



## CURRENT TOPIC / АКТУЕЛНА ТЕМА

**Historical aspects of diabetes, morbidity and mortality**

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**SUMMARY**

It has been an entire century since the introduction of insulin into clinical practice, which, among other led to improvements of fertility and pregnancy outcomes of women suffering from gestational diabetes. The prevalence of diabetes worldwide and in Serbia is high and tends to increase as a consequence of modern lifestyle. Nevertheless, modern diagnostic and therapeutic approaches enable people with diabetes to achieve and complete pregnancies without adverse outcomes. Gestational diabetes can be considered as non-communicable disease and efforts should be made to determine its effects on offspring. In the context of COVID-19 pandemic, diabetes mellitus was identified as an important risk factor for severe forms of the disease.

**Keywords:** diabetes; history; discovery; insulin

**INTRODUCTION**

Just under 100 years ago, in 1923, Banting and MacLeod received a Nobel Prize for the discovery of insulin and just over 100 years ago, Banting reported the discovery to the American Society of Physiology [1]. This marked the end of the so-called pre-insulin era in diabetes [1]. Although, the terminology of diabetes mellitus is commonly believed to originate from ancient Greece, it was in 1822 in Britain that it was recognized as a separate clinical entity [2]. The word ‘diabetes’ did find its place in the ancient Greek medical literature in the second century AD, and famous Avicenna gave the description of the increase in appetite and diabetic gangrene at the end of the first millennium AD, and the Aretaeus was thought to be the one introducing the term ‘mellitus’ [1, 2].

The discovery of the pathophysiological mechanisms in diabetes and insulin itself was a long process, which included numerous anatomists, pathophysiologist, and biologists. The reports on diabetes after the pancreatectomy in dogs fueled the further discoveries on the topic [2]. This work has paved the route for Banting and Best and has enabled the discovery of such an important and widely used treatment that insulin is today [1, 2].

**THE SLOW DECREASE IN MORTALITY AFTER THE INTRODUCTION OF INSULIN**

Before the discovery of insulin, the diagnosis of diabetes, especially of type 1 diabetes, was a death sentence for the patients, with only vague ideas on the possibilities for treatment and control. The study conducted in the 1960s also showed significantly higher mortality rates among patients with diabetes compared to the general population, decades after the introduction of insulin [3]. Nonetheless, throughout the decades after the introduction of insulin, the mortality declined, but between 1945 and 1967 in which the above-mentioned study was published, the decline in mortality was not observed [3]. The improvement in treatment led to the astonishing decline in mortality from 827 per 1000 before the insulin era to 1 per 1000 in the 1960s [4]. Significant factor that attributed to the decline in mortality from diabetes was the discovery and widespread use of antibiotics, so the infections, as a cause of death among patients with diabetes were reduced [4]. As diabetes became chronic and more controlled illness, most of deaths in the 1960s were associated with cardiovascular and renal illnesses, whose proportion in the total death among patients with diabetes increased from around 25% to more than 75%, mainly due to reduction in deaths from acute causes, like ketoacidosis and infections [4].

**Received • Примљено:**  
October 21, 2022

**Revised • Ревизија:**  
January 23, 2023

**Accepted • Прихваћено:**  
January 24, 2023

**Online first:** January 26, 2023

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Newer data shows the further decline in diabetes mortality, although its incidence is rising [4]. The introduction of the intensive insulin treatment has significantly contributed to this, although the effect of socioeconomic status, still cannot be ignored [4].

### **RECOGNITION OF DIABETES IN PREGNANCY**

Even before the discovery of insulin, diabetes in pregnancy was described and recognized as a risk factor for the late pregnancy losses, macrosomia and different congenital malformations [5], especially in the late 19th century, including both gestational diabetes and pre-gestational diabetes although their clinical distinction was not well established.

Pre-gestational diabetes was in the pre-insulin era associated with typical symptoms of poor glycemic control: primary or secondary amenorrhea, oligo or hypomenorrhea, hypoplasia of the genital tract, and functional sterility. The fertility of these patients was about 2%, while today it is equal to that of women without diabetes of the same age [6].

Diabetes in pregnancy was described in the 19th century as well, in a 22-year-old Berlin woman who developed symptoms of diabetes during her fifth pregnancy, as she had given birth to unusually large children in the previous two pregnancies. The child was born alive, unusually large, but died shortly after birth, while the mother gradually recovered [7].

At the turn of the century, researchers had already begun describing the diabetes in pregnancy in published literature, and until 1908, there were total of 57 cases described. Diabetes in pregnancy during the late 19th and early 20th century was associated with high maternal and high neonatal mortality, with the half of the mothers and two thirds of newborns dying at childbirth [8].

### **THE FIRST STEPS IN TREATMENT OF DIABETES IN PREGNANCY**

As the discovery of insulin changed the lives of all patients with diabetes, it changed lives of patients with diabetes in pregnancy as well, and in the first decade of the introduction of insulin, the first report of total of 43 successful term pregnancies among women with diabetes was published in 1927 [9]. Nonetheless, it took decades to achieve the adequate and timely diagnosis and introduction of treatment among pregnant women with diabetes to achieve the low mortality that we have today. Maternal mortality is very low nowadays, but in the 1940s, one out of 20 pregnant women with diabetes died during pregnancy and/or childbirth, which decreased to 1–3% in the 1950s. Neonatal mortality was even higher and was around 40% in the 1940s and decreased to 5% in 1980s. Nowadays, women with diabetes are considered conditionally healthy, with normal fertility, with a slightly higher risk of morbidity and mortality compared to healthy pregnant women,

but we are still fighting to decrease the perinatal mortality as it remains statistically significantly higher even in the most optimal conditions [10].

### **DEVELOPMENT OF THE DIAGNOSTIC CRITERIA**

The first set of gestational diabetes diagnosis criteria were introduced in 1964, by O'Sullivan and Mahan, with the aim of establishing the risk of diabetes after pregnancy, using the 100g Oral Glucose Tolerance Test [5]. These criteria included the establishment of cut-off for blood glucose levels at the more than two standard deviations above the population mean [5]. These criteria were later changed and improved in 1980 and 1982, first by Metzger and then by Carpenter and Coustan [5]. This was followed by the International Workshop conferences on diabetes in pregnancy and, more recently, The Hyperglycemia and Adverse Pregnancy Outcomes Study, that specifically aimed to shift the established criteria for diagnosis of gestational diabetes mellitus (GDM) from the risk of development of maternal diabetes later in life to assessment of the level of hyperglycemia associated with the adverse pregnancy outcomes, both maternal and neonatal [5].

This was in accordance with the knowledge established even earlier when Karlsson and Kjelmer [11] showed the association between the poor neonatal outcomes and the hyperglycemia in pregnancy with the association between the perinatal outcomes and increase in maternal glycemic values. The pathophysiological basis of macrosomia was also described at the time.

### **DIABETES IN PREGNANCY TODAY**

Along with the increase in the prevalence of diabetes in the general population worldwide, there is the increase in the prevalence of diabetes in pregnancy and data shows that one in every six pregnancies worldwide is affected by maternal hyperglycemia [12]. Today, the research is focused on the most adequate approach to screening, diagnosing and treatment of diabetes in pregnancy, especially lowering the future risks for both mother, and neonates, through direct effects of hyperglycemia, but also through its epigenetic effects.

The possibilities for diagnosis or prediction of maternal diabetes earlier in pregnancy have been examined including the commonly used biomarkers like hemoglobin, hematocrit, fasting blood sugar, and red blood cell count [13], but also newly developed methods, like the possibilities for the use of artificial intelligence algorithms [14]. The possibilities for preventing the development of GDM through introduction of Mediterranean diet and exercise in early pregnancy along with the use of metformin and even probiotics are also examined in order to minimize the possible effects of all levels of maternal hyperglycemia on neonatal outcomes [15].

In the context of current Coronavirus Disease 2019 (COVID-19) pandemic a many questions have been raised

about its potential harm to the mother and fetus. Moreover, some parallels between the increase in prevalence of non-communicable disease after the 1918 Influenza pandemic were made in the context of current COVID-19 pandemic [16]. A large multinational study proved that insulin-dependent GDM was associated with COVID-19, while diabetes and obesity were risk factors for COVID-19 diagnosis in pregnancy [17] Another multicenter study investigated whether GDM represents an independent risk factor for adverse pregnancy outcomes in women with SARS-CoV-2 and confirmed same results [18]. These findings have shed additional light on pathophysiology of COVID-19 in adult population.

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## CONCLUSION

The prevalence of diabetes is increasing worldwide and in Serbia, as a consequence of poor diet, lack of exercise, and chronic stress. Nevertheless, modern diagnostic and therapeutic approaches enable people with diabetes to achieve and complete pregnancies without adverse outcomes. GDM can be considered as a non-communicable disease and efforts should be made to determine its effects on the offspring. In the context of COVID-19 pandemic, diabetes mellitus was identified as an important risk factor for severe forms of the disease.

**Conflict of interest:** None declared.

## Историјски аспекти дијабетеса, морбидитет и морталитет

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### САЖЕТАК

Прошло је тачно 100 година од открића инсулина и његовог увођења у свакодневну клиничку праксу, што је довело до повећања фертилитета жена са дијабетесом, и побољшања исхода трудноћа компликованих дијабетесом. Преваленција дијабетеса у свету и у Србији је висока са тенденцијом пораста, што је последица савременог начина живота. Ипак, захваљујући савременим приступима у дијагностици и те-

рапији, жене са дијабетесом могу да остваре трудноће без нежељених исхода. Гестацијски дијабетес се може посматрати као хронична незараznа болест и потребно је уложити напоре да се одреде његови утицаји на потомство. У контексту пандемије ковида 19, дијабетес мелитус је препознат као значајан фактор који је повезан са тешким формама болести.

**Кључне речи:** дијабетес; историја; откриће; инсулин