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REVIEW

History of gestational diabetes mellitus

Dragana Božić [1], Stefan Dugalić [1,2], Maja Macura [1,2], Miloš Milinčić [3], Ivana Novaković [1], Miroslava Gojnić [1,2]

[1]Clinic of Gynecology and Obstetrics, University Clinical Centre of Serbia, Belgrade, Serbia
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia
[3]University of Belgrade, Faculty of Medicine, Institute of Medical Statistics and Informatics, Belgrade, Serbia

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Correspondence to:
Dragana Božić
Clinic of Gynecology and Obstetrics, University Clinical Centre of Serbia,
26 Višegradska Street, 11000 Belgrade, Serbia
E-mail: gagabozic90@gmail.com

Summary

The goal of this paper is to present the chronological development of knowledge about diabetes mellitus from the time of Hippocrates, through Langerhans and White, how it was discovered that inadequate pancreatic function was the cause of diabetes mellitus, and that the kidney was just an organ that became weaker due to unregulated pancreatic function. Studying gestational diabetes mellitus leads to a better control of diabetes in pregnancy, better perinatal outcome with fewer peripartal and perinatal complications. In the second part of the paper, there is a review of literature available on the Web of Science, containing the number of papers published over the years, as well as areas and countries they had been published in.

Keywords: gestational diabetes mellitus; diabetes in pregnancy; literature review

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INTRODUCTION

It was estimated that the number of patients with diabetes would increase from 135 million in 1995 to 300 million in 2025 (1). However, the World Health Organization announced that in 2009, 300 million people worldwide were already suffering from diabetes. There were 422 million people with diabetes worldwide in 2022, most of whom lived in low- and middle-income countries, and diabetes is responsible for 1.5 million fatalities every year (2).

If we go back through human history to the time of Ancient Greece, diabetes mellitus was an issue of great attention even then. Ancient records cite symptoms such as increased fluid intake and frequent urination as evidence of diabetes. The first official record of the disease was found in an Egyptian tomb near the city of Thebes in 1862, written on papyrus (3).

Hippocrates, a Greek physician who lived from 460 BC to 370 BC, was one of the first to suggest that the disease was due to environmental factors such as diet and lifestyle. He believed that physical health could be maintained through proper diet, exercise, fresh air, and personal hygiene. He was also the first to categorize diseases into acute, chronic, endemic, and epidemic. During Hippocrates' time, medicine was still a developing science, and physicians were only able to evaluate a patient's condition and make predictions based on case histories (4).

Hippocrates described diabetes as "producing fluids much and often" while Aristotle termed it "wasting of the body" (5). The term "diabetes" traces back to Demetrius of Apameia (1st or 2nd century BC) and is derived from the Ionic word meaning "to pass or run through" as in a siphon, later becoming the Latin word for "siphon" (6). The sweetness of diabetic urine was first described in ancient Indian texts, and later by Avicenna (980–1037) (7) and Morgagni (1635–1683). In 1674, Thomas Willis (1621–1675) recognized this sweet taste (lat. *quasi melle*) as a sign of diabetes, distinct from other causes of polyuria, and suggested that it was due to sugar in the blood. This was later confirmed by Matthew Dobson (1732–1784), who showed that sweetness originated from sugar in the blood, which passed unchanged into the urine (6).

Willis' careful examination of the symptoms of the disease resulted in naming it "diabetes mellitus". It took more than a hundred years for his argument to be supported by the demonstration of sugar in the blood and urine of diabetics by Robert Wyatt in 1774 and subsequently by more thorough studies of Matthew Dobson (1732–1784) (8). After that, diabetes has become a dietary disorder where there is an excessive buildup of sugar in the bloodstream, leading to its excretion in urine. This initiated a new strategy for managing diabetes through diet, focusing on the digestive organs as the cause of the disease, with a particular emphasis on the absorption of sugary substances in the stomach (6).

At the time of Tiberius, Celsus, a Greek writer, wrote about a condition in which greater amounts of urine were excreted in comparison with the amount of fluid ingested, although painlessly. This concept was echoed by many authors in the Middle Ages (5).

Areteus of Cappadocia provided the earliest known accurate clinical description of diabetes, referring to it as an infrequent condition characterized by "melting down of the flesh and limbs into urine", as well as intense thirst, copious urination, and shortened, uncomfortable life. He believed that it could be caused by other diseases negatively impacting the kidneys and bladder (9).

Cawley was the first to suggest a relationship between the pancreas and diabetes. In 1889, Oscar Minkowski (1858–1931) and Joseph Mering (1849–1908) verified the initial clinical observations by demonstrating that when the pancreas was removed from dogs they developed diabetes, which could be reversed by implanting pancreatic fragments beneath the skin (8–12).

A significant progress was achieved by finding out that the pancreas was the target organ in diabetics. In 1869, Paul Langerhans (1849-1888) identified the distinct morphological characteristics of pancreatic islands, which were subsequently named after him, and this led to a deeper understanding of the specific role of the pancreas (8,10,13).

In 1909, Eugene L. Opie observed that the islands of Langerhans in diabetics had hyaline degeneration, which was later corroborated by a series of experiments. This prompted Edward Sharpey-Schafer in 1916 to postulate that the islands of Langerhans produced a hormone that regulated glucose levels, which he named insulin. Frederick Banting (1891–1941) and Charles Best (1892–1978) isolated this hormone in 1922. It was determined that diabetes was an endocrine disorder, rather than a kidney disease as had been previously thought. However, it was yet to be seen how diabetes caused kidney disease (6).

Paulescu published most comprehensive papers in significant journals describing all the physiological functions and pharmacodynamic characteristics of the new hormone he isolated and named "Pancreine". These papers marked the first-time diabetes not only as a disorder of carbohydrate metabolism, but as a disorder of the entire energy metabolism of the human body, including lipid and protein metabolism. In 1916, he began conducting experiments using a pancreatic extract that he obtained using his own method, and then injecting it intravenously into diabetic dogs which led to the disappearance of diabetic symptoms (14).

Leonard Thompson, a fourteen-year-old boy, was the first person to receive the pancreatic extract. On 21st January 1922, he was hospitalized at Toronto General Hospital in critical condition, when he was injected with pancreatic extracts. His blood glucose was approximately 32 mmol at the time, and after the injection, his glucose levels dropped to about 5.5 mmol. Afterwards sterile

abscess appeared, so the extract was stopped. However, when a higher potency extract was administered between 23rd and 25th January 1922, his glucose levels returned to normal, and his urinalysis was much better (15). Banting and four colleagues wrote a report on the clinical use of insulin in diabetics. For this discovery, Frederic Banting and MacLeod received the Nobel Prize for Medicine in 1923 (16).

First reports of diabetes during pregnancy appeared in the 19th century. In 1824, Heinrich Gottlieb Bennewitz wrote about a pregnant woman who experienced polydipsia, polyuria, and fatigue. This was her fifth pregnancy, and it ended with the birth of a baby that weighed over 6 kg, who unfortunately died during labor. There was a large amount of sugar present in her urine (17). In 1846, Lever reported a similar case (18).

Gestational diabetes mellitus

Research into gestational diabetes mellitus started in the 1940s. In 1954, the term "meta gestational diabetes" appeared, highlighting the fleeting nature of the condition. In 1964, O'Sullivan and Mahan suggested diagnostic criteria for gestational diabetes. In 1979, gestational diabetes was officially identified as a unique type of diabetes and characterized as "Carbohydrate intolerance of variable severity observed during pregnancy" for the first time (19).

Before the invention of insulin in 1922, it had already been known that women suffering from diabetes were often infertile. These women were believed to suffer from infertility due to amenorrhea, atrophy of the uterus and Graafian follicles, and malnutrition (20,21). After insulin was introduced in 1923, pregnancy rate among women with a short history of diabetes skyrocketed, rising by seven times. However, women who had been having diabetes for a long time still had low pregnancy rates or were unable to conceive for many years (22).

In 1882 in London, Duncan reported that out of 16 pregnant women and 22 pregnancies, high rates of maternal and perinatal mortality were recorded, with more than 60% of mothers and 47% of newborns not surviving. He drew several conclusions from his observations and findings about pregnancies, including the fact that diabetes may evolve during the course of pregnancy, may only appear during pregnancy, may cease after pregnancy and recur or develop after parturition, may not develop in pregnancy after it has been cured, woman may conceive when suffering from diabetes, diabetes may not affect the healthy progress of pregnancy and delivery, and pregnancy may be frequently interrupted by fetal death (23).

In 1909, Professor Williams of Baltimore reported 66 cases of diabetes in pregnant women from literature, 55 of which had diabetes before conception, nine developed diabetes during pregnancy, and the onset was unclear in two cases. The mortality rate at delivery was 27%, with an additional 23% dying within two years after delivery. The perinatal mortality rate ranged from 27% to 53% (24). His manuscript primarily discussed how to interpret and use glycosuria as a diagnostic tool for diabetes during pregnancy, since it was the basis for diagnosing the condition at the time. He showed that if a female's urine had 1-3 g/L of sugar, it was likely to be normal, but a greater amount pointed to diabetes, particularly during early pregnancy or in the presence of symptoms. This could have been the first instance of a diabetes screening program being conducted during pregnancy (24).

The source of glycosuria was not identified. It was suggested that the cause could be either alimentary, due to increased absorption of carbohydrates, or toxemic, due to liver abnormalities. In 1898, Brocard discovered pregnant women had lower tolerance for sugar than non-pregnant women, as evidenced by the presence of glycosuria two hours after ingesting 50g of glucose, which was found in 50% of pregnant women compared to just 11% of non-pregnant women (25).

Reports from the 1920s to 1930s suggested that stillborn infants of mothers with diabetes had pancreatic abnormalities, mainly an enlargement of Langerhans' islands. This was believed to occur due to glucose transfer from the mother to the fetus and inadequate maternal glucose control. There was a potential for newborns to experience deadly hypoglycemia within a few days of birth (20,26).

Many authors conducted reports on the efficacy of insulin after its discovery and use in pregnancy. In 1926, Lambie in Edinburgh noted that when diabetes developed during pregnancy, it occured mainly in the fifth or sixth month, and rarely before the fourth or after the eighth month of gestation. He also proposed that the ketogenic-antiketogenic balance be determined using the 50 g oral glucose challenge test (OGCT) (27). In 1933, Skipper made a thorough review of literature regarding the use of insulin during pregnancy and discovered that it led to a marked decrease in maternal mortality and a slight improvement in fetal and newborn survival rates (28). He concluded that insulin use had led to a decrease in maternal mortality; women with diabetes often have glucose intolerance in the later stages of pregnancy; hypoglycemia is common postpartum and can cause severe problems, such as coma; if correctly treated, diabetes during pregnancy should not be harmful; ketonuria is common in untreated women; poor metabolic control, excessive growth of fetus, and congenital abnormalities are the leading causes of fetal death; therefore, any woman with glycosuria should be tested for diabetes, as it can emerge during pregnancy; monitoring glycosuria closely is essential; cesarean section may be necessary when the fetus is macrosomic; and breastfeeding should be encouraged, while sterilization should be considered for women with unstable diabetes, depending on the number of children they already have (28). His conclusions

are still being used today, albeit with some modifications and adaptations.

In 1945, Miller first recorded the presence of obstetric complications in the prediabetic period (29). During the 1950s the idea of gestational diabetes mellitus (GDM) was established, along with the identification of certain risk factors that can lead to the development of abnormal carbohydrate metabolism during pregnancy (30–33). Soon, it was proposed that screening programs be implemented for the early detection of diabetes in pregnancy.

In 1949, Dr. Priscilla White proposed the "White's Classification" which became a standard for classifying diabetes and pregnancy. It was repeatedly modified to distinguish between patients who had gestational diabetes mellitus and those with pre-existing diabetes. The classification was enhanced by the addition of an alphabetic list that considered the onset of diabetes, how long the diabetes had been present, and if any complications were present due to diabetes (34).

First steps in screening for gestational diabetes mellitus

Hoet first noted the heightened obstetrical risks associated with GDM in 1954. During the 1960s, GDM screening was performed solely by obtaining a patient's history (35). In 1957, Wilkerson and Remein (31) proposed that a 3-hour oral glucose tolerance test (OGTT) should be given to patients with risk factors for diabetes, such as family history of diabetes, gestational glycosuria, and having an overdeveloped infant at birth, following Hoet's study (35) and the observation of a large group of women by Dr. John B. O'Sullivan (22). They suggested that women with no known risk factors should have their blood glucose measured one hour after consuming a 50g glucose load. If the value is 130 mg or more, they should undergo a 3-hour OGTT (31).

The best way to screen and diagnose gestational diabetes mellitus was much debated. OGTT criteria for non-pregnant individuals suggested that approximately one-third of pregnant women would be diagnosed with diabetes. O'Sullivan and statistician Claire Mahan conducted 100-g OGTTs on 752 mainly pregnant women in the second and third trimesters and determined standard deviation upper limits for glucose values obtained from this test (36). The maximum values in the 2nd and 3rd hour were higher in pregnant individuals than those found in non-pregnant individuals, which is indicative of impaired glucose tolerance during pregnancy. The O'Sullivan and Mahan criteria were originally devised to predict type 2 diabetes in future, however, in the next few decades, they became an established method for detecting diabetes during pregnancy (36). O'Sullivan and Mahan proposed that fasting values should be 6,1 mmol/L, 1-hour values should be 9,4 mmol/L, 2-hour values should be 6,7 mmol/L and 3-hour values should be 6,1 mmol/L. If two or more of these values were abnormal, it would indicate an abnormal test result (36).

The findings of Pedersen and Priscilla White's studies highlighting the importance of maternal glucose levels in the results of pregnancies for diabetic women have prompted a shift in the focus of diagnosing and treating these women earlier on. It is not only about a future risk of developing diabetes mellitus type 2, but also about the prevention of negative outcomes for the mother and the fetus in the current pregnancy (34,37).

Gestational diabetes mellitus in literature

Bibliometric analysis geared towards a review of literature productivity and an observation of trends in gestational diabetes mellitus is presented in this section of the paper. The data are collected from the Web of Science platform (all sources), using the following search configuration:

TI = (gestational diabetes mellitus) OR TI = (diabetes in pregnancy)

Indexes = SCI-EXPANDED, SSCI, AHCI, CPCI-S, CPCI-SSH, ESCI

Timespan = All years

Data are collected for 10,207 scientific papers.

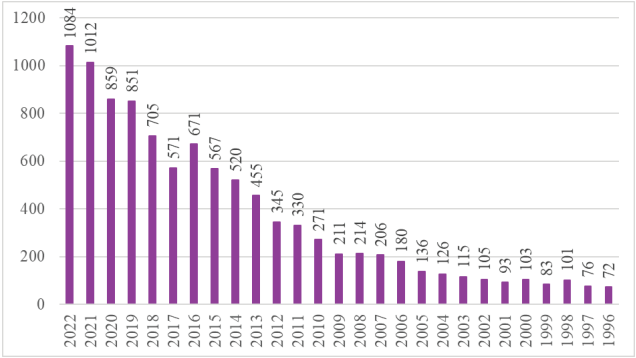

Figure 1. Number of published papers 1996-2022

The number of published papers with key words gestational diabetes mellitus or diabetes in pregnancy rose from 72 in 1996 to 1084 in 2022. A constant growth of the number of papers published with gestational diabetes or diabetes in pregnancy in title is evident.

Table 1 below shows 25 most popular research areas related to gestational diabetes mellitus. The highest number of papers comes from Endocrinology Metabolism research area (3981 papers), followed by Obstetrics Gynecology (2688 papers).

Those 10,207 papers were published in 1,378 journals. **Table 2** presents 25 journals with the highest number of papers published in the observed period. The top contributor is *DIABETES* with 573 papers published, followed by *DIABETOLOGIA* and *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.*

Table 1. Most popular research area related to gestational diabetes mellitus

Research Areas	Number of papers	% of 10,207
Endocrinology Metabolism	3981	39.003
Obstetrics Gynecology	2688	26.335
General Internal Medicine	1015	9.944
Public Environmental Occupational Health	462	4.526
Reproductive Biology	429	4.203
Research Experimental Medicine	398	3.899
Nutrition Dietetics	381	3.733
Biochemistry Molecular Biology	327	3.204
Pediatrics	289	2.831
Pharmacology Pharmacy	217	2.126
Science Technology Other Topics	199	1.95
Environmental Sciences Ecology	171	1.675
Cell Biology	160	1.568
Cardiovascular System Cardiology	157	1.538
Developmental Biology	141	1.381
Nursing	113	1.107
Genetics Heredity	109	1.068
Medical Laboratory Technology	104	1.019
Health Care Sciences Services	99	0.97
Immunology	91	0.892
Physiology	86	0.843
Life Sciences Biomedicine Other Topics	67	0.656
Chemistry	65	0.637
Biotechnology Applied Microbiology	57	0.558
Neurosciences Neurology	50	0.49

Table 2. Most popular journals related to gestational diabetes mellitus

Publication Titles	Number of papers	% of 10,207
Diabetes	573	5.614
Diabetologia	515	5.046
American Journal of Obstetrics and Gynecology	426	4.174
Diabetes Care	389	3.811
Diabetic Medicine	280	2.743
Diabetes Research and Clinical Practice	232	2.273
Journal of Maternal-Fetal and Neonatal medicine	178	1.744
BMC Pregnancy and Childbirth	163	1.597
Obstetrics and Gynecology	154	1.509
Reproductive Sciences	147	1.44
BJOG: An International Journal og Obstetrics and Gynecology	139	1.362
Gynecological Endocrinology	139	1.362
Placenta	123	1.205
PLOS One	114	1.117
Frontiers in Endocrinology	113	1.107
Australian New Zealand Journal of Obstetrics and Gynecology	83	0.813
Acta Diabetologica	81	0.794
Acta Obstetricia et Gynecologica Scandinavica	76	0.745
Nutrients	75	0.735
Journal of Clinical Endocrinology Metabolisam	71	0.696
Irish Journal of Medical Science	70	0.686
Journal of Obstetrics and Gynecology Research	68	0.666
Diabetes Technology Therapeutics	67	0.656
Journal of Diabetes Research	64	0.627
European Journal of Obstetrics, Gynecology and Reproductive Biology	62	0.607

Table 3. Top authors' affiliating countries

Countries/regions	Number of papers	% Of 10,207
USA	1969	19.291
People's R. of China	1754	17.184
Australia	730	7.152
England	699	6.848
Canada	468	4.585
India	361	3.537
Spain	345	3.38
Turkey	332	3.253
Italy	327	3.204
Denmark	278	2.724
Ireland	262	2.567
Iran	260	2.547
Poland	257	2.518
Israel	232	2.273
Brazil	227	2.224
Austria	225	2.204
Germany	222	2.175
Sweden	218	2.136
Netherlands	160	1.568
South Korea	153	1.499
France	150	1.47
Greece	146	1.43
Japan	145	1.421
Finland	132	1.293
Switzerland	122	1.195

Table 3 presents top authors' affiliating countries. The USA and China are dominant in the field, followed by Australia, England, and Canada.

CONCLUSION

The number of people with diabetes mellitus has slowly been increasing due to a longer life expectancy and faster detection of the disease. Modern treatments help to reduce the frequency of complications for those who already suffer from diabetes. Diabetes in pregnancy brings to light a new population, and the babies born from these pregnancies are a part of this group.

The high prevalence of diabetes around the globe is likely a result of changes in the modern lifestyle. This is a contemporary disease that is caused by an abundance of unhealthy food, lack of physical exercise, and obesity, just like Hippocrates suggested a long time ago.

Diabetes is mainly found in urban and industrialized areas, where individuals have access to unhealthy food and lack of physical activity, in addition to experiencing psychological effects of living in a city, such as chronic stress. All these factors combine to create an environment that leads to the development of diabetes.

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ISTORIJA GESTACIJSKOG DIJABETES MELITUSA

Dragana Božić[1], Stefan Dugalić[1,2], Maja Macura[1,2], Miloš Milinčić[3], Ivana Novaković[1], Miroslava Gojnić[1,2]

Sažetak

Cilj ovog rada je da prikaže hronološki razvoj saznanja o dijabetes melitusu od vremena Hipokrata, preko Langerhansa i Vajtove, zatim kako se došlo do saznanja da je neadekvatna funkcija pankreasa uzrok nastanka dijabetes melitusa, a da je bubreg samo organ koji slabi usled neregulisane funkcije pankreasa. Izučavanjem gestacijskog dijabetes melitusa dolazi do bolje kontrole dijabetesa u trudnoći, boljeg perinatalnog ishoda sa manjim brojem peripartalnih i perinatalnih komplikacija. U drugom delu rada dat je osvrt na celokupnu literaturu dostupnu na Web of Science-u, u smislu broja radova koji su objavljeni tokom godina, u kojim oblastima i u kojim zemljama.

Ključne reči: gestacijski dijabetes melitus; dijabetes u trudnoći; pregled literature

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