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Diabetes Mellitus and Planning Conception

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Abstract

Diabetes mellitus is a disease which affects endocrine system and it is considered to beone of the most serious health problems to modern global health. Glycemic control is one of themost important aspects of preconception care; however other aspects such as folic acid supplementation, smoking cessation, screening and treatment of diabetes complications and discontinuing teratogenic medication, are as important for improving maternal and fetal outcomes.

Effective preconception care is associated with improved pregnancy outcomes for women with diabetes. A multidisciplinary team work is essential for preconception care. Outcome becomes fruitful with patient awareness and managing diabetes before pregnancy in an organised manner.

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Advances in Diabetes & Endocrinology

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Diabetes and Fertility- An Overview

Diabetes is a disease that affects millions of people and their families. The WHO estimates that more than 180 million people worldwide have diabetes. This number is likely to become 300 million by 2030 [1].

Diabetes has become a major health burden affecting primarily young adults and women in their reproductive age [2,3]. Type 1 diabetes is rising alarmingly worldwide, at a rate of 3% per year. Some 70,000 children aged 14 and under, develop Type 1 diabetes annually. Type 2 diabetes is also increasing in number among children and adolescents as obesity rates in this population continue to soar, in both developed and developing nations [4].

Given its' prevalence and heavy healthcare and quality-of-life burden [6], there is a great need for better treatment options. Despite improved access and quality of antenatal care, women and their foetuses with pre gestational diabetes are associated with increased risks of adverse pregnancy outcomes [7-11].

The first population-based epidemiological study on fertility rates over time among women with Type 1 diabetes was conducted in Sweden during 1965 to 2004 [12]. The lowest standardized fertility ratios were observed among women who had their first hospitalization for diabetes in the earliest years. The presence of diabetic microvascular or cardiovascular complications was associated with particularly low fertility, essentially regardless of year of first hospitalization.

Infertility risk factors related to diabetes [5]

Menstrual abnormalities

Shortening of reproductive period (late menarche and premature menopause)

Poor glycemic control and presence of diabetes complications

Hyperandrogenism and polycystic ovary syndrome

Autoimmunity (Hashimoto's thyroiditis and antiovarian autoantibodies)

Sexual dysfunction

With changing dietary and lifestyle patterns, the prevalence of obesity is increasing, thus raising the incidence of Type 2 diabetes during the reproductive years. Going in this direction, the disease can be linked to polycystic ovarian syndrome, the most common hormonal disorder among women of reproductive age, and a leading cause of infertility. Legro et al. showed that PCOS women are at significantly increased risk for impaired glucose tolerance and Type 2 diabetes mellitus at all weights and at a young age [13]. A study by A mini et al. showed that PCOS is highly prevalent in Type 2 diabetic patients [14].

Again, obesity is common in both PCOS and Type 2 diabetic women. Studies show that obese women seeking pregnancy experience longer times to conception, unrelated to age and to cyclic regularity, which is suggestive of alterations in ovarian function during the periconceptual period [15-16].

Diabetes and the Preconception Care

Preconception care is defined as a care that aim to identify and modify risks during pregnancy and improves pregnancy outcome through prevention and management. It is very alarming that 50% of all pregnancies are unplanned [17]. Improved preconception care is a mandatory component for women with diabetes.

Diabetes affects women in many ways, and one of them is the focus of the present discussion – the association between diabetes mellitus and planning conception.Women with diabetes should be informed about the benefits of preconception glycaemic control at each contact with healthcare professionals, from adolescence onwards [18]. Many of the complications of diabetes mellitus during pregnancy can be prevented by optimizing maternal health in the preconception period [19].

Periconceptional period is one of the most vital periods in a woman's life especially if she is suffering from any major illness like diabetes. Preconception care for women with diabetes is an effective means to reduce the incidence of adverse pregnancy outcomes [20-23]. Diabetic mothers are vulnerable to early pregnancy losses

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together with an increased incidence of congenital malformations in infants. Therefore, optimal medical care and pre conceptional counselling becomes a must in such patients [24]. This is best accomplished through a multidisciplinary team approach including a diabetologist, obstetrician, a dietitian, and other specialists as and when necessary.

Education in self management skills have a special role in diabetes. This model of care is important for patients to achieve the level of sustained glycemic control necessary to prevent congenital malformations. All diabetic women of child-bearing potential should be counselled about the risks of unplanned pregnancy and their use of appropriate contraception should be assured until metabolic control is achieved and conception is attempted. The first few weeks of pregnancy, when a woman may not be aware of her ongoing pregnancy, are particularly important because diabetic embryopathy induced by hyperglycaemia develop during this time [25-26]. Diabetic embryopathy includes the following congenital malformations in the fetus and are strongly related to the degree of hyperglycaemia in the periconceptional period:

- Congenital heart defects, most common abnormality, comprising 35 to 40 percent of major congenital anomalies, and includes tetralogy of Fallot, transposition of the great arteries, septal defects, and anomalous pulmonary venous return [27].
- Central nervous system defects (anencephaly, spina bifida, encephalocele, hydrocephaly, anotia/microtia)
- Limb defects
- Orofacial clefts
- Defects in the urogenital system [28-29].
- Sacral agenesis/caudal dysplasia (lack of fetal development of the caudal spine and corresponding segments of the spinal cord) accounts for 15 to 25 percent of all cases [30].

In women with advanced complications of diabetes, weighing the risk of a pregnancy to their health versus the desire for child bearing is particularly important.

The Goals and the Roles

Women with diabetes should be empowered to take control of their own disease process. Therefore, its very important that the goals and specific roles of each member of the team should be clear [31]. Women with type 2 diabetes may be less likely to prepare for pregnancy and achieve good glycemic control compared with those with type 1 diabetes [32-33]. While the risk of pregnancy complications may be similar for women with type 1 and type 2 diabetes, women with type 1 diabetes are more likely to have pre gestational micro vascular complications and are at higher risk of developing severe hypo- and hyperglycaemia and diabetic ketoacidosis.

The above constitutes an integrated model of care, demanding coordination of the roles of the different team members. Motivation for intensive self-management is dependent on the team's approach to imparting knowledge and skills to women with diabetes. Comprehensive and ongoing patient education is critical for shared decision-making about management goals and medication changes and for helping patients meet the considerable demands of self-care. Support system, includes family and work environment. Psychosocial status including adherence issues, social support network, and stress factors related to both diabetes and pregnancy should be discussed.

Based on the above information gathered, these professionals will review the patient's current management plan and develop a comprehensive treatment plan.

Contraindications to pregnancy

The NICE guideline states that an HbA1C > 10% is a contraindication to pregnancy. In contrast ADIPS suggests that impaired renal function as measured by a serum creatinine> 0.2 mmol/L should be a contraindication to pregnancy.

Role of Diet and Nutrition Therapy in the Management of Diabetes

Diet is one of the most important behavioural aspects of diabetes treatment. Understanding how different food intakes affect glycemia and developing a food plan of meals and snacks helps women reduce glucose fluctuations and manage fluctuations that occur.

The desired outcome of the preconception phase of careis to lower HbA1C test values to a level associated with optimal development during organogenesis. In order to achieve this goal, diet and nutrition has a great role. Nutrition history includes weight changes, history of eating disorders, gastrointestinal problems, and lifestyle considerations. Diet recall or food diaries may be of benefit in identifying specific problems within the meal plan.

Calculation of caloric needs based on height, weight, age, and activity level with development of a meal plan, including distribution of calories, carbohydrate, fat, and protein to achieve optimal nutrition while maintaining appropriate weight and acceptable glycemic control is the need of the hour.

Medical Nutrition Therapy for Diabetes should consider the following key aspects:

- Consistency in day-to-day carbohydrate intake at meals and snacks
- Weight management and increased physical activity
- Caloric intake (balanced with caloric expenditure)
- Nutritional content (balance of selected protein, carbohydrates, and fats)
- Timing of meals and snacks
- Adjusting insulin (in case of Type 1 diabetics) for variations in blood glucose, food, or activity
- Meal-insulin timing

Rallis in his study [51]concluded that a high-fat, low-carbohydrate, ketogenic diet may prove to be a more effective dietary intervention in the treatment of type 2 diabetes mellitus [52-53], whereas the present nutritional guidelines appear biased towards the promotion of carbohydrate-rich diets as mentioned above. The concept behind a ketogenic diet uses the idea that dietary macronutrient content modification promotes a shift from a carbohydrate to a lipid dominant metabolism. In order to achieve a ketogenic state, carbohydrate

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Diabetologist	Obstetrician	Dietician
Detailed history of any acute complications, including history of infections, ketoacidosis, and hypoglycaemia (including frequency, severity, signs and symptoms, and self-treatment) Chronic diabetic complications, such as retinopathy, nephropathy, hypertension, atherosclerotic vascular disease, and autonomic and peripheral neuropathy should be looked into.	Menstrual/pregnancy history; contraceptive use. Discussion regarding the effect of diabetes on pregnancy and how pregnancy affects diabetes.	Using an appropriate meal plan. Discuss if any Medical Nutrition Therapy (MNT) was previously followed.

Help the patient lower her glycated haemoglobin. Blood glucose testing and urine ketone testing should be done at each visit.
 	
Since it takes two to three months to turn over HbA_1C, women with diabetes should be encouraged to allow a minimum of six months to achieve optimal glucose control before trying to conceive, in case diabetes is not already well controlled.
 	
The following preconception glucose targets are reasonable to attempt to achieve:
• HbA1C <6.5 %
• Fasting capillary blood glucose concentration 80 to 110 mg/dL (4.4 to 6.1 mmol/L)
• Two hour postprandial glucose concentration <155 mg/dL (8.6 mmol/L)
	Explain the patient the various risks
	(maternal and fetal) including fetal malformations and means of prevention [34]
	
	***Risks to the mother*:**
	• Increased risk of miscarriage (2-3 fold higher in women with pregestational diabetes)
	• Preeclampsia/gestational hypertension (The risk may be higher in women with type 1 diabetes due to their higher risk of pre-existing microvascular disease;however, evidence suggests that glycemic control decreases the risk of developing preeclampsia) [36-37]
	• Increased risk of hypoglycaemia in early pregnancy in women on insulindue in part to the lower glucose targets in pregnancy, and possibly to the contribution of erratic meals due to morning sickness. She should be instructed to carry a snack at all times.
	• Increased weight gain in pregnancy
	• Preterm labour/delivery (both indicated and spontaneous preterm delivery)
	• Worsening of retinopathy in those with pre-existing proliferative retinopathybecause of pregnancy-related vascular and volume changes
	• Increased risk of caesarean section
	• Labour inductions are increased
	• Obstructed labour
	• Traumatic vaginal delivery
	• Traumatic postpartum hemorrhage
	• Interventional delivery
	• Complications associated with coagulopathy (in cases of prolonged retention of dead fetus)
	• Risk of developing postpartum prediabetes, Metabolic syndrome and Type 2 diabetes in future.
	***Risks to the fetus*:**
	• Fetalmacrosomia/large for gestational age [39]
	• Fetal malformations (epigenetic changes in gene expression may be influenced by pregestational diabetes; this is an area of ongoing investigation) [40]
	• Stillbirth/perinatal mortality risk begins to increase at A1C levels between 6-6.9% [25,41]
	• Prematurity
	• Intrapartum asphyxia
	• Birth trauma
	  • Shoulder dystocia
	  • Bone fracture (clavicle)
	  • Nerve palsy (brachial plexus injury)
	***Risks in Newborn*:**
	• Respiratory distress syndrome
	• Admission to NICU
	• Hypoglycaemia (because of high insulin levels in fetus)
	• Hypocalcemia
	• Hypomagnesemia
	• Hyperviscosity
	• Polycythemia
	• Hyperbilirubinemia
	• Hyperinsulinaemia
	• Cardiomyopathy
	Risk to Children Born to Diabetic Mothers [42-45]:
	• Obesity
	• Impaired glucose tolerance
	• Type 2 diabetes in adulthood
	• Metabolic syndrome (adverse cardiometabolic outcomes)
	• Pregestational diabetes and gestational diabetes have been linked with an increased risk for autism in offspring [46-47]
		NICE recommendsweight reduction for women with a BMI >27 kg/m^2 [35]
		Provision of dietary advice such as consuming a dietwith high levels of complex carbohydrates, solublefibre and vitamins, and reduced levels of saturated fats is also recommended [37-38].
		.

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Assessment of other medical complications or diseases especially, thyroid status. Measurement of serum thyroid stimulating hormone and/or free thyroxine level in women with type 1 diabetes is important because of the 510 % coincidence of hyper- or hypothyroidism	Contraception, timing of conception needs to be discussed in detail	Timing meals and snacks (discussed below)
Diabetes management, including insulin regimen, prior or current use of oral glucose-lowering agents, needs to be discussed	In cases of patients with polycystic ovarian syndrome, well controlled on metformin, the drug need not be stopped at conception	
Choosing time and site of insulin injections	Patients with Impaired glucose tolerance, Impaired Fasting Glucose, or patients with an HbA_1C of 5.7–6.4 % should undergo following interventions before pregnancy: • Weight loss ≈ 7% of body weight (therefore, physical activity becomes a must especially in obese patients) • Increasing physical activity to at least 150 min/week of moderate activity such as walking • Metformin therapy for prevention of type 2 diabetes may be considered in those with: • BMI > 35 kg/m^2 • Women with prior GDM Women with HbA1c above 86mmol/mol should be strongly advised to avoid pregnancy because of the associated risks.	
Testing capillary blood glucose	Folic acid 5 mg/day at least 3 months prior to conception [48]	Using carbohydrate and glucagon for hypoglycaemia
Self-adjusting insulin doses	Systemic examinations to be done (in case of Type 1 diabetes) [51] • Fundus examination • Renal function testsby measurement of serum creatinine and urinary microalbumin measurement (albumin-to-creatinine ratio or 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance) is undertaken before conception • Hypertension • Any infections to be treated well before (UTI, dental caries)	Refrain from smoking and alcohol
Oral hypoglycaemics to be switched over to insulin in case of Type 1 diabetics. Useof metformin as an adjunct or alternative for diabetic treatment preconceptionally when insulin treatment is refused or a patient develops resistance, is recommended [35,49,50]	Reducing stress, coping with denial	
	Immunity to rubella should be checked	

intake must be restricted to about 10% of total dietary intake. Protein and fat should make up ~20% and ~70% of the diet, respectively [54]. Under these conditions, the body begins to upregulate lipolytic enzymes and bypass the dependence on glucose for energy [55].

Hallberg et al did assess compliance of the ketogenic diet among diabetic patients using objective serum ketone monitoring and demonstrated that 87% of their participants were able to maintain a ketogenic diet for at least a year [56]. Dietary fats appear to play a role in mood stability [57], and endogenously produced ketone bodies (by-product of a ketogenic diet) naturally suppress appetite [58] both of which may assistin improving patient satisfaction and compliance with this nutritional methodology. A recent meta-analysis by Sainsbury et al however found that while carbohydrate-restricted dietsproduced greater reductions in HBA1C at 3 and 6 months, there was no statistically significant difference at 12 or 24 months [59].

Associated Complications and Management

High risk of diabetic complications and potential risks for pregnancy-related complications [60] require a detailed physical examination initiating with a blood pressure measurement (including orthostatic changes) before conception with special emphasis on the following [10]:

Counselling and Continued Care

The counselling sessions are important primarily for patient education, motivation, and instruction in more effective management strategies. At each visit, it is extremely important to make sure that the patient has understood what is being discussed and instructed. Evaluation of self monitoring of blood glucose; observation of technique used by the patient and to correlate test with the laboratory; testing log of the patient should be reviewed for appropriate timing of testing, frequency of testing, and values. Make sure that the patient has understood the insulin algorithms, identify the problem areas and reinstruct.

Evaluation of frequency, duration and timing of hypoglycaemic and hyperglycaemic episodes with an attempt to identify its' cause, are reviewed. Monthly HbA1C measurements prior to pregnancy are needed. Review the exercise plans, including timing, duration, and intensity as it relates to her tolerance of the activity.

Review with the nutritionist/dietician is extremely important. Root cause of many of the associated complications can be identified tracking the food records of each day (with timings), the blood glucose values before and after those particular meals and the amount of insulin injected. Review weight changes and determine the appropriateness of the prescribed meal plan and adjust as necessary.

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Complication	Inferences
Hypoglycemia [35,50]	Repeated and/or frequent episodes may be associated with: • Defective counterregulation • Unawareness of the complication • Insulin dose errors • Excessive alcohol intake • Unexplained Complete awareness, means of prevention and immediate management, be provided to the woman and her family members. Aim to achieve the following goals: • Preprandial whole blood glucose 70–100 mg/dl (3.9–5.6 mmol/l) OR • Preprandial plasma glucose 80–110 mg/dl (4.4–6.1 mmol/l) • Postprandial whole blood glucose 1 h <140 mg/dl (<7.8 mmol/l) 2 h <120 mg/dl (<6.7 mmol/l) OR • Postprandial plasma glucose 1 h <155 mg/dl (<8.6 mmol/l) 2 h <135 mg/dl (<7.5 mmol/l) • Aglycatedhemoglobin value within or near the upper limit of normal for the laboratory or within three standard deviations of the normal mean. All blood glucose meters give a glucose result that is a plasma value. Plasma values are approximately 11-12% higher than whole blood values.
Hypertension	Patients with type 1 diabetes frequently develop hypertension in association with diabetic nephropathy as manifested by the presence of microalbuminuria or albuminuria. Patients with type 2 diabetes more commonly have hypertension as a concomitant disease. Therefore, aggressive monitoring and control of hypertension in the preconception state is imperative.
Diabetic Retinopathy	Dilated retinal examination as the condition has a potential to worsen during pregnancy.A baseline dilated comprehensive eye examination is necessary before conception, in addition to achievement of good metabolic control. If deemed necessary, laser photocoagulation can be undertaken.
Diabetic Nephropathy	In less severe nephropathy, renal function worsens during pregnancy in only 8–30%, therefore, it should not be considered a risk to conception. In severe cases or those with incipient renal failure (serum creatinine >3 mg/dl or creatinine clearance <50 ml/min) pregnancy should be avoidedunless renal function can be stabilized by renal transplantation.
Cardiovascular complications	Thorough cardiovascular assessment is essential especially in those with long standing diabetes (> 10 years)or with other coronary artery disease risk factors.Untreated cardiovascular disease is associated with a high mortality, and should be excluded [61].
Neurological examination	Neurological assessment, including autonomic function is necessary. The following manifestations should be identified, appropriately evaluated and managed before conception is contemplated: • Gastroparesis, • Urinary retention, • Hypoglycaemic unawareness, or • Orthostatic hypotension
Lower extremity examination	For evidence of vascular disease, neuropathy, deformity, or infection
Pelvic examination	Including pap smear. Look for any repeated vulvovaginal infections including excessive leucorrhea
Hospitalizations	Occasionally it becomes necessary to hospitalize for treatment of intercurrent illness and acute diabetic complications such as diabetic ketoacidosis, hyperosmolar nonketotic syndromes, or severe hypoglycaemia.

Unfortunately, unplanned pregnancies occur in about two-thirds ofwomen with diabetes, precluding adequate preconception care and leading to apersistent excess of malformations in their infants [62]. There are no contraceptive methods that are specifically contraindicated in women with diabetes.

Compliance is the sole issue seen in many patients. Again, counselling has a key role in overcoming the patient's resistance. Stress issues should be discussed in detail. Explore ways and give suggestions on how to cope with it.Reinforce the importance of the overall treatment plan with the patient.

In the end, the importance of carefully planning a pregnancy and the need for effective contraceptionand avoiding pregnancy until a good glycemic control is achieved, should again be elaborated. The contraceptive methods with proven high degrees of effectiveness are to be preferred. Together with this, there is a need to review the current medications and their safety in pregnancy.

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