city (4.6%) with parity 5 compared with rural areas (2.8%) (p = 0.030).

Studyings of blood sugar level, showed that mean fasting glucose value significantly higher in urban group 4.97 ±0.6 mmol/L, compare to the rural group 4.82 ±0.6 mmol/L (p <0.001). However, mean glucose concentration after 2 hour glucose load significantly higher in rural group 6.68 ±1.1 mmol/L compare to urban group 5.63 ±0.6 mmol/L (p<0.001). No significant differences noted in blood glucose level after 1 hour glucose load between urban and rural areas (p = 0.363).

In medical history, women from the rural were significantly more likely to suffer from anemia of varying severity (100%) and iodine deficiency (84.3%) compared to urban 45.7 and 18.0%, respectively (p<0.001 and p<0.001).

Comparative analysis of family history showed that women in the rural had relatives with DM (14.9%) and AH (34.4%) significantly more common than in the urban (7.8 and 11.7%, respectively) (p<0.001 and p<0.001).

Table 4.7: Maternal characteristics differences between urban and rural study participants

Parameter	URBAN (n = 1610)			RURAL (n = 828)			*p* value
	n	%	Mean ±SD	n	%	Mean ±SD	
Age (yr)			25.02 ±5.0			24.37 ±5.0	0.001
Weight (kg)			60.27 ±11.1			58.25 ±11.0	<0.001
Height (cm)			159.08 ±5.6			160.3 ±6.3	<0.001
BMI (kg/m^2)			23.797 ±4.1			22.645 ±4.0	<0.001
SBP (mm of Hg)			100.21 ±8.6			101.33 ±12.5	0.700
DBP (mm of Hg)			63.0 ±6.3			64.65 ±9.0	<0.001
Parity							
1	517	32.1		295	35.6		0.081
2	457	28.4		234	28.3		0.949
3	349	21.7		187	22.6		0.608
4	190	11.8		78	9.4		0.075
5	74	4.6		23	2.8		0.030
6	16	1.0		8	1.0		0.948
7	3	0.2		3	0.4		0.406
8	4	0.2		0			0.151
Plasma glucose (mmol/l)							
Fasting			4.97 ±0.6			4.82 ±0.6	<0.001
1 hour			5.79 ±0.7			5.79 ±0.9	0.363
2 hour			5.63 ±0.6			6.68 ±1.1	<0.001
Medical history of anemia	735	45.7		828	100		<0.001
Medical history of thyroid gland diseases	290	18.0		698	84.3		<0.001
Family history of hypertension	189	11.7		285	34.4		<0.001
Family history of diabetes	125	7.8		123	14.9		<0.001

Data presented as n (%) or as Mean ± Standard Deviation. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

In a comparative analysis of obstetric outcomes was noted that participants of the rural setting gave birth earlier 38.62 ±3.3 weeks than urban setting 39.43 ±1.9 weeks ($p < 0.001$). The proportion of vaginal delivery significantly higher in urban (92.5%) compared to rural (88.3%) ($p<0.001$). Emergency CS was more often carried out in the rural setting (11.5%) in comparison with the urban (3.0%) ($p < 0.001$). However, according to the results obtained, it turned out that the planned CS was carried out only in the urban setting.

Premature rupture of membranes is more common in pregnant women from the rural (19.3%) compared to those from the urban (9.8%) ($p < 0.001$). Induced delivery significantly more often prevailed in the rural (9.7%) as compared to the urban (1.4%) ($p<0.001$).

No statistically significant differences in mean values of the weight of newborns between urban and rural areas. However, urban newborns of 50.88 ±2.8 cm distinguished by a slightly higher height compared to rural newborns of 50.47 ±5.4 cm ($p < 0.001$). Also, an identical difference was noted in the mean head circumference of newborns (34.48 ±1.4 and 33.52 ±3.1 cm, respectively, $p < 0.001$).

Analysis of blood glucose indicators at the 30th minute after birth in newborns showed significant mean value prevailed in children from urban of 3.42 ±0.6 mmol/l compared to rural area 3.23 ±1.2 mmol/l ($p=0.003$).

Table 4.8: Obstetric and newborn outcomes differences between urban and rural study participants

Parameter	URBAN (n = 1610)			RURAL (n = 828)			*p* value
	n	%	Mean ±SD	n	%	Mean ±SD	
Obstetrical outcome							
Gestational weeks at time of delivery			39.43 ±1.9			38.62 ±3.3	<0.001
Vaginal delivery	1490	92.5		731	88.3		<0.001
Planned cesarean section	71	4.4		0			<0.001
Emergency cesarean section	48	3.0		95	11.5		<0.001
Vacuum extraction	1	0.1		2	0.2		0.231
Rupture of membranes	157	9.8		160	19.3		<0.001
Induced delivery	23	1.4		80	9.7		<0.001
Newborn characteristics							
Birth weight (g)			3244.87 ±525.9			3186.90 ±765.8	0.336
Height (cm)			50.88 ±2.8			50.47 ±5.4	<0.001
Head circumference (cm)			34.48 ±1.4			33.52 ±3.1	<0.001
Neonatal outcome							
5-min APGAR (points)			7.89 ±0.6			7.89 ±1.0	0.001
30-min glucose (mmol/l)			3.42 ±0.6			3.23 ±1.2	0.003

Data presented as n (%) or as Mean ± Standard Deviation. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

4.3. Risk factors for GDM in study population

Analysis of the data among study participants based on the glucose level, pregnant women with GDM 25.32 ±5.3 statistically differed with older age from comparison group 24.55 ±4.9 (p = 0.001). Proportion of women under the age of 20 was significantly higher (14.0%, p = 0.013) in group with no-GDM. Nevertheless, statistically more subjects with age ≥30 years noted in the GDM group (20.7%) compared to no-GDM group (16.3%) (p = 0.008).

Comparative analysis in the groups showed that women with GDM 60.66 ±11.4 kg had more weight compared with no-GDM 59.07 ±10.9 kg (p=0.001). Proportion of pregnants weighing more than 60 kg significantly higher in GDM group (42.2%) compared to no-GDM (36.4%) (p=0.006).

There were no statistically significant differences in the height of the subjects between the groups of GDM (159.68 ±5.8 cm) and those without GDM (159.42 ±5.9 cm) (p = 0.459). However, it should be noted that women with a height >170 cm (3.2%) prevailed in the GDM group, and with height ≤150 cm - in the group of without GDM (7.3%).

BMI data in the groups showed that, high BMI indicators found in the GDM group (23.787 ±4.3) compared to without GDM (23.222 ±4.0) (p = 0.002). In cluster analysis of the data, it was noted that the group with GDM (8.8%) was distinguished by the highest proportion of women with BMI ≥30.0 in comparison with no-GDM (6.4%) (p = 0.031).

Comparative analysis of blood pressure parameters did not show differences between groups.

Also, no significant differences in parities 1,2, and 3 between groups. It should be noted that the proportion of pregnant women with a parity of ≥4 were statistically more higher in GDM (19.1%) compared to no GDM group (15.1%) (p = 0.012).

There were no statistically significant differences in mean of gestational weeks OGTT performance between groups. Thus, a comparative analysis showed that the significantly higher mean increase observed in the concentration of glucose in fasting blood plasma (5.57 ±0.4 mmol/L), at 1 hour (6.40 ±0.7 mmol/L) and 2 hours (6.42 ±1.1 mmol/L) after glucose load was noted in the GDM group than in the group with no-GDM (p <0.001).

In medical history, anemia and iodine deficiency status were most often noted in the group with no-GDM than with GDM.

Analysis of family history in the study of diseases such as diabetes and hypertension between groups did not reveal statistically significant differences.

Table 4.9: Characteristics of study participants with GDM and no-GDM

Parameters	GDM N = 791				no-GDM N = 1647				*p*-value
	n (%)	Mean ±SD	Median	25q-75q	n (%)	Mean ±SD	Median	25q-75q	
Age (years)		25.32 ±5.3	24	21-28		24.55 ±4.9	24	21-27	0.001
<20	82 (10.4)				230 (14.0)				0.013
20-24	325 (41.1)				694 (42.1)				0.623
25-29	220 (27.8)				454 (27.6)				0.898
≥30	164 (20.7)				269 (16.3)				0.008
Weight (kg)		60.66 ±11.4	58	53-66		59.07 ±10.9	57	51-65	0.001
≤40	4 (0.5)				21 (1.3)				0.078
41 – 50	128 (16.2)				340 (20.6)				0.009
51 – 60	325 (41.1)				686 (41.7)				0.791
>60	334 (42.2)				600 (36.4)				0.006
Height (cm)		159.68 ±5.8	160	156-164		159.42 ±5.9	160	155-164	0.459
≤150	47 (5.9)				121 (7.3)				0.200
151-160	444 (56.1)				880 (53.4)				0.210
161-170	275 (34.8)				601 (36.5)				0.406
>170	25 (3.2)				45 (2.7)				0.553
BMI (kg/m^2)		23.787 ±4.3	23.1	20.8-25.7		23.222 ±4.0	22.6	20.4-25.2	0.002
<18.5	45 (5.7)				127 (7.7)				0.068
18.5 – 24.9	506 (64.0)				1066 (64.7)				0.716
25.0 – 29.9	170 (21.5)				348 (21.1)				0.838
≥30.0	70 (8.8)				106 (6.4)				0.031

SBP (mm of Hg)		101.0 ±10.7	100	90-100		100.4 ±9.7	100	90-100	0.231
<120	723 (91.4)				1526 (92.7)				0.280
120-139	58 (7.3)				105 (6.4)				0.376
≥140	10 (1.3)				16 (1.0)				0.510
DBP (mm of Hg)		63.75 ±7.8	60	60-70		63.47 ±7.1	60	60-70	0.623
<60	20 (2.5)				39 (2.4)				0.809
60-89	759 (96.0)				1590 (96.5)				0.471
≥90	12 (1.5)				18 (1.1)				0.374
Parity									
1	252 (31.8)				560 (34.0)				0.293
2	204 (25.7)				487 (29.6)				0.053
3	184 (23.3)				352 (21.4)				0.292
≥4	151 (19.1)				248 (15.1)				0.012
Gestational weeks at time of OGTT		26.28 ±2.7	26	24-28		26.28 ±2.5	26	24-28	0.855
Plasma glucose (mmol/l)									
Fasting		5.57 ±0.4	5.5	5.2-5.8		4.61 ±0.4	4.8	4.4-5.0	<0.001
1 hour		6.40 ±0.7	6.4	5.9-6.8		5.50 ±0.6	5.6	5.0-5.8	<0.001
2 hour		6.42 ±1.1	6.2	5.8-6.7		5.78 ±0.8	5.7	5.2-6.1	<0.001
Medical history of thyroid gland diseases	273 (34.5)				715 (43.4)				<0.001
Medical history of anemia	445 (56.3)				1118 (67.9)				<0.001
Family history of diabetes mellitus	81 (10.2)				167 (10.1)				0.939
Family history of hypertension	152 (19.2)				322 (19.6)				0.845

Data presented as n (%) or as Mean ±Standard Deviation, Median and Interquartile Range. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

In the urban area, women with GDM were older 25.29 (95% CI 24.89 - 25.70) compared to no GDM 24.86 (95% CI 24.55 - 25.17), without statistically significant differences between groups.

Pregnant women in group with GDM had more weight 61.03 (95% CI 60.12 - 61.94) than in the group without GDM 59.81 (95% CI 59.14 - 60.48) ($p = 0.047$).

The height of women with GDM 159.50 (95% CI 159.05 - 159.95) was slightly higher than in the group without GDM 158.82 (95% CI 158.48 - 159.16) ($p = 0.039$).

There were no statistically significant differences in BMI between the groups.

According to the results of a comparative analysis, the GDM group had higher mean of DBP values of 63.36 (95% CI 62.86 - 63.86) compared to without GDM group 62.78 (95% CI 62.39 - 63.17) ($p=0.036$). However, no statistically significant differences were found in the SBP values.

There were no statistically significant differences in parity between the two groups.

In the family history, relatives with DM (8.7%) and AH (12.8%) were most often noted in the group of GDM than in the group without GDM (7.2 and 11.1%, respectively).

Table 4.10: Maternal parameters of the study participants based on glucose status in urban setting

Parameters	GDM N = 609		no-GDM N = 1001		*p*-value
	n (%)	Mean (95% CI)	n (%)	Mean (95% CI)	
Age (years)		25.29 (24.89 – 25.70)		24.86 (24.55 – 25.17)	0.100
<30	493 (81.0)		816 (81.5)		
≥30	116 (19.0)		185 (18.5)		
Weight (kg)		61.03 (60.12 – 61.94)		59.81 (59.14 – 60.48)	0.047
≤40	2 (0.3)		5 (0.5)		
41 – 50	91 (14.9)		178 (17.8)		
51 – 60	250 (41.1)		426 (42.6)		
>60	266 (43.7)		392 (39.2)		
Height (cm)		159.50 (159.05–159.95)		158.82 (158.48–159.16)	0.039
≤150	34 (5.6)		72 (7.2)		
151-160	358 (58.8)		604 (60.3)		
161-170	198 (32.5)		303 (30.3)		
>170	19 (3.1)		22 (2.2)		
BMI (kg/m^2)		23.982 (23.641–24.323)		23.684 (23.438–23.930)	0.203
<18.5	30 (4.9)		45 (4.5)		
18.5 – 24.9	383 (62.9)		647 (64.6)		
25.0 – 29.9	138 (22.7)		234 (23.4)		
≥30	58 (9.5)		75 (7.5)		
SBP (mm of Hg)		100.56 (99.89 – 101.23)		100.0 (99.47 – 100.54)	0.189
<120	565 (92.8)		940 (94.0)		
120-139	44 (7.2)		59 (5.9)		
≥140			2 (0.2)		
DBP (mm of Hg)		63.36 (62.86 – 63.86)		62.78 (62.39 – 63.17)	0.036
<60	8 (1.3)		19 (1.9)		

60-89	600 (98.5)		979 (97.8)		
≥90	1 (0.2)		3 (0.3)		
Parity					
1	185 (30.4)		332 (33.2)		0.245
2	187 (30.7)		270 (27.0)		0.107
3	132 (21.7)		217 (21.7)		0.999
4	69 (11.3)		121 (12.1)		0.648
5	27 (4.4)		47 (4.7)		0.808
6	6 (1.0)		10 (1.0)		0.978
7			3 (0.3)		0.176
8	3 (0.5)		1 (0.1)		0.125
Gestational weeks at time of OGTT		26.38 (26.17 – 26.60)		26.28 (26.12 – 26.45)	0.561
Family history of diabetes mellitus	53 (8.7)		72 (7.2)		0.272
Family history of hypertension	78 (12.8)		111 (11.1)		0.299

Data presented as n (%) or as Mean, 95% Confidence Interval for Mean. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

In rural area, pregnant women with GDM were older of 25.40 (95% CI 24.55 - 26.25) compared to those without GDM (95% CI 23.71 - 24.45) (p = 0.019). Women from the group with GDM had higher weight 59.42 (95% CI 57.77 - 61.07) than from the group without GDM 57.62 (95% CI 57.08 - 58.77), but no statistically significant differences. Between groups, there were no statistically significant differences in BMI, blood pressure, parity, family history of diabetes, or hypertension.

Table 4.11: Maternal parameters of the study participants based on glucose status in rural setting

Parameters	**GDM N = 182**		**no-GDM N = 646**		***p*-value**
	n (%)	**Mean (95% CI)**	**n (%)**	**Mean (95% CI)**	
Age (years)		25.40 (24.55 – 26.25)		24.08 (23.71 – 24.45)	0.019
<30	134 (73.6)		562 (87.0)		
≥30	48 (26.4)		84 (13.0)		
Weight (kg)		59.42 (57.77 – 61.07)		57.62 (57.08 – 58.77)	0.095
≤40	2 (1.1)		16 (2.5)		
41 – 50	37 (20.3)		162 (25.1)		
51 – 60	75 (41.2)		260 (40.2)		
>60	68 (37.4)		208 (32.2)		
Height (cm)		160.25 (159.36 – 161.13)		160.35 (159.87 – 160.84)	0.824
≤150	13 (7.1)		49 (7.6)		
151-160	86 (47.3)		276 (42.7)		
161-170	77 (42.3)		298 (46.1)		
>170	6 (3.3)		23 (3.6)		
BMI (kg/m^2)		23.135 (22.523 – 23.746)		22.507 (22.204 – 22.810)	0.061
<18.5	15 (8.2)		82 (12.7)		
18.5 – 24.9	123 (67.6)		419 (64.9)		
25.0 – 29.9	32 (17.6)		114 (17.6)		
≥30	12 (6.6)		31 (4.8)		

SBP (mm of Hg)		102.45 (100.29 – 104.60)	101.01 (100.11 – 101.92)	0.583
<120	161 (88.5)		26 (4.0)	
120-139	12 (6.6)		604 (93.5)	
≥140	9 (4.9)		16 (2.5)	
DBP (mm of Hg)		64.35 (63.69 – 65.01)	65.71 (64.18 – 67.25)	0.277
<60	6 (3.3)		26 (4.0)	
60-89	166 (91.2)		604 (93.5)	
≥90	10 (5.5)		16 (2.5)	
Parity				
1	66 (36.3)		229 (35.4)	0.839
2	44 (24.2)		190 (29.4)	0.166
3	41 (22.5)		146 (22.6)	0.983
4	22 (12.1)		56 (8.7)	0.163
5	7 (3.8)		16 (2.5)	0.321
6	1 (0.5)		7 (1.1)	0.515
7	1 (0.5)		2 (0.3)	0.634
Gestational weeks at time of OGTT		26.23 (25.84 – 26.61)	26.19 (26.01 – 26.37)	0.764
Family history of diabetes mellitus	27 (14.8)		96 (14.9)	0.993
Family history of hypertension	70 (38.5)		215 (33.3)	0.194

Data presented as n (%) or as Mean, 95% Confidence Interval for Mean. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

There were no statistically significant differences in age and weight between women with GDM in urban and rural locations. However, the mean height of women from the rural area 160.25 ±6.0 cm was higher than from urban 159.50 ±5.7 cm (p = 0.040).

Mean BMI significantly higher in the group of women from urban area 23.982 ±4.3 compared to rural area 23.135 ±4.2 (p = 0.008).

In terms of BP, DBP significantly higher in group of subjects from rural area 65.71 ±10.5 mm of Hg compared to urban 63.36 ±6.3 mm of Hg (p = 0.026).

Comparative analysis of the parity parameter did not reveal any significant differences. Although, there were more primiparas in the rural (36.3%), and with parity 2 in the urban (30.7%).

The mean fasting glucose value 5.48 ±0.4 mmol/L, after 1 hour 6.60 ±1.1 mmol/L and after 2 hours 7.78 ±1.4 mmol/L significantly higher in rural group, compared to urban 4.62 ±0.3 mmol/L; 5.43 ±0.5 mmol/L and 5.50 ±0.4 mmol/L, respectively (p <0.001).

Comparative analysis of family history showed that women in rural setting had DM (14.8%) and AH (38.5%) among relatives significantly more often than in urban setting (8.7 and 12.8%, respectively) (p=0.016 and p<0.001).

Table 4.12: Differences in maternal characteristics between urban GDM and rural GDM study participants

Parameter	**URBAN (n = 609)**			**RURAL (n = 182)**			
	n	**%**	**Mean ±SD**	**n**	**%**	**Mean ±SD**	***p* value**
Maternal characteristics							
Age (yr)			25.29 ±5.1			25.40 ±5.8	0.698
Weight (kg)			61.03 ±11.4			59.42 ±11.3	0.063
Height (cm)			159.50 ±5.7			160.25 ±6.0	0.040
BMI (kg/m^2)			23.982 ±4.3			23.135 ±4.2	0.008
SBP (mm of Hg)			100.56 ±8.4			102.45 ±14.7	0.850
DBP (mm of Hg)			63.36 ±6.3			65.71 ±10.5	0.026
Parity							
1	185	30.4		66	36.3		0.134
2	187	30.7		44	24.2		0.089
3	132	21.7		41	22.5		0.807
4	69	11.3		22	12.1		0.779
5	27	4.4		7	3.8		0.732
6	6	1.0		1	0.5		0.582
7	0			1	0.5		0.067
8	3	0.5		0			0.343
Plasma glucose (mmol/l)							
Fasting			4.62 ±0.3			5.48 ±0.4	<0.001
1 hour			5.43 ±0.5			6.60 ±1.1	<0.001
2 hour			5.50 ±0.4			7.78 ±1.4	<0.001
Family history of hyper-tension	78	12.8		70	38.5		<0.001
Family history of diabetes	53	8.7		27	14.8		0.016

Data presented as n (%) or as Mean ± Standard Deviation. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

In a comparative analysis of the data, depending on the glucose status after OGTT, pregnant women with slightly elevated fasting (fasting group) blood glucose value had high mean age of 25.4 ±5.3 than a group of high glucose value after 1 or/and 2 hours load (severe group) 24.3 ±5.2 and normal blood glucose value (GDM negative group) 24.6 ±4.9 (p=0.001).

Mean weight of women from fasting group higher 60.8 ±11.4 kg than from severe group 58.8 ±11.7 kg and GDM negative group 59.1 ±10.9 (p=0.001).

No statistically significant differences in height parameters between groups.

The mean weight women from fasting group higher 23.9 ±4.3, than from severe group 23.0 ±4.2 and GDM negative group 23.2 ±4.0 (p=0.001).

SBP and DBP in women with severe group higher 107.4 ± 17.0 and 69.0 ± 11.6 than fasting group 100.4 ± 9.8 and 63.3 ± 7.1 and GDM negative group 100.4 ± 9.7 and 63.5 ± 7.1 (p = 0.001 and p <0.001).

In parity data, the proportion of primiparas was statistically higher in severe group 44.1% than in fasting group 30.7% and GDM negative group 34.0% (p = 0.046). No statistically significant differences were found in parity of 2 and 3 between the groups. The proportion of pregnant women with parity ≥4 was significantly higher in fasting group 19.9% than in GDM negative group 15.1% and severe 10.3% groups (p = 0.005).

In the family history, the proportion of relatives with AH significantly higher in the severe 41.2% than in GDM negative 19.6% and fasting groups 17.2% (p=0.005).

No statistically significant differences found in family anamnesis of having relatives with DM between groups.

Table 4.13: Parameters of study participants according to glucose status

Parameters	GDM-negative N = 1647			GDM-fasting N = 723			GDM-severe N = 68			*p*-value
	n (%)	Mean ±SD	25q-75q	n (%)	Mean ±SD	25q-75q	n (%)	Mean ±SD	25q-75q	
Age (years)		24.6 ±4.9	21.0-27.0		25.4 ±5.3*	21.0-29.0		24.3 ±5.2	20.0-27.0	0.001
Weight (kg)		59.1 ±10.9	51.0-65.0		60.8 ±11.4*	53.0-66.0		58.8 ±11.7***	50.25-66.0	0.001
Height (cm)		159.4 ±5.9	155.0-164.0		159.7 ±5.7	156.0-164.0		159.9 ±6.0	156.0-163.75	0.722
BMI (kg/m^2)		23.2 ±4.0	20.4-25.2		23.9 ±4.3*	21.0-25.7		23.0 ±4.2***	20.15-24.9	0.001
SBP (mm Hg)		100.4 ±9.7	90.0-100.0		100.4 ±9.8	90.0-100.0		107.4 ±17.0**(***)	100.0-110.0	0.001
DBP (mm Hg)		63.5 ±7.1	60.0-70.0		63.3 ±7.1	60.0-70.0		69.0 ±11.6**(***)	60.0-80.0	<0.001
Parity										
1	560 (34.0)			222 (30.7)			30 (44.1)			0.046
2	487 (29.6)			189 (26.1)			15 (22.1)			0.118
3	352 (21.4)			168 (23.2)			16 (23.5)			0.573
≥4	248 (15.1)			144 (19.9)			7 (10.3)			0.005
Family history for hypertension	322 (19.6)			124 (17.2)			28 (41.2)			<0.001
Family history for diabetes	167 (10.1)			72 (10.0)			9 (13.2)			0.692

Data presented as n (%) or as Mean ±Standard Deviation and Interquartile Range. Chi-square test used to compare categorical variables and Kruskal Wallis Test or Mann-Whitney U Test used for comparing continuous variables between groups. P values < 0.05 for two-tailed test considered statistically significant.
*p value < 0.001 (comparison between GDM-negative and GDM-fasting groups)
**p value < 0.001 (comparison between GDM-negative and GDM-severe groups)
***p value <0.05 (comparison between GDM-fasting and GDM-severe groups)

4.4. Obstetrical outcomes

There were no statistically significant variations in mean gestational weeks at time of birth between the GDM and no GDM groups, according to a comparative analysis of obstetric outcomes.

There were no significant variations in the percentage of vaginal deliveries across the groups. However, the obtained results showed that planned CS was performed more often in women with GDM (3.9%) compared with no-GDM (2.4%) (p = 0.040).

Emergency CS more often performed in the group of no-GDM (6.2%) compared with GDM (5.2%). Vacuum extraction used in two (0.3%) cases in the GDM group versus one (0.1%) case in the group of without GDM. Induced labor more often prevailed in the group with no-GDM (4.6%) compared with GDM (3.5%). Premature rupture of membranes is more likely in GDM pregnant women (13.7%) than in no-GDM pregnant women (12.7%).

Table 4.14: Obstetrical outcomes of study participants with GDM and no-GDM

Parameters	**GDM N = 791**		**no-GDM N = 1647**		***p*-value**
	n (%)	**Mean ±SD**	**n (%)**	**Mean ±SD**	
Gestational weeks at time of delivery		39.09 ±2.6		39.18 ±2.5	0.635
Vaginal delivery	717 (90.6)		1504 (91.3)		0.585
Planned CS	31 (3.9)		40 (2.4)		0.040
Emergency CS	41 (5.2)		102 (6.2)		0.321
Vacuum extraction	2 (0.3)		1 (0.1)		0.205
Induced delivery	28 (3.5)		75 (4.6)		0.244
Rupture of membranes	108 (13.7)		209 (12.7)		0.508

Data presented as n (%) or as Mean ±Standard Deviation. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

Women from rural area earlier admitted to the delivery 38.24 ±3.7 in comparison with women from the urban area 39.57 ±1.7 (p <0.001). Vaginal delivery significantly higher in women from urban 93.1% than in rural area 84.6% (p <0.001). Planned CS carried out only among women of the urban setting 4.4%. Emergency CS performed more often in women from rural area (14.3%) than in urban area (2.3%) (p <0.001). Premature rupture of membranes more often observed in women from rural area (22.0%) compared to urban (11.2%) (p <0.001). Induction of labor significantly higher performed in women with GDM in rural area (9.9%) compare to in urban area (1.1%) (p <0.001).

Table 4.15: Differences in obstetric outcomes between urban GDM and rural GDM study participants

Parameter	**URBAN (n = 609)**			**RURAL (n = 182)**			
	n	**%**	**Mean ±SD**	**n**	**%**	**Mean ±SD**	***p* value**
Gestational weeks at time of delivery			39.57 ±1.7			38.24 ±3.7	<0.001
Vaginal delivery	567	93.1		154	84.6		<0.001
Planned cesarean section	27	4.4		0			0.004
Emergency cesarean section	14	2.3		26	14.3		<0.001
Vacuum extraction	1	0.2		2	1.1		0.072
Rupture of membranes	68	11.2		40	22.0		<0.001
Induced delivery	7	1.1		18	9.9		<0.001

Data presented as n (%) or as Mean ±Standard Deviation. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

In the course of pregnancy, significantly higher proportion of women with any complications observed in the severe group (57.4%, p<0.001) compare to GDM-negative (28.0%) and GDM fasting groups (15.4%). Among complications prevailed proportions of threatening miscarriage, preeclamsia and infection of urinary tract (all p<0.001). Mean gestational week at time of delivery significantly lower in the severe group compare to fasting and GDM-negative groups. In a comparative analysis of obstetric data depending on glucose status, the subjects in fasting group (4.3%) underwent planned CS more often than from GDM-negative group 2.4% (p = 0.016). Emergency CS more often performed in the severe group (13.2%) than in fasting group (4.4%) and in GDM-negative group (6.2%) (p = 0.008). Induction of labor was significantly more often performed in severe group 20.6% than in fasting group 1.9% and in GDM-negative group 4.6% (p <0.001). Premature rupture of membranes significantly more often observed in the severe group 29.4% than in fasting group 12.2% and in GDM-negative group 12.7% (p<0.001). No significant difference observed among mothers with with healthy status at time of discharge between groups, however sick mothers proportion slightly higher were in the fasting group (2.9%, p=0.017) compared to negative group (1.5%).

Table 4.16: Obstetric parameters of study participants according to glucose status

Parameters	**GDM-negative N = 1647**	**GDM-fasting N = 723**	**GDM-severe N = 68**	***p*-value**
Pregnancy				
Any complication	461 (28.0%)	111 (15.4%)	39 (57.4%)	<0.001
Threatening miscarriage	278 (16.9%)	56 (7.7%)	21 (30.9%)	<0.001
Preeclampsia / eclampsia	26 (1.6%)	5 (0.7%)	7 (10.3%)	<0.001
Urinary tract infection	80 (4.9%)	13 (1.8%)	6 (8.8%)	<0.001
Delivery				
Gestational weeks at delivery	39.2 ±2.5	39.3 ±2.2	37.2 ±4.6	<0.001
Vaginal delivery	1504 (91.3)	659 (91.1)	58 (85.3)	0.232
Planned CS	40 (2.4)	31 (4.3)	0	0.016
Emergency CS	102 (6.2)	32 (4.4)	9 (13.2)	0.008
Vacuum extraction	1 (0.1)	1 (0.1)	1 (1.5)	0.069
Induced delivery	75 (4.6)	14 (1.9)	14 (20.6)	<0.001
Rupture of membranes	209 (12.7)	88 (12.2)	20 (29.4)	<0.001
Mother status				
Healthy	1623 (98.5%)	702 (97.1%)	68 (100%)	0.316
Sick	24 (1.5%)	21 (2.9%)	0	0.017
Dead	0	0	0	

Data presented as n (%) and Mean ±SD. Chi-square test used to compare categorical variables. Kruskal Wallis Test used for comparing continuous variables between groups.
P values < 0.05 for two-tailed test considered statistically significant.

4.5. Anthropometric data of neonates and neonatal outcomes

No statistically significant differences in the mean values of weight of newborns between the GDM group and those without GDM. Proportion of neonates with birth weight <2500 g identical in both groups. Proportion of newborns born with birth weight ≥4000 g higher in the group of GDM (9.0%) compare to no GDM (8.2%).

No statistically significant differences in the mean values of height of newborns.

However, mean neonatal head circumference prevailed in the GDM group 34.21 ±2.2 cm than in without GDM 34.14 ±2.2 cm (p = 0.037).

Significant predominance noted in the mean value of the Apgar score at 5-minute in group of no- GDM 7.91 ±0.8 points compared with GDM group 7.85 ±0.8 points (p = 0.034). Proportion of newborns at 5-minute Apgar score <7 points higher in GDM group (4.9%) compare to no- GDM group (3.5%).

No statistically significant differences in mean at 30-min glucose value between GDM and no-GDM groups (3.40 ±0.7 and 3.38 ±0.8 mmol/L, respectively)

Table 4.17: Anthropometric data of neonates and neonatal outcomes of study participants with GDM and no-GDM

Parameters	GDM N = 791				no-GDM N = 1647				*p*-value
	n (%)	Mean ±SD	Median	25q-75q	n (%)	Mean ±SD	Median	25q-75q	
Birth weight (g)	791	3216.5 ±641.5	3200	3000-3580	1646	3229.4 ±607.0	3205	3000-3600	0.737
<2500	53 (6.7)				111 (6.7)				0.971
≥2500	738 (93.3)				1535 (93.2)				0.927
≥4000	71 (9.0)				135 (8.2)				0.517
<4000	720 (91.0)				1511 (91.7)				0.551
Height (cm)	791	50.63 ±3.8	51	50-52	1644	50.80 ±3.9	51	50-53	0.184
Head circumference (cm)	790	34.21 ±2.2	34	34-35	1628	34.14 ±2.2	34	34-35	0.037
5-min APGAR (points)	776	7.85 ±0.8	8	8-8	1584	7.91 ±0.8	8	8-8	0.034
5-min APGAR <7	39 (4.9)				58 (3.5)				0.096
5-min APGAR ≤8	733 (92.7)				1458 (88.5)				0.002
30-min glucose (mmol/l)	696	3.40 ±0.7	3.35	3.0-3.7	1253	3.38 ±0.8	3.3	3.0-3.7	0.451
≤2.5	39 (4.9)				83 (5.0)				0.908

Data presented as n (%) or as Mean ±Standard Deviation, Median and Interquartile Range. Chi-square test used to compare categorical variables. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

Comparative analysis did not show significant differences in the parameters such as mean weight and height among newborns from urban and rural area. However, it was noted predominance of mean head circumference in newborns from the urban (34.56 ±1.2 cm) compared to rural (33.36 ±3.5 cm) (p <0.001).

Analysis of glucose value at 30th minute after birth in newborns, showed that mean value significantly lower in children from rural area 3.16 ±1.2 mmol/L compared to the urban area 3.48 ±0.6 mmol/L (p = 0.007).

Table 4.18: Differences in anthropometric data of neonates and neonatal outcomes between urban GDM and rural GDM study participants

Parameter	**URBAN (n = 609)**	**RURAL (n = 182)**	***p* value**
	Mean ±SD	**Mean ±SD**	
Birth weight (g)	3258.54 ±496.4	3142.97 ±879.3	0.939
Height (cm)	50.94 ±2.5	50.02 ±5.7	0.218
Head circumference (cm)	34.56 ±1.2	33.36 ±3.5	<0.001
Neonatal outcome			
5-min APGAR (points)	7.89 ±0.6	7.80 ±1.1	0.396
30-min glucose (mmol/l)	3.48 ±0.6	3.16 ±1.2	0.007

Data presented as Mean ± Standard Deviation. Mann-Whitney U Test used to compare continuous variables. P values < 0.05 for two-tailed test considered statistically significant.

In a comparative analysis of neonatal data depending on glucose status, mean weight of newborns from severe group (2898.82 ±1003.4) significantly lower from fasting group (3246.38 ±588.6, p <0.05) and GDM-negative group (3229.38 ±606.9, p <0.05).

No statistically differences in mean height between groups.

Mean head circumference statistically higher in fasting group (34.35 ±1.7), compare to severe group (32.63 ±4.8) and GDM-negative group (34.14 ±2.2).

Analysis of Apgar score showed that, newborns from severe group (6.68±1.30, p<0.001) had significantly lower 1-min and 10 min Apgar (8.65±1.49, p<0.001) compare to the other groups. However, mean 5-min Apgar score statistically lower in fasting group compare to GDM-negative group 7.86 ±0.7 and 7.91 ±0.8 p <0.05, respectively.

Mean 30-min glucose value significantly lower in the severe group (2.97 ±1.3), compare to fasting (3.41 ±0.6, p <0.05) and GDM-negative groups (3.38 ±0.8 p <0.05).

Table 4.19: Neonatal parameters of study participants according to glucose status

Parameters	GDM-negative N = 1647			GDM-fasting N = 723			GDM-severe N = 68			*p*-value
	Mean ±SD	Median	25q-75q	Mean ±SD	Median	25q-75q	Mean ±SD	Median	25q-75q	
Birth weight (g)	3229.38 ±606.9	3205	3000-3600	3246.38 ±588.6	3200	3000-3570	2898.82 ±1003.4 **(***)	3100	2600-3600	0.107
Height (cm)	50.80 ±3.9	51	50-53	50.83 ±3.3	51	50-52	48.49 ±6.9	51	47-53	0.171
Head circumference (cm)	34.14 ±2.2	34	34-35	34.35 ±1.7 *	34	34-35	32.63 ±4.8 ***	34	33-35	0.003
1-min APGAR	7.21±0.91	7	7-8	7.28±0.91*	7	7-8	6.68±1.30**(***)	7	7-7	<0.001
5-min APGAR	7.91 ±0.8	8	8-8	7.86 ±0.7 *	8	8-8	7.68 ±1.3	8	8-8	0.105
10-min APGAR	8.65±0.94	9	8-9	8.47±0.86*	8	8-9	8.65±1.49**(***)		9-9	<0.001
30-min glucose	3.38 ±0.8	3.3	3.0-3.7	3.41 ±0.6	3.4	3.0-3.7	2.97 ±1.3**(***)	3.0	1.9-4.0	0.055

Data presented as Mean ±Standard Deviation, Median and Interquartile Range. Kruskal Wallis Test or Mann-Whitney U Test was for comparing continuous variables between groups. P values < 0.05 for two-tailed test considered statistically significant.
*p value <0.05 (comparison between GDM-negative and GDM-fasting groups)
**p value <0.05 (comparison between GDM-negative and GDM-severe groups)
***p value <0.05 (comparison between GDM-fasting and GDM-severe groups)

Comparative analysis of neonates parameters according to glucose status showed higher proportion of antenatal and postnatal death among GDM severe group offsprings compared to GDM fasting and GDM negative groups (all p<0.001). Proportion of alive at birth and discharged alive offsprings were lower in the severe group compare to other groups (all p<0.001).

Proportion of macrosomia newborns were higher in fasting group, however proportion of offsprings with weight <1500 g significantly higher in severe group.

The proportion of Apgar score assessed less that 7 points observed in GDM severe group compare to fasting and GDM-negative groups.

Hypoglycemia more often observed among offsprings from severe group compare to other groups.

Table 4.20: Neonates outcomes according to glucose status

Parameters	**GDM-negative N = 1647**	**GDM-fasting N = 723**	**GDM-severe N = 68**	***p*-value**
Neonates				
Alive at birth	1624 (98.6)	719 (99.4)	61 (89.7)	<0.001
Antenatal death	23 (1.3)	4 (0.6)	4 (5.9)	0.001
Postnatal death	45 (2.7)	13 (1.8)	11 (16.2)	<0.001
Discharged alive	1599 (97.1)	710 (98.2)	57 (83.8)	<0.001
Birth weight				
>4000 g	135 (8.2)	65 (9.0)	6 (8.8)	>0.05
<1500 g	40 (2.4)	15 (2.1)	12 (17.6)	<0.001
APGAR < 7 points				
At 1^{th} min	111 (6.7)	49 (6.8)	11 (16.2)	>0.05
At 5^{th} min	150 (9.1)	73 (10.1)	11 (16.2)	>0.05
At 10^{th} min	36 (2.2)	14 (1.9)	4 (5.9)	>0.05
30 –min glucose				
<2.0 mmol/L	60 (3.6)	14 (1.9)	9 (13.8)	<0.001

Data presented as n (%). Chi-square test used to compare categorical variables.
P values < 0.05 for two-tailed test considered statistically significant.

5. DISCUSSION

5.1. Prevalence of gestational diabetes in Tajikistan

Gestational diabetes mellitus, being an extragenital pathology, occupies one of the leading places in the structure of the causes of maternal morbidity and mortality and represents one of most public health problem worldwide [4-7].

Any pregnancy that is physiological is a diabetogenic factor. When it occurs, metabolic processes change significantly. This is due to the development and active functioning of a new organ, the placenta, which has an impact on the fetus's development as well as the health of the unborn kid. The role of the fetoplacental complex can hardly be overestimated. The placenta develops continuously throughout pregnancy, including periods of branched angiogenesis, unbranched angiogenesis, trophoblast differentiation, and syncytium production [69]. With the onset of the second trimester of pregnancy, the consumption of high-energy substrates (including glucose) by the placenta and the fetus increases. The uteroplacental and fetoplacental blood flows perform an important function in the delivery and removal of metabolic products. After 28 weeks of gestation, metabolic changes are aggravated, reaching a maximum by 32 weeks of gestation.

According to the literature analysis, there were few research in the Republic of Tajikistan on the prevalence, risk factors, obstetric and neonatal outcomes in women with GDM.

Based on the above information, The purpose of this study was to investigate the prevalence, risk factors, obstetric and neonatal outcomes in pregnant women with GDM, as well as the application of the findings in national standards and guidelines for ensuring safe motherhood in the Republic of Tajikistan [141].

The prevalence of GDM in the study was 32.4%. It should be noted that 29.7% of the subjects only had an increase in fasting blood sugar, while 2.8% had an increase in blood sugar after 1 hour and / or 2 hours of glucose load.

The high frequency of GDM detection in this study can be associated to the one-step diagnostic method used in this study. According to Nguen C. L. et al. (2018), a study from Thailand showed a high prevalence of GDM among women with a one-step GDM study using 75g glucose, compared to a two-step method using 100 g glucose. The frequency of GDM with a one-step test was 32.0%, and with a 2-step test - 10.3% [21]. At the same time, It should be noted that the authors are confident that the use of a one-step test with lower thresholds compared to a two-step

test for diagnosing GDM will lead to an improvement in financial costs in the health care system, which is associated with complications leading to this disease [21].

In urban area, prevalence of GDM is 37.8%, in rural area - 22.0%. In general, in many countries of the world, prevalence of GDM is increasing, which most often occurs in women of late reproductive age, who have a history of GDM, or high BMI, of different racial and ethnic groups [142, 143]. According to the results of our research, prevalence of GDM in urban setting is higher than in rural. Our data are consistent with the results of a study conducted in India, which also have higher frequency of GDM in urban than in rural areas [144, 145]. It can also be reduced to the fact that urban life differs from rural life, where residents are mainly engaged in agriculture. Whereas in the city women do light housework. A study in Cameroon confirms that high energy expenditures are observed with physical activity in rural areas compared to urban areas [146]. The rise in obesity and metabolic syndrome is most likely due to changes in food habits and sedentary lifestyles seen in developing countries [147, 148], as well as the rise in GDM incidence we've seen in Tajikistan.

5.2. Risk factors for gestational diabetes

Women with GDM in Tajikistan older age (≥30 years), had higher mean weight, higher BMI, and a high proportion of parity ≥4, compared with those without GDM. Our findings are in line with those of Gibson K.S. et al. (2012), who discovered a strong link between an increase in the proportion of GDM and an increase in the incidence of obesity in the female population [13]. In addition, Wallace J.M. et al. (2012), found a positive relationship between an increase in BMI and the presence of GDM [8]. The data obtained by us could use to improve the prognosis of GDM among women at risk in accordance with age, BMI and parity before pregnancy. In addition, they are useful in counseling young non-pregnant women about their high risk of developing GDM if they are overweight or obese, and in motivating them to lose weight.

From the results obtained, both in the urban and in the rural, the subjects showed an increase in DBP among pregnant women with GDM. Increases in BP in GDM have also reported in studies in other parts of the world [149-151].

Rural participants were more likely to have relatives with diabetes mellitus in their family. Our findings are in line with the findings of a number of investigators, who found that the existence of T2D is linked to the development of GDM as one of the risk factors. [6, 7, 10-13].

5.3. Obstetrical outcomes in women with gestational diabetes

Planned CS was performed reliably more often in women with GDM compared to no-GDM. Emergency CS more often performed in women from rural area than in urban area. Women from the rural with GDM admitted to childbirth earlier in comparison with women from the urban. Premature rupture of membranes more often observed in women in rural area than in urban area. Induction of labor significantly frequent in women with GDM in rural area than in urban area.

A number of studies also confirm our results, indicating that the course of pregnancy with GDM complicated by deterioration of the condition of the pregnant woman and fetus, which requires early delivery, followed by an increase in the number of premature births [96]. The frequency of abdominal delivery in pregnant women with GDM ranges from 28.8% to 46.6% [97]. According to the results of many studies, hypertensive disorders during pregnancy, childbirth by CS and low frequency of breastfeeding predominate among early maternal complications [39, 100].

5.4. Neonatal outcomes in women with gestational diabetes

According to the results of assessing the state of newborns by using Apgar score at the 5-minute, newborns from mothers with GDM had lower indicators than the group of newborns from mothers without GDM. Hypoglycemia more often observed in newborns from rural areas than in urban areas.

At the same time, a team of scientists in the study HAPO among 25505 pregnant women from nine countries of the world, revealed a correlation between the development of hyperglycemia in the mother, weight of the newborn over 90th percentile, level of C-peptide in serum blood taken from the umbilical cord more than 90th percentile and presence CS and neonatal hypoglycemia [99]. Frequent perinatal complications in GDM are the birth of a large baby, development of neonatal hypoglycemia, hyperbilirubinemia, shoulder dystocia, and an increased percentage of fat in newborns compared with the absence of GDM [103]. The development of perinatal pathology and death in newborns with GDM is greatly influenced by the occurrence of disorders that occur during the period of intrauterine development of the fetus and functional changes in FPC [104-106]. P. Jamurzek et al. (2015), in their study, found that in overweight or obese pregnant women with GDM, pregnancy was most often associated with adverse perinatal outcomes, such as macrosomia, birth trauma, neonatal hypoglycemia and RDS [81].

5.5. Prevalence and pregnacy outcomes in study participants depending on Glucose Status

In the study, the prevalence of GDM is 32.4%. This prevalence is high compared to a previous study in Tajikistan, in which the prevalence was 16.2%[5]. According to the literature review among countries of Central Asia the prevalence of GDM in Turkmenistan is 6.3% [25] and in Uzbekistan – 10,5% [152]. Some of the discrepancy explained by differences in diagnostic methods used to detect of hyperglycemia, such as two-step GCT (glucose challenge test) and OGTT in Turkmenistan, threshold diagnostic criteria in previous research in Tajikistan, characteristics of the studied population and research design in Uzbekistan. According to research findings, it is also possible that the current study population has a higher level of insulin resistance. It should be mentioned that in the current study, 723 (91.4%) of the 791 (100%) patients with GDM were diagnosed with GDM based on a fasting blood sample. Our findings are in line with those of a major Danish study that identified a large number of cases of GDM based on slightly higher fasting glucose levels [153]. Furthermore, the findings are in line with a cross-sectional study conducted in North India, which included over 5.000 pregnant women and detected more than 94% of instances of GDM based on fasting venous plasma level (FVPL) [154]. Similar results were obtained in a study conducted in Tanzania, which also noted a high incidence of GDM in the population - 39%, in which a large number of cases of GDM based on fasting glucose results - 94.1% [155].

GDM is to some extent considered a postprandial clinical disorder, OGTT is essential for effective screening and diagnosis of GDM [156]. M.M. Agarwal et al. (2010) investigated the efficacy of FVPL as a GDM screening test and found that it is significantly dependent on diagnostic criteria [156]. He was correct in arguing that FVPL, as an initial part of OGTT, cannot be used as a screening test for GDM. In addition, the specificity of FVPL remains low, and its elevation achieved by increasing the sensitivity. The IADPSG has defined an FVPL level <5.1 mmol/L as a new universal screening method that avoids OGTT. Contrary to the known links in the pathogenesis of GDM, IADPSG also proposed the definition of FVPL as a criterion for diagnosing GDM in early pregnancy [10, 157, 158]. The application of these criterias bring to increase detection of GDM by 3.5 times. [159]. According to some authors [158, 160] HAPO study by recommending diagnostic threshold values allowed to overdiagnosis of GDM. The authors mainly criticized the arbitrarily chosen diagnostic boundaries of glucose levels, especially with a very high sensitivity of the FVPL (> 5.1 mmol/L), acting as an independent diagnostic criterion, which led to overdiagnosis of GDM [161]. Interestingly, when GDM recorded among the 15 re-

search centers that participated in the HAPO study, variations observed that at time of measurement of glucose levels corresponds to the threshold values of GDM. [162]. More than 70% of women in regions like Bellflower and Providence in the US and Barbados were diagnosed with GDM based on fasting blood glucose, but GDM was diagnosed based on 1 hour in 64% of Bangkok cases and 2 hours in 29% of Hong Kong instances [155, 162]. The degree of obesity and abnormal glucose tolerance of the population evaluated in the HAPO research centers, according to the authors, were associated with these center-to-center variances [99, 155]. In contrast to this observation, a number of researchers found in a retrospective cohort study that plasma glucose greater than 10.0 mmol/L made the most significant contribution to the increase in the frequency of diagnosis of GDM [158]. According to the US National Institute of Health (NIH), the HAPO criteria are responsible for a manifold increase in the prevalence of GDM without a clear decrease in the characteristic complications of pregnancy. In addition, according to some authors, it may be necessary to adapt the diagnostic criteria for HAPO for some ethnic groups or geographic regions, since HAPO studies do not include participants from all regions of the world [156, 158, 163, 164].

Meanwhile, Hughes R.C.E. et al. (2014) hypothesized that finding HbA1c>5.9% in early pregnancy and early OGTT at <20 weeks of gestation could be a viable strategy for identifying women with GDM and an elevated risk of severe pregnancy outcomes [165]. Another group of authors found that HbA1c levels are highly dependent on insulin resistance, gestational age, and ethnicity [166, 167]. Although HbAlc measurement has a lower predictive value [168] compare to FVPL and OGTT for GDM, its measurement in pregnant women should not be completely discontinued due to the fact that increased values can be a simple and rapid screening test for GDM [163, 169]. Necessary to note that even in cases where GDM not diagnosed, judging by the normal OGTT value, hyperglycemia due to excessive consumption of carbohydrates and food with a high glycemic index can often cause perinatal complications. Normalization of glycemia after 2 hours cannot always guarantee absence of specific complications. In these cases, an elevated HbA1c is usually a reliable indicator of ongoing hyperglycemia and its complications. It is important to conclude that more appropriate to designate specific complications during pregnancy as hyperglycemic complications, and not solely due to GDM. Most important to detect episodes of hyperglycemia during pregnancy [158].

Women with higher FVPL were not shown to have a significant rate of unfavorable obstetric and neonatal outcomes in the current investigation. Whereas, women with abnormal blood glucose concentration after 1 and/or 2 hours glucose load, have significantly higher rate of

poor outcomes, such as premature rupture of membranes, induction of labor, emergency CS and low mean weight of newborns. Our results are consistent with data from a study conducted in Denmark, where there are minimal adverse outcomes, in women who have slightly elevated FVPL [153]. In China, an increase in the GDM population based on elevated FVPL results was not significantly associated with increased obstetric and neonatal morbidity [170]. According to Ryan EA. (2011), maternal glucose is a poor predictor of large-baby birth, and single-step OGTT is poorly repeatable, therefore the intervention's projected benefit will be minor at best [160]. Based on large for gestational age risk in pregnancy, Jensen RC et al. (2021) determined an FVPG cut point between 5.5 and 5.7 mmol/L [171].

The most obvious issues will be health-care expenses associated with these additional diagnoses, as well as adverse perceptions of pregnancy's "medicalization". Some national health-care systems may be hesitant to embrace a consensus approach because of the expected cost rise. It may also lead to the adoption of a different odds ratio for risk categorization, resulting in a lower percentage of women being diagnosed for pragmatic reasons [172].

Therefore, in a number of the above studies, as well as in the present study, most of the diagnosis of GDM classified based on FVPL results, and not OGTT. As a result, the applicability of an OGTT for the diagnosis of GDM in some countries may be questioned because to its higher cost and longer duration. As a result, the one-size-fits-all approach to GDM diagnosis is controversial [153].

5.6. Strengths of the study

For the first time the problem of GDM was addressed in a large study in two different settings of Tajikistan. Present study used universal screening with clearly defined inclusion and exclusion criterias. Citrate tubes were used to collect blood to prevent glycolysis and improve the diagnostic accuracy of blood test results. Anhydrous glucose was used in OGTT. Despite of different locations of reproductive health centers and delivery departments, a large amount of data was collected qualitatively on time. For the first time determined the prevalence of GDM in Tajikistan, also in two different settings (urban and rural), described main risk factors, as well as obstetric and neonatal parameters; obtained scientifically interesting data to improve the GDM management in Tajikistan.

5.7. Limitations of the study

The limitations of this study include lack of data on potential risk factors for GDM, such as socioeconomic status, educational level, sedentary time, physical activity and dietary habits. Despite the fact that the participants in this study were carefully instructed on how to fast properly, there is always a risk of not following the instructions, which in turn is also not excluded in this study. Especially in urban areas, fasting blood glucose values were similar and glucose values at 1 and 2 hours were often actually lower. Measurements of glucose levels may not have been very precise as photometric results were directly read by a technician from the photometer.

In the beginning of the current study, we had problems in recruitment of subjects because we had difficulties in motivating the women to participate. Despite the fact that the OGTT performed on time in most women, some participants missed date of their last menstrual period, we therefore do not know whether the OGTT was always performed during weeks 24 to 28. In some women we could not collect data on childbirth in women and parameters of newborns, because delivery occurred at home or in different delivery departments. However, we have no indication that this introduced a systematic error. Furthermore, we did not investigate HbA1c levels, which is also valuable indicator without considering traditional risk factors.

6. CONCLUSION

The prevalence of gestational diabetes mellitus is high, due to the increased incidence of fasting hyperglycemia. Our results are relevant with studies from other parts of the world [153-155, 170]. In the capital prevalence of GDM is higher than in the southern part of the country.

Risk factors for GDM such as age, BMI, parity found in population are consistent with research findings from other studies [173-177].

The one-step OGTT using threshold values recommended by WHO (2013) revealed a large number of cases with fasting hyperglycemia only, and a very small number of cases with elevation of blood sugar value above the threshold level in 60 and/or 120 minutes. Cases with an increase in fasting glucose value only, in whom observed slightly elevation of glucose level (basically between 5.1-5.6 mmol/L) represented a group of women with mild GDM, while an increase in glucose value after post-prandial load - women with severe GDM. Nevertheless, no difference observed in obstetric and neonatal outcomes between mild GDM and normal blood sugar level groups. Our trial results are in good agreement with recently published studies [153, 154, 170, 178-184]. However, in the group with severe cases of hyperglycemia the course of pregnancy, childbirth and perinatal outcomes were characterized by a high rate of a threatening miscarriage, preeclampsia, urinary tract infection, premature rupture of membranes, emergency caesarean section, low birth weight, Apgar score at 1, 5 and 10 minutes, hypoglycemia, antenatal and postnatal deaths.

Therefore, the application of the above described approach results in the detection of a large number of cases with mild hyperglycemia, which do not seem to be clinically relevant. This is in good agreement with studies in some countries, in which a two- versus one-step approach was compared, leading to the notion that mild forms of GDM may not translate into practical problems [180, 185-187].

Thus, according to the results of this study alternative screening strategies may be suitable in order to identify clinically significant forms of GDM. With the aim of a universal screening, one of the versions may be using variations of the two-step approach. First step during 24 to 28 weeks of gestation performing GCT with 50 g of glucose in non-fasting state, in cases of positive value followed by second step until 32 weeks of gestation, where conduct standard OGTT with 75 or 100 g of glucose with slightly different threshold values diagnosing GDM [127, 188-191]. Second option can be using of one step approach based on prospective study of Diabetes In Pregnancy Study group of India (DIPSI), which recommends performing GCT with 75 g of glucose regardless of the time of the last meal, and GDM is diagnosed if plasma glucose after 2

hours is ≥140 mg / dL (7.8 mmol/L) [192]. The Indian Ministry of Health, the World Health Organization, the International Development Foundation, and the International Federation of Gynecology and Obstetrics (FIGO) have all supported this guideline. Third option use of HbA1c in different gestational months with slightly different threshold values for diagnosing GDM [191, 193-195], or/and in combination with fasting plasma glucose value [191, 196]. An alternative option would be the use of a selective screening in women with risk factors, which is also supported by some studies [197, 198]. Finally, another screening strategy would be based on clinical guidelines, where the detection of carbohydrate metabolism disorders is mandatory, at least twice per pregnancy [199, 200]. Of course, to implement such algorithm, a national standard needed, which is not yet available in the republic. It's important to remember that each of the suggested approaches has its own set of limitations, and none of them has been approved in Tajikistan [188].

In conclusion, GDM remains a relevant pathology, with effects on both maternal and offspring health. Therefore, research of high quality is required to solve the problems related to the current approaches. Future studies should focus on various strategies for screening clinically relevant cases, predictors of poor outcomes in women with GDM and development of standards with further implementation.

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8. APPENDIX

Appendix 1 Questionnaire

Project Gestational Diabetes in Central Asia

Center:_____ rural ☐ urban ☐ **Patient Nr.:** _____ **Consent form:** yes☐no☐

Name:_____ **Surname:**_____ **Maidenname:**_____ **DoB:**_____

Visit 1

Date of visit:_____ **Inclusion criteria:**☐ yes☐no **Exclusion criteria:**☐ yes☐no

G _____ **P** _____ **Last menstrual period:** _____ **EDD** _____

Previous pregnancy problem:☐ yes☐ no If yes, comment: _____

Weight (kg): _____ **Height (cm):**_____ **BP(mmHg):**_____ **Planned date visit 2:** _____

Visit 2

Date of visit:_____ **Week 24-28:**☐ yes☐no **Fasting:**☐ yes☐no

Weight (kg): _____ **BP (mmHg):**_____ **Pregnancy problem:**☐ yes☐no, if yes,

Med. Hist.: HTN ☐ yes☐ no
DM ☐ yes☐ no
Thyroid ☐ yes☐ no
Other ☐ yes☐ no

Fam. Hist.: HTN ☐ yes☐ no
DM ☐ yes☐ no
Malign. ☐yes☐ no

Consanguinity: ☐ yes☐ no

Oral glucose tolerance test: **Glucose:**0 (min.):_____ 60 (min.):_____ 120 (min.):_____

Additional fasting sample:☐ yes☐no

Visit 3 A (mother-delivery)

Date of admission: _____ **Time of admission:**_____

Date of delivery:_____ **Time of delivery:**_____

Rupture of membranes Date:_____ Time:_____ **Estimated blood loss (ml):**_____

Delivery mode:☐Spont☐CS ☐Vac/Forc ☐Emergency CS

Presentation:☐Cephalic☐Breech **Induction:**☐ none☐Oxytocin ☐Prostagland.☐Anmiocent.

Discharge of mother: Date_____ **Status:**☐Healthy☐ Sick ☐ Dead

Additional placental sample:☐yes ☐no

Visit 3 B (Child)

Alive:☐yes ☐no **Sex:**☐male ☐female **Healthy:**☐yes ☐no;if no, comment_____

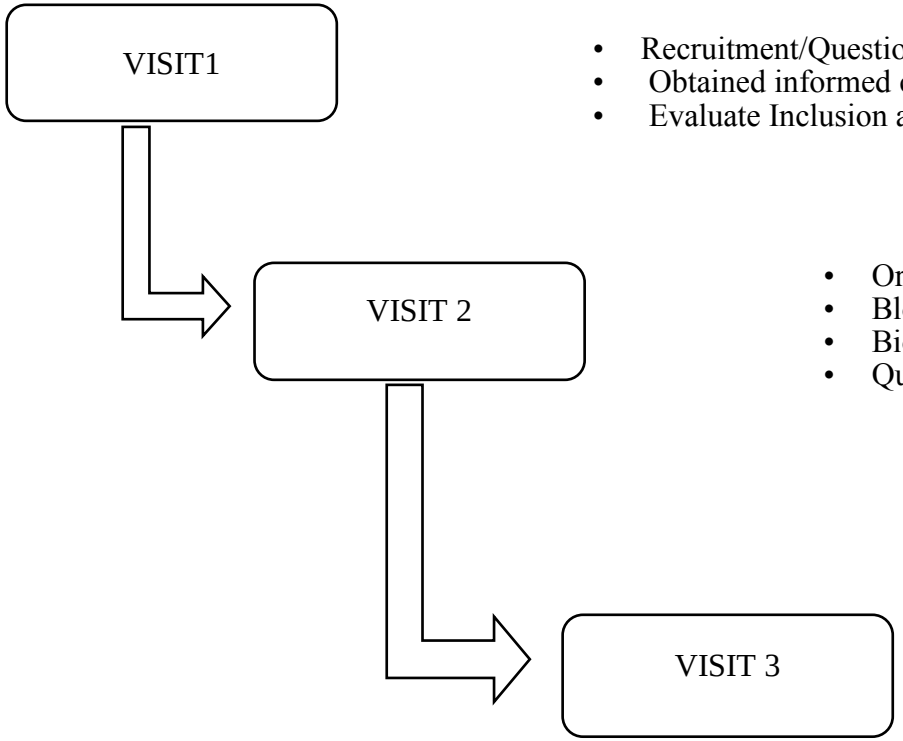
Birth weight (g):_____ **Height (cm):**_____ **Head circumference: (cm)**_____

APGAR minutes: 1(min):_____ 5 (min):_____ 10 (min):_____ 30 (min):_____

Glucose (30 min).:_____ **Therapy:**☐no ☐oral ☐IV

Discharge of baby date: _____ **Status:**☐Healthy ☐Sick ☐Dead

Appendix 2 Visits



- Recruitment/Questionnaire
- Obtained informed consent
- Evaluate Inclusion and Exclusion criteria

- Oral glucose tolerance test
- Blood sampling
- Biometric parameters
- Questionnaire

Evaluation of the Delivery

- According to the National Standards
- Biometric parameters

Evaluation of the neonates

- Apgar Scale
- Glucose consentration of a newborn in 30 minutes after birth
- Biometric parameters
- Questionnaire

9. ANNEX

List of Publications

Research article

Published

Pirmatova DA, Dodkhoeva MF. Prevalence and medico-social characteristics of pregnant women with gestational diabetes mellitus in combination with anemia *J. Avicenna Bulletin* 2019; 2:206-213. doi: 10.25005/2074-0581-2019-21-2-206-213

Pirmatova DA, Dodkhoeva MF, Masaidova LV. Features of the morphological structure of the placenta of puerperas with gestational diabetes mellitus and anemia *J. Avicenna Bulletin* 2019; 4:556-564. doi: 10.25005/2074-0581-2019-21-4-556-564

Pirmatova DA, Dodkhoeva MF, Parhofer KG, Khaknazarova MA. Events for optimization of diagnostics and management of pregnant women with gestational diabetes mellitus *J. Bulletin of the Academy of Medical Sciences* 2020; 1:36-43. doi: 10.31712/2221-7355-2020-10-1-36-43

Pirmatova DA, Dodkhoeva MF, Parhofer KG. Peculiarities of the course of pregnancy and childbirth in women with gestational diabetes mellitus *J. Bulletin of the Academy of Medical Sciences* 2020; 2:163-167. doi: 10.31712/2221-7355-2020-10-2-163-167

Under review:

Pirmatova D, Dodkhoeva M, Hasbargen U, Flemmer AW, Abdusamatzoda Z, Saburova Kh, Salieva N, Radzhabova S, Parhofer KG. Screening for Gestational Diabetes mellitus in Tajikistan. Submitted to peer review journal.

Statement on Pre-release and Contribution

I, Dilnoza Pirmatova, declare that the material in this thesis is original research carried out by me. I also declare, that I was responsible for the structure, design, data collection and organization, statistical analysis, data interpretation and writing of this thesis.

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Affidavit

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I hereby declare, that the submitted thesis entitled

Gestational Diabetes Mellitus in Tajikistan: Prevalence and Management

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Dushanbe, 02.11.2022

Place, date

Pirmatova Dilnoza

Signature doctoral candidate

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Confirmation of congruency between printed and electronic version of the doctoral thesis

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I hereby declare that the electronic version of the submitted thesis, entitled
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