

A Historical Perspective on Gestational Diabetes Mellitus- A Review

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Abstract - Gestational diabetes mellitus (GDM) is a form of diabetes affecting the pregnant women who develops the diabetes for the first-time during pregnancy. Diabetes increases pregnancy risks difficulty in conceiving, miscarriages, malformed babies and an overall poor outcome in pregnancies and are the major impacts of diabetes in women. According to the International Diabetes Federation (IDF) one in ten women are living with diabetes, many of whom do not have access to health care and lack awareness about the diseases. Diabetes in women is one of the lesser discussed topics. This therefore becomes a high priority to control the disease at its earlier stages. What needs to be done is that all the women with diabetes should have access to the essential diabetes medicine, technologies and screening facilities.

keywords - Gestational diabetes mellitus, glucose tolerance, insulin and pregnancy.

ABBREVIATIONS:

FULL TERM	DEFINITION
GDM	Gestational Diabetes Mellitus
IDF	International Diabetes Federation
WHO	World Health Organization
ATP	Adenosine triphosphate
OGTT	Oral Glucose Tolerance test
BMI	Body Mass Index
JSOG	Japan Society of Obstetrics and Gynecology
VLDL	Very Low-Density Lipoproteins
LDL	Low-Density Lipoproteins
HDL	High-Density Lipoprotein
GLUT-4	Glucose Transporter Type-4
ROS	Reactive Oxygen Species
MCV	Mean Corpuscular Volume
PCV	Packed Cell Volume
MCH	Mean Corpuscular Hemoglobin
MPV	Mean Platelet Volume
TG	Triglycerides
FFA	Free Fatty Acids
FTIR	Fourier-Transformer Infrared Spectroscopy
IRS-1	Insulin Receptor Substrate-1
B3-AR	Beta-3- Adrenergic Receptor

1. INTRODUCTION:

Diabetes mellitus is a chronic disease that occurs due to high sugar levels in the blood of Type-1 and Type-2 occurs in large number of people. World Health Organization (WHO) has reported in year 2000 that about 172 million people around the world are suffering from diabetes and has estimated the numbers to increase to 367 million in forthcoming years. India has been reported as the country with the maximum diabetic patients. The study of GDM emphasizes on the various biochemical alteration that occur during second trimester of pregnancy. Understanding the mechanism of these biochemical and genetic risk factors could be helpful to determine an appropriate management technique for GDM. Medications for GDM should be in such a way

that there is an increase in insulin response by the receptor and preventive against the development of type 2 Diabetes mellitus in future. Regarding GDM screening has primarily focused on the benefit of the fetus. Future research should focus on the applicability of many preventive and prognosis measures in the GDM subjects so that future onset of type 2 diabetes is avoided or managed.

2. HISTORY AND EPIDEMIOLOGY OF GESTATIONAL DIABETES MELLITUS (GDM):

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose tolerance with onset or first recognition during pregnancy. GDM occurs in pregnant women who need 2-3 times more insulin than normal and the body is unable to produce the needed insulin. A total of 200,000 cases of gestational diabetes mellitus are reported every year. GDM has not only associated with acute risk for complication of pregnancy but also long-term risks for both mother and baby. GDM affects at least 7% and possibly as many as 18% of pregnancies in the United States. Using new diagnostic criteria, an international and multi-center study of GDM found that the pregnancies were affected by gestational diabetes mellitus [11].

[17] demonstrated that ethnicity as well as maternal age and degree of obesity must be taken into an account in comparing the prevalence of GDM in different population. The risk for GDM was higher in black and Hispanic women than in white women. Furthermore, a significant effect on birth weight with maternal body as a significant co-variance. These findings were supported by a study showing that Asian women were more likely to have GDM than White women [32].

The clinical studies demonstrated that an approximate 30% reduction in basal rates of muscle mitochondrial ATP synthesis and reduced mitochondrial numbers was observed in healthy, young and insulin resistant offspring of parents with Type-2 diabetes [43].

Thus, long standing decrease in mitochondrial activity may ultimately contribute to an increase in the percentage of saturated fatty acids or a decrease in the percentage of poly unsaturated

fatty acids of membrane lipids. This concept is consistent with the results of [54], and studied the membrane lipid fatty acids in control individuals and women with GDM. The insulin resistant a characteristic of gestational diabetes is correlated with fatty acid profile of erythrocyte and skeletal muscle cell membrane. It was found that appreciable reduction in arachidonic acid and docosa hexaenoic acid were associated with a substantial increase in saturated fatty acids in erythrocyte membrane of GDM women compared with control individuals [54].

In Clinical studies, screening for GDM typically occurs between 24 and 28 weeks of gestation with one-hour glucose challenge test. If this screen test is abnormal the diagnosis of GDM is confirmed with glucose test in the late second and third trimester.

The diagnosis of GDM can be somewhat challenging. The pathology may be too sufficiently established for treatment to be effective in reducing significant maternal and fetal risks.

3. SCREENING AND DIAGNOSIS:

[46, 22] evaluated the screening and diagnosis the protocol for GDM. The final diagnosis is based on the results of OGTT. There is no agreement on the performance or interpretation of OGTT in pregnant women. The fourth international workshop and conference on GDM [39] the WHO diabetes mellitus 1985 and the European diabetic pregnancy study group [50] proposed different criteria for interpreting the results of 100g-3hours of OGTT or 75g-2hours of OGTT. [20] evaluated the accuracy of diagnosing GDM by a 2hours blood glucose value of nearly 9.0 mmol/l in the 75g-OGTT.

4. COMPLICATIONS OF GDM:

The body of the baby is abnormally large a condition known as macrosomia. Such babies are more likely to be delivered through Caesarian section rather than vaginal birth. The baby may have low blood sugar levels a condition known as hypoglycemia. The skin of the baby gets a yellowish blue. The white region of the eye will also change in color. This condition can be treated effectively but not serious in nature. The newly born baby may experience discomfort while breathing and this condition is known as Respiratory Distress Syndrome. The baby may possess low levels of minerals, may be administered to the baby in such situations.

5. ADVERSE CONSEQUENCES OF GDM:

GDM can have deleterious consequences for the mother as well as the off springs. These consequences may be observed at the time of delivery which will be referred as immediate consequences or they may appear later in life which will be referred as long-term consequences. Women with uncontrolled plasma glucose levels during pregnancy have immediate adverse consequences such as pre-eclampsia, pre term deliveries, still births, caesarian sections and insulin treatment [10]. Indian women diagnosed with GDM up to 8.2% preterm deliveries have been reported [1]. Moreover, one in six Indian women studied who were diagnosed as having GDM continued to have Diabetes even after pregnancy was over [45]. During pregnancy, the GDM women develop the changes in their fasting lipid level, blood pressure, large and small vessel function which causes pregnancy induced hypertension. This metabolic syndrome is a condition which involves central obesity with raised triglyceride levels, reduced HDL cholesterol, raised blood pressure and raised fasting plasma glucose levels [40]. Several studies have shown that the association of GDM with congenital malformation such as cardiac defect, hypospadias, polydactyl and central nervous system defects [51]. It has been reported that neonates of women with GDM had greater than average head, chest and abdominal measurement compared to neonates without GDM [27]. Women with a history of GDM are at a greater risk of developing various chronic diseases in life such as Diabetes Mellitus (DM), Metabolic syndrome and cardio vascular diseases compared to women who do not develop GDM in pregnancy [31].

In a comparison of offspring of mother with GDM with those of diabetic father and offspring of parents who do not have diabetes, BMI of offspring of mothers of GDM has significantly higher than that of the controlled group [24]. In the early phase of intrauterine development of the fetus in women with GDM, there is increased defect in organogenesis and physiologic function development and increased levels of amino acids, glucose and fatty acids. In the case of women with diabetes during pregnancy there are risks of diabetic retinopathy, diabetic nephropathy and ketoacidosis could increase. Prenatal complications exhibited

are increased and delayed intrauterine fetal development, neonatal complications in GDM subjects and there is a increased risk of the mother developing Type-2 diabetes in future.

6. MANAGEMENT OF GDM:

The importance of education in women with GDM and their parents about the condition and its management cannot be over emphasized. The compliance with the treatment plan depends on the patients understanding of

- Diet and exercise
- Self-administration of insulin
- Identification and treatment of hypoglycemia
- Physical activity
- Reduce the stress and anxiety

It has been reported that in GDM patients undergoing Insulin therapy where fetal development is thought to be within the normal range. GDM patients for whom labor is induced at 38-39 weeks and Insulin treated GDM patients who electively waited for labor and child birth to take their natural course. In the case of GDM patients has good blood glucose control and fetal development is thought to be in natural range, it is considered that the pregnancy of GDM patients may be managed in the same manner as those of normal glucose tolerant women. Special care is needed as the amount of insulin required during pregnancy, during delivery and after birth differs tremendously. Thus, Insulin requirements at the end of the pregnancy increases by approximately two-fold. Accordingly, attention needs to be paid to such changes is required in Insulin amounts during pregnancy and the amount of Insulin administered reduce to half following delivery.

In many cases, at the onset of labor the patient is administered an electrolyte fluid containing 5% glucose at a rate of 100-120 ml/hour, then administered Insulin intravenously via an infusion pump. Depending on individual cases, blood glucose is measured at intervals of one to two hours. Insulin administration with the dosage of 0.5 units per hour and Insulin dosing rate is determined based on fluctuations in blood glucose levels. Obesity is an important risk factor for GDM and so prior to pregnancy not only it is necessary for patients to take special care with their lifestyle, especially diet, but it is also vital that women suffering from infertility be checked for glucose Intolerance. For women with carbohydrate complications of obesity it is also necessary that the GDM subjects make lifestyle improvements after the birth.

7. TREATMENT OF GDM:

In the majority of GDM cases, the frequencies of the various complications that may affect the mother and child can be controlled with appropriate diagnosis and treatment. The subjects who received treatment like diet therapy, self-monitoring of blood glucose, Insulin therapy have a lower incidence of complications for both the mother and newborn than for subjects receiving no treatment intervention. Depending on the degree of hyperglycemic disorder in pregnancy, self-monitoring of blood glucose is carried out by the patient at a frequency of 4-7 times per day. The target blood glucose levels are venous plasma glucose values 100mg/dl or lower before meals and of 120mg/dl or lowers 2 hours after meals. If the target values cannot be achieved, the diet and Insulin therapies are implements. Furthermore, if the patient is hospitalized regular check-ups should be made, to ensure that the difference between blood glucose levels obtained through self-monitoring and by laboratory testing is no more than around 10%.

8. DIET THERAPY OF GDM:

The key strategies for achieving control of blood glucose level are first of all frequently self-monitoring of blood glucose, followed by appropriate diet therapy which is extremely important. During pregnancy, as pregnant women patients need to consume adequate energy, proteins, and minerals. In Japan, according to the diet therapy recommended by the 'JSOG' committee on nutrient and metabolism problems- the dietary intake for ideal pregnancy weight is 25-30 kcal/kg+350 kcal the additional calorie intake recommended for pregnant women which is according to the diet reference intakes prescribed by the Ministry of Health and Welfare. Under the nutritional guidelines recommended by the Ministry of Health and Welfare in 2010-2012an additional caloric intake of 50kcal, 250kcal, 450kcal is recommended for pregnant women during first, second and third trimester respectively.

9. INSULIN THERAPY OF GDM:

Pregnancy is characterized by peripheral Insulin resistance which is compensated by an increase in Insulin secretion to maintain glucose homeostasis. Gestational Diabetes Mellitus (GDM) which occurs in about 4% of pregnancies, develops if insulin secretion fails to overcome Insulin resistance. In the United States nearly 4% of patients were reported to have diabetes. 88% of these women have GDM (45,000 per year) and the remaining 12% have either Type-1(12,000) Type-2(50,000) pregnancy is a diabetogenic condition characterized by Insulin resistance with a compensatory increase in B cell receptor and hyperinsulinemia which likely plays a role in ensuring that the fetus had an adequate supply of glucose. Pregnant women with diabetes are associated with an increased incidence of congenital abortions in women with poor glycemic control. Pregnancy is potentially a diabetogenic condition. Normal human pregnancy is associated with hyperinsulinemia a progressive decline in insulin sensitivity [28]. There is an average 60% decrease in Insulin sensitivity with advancing gestation in women with normal as well as abnormal glucose tolerance [42].

In case that target blood, glucose levels cannot be achieved, Insulin therapy should be actively implemented. In Insulin therapy condition, due to the need for strict blood glucose control, it is important to keep blood Insulin concentrations as close as possible to physiological Insulin secretion patterns. Basal Insulin secretion, after meals Insulin secretion, intensive Insulin therapy is carried out by means of multiple injections of intermediate acting and rapid acting Insulin or ultra-rapid acting Insulin analog. It is clear that nutrition-based interventions are effective for GDM. The results showed that women receiving treatment had a reduction in birth weights, lower frequency of large for gestational age birth and less pre-eclampsia compared with women receiving usual care. Many organizations recommended moderate physical activity, including brisk walking or arm exercises while seating in a chair, as part of the treatment program for women with GDM who are participating in therapy. These

recommendations are based on small studies suggesting that exercises lower fasting and postprandial glucose levels and may reduce the number of women with GDM taking Insulin therapy.

The goal of GDM treatment is to maintain blood glucose at levels that will minimize risk of adverse prenatal outcomes. The use of Insulin during pregnancy, heavily depends on patient treatment preference and the success of their lifestyle interventions. Diagnosis of GDM may depend on the screening protocols at a particular site which may explain how it was associated. Detailed studies of women with glucose tolerance, which is first detected during pregnancy provided three types of information regarding the relationship between GDM and Type-2 diabetes. First, virtually all women with GDM appear to have a large B cell defect against a background of chronic and more resistance to Insulin's ability to stimulate glucose utilization [49]. [38] in a study of 94 patients with GDM are reported that, the most significant predictor of 6 weeks diabetes was Insulin requirement followed by poor glycemic control. All these factors probably represent the magnitude of the Insulin resistance, which is the hallmark of future diabetes and other complications.

10. ROLE OF LIPIDS IN GDM:

Obesity is the most prominent risk factor for GDM patients and is linked to cardiovascular risk [12]. Transport of apolipoproteins and cholesterol is vital adaptive mechanism in pregnancy that support fetal development. Pregnancy is a hyperlipidemic state in which the placenta and fetal neuronal and membrane development [9]. The biochemical changes in GDM cases reflect fundamental alterations in the balance between carbohydrate and lipid metabolism. In GDM, disruptions in the balance of VLDL/LDL/HDL associated fetal and maternal morbidities. Very few investigators were demonstrated the changes in lipid metabolism during pregnancy complicated with GDM [26].

GDM is characterized by Insulin resistance is associated with cardiovascular diseases. Metabolic and biochemical changes that increase the risk of cardiovascular disease in GDM subjects with atherogenic dyslipidemia by increased concentrations of LDL particles, decreased HDL and increased triglycerides [25]. It was observed that triglycerides (TAG) and low HDL levels in GDM patients were related to diabetic dyslipidemia. Previous studies have shown that GDM is associated with an increased risk of hypertension. A significant increase in the incidence subjects was reported and the risk of pre-eclampsia in pregnant women is increased with elevated sugar and Insulin levels [8].

11. ROLE OF MINERALS IN GDM:

Diabetes Mellitus is characterized by hyperglycemia and is closely related to trace elements investigations of the changes of elemental contents in serum of the pregnant women with GDM which is significant. Iron is essential ion for life, playing a central role in many metabolic processes. Many enzymes in metabolic pathways are iron dependent thus iron making iron necessary for essential processes such as DNA synthesis, ATP synthesis as well as several neurotransmitters like serotonin and oloparmine [53]. Increased tissue iron levels are associated with diabetes both in human hereditary (HH) and in dietary iron overload [33]. However, the effect of iron is to increase glucose uptake, and high body iron levels are associated with increased level of oxidative stress and may elevate the risk of Type-2 diabetes. Calcium is essential for Insulin mediated intracellular processes in Insulin responsive tissues such as skeletal muscle and adipose tissue [19] and very narrow range of Ca²⁺ needed for optimal mediated functions [7]. Changes in Ca²⁺ in primary Insulin target tissues may contribute to peripheral Insulin resistance [41] via impaired Insulin signal transduction [13] leading to decreased GLUT-4 activity [29]. Advance research studies describe high mortality with high sulfur-calcium [21]. Women with Type-2 diabetes had in addition to their lower serum Mg significantly higher serum Ca compared with Type-2 diabetes and non-diabetic women at baseline. It was reported that zinc is involved in the synthesis storage, secretion and conformational integrity of Insulin [5]. Lower levels of zinc may affect the ability of pancreatic Islets cells for the production and secretion of Insulin in Type-2 diabetes [44]. A physicochemical relationship exists between Insulin and zinc. Since 1970s investigators regarding the biochemical pathway and structure of Insulin been known.

The role of zinc in gestational diabetes is not well established. Studies on diabetic pregnant rats suggested that the zinc transport to the fetus is reduced either because of decrease in placental transport or altered maternal or fetal zinc binding ligands [30]. In humans no difference was observed between Insulin dependent diabetic women and control subjects [35] further research is needed to establish zinc status on glucose homeostasis in women with GDM. Magnesium is the second most plentiful in human being living cells. Magnesium is the fourth most abundant cation in human body, and the second most abundant intracellular cation. It serves as a cofactor for an enzymatic reaction that require ATP as a key component in various reactions that require kinase. Magnesium has been found to regulate and improve blood sugar control, plays a vital role in the secretion and the function of Insulin and is necessary for Insulin and helps the body digest, absorb, utilize proteins fats and carbohydrates. Magnesium also plays a role in the release of Insulin and the maintenance of the pancreatic B cell cycle [18]. GDM subjects with higher fasting glucose levels had lower blood magnesium levels and higher urine levels of magnesium decreases in serum magnesium and increased urinary losses of magnesium were reported in Type-1 diabetes and GDM. Historically, one of the earliest recognized effects of copper deficiency, was the glucose tolerance in animals observed [34]. It is also known that production of Reactive Oxygen Species (ROS) is facilitated in the presence of copper ion through Fenton reaction [6].

12. STATUS OF ANTIOXIDANTS:

Oxidative stress peaks by the second trimester of pregnancy, ending what appears to be a vulnerable period for fetal health and gestational progress. Conditions are restricted to pregnancy, such as gestational hypertension, Insulin resistance which exhibit exaggerated indications of free radical damage. Elevated glucose levels can induce oxidative stress in gestational diabetic mothers [52]. Several studies found associations among diabetes in pregnancy and different markers of oxidative stress [16]. During pregnancy, the synthesis rate of lip-peroxides appears to exceed their decomposition rate, causing oxidative stress. It has been demonstrated that non pregnant patients with Type-1 diabetes have lower total antioxidant activity, the reduction of antioxidant levels may be linked to an increase in free radical mediated lipid per-oxidation.

13. HEMATOLOGICAL PARAMETERS OF GDM:

Gestational diabetes mellitus (GDM) is influenced by hemoglobin level (Hb) and mean corpuscular volume (MCV) before 14 weeks gestation in GDM women. The incidence of GDM in women with iron deficiency anemia has been reported to be 50%

of that seen in non-anemic women [14]. Previous studies have shown that MPV was increased in subjects with arterial thrombosis and at a risk for cardiovascular disease associated with diabetes and hypertension [4].

14. STUDY OF INSULIN HORMONE AND RECEPTORS:

Pregnancy is characterized by peripheral Insulin resistances, which is compensated by an increase in Insulin secretion to maintain glucose homeostasis. Gestational diabetes mellitus (GDM) which occurs in about 4% of pregnancies, develops of Insulin secretion fails to overcome Insulin resistance. Therefore, GDM shares many features with Type-2 diabetes mellitus, including not only glucose intolerance, impaired Insulin secretion but also association with similar risk factors, obesity and family history of diabetes.

In the United States nearly 4% of patients were reported to have Diabetes Mellitus. 88% of these women have GDM 45,000 women per year, and the remaining 12% have either Type-1 or Type-2 diabetes. Pregnant women with diabetes are associated with an increase incidence of congenital abortions of women with poor glycemic control [47]. Pregnancy is a potentially diabetogenic condition. Normal human pregnancy is associated with hyperinsulinemia and a progressive decline in Insulin sensitivity [28]. There is an average 60% decrease in Insulin sensitivity with advancing gestation in women with normal as well as abnormal glucose intolerance [42]. A measure of this Insulin sensitivity and the Insulin response to glucose was investigated [35]. Insulin receptor binding increased significantly in the women with GDM after dietary treatment had been instituted [2]. The changes in the receptor binding to monocytes and adipocytes may be secondary to various pregnancies associated endocrine and metabolic factors.

15. STUDY OF LIPID LDL PARTICLE:

Some investigators attributed the increased risk of developing Type-2 Diabetes Mellitus and hypertension in women with history of GDM with their dyslipidemia profiles [31]. Low density lipoproteins LDL particles are the major carriers of plasma cholesterol in humans. LDL exhibits substantial heterogeneity based on measures of size, density and chemical compositions. [37] categorized LDL particles into two major classes phenotypes denoted as A and B. Subjects with subclass phenotype B tend to have atherogenic lipoprotein profiles, including higher plasma TG, VLDL, apoprotein B concentrations and lower concentrations of apoprotein AI and HDL and an increased fraction of small LDL are frequent lipoprotein abnormalities and in subjects with Insulin resistance and Type-2 Diabetes Mellitus.

16. CLINICAL FEATURES OF GDM:

Gestational Diabetes Mellitus GDM is defined as glucose intolerance that is first detected during pregnancy. A significant increase in the levels of cholesterol, TG and FFA were observed GDM subjects. There is a linear correlation between GDM and inborn plasma TG levels [13], increased lipid concentration may increase the risk of cardiovascular disease especially with multiple pregnancies. Calcium, copper, magnesium concentrations in serum that has been found to be increased in GDM subjects. Increased levels were found to be strongly associated with zinc and copper deficiency, patients with Diabetes Mellitus has altered metabolism of copper, zinc and magnesium which is related to increased values of neutrophils, eosinophils, ESR and glycated hemoglobin. No significant alterations were observed in the levels of RBC & Hb, PCV, MCV, MCH, WBC and lymphocytes in GDM subjects.

It was observed that the levels of Insulin in GDM group was decreased. [5] stated that increased carbohydrates intolerance in women without over gestational diabetes was associated with graded increase in the incidents of macrosomia. There is an alteration in the Insulin receptor gene and an increasingly evidence of genetic polymorphism such as Insulin receptor substrate 1 (IRS-1), B3-AR in GDM subjects.

The levels of LDL were found to be increased in GDM subjects whereas levels of HDL is lowered [37]. FTIR spectral study of LDL particle shown significant changes suggesting alterations with the structure of LDL and thereby the function [55].

17. CONCLUSION AND FUTURE DIRECTIONS:

Prevalence of diabetes is increasing among world population. According to the International Diabetes Federation, South East Asia is having one of the largest populations of diabetes which is not only a health burden. The themes for diabetes in women is our right to be healthy future. With a very evident neglect of health issues faced by women, experts say that gestational diabetes present a much greater risk. Women diabetes our right to a healthy future. According to the International Diabetes Federation IDF, one in 10 women are living with diabetes, many of whom do not have access to healthcare and lack awareness about the disease. An even bigger problem is diabetes during pregnancy-one in seven births is affected by gestational diabetes. Diabetes is also ninth leading cause of death in women globally, causing 2.1 million deaths per year. Medical experts observe that in the gestational or pre-gestational diabetes, maternal sugar gets transferred to the fetus. The unborn baby is not supposed to produce any Insulin. But due to the sugar passed on by the mother, fetal Insulin is produced. The fetal Insulin trigger various abnormalities in the child, like defects in the spinal cord, a large head, heart abnormalities. Adding that if diabetes is detected well in time, the sugar levels can be brought under control, and the pregnancy can be planned afterwards by withdrawing contraception. Regular screening and timely diagnosis is this very essential. According to medical investigators, a diabetic female faces four times higher risk of developing heart ailments than normal subjects. The present research interest in the clinical disease GDM increase awareness in the world population. Understanding the mechanism of biochemical and genetic risk factors could be helpful to determine an appropriate management for GDM. Screening for GDM will be used for its value of identifying mothers at higher risk for Type-2 diabetes. Medical management acknowledges that women, who juggle many different roles at home and work, approach the doctors very late. There is a tendency to ignore their health problems and an obvious lack of care at home and registered a delay in diagnosis is seen at least 40% of cases. Future research should examine the applicability of many preventive and prognosis measures in GDM subjects so that future onset of Type-2 diabetes is avoided or managed. All women with GDM should be encouraged to engage in preventive behaviors such as increased physical activity healthy diets, regular monitoring of blood glucose levels and maintenance of normal body weight.

“PRECISION DIABETES IN WOMEN IS BOON”

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