Can 'Gestational Diabetes Mellitus' be prevented?

Thesis Report

Submitted by

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World Journal of Research and Review

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Acknowledgment

I would like to express the deepest appreciation to my supervisor professor Colin Dayan, who has shown the attitude and the substance of a genius.

Without his meticulous supervision and constant help this dissertation would not have been possible.

List of Abbreviations

GDM- Gestational Diabetes Mellitus
HOMA-IR- Homeostasis Model Assessment of Insulin Resistance
PCOS- Poly cystic Ovarian Syndrome
MI- Myo-Inositol
FPG- Fasting Plasma glucose
SBGH- Sex binding globulin hormone
OGTT- Oral Glucose Tolerance Test
MET- Metabolic Equivalent of Task (MET)
HAPO- Hyperglycemia and Adverse Pregnancy Outcome
ACHOIS- Australian Carbohydrate Intolerance Study In Pregnant Women
MFMU- Maternal Fetal Medicine Units
NICE- National Institute for Health and Care Excellence
ACOG- American College of Obstetricians and Gynecologists
PPG- Postprandial plasma glucose
OR- Odds Ratio
RR- Relative Risk
BMI- Body Mass Index

Abstract

Gestational Diabetes Mellitus [GDM] constitutes a major health problem worldwide and the incidence of which is escalating tremendously, paralleling the high incidence of obesity and sedentary lifestyle. The adverse pregnancy outcomes reflect the negative impact of gestational diabetes mellitus on the fetus and the mother. The primary objective of this research is to study the risk factors among 50 patients with Gestational Diabetes Mellitus and the secondary objective is to study the feasible opportunities for prevention of Gestational Diabetes in these patients. Data collection was done as a retrospective study. The medical records of these patients were reviewed. This study was conducted at Hamad Medical Corporation -Al Khor Hospital in State of Qatar.

On analysis, the results revealed that around 68% of patients were expatriates and amongst these 70% were found to be obese and that the - Maternal age > 25 years was seen in 54% of patients. The significant risk factors for Gestational Diabetes Mellitus for individuals of maternal age above 25 years are Obesity, family History of diabetes mellitus. The preventive measures for these individual who are under the risk are Physical Activity, Dietary Modifications, Counseling and administration of drugs like Metformin, Inositol Therapy.

1. Introduction

Gestational Diabetes mellitus (GDM), a condition characterized by glucose intolerance during pregnancy, is associated with a variety of adverse birth outcomes, including excessive fetal weight gain and related increases in the rate of cesarean delivery and perinatal injury.[Gestational Diabetes Mellitus , AADE Practice Advisory ,Issued December 19, 2013]

Gestational Diabetes Mellitus [GDM] constitutes a major health problem worldwide and the incidence of which is escalating tremendously, paralleling the high incidence of obesity and sedentary lifestyle. The adverse pregnancy outcomes reflect the negative impact of gestational diabetes mellitus on the fetus and the mother.Insulin resistance is associated with pregnancy and explains the incidence of Gestational Diabetes Mellitus. It is caused by the placental secretion of several insulin-antagonist hormones, including growth hormone (GH), corticotrophin- releasing hormones. These hormones provide the fetus with the adequate nutritional supply needed during the intrauterine period. Gestational Diabetes Mellitus has been associated with various maternal and perinatal adverse outcomes. Screening and subsequent treatment are associated with short term benefit.

With the recent recommended diagnostic criteria by the International Association of Diabetes and Pregnancy Study Groups and increasing rate of obesity, the prevalence will continue to rise. [http://omicsonline.org/gestational-diabetes-mellitus-update-and-review-of-literature-2161-038X.S2-002.pdf]

Objectives

The objective of the study is:

1. To study the risk factors among 50 patients with Gestational Diabetes Mellitus (GDM) at Alkhor Hospital. State of Qatar.
2. To study the potential opportunities for prevention of gestational diabetes mellitus in review of these patients.

2. Review of Literature

2.1. Definition

The American College of Obstetricians and Gynecologists (ACOG) defines the Gestational Diabetes Mellitus as ''the occurrence of glucose intolerance discovered for the first time during pregnancy''. (1, 2) The International Association of Diabetes and Pregnancy Study Group (IADPSG), and World Health Organization have put in efforts to distinguish women with preexisting diabetes from cases with the transient disease due to pregnancy – induced insulin resistance. (3-5)
The above organizations use the term Gestational Diabetes Mellitus to define diabetes diagnosed during second half of pregnancy, and overt diabetes or diabetes mellitus in pregnancy to describe early onset of diabetes occurring during pregnancy, before the influence of insulin resistance becomes evident.(6)

2.2. Prevalence

The prevalence of Gestational Diabetes Mellitus in the U.S. is 6% to 7% but the range can be from 1 to 25 %.(7, 8). The prevalence varies considerably worldwide, almost in parallel with that of type 2 Diabetes Mellitus. (9). This variation is attributed to different screening methods, population characteristics, methodologies of the performed tests, and the criteria for diagnosis. Prevalence is observed to be high, reflecting the rise in the weight of the pregnant women and their age. (10 – 14). In 2010, the IADPSG developed new screening and diagnostic criteria for Gestational Diabetes Mellitus that has resulted in an incremental rise of the prevalence to 18%. These resulted in adverse effects on the foetal growth. These are Fetal Macrosomia is newborns with excess birth weight and large gestational age; Fetal organomegaly (hepatomegaly, cardiomegaly), Neonatal respiratory and metabolic complications (hypoglycemia, Hyperbilirubinemia, hypocalcaemia, erythemia); Fetal birth trauma, Perinatal mortality, Shoulder dystocia increases with obesity and Gestational Diabetes Mellitus. The increased risk was attributed to anthropometric abnormalities in Gestational Diabetes Mellitus [GDM] infants. To minimize these complications pertinent to gestational diabetes mellitus, Caesarean delivery has been recommended. Gestational Diabetes Mellitus in pregnancy induces excess fetal growth, decreased insulin sensitivity, and decreased insulin secretion. These changes result in impaired glucose tolerance during early youth and adolescence.

Maternal effects include Preeclampsia, Hydramnios, Maternal trauma, and Operative delivery. Women with Gestational Diabetes Mellitus have high incidence of hypertensive disorders during pregnancy, especially chronic hypertension which ranges between 2.5-5%, preeclampsia between 5-15% and for gestational hypertension around 6%. These conditions explain the association between Gestational Diabetes Mellitus and preterm delivery in Hyperglycemia and Pregnancy Outcome [HAPO] study, 16% of women with gestational diabetes mellitus have had primary Caesarean section, increased Fasting plasma glucose [FPG] and Postprandial plasma glucose [PPG] were associated with increased odds of primary Cesarean Section.

The risks of the above outcomes escalate as maternal fasting plasma glucose level exceeds 4.2 mmol/L and as the one-hour and two-hour oral glucose tolerance tests [OGTT] values increase.

There is no obvious threshold that defines patients at increased risk of adverse outcomes. (16-25). If maternal hyperglycemia persists during organogenesis, especially in patients with pre-gestational diabetes, the risks of miscarriage and congenital malformations are increased. In the long-term perspective; subjects with Gestational Diabetes Mellitus are candidates for developing overt diabetes mellitus and Cardio Vascular Disease as a result of the reduction of the maternal pancreatic beta-cell reserve. It has been found that women with Gestational Diabetes Mellitus even with a normal postpartum Glucose Tolerance Test are at seven-fold higher risk for future diabetes than those without history of Gestational Diabetes Mellitus.

2.3. Risk Factors

The risk factors identified in developing Gestational Diabetes Mellitus include, Personal history of impaired glucose tolerance or past history of Gestational Diabetes Mellitus, member of one of the known ethnic groups which have a high prevalence of type 2 Diabetes Mellitus, family history of diabetes, especially among first degree relatives. (27), Body Mass Index>30 kg/m2, significant weight gain in early adulthood and between pregnancies (28), or excessive gestational weight gain (29-31). Maternal age more than 25 years of age, previous delivery of a baby > 9 pounds (4.1 kg), previous unexplained perinatal loss or birth of a malformed infant, maternal birth weight > 9 pounds or less than 6 pounds, glycosuria at the first prenatal visit. Medical conditions associated with diabetes, like metabolic syndrome, polycystic ovary syndrome (PCOS), current use of steroids, hypertension. On the other hand, the factors which are associated with low risk for developing Gestational Diabetes Mellitus, are include Age < 25 years, normal body mass index, no past history of abnormal Oral Glucose Tolerance Test or complicated pregnancy course related to Gestational Diabetes Mellitus and no history of diabetes mellitus among family members.

The independent risk factors for Gestational Diabetes Mellitus are BMI above 30 kg/m2, earlier or previous macrosomic baby weighing 4.5 kg or above, previous history of Gestational Diabetes Mellitus, family history of diabetes, family origin with a high prevalence of diabetes, prevalence in South Asians especially those from India, Pakistan, and Bangladesh, natives from Black Caribbean region, women from Middle Eastern (women originally from Saudi Arabia, UAE, Iraq, Jordan, Syria, Oman, Qatar, Kuwait, Lebanon or Egypt).

Torloni et al had studied pre-pregnancy Body Mass Index and the risk of Gestational Diabetes Mellitus through a systematic review of the literature with meta-analysis. The design used was a systematic review studying several clinical trials over the last 3 decades (1977-2007), using 4 electronic databases, which had looked into the pertinent topics. Body mass index was used to represent a reliable indicator of obesity. Standard diagnostic criteria for Gestational Diabetes Mellitus were considered. Trials advocating selective screening for Gestational Diabetes Mellitus were eliminated.1745 citations, 671945 subjects were reviewed over 70 studies. Cohort studies included 59 subjects and case controls are 11. The quality of these trials is found to be high. The Odds Ratio of the overweight women having Gestational Diabetes Mellitus was 0.75 (95% CI 0.69 to 0.82) in comparison with subjects of normal body mass index. The Odds Ratio for overweight, moderately obese and morbidly obese women were 1.97 (95% CI 1.77 to 2. 19), 3.01 (95% CI 2.34 to 3.87), and 5.55 (95% CI 4.27 to 7.21) respectively. It had been reported that an incremental rise of body mass index by 1kg/m2 increases Gestational Diabetes Mellitus

risk by 0.92%. The conclusion was the risk of developing Gestational Diabetes Mellitus was directly proportional to the weight status prior to conception. Such knowledge is crucial in order to plan for favorable and safe pregnancy outcome. (39).

2.4. Screening of Gestational Diabetes Mellitus

Screening gestational diabetes mellitus using risk factors is recommended in a healthy population. At the time of appointment booking, the following risk factors for Gestational Diabetes Mellitus should be determined by BMI > 30kg/m2, previous macrosomic baby weighing 4.5 kg or above, previous Gestational Diabetes Mellitus ,family history of diabetes (first- degree relative with diabetes), family history of a high prevalence of diabetes, women with at least one risk factor of those mentioned above must be considered for appropriate tests used in the diagnosis of Gestational Diabetes Mellitus. In order to create a valid informed plan regarding screening methods and valid tests for the diagnosis of Gestational Diabetes Mellitus, the patient must be informed that GDM in the majority of patients can be effectively prevented by dietary measures and physical activity, treatment with oral hypo-glycemic medications or the use of insulin is needed by 10-20% of the pregnant women, in case if the dietary measures and physical activity failed to control gestational diabetes mellitus, failure of detection of Gestational Diabetes Mellitus and failure to control it, is associated with perinatal complications, including shoulder dystocia, continuous monitoring and intervention are needed throughout pregnancy and labour, if the diagnosis of Gestational Diabetes Mellitus had been established. Some screening tests are not recommended for Gestational Diabetes Mellitus, like Fasting blood glucose, random blood glucose 1-hour glucose challenge test, Urinary glucose.

The only diagnostic test for Gestational Diabetes Mellitus that should be used is the 2-h 75g Oral Glucose Tolerance Test [OGTT] The WHO diagnostic criteria for Gestational Diabetes Mellitus have to be used. Blood glucose monitoring by the patient or Oral Glucose Tolerance Test at 16 to 18 weeks gestation should be considered for patients with past history of Gestational Diabetes Mellitus. In case this test is normal, the patient should have to get another Oral Glucose Tolerance Test at 28 weeks gestation. Women with risk factors for Gestational Diabetes Mellitus should do Oral Glucose Tolerance Test [OGTT] at 24 to 28 weeks gestation. Gestational Diabetes Mellitus patients should be encouraged to perform regular blood glucose monitoring. Recent ADA recommendations encouraged optional screening for Gestational Diabetes Mellitus according to the existence of risk factors. There was a debate concerning the appropriate approach for Gestational Diabetes Mellitus screening. The selective screening considers the different risk factors gestational diabetes mellitus as the main basis. The universal screening considers the blood glucose measurements as the mainstay for screening.

David Simmons et al conducted a study aiming at comparing the divers' strategies involving the diagnosis and management of Gestational Diabetes Mellitus, which was advocated by the ADA, the American College of Obstetricians and Gynecologists (ACOG), and NICE guidelines. NICE guideline refuted some risk factors in view of cost-effectiveness, but emphasized the beneficial impact of screening, which limits several complications regarding Gestational Diabetes Mellitus outcomes that may add more costs and burden to health system. According to NICE, several speculations are unrealistic when considering cost-effectiveness and the actual costs and impact were underestimated. NICE does not support the universal screening and refutes certain risk factors of Gestational Diabetes Mellitus, like the presence of diabetes mellitus among family

members. There was no concrete evidence found by the 2002 NICE Health Technology Assessment to support universal screening for Gestational Diabetes Mellitus during pregnancy, but it showed the negative impact of maternal high blood glucose on the fetal outcomes. The NICE 2008 guideline on diabetes in pregnancy advocated programmes encouraging screening women with high risk factors.

In conclusion, the comparison between the different guidelines has shown important discrepancies in screening methodologies, diagnostic tools and the entire management of Gestational Diabetes Mellitus. (47). The multinational Hyperglycemia and Pregnancy Outcome (HAPO) study demonstrated the intimate association between maternal hyperglycemia and the development of adverse neonatal outcomes in about 23000 pregnant patients. The findings of this study constituted an important template that had led to the development of a consensus report published in 2010 involving the diagnosis and screening for diabetes. In 2009, another study had been conducted, assessing the impact of Gestational Diabetes Mellitus treatment on pregnancy outcomes. Ethnicity is considered to be a major risk factor when planning for Gestational Diabetes Mellitus screening, as it was found significantly prevalent in a great proportion of pregnant women with Gestational Diabetes Mellitus. The risk factors related to Gestational Diabetes Mellitus were derived mostly from European background, so few clinical trials were studying ethnicity in non-Europeans. The authors have performed a trial aiming to evaluate the impact of classic risk factors for Gestational Diabetes Mellitus on Asians and tried to assess the feasibility and role of the risk factors as indicators in screening and testing women for Gestational Diabetes Mellitus.

Data of patients were originally from China, Philippines, Sri Lanka, and Vietnam attending the Obstetrics and Gynaecology unit at Westmend hospital in Australia were studied during the time between 1988- 1996. All pregnant women received 50 g glucose randomly between weeks 24 to 26 gestation. When the blood glucose at 1- hour exceeds 140mg/dl, then the patient had to report again for the standard 75 g glucose tolerance test and would be labelled to have Gestational Diabetes Mellitus if blood glucose exceeds or equal to 108, 180 , 145 mg/dl at zero, 1 hour , or 2 hour, respectively. Gestational Diabetes Mellitus status and the several risk factors, comprising age group, the recorded weight of the patient at the time of the initial out-patient visit, body mass index, status of gravida, status of parity, history of diabetes mellitus among family members, history of large-for-gestational-age newborn, past history of gestational hypertension, past history of abortions or fetal loss, and past history of fetal anomalies, all these are reported in the study population.

The medical data of 2,797 full-term pregnancies were reviewed. 2,139 women of Asian origin were studied. Patients who have had multiple pregnancies, abortions, those in whom pregnancy was terminated, those with pre-Gestational Diabetes Mellitus were not included in the study. 9.2% of patients with Gestational Diabetes Mellitus were reported among ladies who were born in China. 8.6% of cases with Gestational Diabetes Mellitus were originally from the Philippines, 10.5% of Gestational Diabetes Mellitus patients were found to be originally from Sri Lanka, while 10.6% of cases were basically from Vietnam. These results of Gestational Diabetes Mellitus incidence were similar to those recorded in other studies performed in Asian Indians in other developed countries. Some results reported lesser incidence of Gestational Diabetes Mellitus in Asia than in the developed countries. There were remarkable differences when

changing the target levels of tests used in the screening for Gestational Diabetes Mellitus. Basically, the required Gestational Diabetes Mellitus numbers of selected women to be tested for GDM and the reliability of utilizing the risk factors as tools to recruit women for Gestational Diabetes Mellitus testing differ based on the target levels.

In order to detect 97% of patients with Gestational Diabetes Mellitus through utilizing the age of 25 years and more and those with body mass index exceeding 30kg/m2, we need to test around 91% of the whole population of pregnant women. All gestational diabetes mellitus risk factors that had been examined were found predictive for GDM, especially when the logistic regression analysis was utilized. The most prevalent and significant risk factor for Gestational Diabetes Mellitus among all groups was found to be past history of Gestational Diabetes Mellitus with a probability of 14.5% in the entire groups. Based on the above finding, selecting patients to be tested for Gestational Diabetes Mellitus based only on risk factors might be insufficient, and many patients may be missed. Several women from Asian origin have no risk factors at all. It is always better to perform global screening tests in developed countries in order to screen the majority of Asian ethnic groups. Performing selective tests may lead to underestimation of small number of patients for testing and so the results would be inappropriate. The authors concluded that their findings were matching the same policies pertinent to universal screening for Gestational Diabetes Mellitus in Asian pregnant subjects living in developed countries. In communities where the incidence of gestational diabetes mellitus is low, using risk factors as the selection tool for testing is appropriate. (42)

ADA recommendations for detection and diagnosis of gestational diabetes mellitus include screening for undiagnosed type 2 diabetes at the first prenatal visit in those with risk factors, screening for Gestational Diabetes Mellitus at weeks 24 to 28 gestation the previously known to have gestational diabetes mellitus, screening women with Gestational Diabetes Mellitus for persistent diabetes at week's 6 to 12 post- delivery, using the OGTT, subjects with a history of Gestational Diabetes Mellitus should have lifelong screening for the development of diabetes., subjects with a history of Gestational Diabetes Mellitus found to have pre-diabetes should receive lifestyle intervention and to have a standard diagnostic tool for the detection of Gestational Diabetes Mellitus, future research is required to resolve this issue.

In Scotland, the guideline set by the Scottish Intercollegiate Guidelines Network (SIGN) followed the same diagnostic criteria operated by the International Consensus. The 75-g OGTT was used by SIGN for patients with high risk. On the other hand, fasting plasma glucose was used in the low risk population. The ACOG showed the increased risk of type2 in women with gestational diabetes mellitus but still not recommending postpartum screening, data suggest that a large proportion of women with gestational diabetes mellitus do not receive appropriate postpartum screening. The failure of postpartum screening may be due to; lack of adequate knowledge about that, differences in recommendations by different organizations, and the prolonged timeframe needed for OGTT for a busy mother. In order to improve outcomes of pregnancy in patients with gestational diabetes mellitus, some concepts should be adopted, including new approaches to address the maternal glycemic control, the clinical assessment and method of delivery need to be modified, risk factors for developing future diabetes should be identified.

Improving the implementation of postpartum screening in women with gestational diabetes mellitus might help to discover a larger number of women at risk of type2 diabetes in whom primary prevention could be achieved. Screening can be delayed beyond 6 weeks, so large number of patients could receive counseling on lifestyle changes, moreover those with negative screening tests will benefit from lifestyle modifications and hence the risk of developing gestational diabetes mellitus in later pregnancies might be reduced. Expert consensus adopted a 2-step blood glucose testing, starting with a random 50-g 1- hour challenge test at a period between week 24 to week 28 of pregnancy. Checking blood glucose levels in the fasting or random states is not advised, due to lack of certainty and accuracy. Most authorities advised a meal, which is rich in carbohydrates, to be continued for the preceding 3 days prior to the day of testing. On the other hand, several studies reported no difference in blood test values on meals with variable amounts and types of carbohydrates. The diagnosis of Gestational Diabetes Mellitus is established if only one or more blood glucose values are equal or above the targets such as Fasting plasma glucose is 5.1mmol/l, one-hour is 10mmol/l, and two-hours of 8.6 mmol/l.

2.5. Approaches for Prevention of Gestational Diabetes Mellitus

2.5.1. Exercise and weight loss. The prevalence of Gestational Diabetes Mellitus in Australian population was found to be around 1.7 - 9.6%.(44).Over 30% of Australian pregnant ladies were reported to fall under the slim category; obesity was not seen frequently among pregnant women. The prevalence of Gestational Diabetes Mellitus was found relatively higher in pregnant women who live in countryside and remote regions compared to urban societies. North-east Victoria showed a higher obesity prevalence amounting to 65.5% among pregnant women. The high incidence of obesity is escalating globally and the identifications of efficient policies to minimize the prevalence of Gestational Diabetes Mellitus and enhance healthier attitudes among obese patients, this may result in better lifestyle. This can be achieved by adopting weight reduction strategies and adhering to BMI targets, through structured educational programmes.

30-50% of the overweight women were reported to fulfill the prescribed weight during pregnancy; this was shown from previous randomized clinical trials. No concrete evidence was supporting the positive impact of lifestyle modifications, exercise, and dietary advice on the prevention of perinatal complications in obese pregnant patients. Dodd et al conducted a meta-analysis comprising 9 clinical trials including 743 women aiming to study the beneficial effects of physical activity and lifestyle modifications during pregnancy.(15) The investigators reported inconclusive results on that. No conclusive data was obtained regarding the role of interventions in preventing the development of Gestational Diabetes Mellitus. One clinical trial examined the impact of interventions compared to routine care in the prevention of Gestational Diabetes Mellitus. The provided interventions comprised of checking weight changes at every out-patient clinic visit, assessment by a dietitian for a period of 5 minutes. There was an evaluation by a psychologist through a special interview.

It is reported that the trend of repeating the intervention on regular basis had resulted in favorable outcomes. The authors have developed a composite intervention, including constant interviews with these patients every week. An intervention called the EDGE (Educate, Develop Goals, Engage), which describes specifically, the continuity of keeping in regular contact with patients, the fortification of behavioral changes, and creation of standards which suit the low

socioeconomic areas, this program continued until birth of the newborn. The authors were aiming at studying the role of the EDGE concept in comparison with the routine care in the prevention of Gestational Diabetes Mellitus in obese pregnant subjects, as well as, in the overweight women The study is supposed to be performed in the primary care centres of Barwon South West, Victoria, Australia.

A randomized controlled trial is implemented; randomization involves the intervention and the routine care groups. This study is performed and recorded utilizing the CONSORT format. The investigators were aiming at comparing the intervention group with the usual care group with regards to the incidence of Gestational Diabetes Mellitus in the obese and overweight population. The primary assumption was that the intervention group will have fewer incidences of Gestational Diabetes Mellitus by around 10% in comparison with the usual care group, as well, 4 additional goals were considered. Recording the discrepancies in the levels of blood glucose when performing oral glucose tolerance test and improving the patients psychologically, through provision of effective interventions. Recruitment criteria include pregnant patients who are below 14 weeks gestation and with BMI>25kg/m2.

Women with a singleton pregnancy will be included if their gestation is less than 14 weeks and their BMI> 25.The exclusion criteria will comprise patients known to have diabetes mellitus, with previous history of Gestational Diabetes Mellitus, patients who do not understand English and therefore cannot sign the consent form, those with bleeding during the recruitment phase, and those with other co-morbid illnesses that may hinder them from performing the proposed physical activity efficiently. Participants assigned for recruitment are selected from 30 public health facilities in countryside and regions around Geelong and Victoria cities. All the enrolled women in the study will be provided by a trial package, given by the assigned medical personnel or the nursing staff containing the first questionnaire and the consent form. Randomization will be through a computer generated randomization sequence. Women in the EDGE program will receive a weekly phone call, encouraging and promoting their capabilities through the discussion about certain points pertinent to the study that aims that the control group will receive usual care. The aim of the study is to find out the number of patients identified to have Gestational Diabetes Mellitus in between 24-28 weeks gestation, and the diagnostic tools are based on the management recommendations of the Australian Diabetes in Pregnancy study (ADIPS), as well as, the diagnostic criteria set by the International Association of Diabetes and Pregnancy Study Groups (IADPSG).The secondary outcomes include gestational weight gain, where in the Institute of Medicine recommends women with BMI>25 to 29.9 kg/m2 gain 7- 11.5 kg and women with a BMI> 30 kg/m2 gain 5 – 9 kg and the other outcome is Large gestational age-defined as Newborn's birth weight that exceeds 90th centile for gestational age and sex, together with newborn's weight > 4 kg, such information will be collected from the records of the patients and will be recorded by utilizing the two mentioned diagnostic tools.

Parameters like depressive episodes, anxiety status, self-assessment of psychological status and the feasibility of changing the behavior of the participants effectively are studied. Such parameters are checked at the beginning of the recruitment phase, and another measurement will be performed at 36 weeks gestational age by utilizing written questionnaires. The assessment of anxiety state is analyzed with a special scale, named Speilberger State-Trait anxiety inventory Assessment of depression is performed with the help of Beck Depression Inventory II. Its use

during pregnancy has been well-validated, differences among the groups will be assessed and comparison will be recorded. Changes related to dietary habits and physical activity will be assessed and comparison between the different groups will be reported. This reveals the personal benefits and gains achieved by the patients from the interventions. The effectiveness of exercise scale and its impact on the patients is evaluated through a range of 9 points, starting from 0 to 10, based on the patient's score. Oral glucose tolerance test will be performed and the differences in the levels of the fasting, one hour and post prandial plasma glucose level at 2 hour are recorded, and comparison between groups is made by utilizing the above mentioned diagnostic criteria. 370 pregnant patients need to be enrolled, knowing that the percentage of obese patients discovered to have Gestational Diabetes Mellitus is 17%.

Leonie et al conducted a study examining the potential opportunity of the physical activity in the prevention of Gestational Diabetes Mellitus among overweight and obese patients during pregnancy. Obese patients had been recruited at weeks 12 gestation and followed up throughout pregnancy. Complete data is collected at 12, 20, and 30 weeks gestation. Energy expenditure of 900kcal per week was accomplished by the intervention group through a special exercise program. The control group received the usual care. Fasting plasma glucose and fasting insulin is checked on regular basis. 2-h 75g OGTT is performed at the initial visit and at 28 weeks gestation. Insulin resistance was assessed by utilizing Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]. The diagnosis and the management of Gestational Diabetes Mellitus are achieved through the implementation of the Australian Diabetes in Pregnancy Society guidelines. The investigators have randomized 50 obese pregnant subjects into two equal groups, intervention or control group, both recruited for 7 months. The rate of recruitment among eligible subjects is 12%, all attended the out-patient department at the Royal Brisbane and Women's Hospital. Both groups have comparable baseline characteristics, with the trend of achieving the diagnosis of gestational diabetes mellitus earlier on in the intervention group.

Exercise duration and intensity differed significantly; weekly energy expenditure [EE] was greater at weeks 28 and 36 gestation in the intervention category At 28 weeks gestation, 73% of the intervention group achieved the exercise target in comparison with only 42% in the usual care group, p value of 0.047 Fasting Plasma Glucose was much lower in the intervention arm at 28 weeks gestation and the insulin level was lower at 36 weeks gestation in the same group. The gist reveals that the targeted physical activity intervention performed in the obese pregnant population was found feasible and beneficial. The rates of recruited pregnant women were considered quite satisfactory, interventions are satisfactory appreciated by participants and are implemented fully in this study, Women in the interventional group were performing sufficient exercises at 20 weeks and were meeting the exercise goal. Based on the results, the authors suggested that exercise and dietary intervention were very beneficial and quite effective in preventing Gestational Diabetes Mellitus and improving the element of insulin resistance. (40)Deirdre K et al conducted a systematic review aiming to study the relationship between exercise and the incidence of Gestation Diabetes Mellitus.

Data is collected using the Medline database searching the pertinent English- language articles, EMBASE, and Cochrane Reviews through March 2010 and by a manual bibliography check. Evaluation is made for the whole set of articles on a specific criteria that had created a priori. Researchers have had utilized all the available manuscripts related to the trial. No restriction had

been made on the assessment of exercise and its timing. The authors excluded all the studies reporting only Impaired Glucose Tolerance [IGT], and the combination of Gestational Diabetes Mellitus and Impaired Glucose Tolerance end point. The idea behind setting such exclusion was because patients with Gestational Diabetes Mellitus can embark on therapeutic interventions including physical activity which leaves a chance for reverse causation. In order to provide a comparable exposure among the studies, elaborated analysis had been performed regarding the relative risks between the maximum and minimum physical activity. The authors used the Cochrane Q test in order to record any heterogeneity. Egger [linear regression method] and Begg's test (rank correlation method) were used to assess the publication bias, considering p value was significant if less than 0.05. Dempsey et al showed couple of findings in 2 clinical trials, namely the OMEGA Study and Alpha Study, considering physical activity a very useful intervention during early pregnancy or even prior to pregnancy in the prevention of Gestational Diabetes Mellitus. Rudra et al updated the results of the pre-pregnancy exposure. The eight studies involved 34,929 subjects, with 2,855 total cases of Gestational Diabetes Mellitus, of these, 5 were prospective cohort studies, 2 retrospective case- control studies, and two cross-sectional surveys. Harizopoulou and colleagues performed their study among women from Greece, all other studies were carried out in women from United States of America. In certain studies, patients were questioned during their postnatal stay in hospital through valid questionnaire about physical activity.

The physical activity units were expressed as number of hours spent during the week. The magnitude of burnt energy was described as Metabolic Equivalent of Task (MET), [is a physiological measure expressing the energy cost of physical activities and is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific physical activity to a reference metabolic rate, set by convention to 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$] MET-hours/week. The type of exercise was defined as mild, moderate, and high intensity. 7 trials showed the relationship between Gestational Diabetes Mellitus and physical exercise. The investigators reported unremarkable differences in the incidence of gestational diabetes mellitus when the different parameters have been controlled, namely presence of diabetes mellitus among family members, history of smoking, ethnicity, and social background. P values were 0.97, 0.23, 0.33, and 0.47 respectively. The relationship between exercise in the first trimester and the incidence of Gestational Diabetes Mellitus was assessed by several studies. There was an inverse relation between the intensity of exercise and the incidence of Gestational Diabetes Mellitus The beneficial effects were seen in pregnant women who were involved in walking and climbing the stairs. This was reported by 4 trials.

Outcomes of these trials revealed that performing intensive exercise prior to pregnancy or even during the first trimester of pregnancy had an important positive impact on the development of Gestational Diabetes Mellitus risk Women performing high intensity exercise during early pregnancy showed a 25% reduction in the risk of developing Gestational Diabetes Mellitus The third trimester of pregnancy is associated with metabolic stress, resulting in insulin resistance in maternal muscles that lead to the development of Gestational Diabetes Mellitus. In non-pregnant women, glycemic control improves by exercise as a result of increased Glucose transporter type 4-GLUT 4 levels [GLUT4 is the insulin-regulated glucose transporter found primarily in adipose tissues and striated muscle (skeletal and cardiac].

Physical activity has an impact on oxidative stress and endothelial function, so the decrease in fat mass and increase in muscle mass improves the glycemic profile and helps in Gestational Diabetes Mellitus prevention Physical activity was assessed through self-report in questionnaires and hence considered as a limitation in this meta-analysis. The study design has no influence on the relationship between exercise and Gestational Diabetes Mellitus risk The limited number of the published studies rendered the assessment of heterogeneity in the pooled Odds Ratio [ORs] more difficult. It is not known whether starting physical activity in early pregnancy in previously sedentary women can result in Gestational Diabetes Mellitus prevention or not. (50)

In a population-based cohort study, obese women who lost around 10 pounds or less between their pregnancies tend to get low risk of developing Gestational Diabetes Mellitus compared with those who lost <10 pounds (the relative risk 0.63; 95% CI 0.38-1.02, adjusted for age and weight gain during pregnancy intervals).(32). Another study comparing the occurrence of Gestational Diabetes Mellitus among 346 patients who delivered before bariatric surgery with the incidence in 354 women that delivered post-surgery, the incidence of Gestational Diabetes Mellitus was less in the surgical group (8 vs. 27%, Odds Ratio 0.23, 95% CI 0.15-0.36). (33)
In non-pregnant women, regular moderate exercise has been found to reduce the risk of Type 2 Diabetes Mellitus compared with women of sedentary lifestyle In 2011, meta-analysis involving seven pre-pregnancy and five early pregnancy observational studies (34),revealed that women with the highest number of units of pre-pregnancy physical activity had prone to half the risk of developing Gestational Diabetes Mellitus compared to those with the lowest number of units (Odds Ratio 0.45, 95% CI 0.28- 0.75); units of physical activity describes frequency in number of hours per week, and the level of exertion or intensity. Physical activity in early pregnancy was reported to be protective (Odds Ratio 0.76, 95% CI 0.70-0.83). A 2014 meta-analysis of 6 Randomized Controlled Trials including 1089 women concluded that starting an exercise program during pregnancy did not significantly reduce the risk of Gestational Diabetes Mellitus in comparison with routine care (Relative Risk [RR] 0.91, 95% CI 0.57-1.44).(35Several studies have examined the role of diet in the prevention of Gestational Diabetes Mellitus, namely low intake of red and processed meat, saturated fat, sugar-sweetened soda, and refined grains, but this remains unproven. Healthy diet enhances weight loss, which is proven to prevent Gestational Diabetes Mellitus. (36) Leonie K.et al has revealed the possibility of an individual's physical activity program aids in the prevention of Gestational Diabetes Mellitus in overweight pregnant subjects. Women at their 12 weeks' gestation were considered and had followed them throughout the pregnancy till they delivered and collected data at 12, 20, 28 and 36 weeks of gestation.

The exercise group had been offered physical activity program, aiming at expending energy with a goal of 900 kcal per week, whereas the usual care group received ordinary obstetric care. Fasting blood sugar and fasting insulin were assessed at every visit, and the element of insulin resistance was assessed by using the 'Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Oral glucose tolerance test at 2-hour using 75-g was done at baseline at 28 weeks gestation. 50 overweight women were studied, 25 women as intervention group and another 25 were assigned as controls. The eligibility of those who were recruited was around 12%. All attended the obstetric unit at the Royal Brisbane and Women's Hospital. Arrangement was made for the intervention group to visit the maternity care unit around 6 times during the study, other means like email and direct phone contacts were also used. Physical activity timing and types differed greatly with more efforts being exerted by the exercise arm, namely at weeks 28 and 36

gestation. Around 16 patients out of the total of 22 women, representing 73% of the cases exceeded the goal of > 900 kcal per week at 28 weeks in comparison with only 8 women out of 19 in the control arm, representing 42%, p value was 0.047. 'Homeostasis Model Assessment of Insulin Resistance [HOMA-IR] was similar in both arms.

Fasting Plasma Glucose was found to be lower at 28 weeks' gestation, as well as fasting insulin level at 36 weeks' gestation in the intervention group in comparison to the routine activity arm. Feedback obtained from both the groups revealed that almost all pregnant ladies in the exercise group gave positive feedback, but reported difficulty in coping with exercise due to the burden of pregnancy symptoms, child care, and work obligations. Regular physical exercise in non-pregnant women improves glucose homeostasis and insulin sensitivity, due to increased responsiveness of muscle uptake to insulin in relation to increased GLUT-4 expression. Insulin resistance in pregnancy occurs at the skeletal muscle level, the physiological and molecular mechanisms seen during exercise explain the benefits in non-pregnant women, and in pregnant women. Physical activity-based interventions may affect glucose and insulin metabolism without influencing gestational weight gain, supporting the independent effect of physical activity on glucose and insulin through its direct effect on skeletal muscle cell adaptations. In order to obtain successful prevention related to exercise, pregnant women should follow a regular exercise program at least three times per week of moderate intensity for 30 minutes or more.

Dietary advice is aiming at preventing maternal hyperglycemia, attenuating the IR of the pregnancy in order to prevent the occurrence of Gestational Diabetes Mellitus. The dietary recommendations favor a low glycemic index diet, which has been shown to be very beneficial in diabetic patients. The dietary advice started usually in the first 90 days of pregnancy, comprising 30% fat and 55% carbohydrates as total caloric intake during pregnancy. Women with the low GI diet were at lower risk for having large-for-gestational-age infants, babies born to mothers on the low GI diet were less heavy and with lower ponderal indexes than those born to mothers on high GI diet. The effect of the low GI diet on Gestational Diabetes Mellitus prevention was evidenced by the lower maternal Fasting Plasma Glucose. The authors suggested more studies with larger population size and another maternal outcome than Fasting Plasma Glucose to reveal additional evidence for a decreased incidence of Gestational Diabetes Mellitus. These studies revealed that at week 20, the exercise group were accomplishing enough physical activity and women in the physical activity group were evidently have more chances to perform physical activity greater than 900 kcal per week compared to women in the control group. Women in the intervention group achieved lower Fasting Plasma Glucose at 28 week and fasting insulin at 36 weeks, compared with the control group, and there was no difference in Homeostasis Model Assessment of Insulin Resistance [HOMA-IR] between the two groups. Exercise as the only physical activity during pregnancy might not influence insulin resistance, combination of exercise and dietary intervention constitutes an important measure in improving insulin resistance and thereby preventing Gestational Diabetes Mellitus (40) Hence, exercise has a major role in preventing both Gestational Diabetes Mellitus and type 2 diabetes mellitus. There is now convincing evidence that the impact of a diabetic intrauterine environment continues into postnatal life.

Babies of mothers with Gestational Diabetes Mellitus are more likely to be overweight or obese in childhood and may develop type 1 or 2 diabetes mellitus in the future. It is very clear that

regular exercise helps in reducing the future risk of obesity in the offspring of Gestation Diabetes Mellitus in women by optimizing the fetal growth and hence reducing the future risk of diabetes mellitus among them, as experts predict that around 70% of women may be classified as overweight or obese by the end of the next decade. (54)
Glazer et al have had conducted a population-based cohort study, they concluded that obese women who lost at least 10 pounds (4.5 kgs) between pregnancies had a lower risk of gestational diabetes mellitus compared to those who lost less than10 pounds.(relative risk 0.63; 95% ci 0.38-1.02, adjusted for age and weight gain during each pregnancy). Burke et al performed a study enrolling 346 women who delivered before bariatric surgery and 354 women who delivered after bariatric surgery, comparing the incidence of gestational diabetes mellitus among the two groups. They concluded that the incidence of gestational diabetes mellitus was lower after surgery (8 versus 27%, or0.23, 95% ci 0.15-0.36).bariatric surgery was found to be an important contributory factor in inducing hormonal changes that may lower the risk of gestational diabetes mellitus independent of weight loss. In 2011, a meta-analysis including 7 pre pregnancy and 5 early pregnancy clinical trials was performed (35). Women with the highest number of units of pre pregnancy physical activity by self-report had approximately one half the risk for getting gestational diabetes mellitus compared to the women with the lowest number of units (or 0.45, 95%ci 0.28-0.75); physical activity was expressed as hours / week.

Exercise in early pregnancy was found preventive against the development of gestational diabetes mellitus (odds ratio 0.76, 95% ci 0.70-0.83). In 2014, meta-analysis of 6 randomized trials involving 1089 women concluded that starting exercise during pregnancy did not significantly reduce the risk for gestational diabetes mellitus compared with routine care. (rr 0.91, 95% ci 0.57-1.44).the explanation of that was in 702 women the exercise started late in pregnancy (18 to 22 weeks of gestation), which may have justified the lack of beneficial effect. (36) Leonie et al conducted a pilot randomized controlled study with an objective of examining the possibility of preventing gestational diabetes mellitus in obese pregnant women through an individualized exercise program. Recruitment of obese subjects started at weeks12 gestation and follow-up continued throughout pregnancy, data collected at 12, 20, 28, and 36 weeks' gestation. The intervention group received an individualized exercise program with an energy expenditure (EE) goal of 900kcal/ week, the control received routine care. The primary outcome was described as weekly metabolic equivalent hours and kilocalories/ week.

Assessment was performed using the pregnancy physical activity questionnaire (PPAQ).The diagnosis of gestational diabetes mellitus was established by using the Australian Diabetes In Pregnancy Society Criteria. Recruitment lasted for 7 months where 50 overweight subjects were allocated as intervention group and control, their baseline characteristics were similar. The intensity and duration of exercise differed significantly between individuals, being more intense in the intervention arm at 28 and 36 weeks of gestation. It was concluded that a combination of exercise and dietary intervention resulted in a positive effect on IR and ultimately prevented the incidence of gestational diabetes mellitus, evidenced by improvement in fasting plasma glucose and fasting insulin levels. The authors suggested some barriers to physical activity during pregnancy including pregnancy symptoms, busy home affairs (children care), and work commitments. All women in the intervention group have had a positive feedback, especially for receiving proper nutritional support and advice, as well as extra care throughout pregnancy. (40)

Emilio g et al reviewed the potential strategies for gestational diabetes mellitus prevention and found that regular exercise results in improvement in glucose homeostasis and insulin sensitivity, by increasing the response of muscle uptake to insulin through enhancing GLUT-4 expression. Lifestyle interventions including physical activity and dietary measures are of paramount importance in preventing gestational diabetes mellitus.

Deirdre k et al conducted a meta-analysis aiming at systematically reviewing and presenting concrete evidence regarding the relationship between exercise and the prevention of gestational diabetes mellitus. They reviewed 442 citations. The total number of studies was 8, including both prepregnancy and early pregnancy, represented a total of 34,929 patients. These included five prospective cohort studies, two retrospective case- control studies, and two cross-sectional surveys. 7 clinical trials showed the relationship between starting exercise prior to pregnancy and the risk of gestational diabetes mellitus. A meta-analysis reported a 55% reduction in gestational diabetes mellitus risk in women performing high intensity exercise compared to those performing low intensity types. (or 0.45, 95% ci 0.28-0.75, p=0.002). Five studies indicated the link between prepregnancy exercise and the risk of developing gestational diabetes mellitus. A 24% lower risk of gestational diabetes mellitus found in the highest activity group compared with the lowest activity group (or 0.76, 95% ci 0.70- 0.83, p<0.0001). The association between walking and gestational diabetes mellitus risk was assessed in three studies. Subjects performing prolonged brisk exercise (>2 miles/day and for more than 30 minutes/day) had less risk of gestational diabetes mellitus compared with those performing slow and short walking. Two studies reported an inverse relationship between the incidence of gestational diabetes mellitus and the highest class of climbing stairs (>10 flights/day) compared to women who did not climb stairs. Four studies reported an inverse relationship between high intensity exercise compared with low intensity type in the period prior to pregnancy (or 0.47, 95%ci 0.19- 0.75). Oken et al showed a higher risk of gestational diabetes mellitus in the sedentary group both prior to pregnancy and during the first trimester of pregnancy (or 1.4, 95%ci 0.7-3.0) and early pregnancy (or1.4, 95%ci 0.8-2.6). (50)

In 2013, Barakat et al performed a randomized controlled trial on 510 pregnant women, 255 were randomized to aerobic, strength and flexibility exercise started at 10-12 weeks (3x50-55 min/week at<70% hr max, adherence:>95%),another 255 women were controls. They reported a reduced 2-h blood glucose (116.8 vs. 123.9 mg/dl; p=0.012). Ong et al (2009) conducted an randomized controlled trials on 6 exercise group (started at week 18 gestational age as home-based stationary cycling, 3x35-50 min/week at 55-65% hr max with adherence:94%, 6 pregnant women were control. They reported increased 1-and2-h blood glucose in control group only (p=0.072).

Retnakaran et al studied glucose tolerance, insulin sensitivity and beta-cell function in 851 pregnant women who underwent a glucose challenge test and 3-h OGTT in late pregnancy. They concluded that glucose tolerance status improved across increasing quartiles of self-reported physical activity in the 12 months before pregnancy (p=0.02). (54) Moderate-intensity exercise was reported to reduce the co- morbidities of gestational diabetes mellitus, as it reduced by one-third the risk of undergoing acute or elective cesarean delivery in women with gestational diabetes mellitus(exercise or:1.30;95% ci:0.44-3.84 vs. Control or:0.98-4.06). Diet: High-fiber diets and low-GI diets have been shown to improve insulin sensitivity and glucose tolerance. The

combination of both was found to reduce the risk of gestational diabetes mellitus by 50%. Chen et al had the hypothesis that increasing consumption of sugar-sweetened beverages was associated with increased risk of developing gestational diabetes mellitus in the Nurses Health Study II. When cola beverages were omitted from some types of sugar-sweetened beverages, no increased risk of gestational diabetes mellitus was observed.

The authors suggested that the caramel colors and flavours in cola drinks might translate to higher intake of advanced glycated end products (AGEs) which have potential adverse effects on beta-cell function. Women drinking non-caloric cola drinks did not have a higher risk. It has been suggested that that the increased glucose portion in the high glycemic index diet and sugar-sweetened beverages was the culprit for the increased incidence of weight gain, diabetes, and Gestational Diabetes Mellitus. High intake of sugar-sweetened beverages is often linked to high consumption of canned meats, refined grains, and less consumption of vegetables, leading to oxidative stress and high risk of both Gestational Diabetes Mellitus and type2 diabetes mellitus. A study involving 1,733 A American subjects showed no association between diet and the risk of developing Gestational Diabetes Mellitus. (56)
Based on the above data, maintenance of exercise in pre-pregnancy and in the first trimester has a positive impact in preventing the risk of Gestational Diabetes Mellitus. In the gulf region, until recently the out-door exercise was not culturally acceptable; therefore the majority of women in the past were reluctant to exercise. This is identified as a major contributory factor in the high prevalence of Gestational Diabetes Mellitus. Recently, and with the increasing diabetes prevention awareness campaigns supported significantly by the government, there is a general trend towards exercise. This trend showed a positive impact on the prevention of Gestational Diabetes Mellitus as evidenced by the above mentioned clinical trials. There is a current trend and fashion among many young obese citizens in the gulf region for bariatric surgery more than that of physical activity. The majority of these people do not have chronic medical problems but they have a strong family history of diabetes, due to high rate of inter-marriage between family members. Such high rate of bariatric surgery among the citizens may contribute significantly in the prevention of Gestational Diabetes Mellitus, as evidenced by clinical trials. (34) As regular prenatal exercise confers protection against the development of Gestational Diabetes Mellitus, it helps to prevent the future development of diabetes mellitus, especially if women continue exercise postpartum and remain active. The Diabetes Prevention Program showed that intensive lifestyle intervention, including weight loss and regular exercise in women with previous Gestational Diabetes Mellitus, achieved a 53% reduction in the development of type 2 diabetes mellitus.

2.5.2. Medications:

Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance with onset or first recognition during pregnancy. When medical nutrition therapy is not successful in maintaining target glucose values during pregnancy complicated by gestational diabetes mellitus, medication is required. Insulin has been the traditional treatment under such circumstances. The use of oral antidiabetic medications in the management of gestational diabetes has increased over the past several years. Recent studies have shown the equivalence to insulin of both glyburide and metformin in terms of pregnancy outcomes in gestational diabetes

mellitus.[http://www.ncbi.nlm.nih.gov/pubmed/19640341] Commonly prescribed medications include Metformin and Inositol.

Metformin:

In a study with 98 patients diagnosed as polycystic ovary syndrome were administered Metformin dose between 1700 to 3000 mg per day was given before pregnancy and continued up till 37 weeks gestation, another 110 normal were given the same (control group). The results revealed a tremendous decrease in the prevalence of Gestational Diabetes Mellitus among the intervention group.(37)Metformin is linked to many metabolic elements of Poly Cystic Ovarian Syndrome, including the improvement in the sensitivity of insulin, blood glucose levels, and lipid levels. Patients with polycystic ovary syndrome were found to be at high risk for the development of Gestational Diabetes Mellitus, so the use of metformin in these patients throughout pregnancy has beneficial effects on the development of Gestational Diabetes Mellitus. In a study, performed on 137 women with polycystic ovary syndrome, the use of metformin throughout pregnancy has resulted in the reduction of the incidence of Gestational Diabetes Mellitus, fetal growth restriction and preterm labor. The metformin group did not show fetal malformations, intrauterine fetal loss or abortion. (38) Diabetes Prevention Program Outcome Study demonstrated the importance of metformin use in patients with Gestational Diabetes Mellitus in preventing the progression to overt diabetes. Several authors reported the protective role of metformin on pancreatic beta cell's reserve reducing the secretory demands triggered by chronic insulin resistance and this can slow or cease the progression to type 2 diabetes.

It has been suggested that the same mechanism explains the decrease in Gestational Diabetes Mellitus and the good glycemic control throughout pregnancy by the pre-conception metformin intake in patients with Poly Cystic Ovarian Syndrome. Metformin crosses the placenta exposing the fetus to concentrations similar to that of the mother, but many recent studies verified the safety of metformin during pregnancy. Kumar P et al reported that there was an important association between history of recurrent abortions and abnormal Glucose Tolerance Tests in Poly Cystic Ovarian Syndrome patients. A Randomized Controlled Trial was performed prospectively assessing the use of metformin therapy in women with impaired glucose tolerance test and previous recent history of fetal loss. The study reported the beneficial effect of metformin in reducing the incidence of miscarriage during early pregnancy and improving pregnancy outcomes significantly. High circulating levels of androgens and LH were found to be highly associated with polycystic ovary syndrome. Using metformin therapy throughout pregnancy revealed positive impact on the levels of androgen and Luteinizing Hormone there by leading to successful pregnancy outcomes, especially when used before conception.

The above mentioned positive impact on Luteinizing Hormone levels was supported by a randomized controlled clinical trial conducted on 32 patients with polycystic ovary syndrome and a similar number of normal women. Both groups were administered metformin in a dose of 850 mg bid. The study revealed a significant decrease in the levels of Luteinizing Hormone was reported in Poly Cystic Ovarian Syndrome patients but no changes were observed in the levels of follicular stimulating hormone and thyroid stimulating hormone. As well, there was a significant decrease observed in the levels of prolactin in comparison to the higher levels prior to treatment

with metformin. These findings highlighted and signified the positive impact of metformin therapy on the pituitary hormones. Women with Poly Cystic Ovarian Syndrome are known to have insulin resistance compared to those with healthy ovaries.10 to 15% of the less obese and thin built cases tend to have an element of insulin resistance compared to 20 to 40% of fat subjects with polycystic ovary syndrome, as well they were more prone to develop frank diabetes mellitus in the future.

Obesity is linked to diverse grave outcomes and negative impact on conception and response to fertility. Weight loss of about 5-10% before pregnancy with or without metformin has improved the defective metabolic markers. Metformin use throughout pregnancy in patients with polycystic ovarian syndrome has been proven to reduce the risk of Gestational Diabetes Mellitus by about 9 – folds. Its use during pregnancy helps in primary and secondary prevention of Gestational Diabetes Mellitus; this was attributed to variety of effects including the metabolic derangement, vascular disorders, and inflammatory processes. Another study on 360 patients with polycystic ovary syndrome without history of diabetes mellitus who got pregnant on metformin therapy and had been followed prospectively, randomized to metformin or placebo. The results were favoring metformin use in reducing or preventing the incidence of Gestational Diabetes Mellitus. A study enrolled 200 patients with Gestational Diabetes Mellitus, randomized to 100 patients on metformin alone and the other 100 patients on insulin. The two groups were matched for age group, body weight, and ethnic background, demonstrated similarity in the risk for Gestational Diabetes Mellitus in both groups, in the prevalence of pregnancy-induced hypertension with its complications, frequency of assisted deliveries, and number of cesarean deliveries. The only difference was the high incidence of increased body weight among the insulin treated arm.

Regarding the metformin group, the results showed significant reduction in the development of preterm deliveries, rate of neonatal hyper-bilirubinemia and the number of neonatal admission to neonatal intensive units. A significant positive impact on neonatal hospital course and outcome was seen in the metformin group over the insulin group. A recent randomized controlled trial, done on 100 patients with Gestational Diabetes Mellitus, were randomized to metformin and insulin, the results showed the superiority of metformin when compared to insulin in preventing large-for-gestational-age , particularly in slim or mildly overweight patients who developed Gestational Diabetes Mellitus in the last trimester of pregnancy.

Obese women with high fasting plasma glucose and who required early therapy were found to have more benefit on insulin compared to metformin. The positive impact of metformin therapy in patients with polycystic ovary syndrome is on the significant reduction of weight. The authors concluded that metformin use during pregnancy improved several metabolic profiles of Poly Cystic Ovary Syndrome, like insulin sensitivity, plasma glucose and lipid profile, reduces pregnancy-related complications, namely Gestational Diabetes Mellitus and gestational hypertension, and reduces first trimestric abortions, premature delivery, and prevents or reduces intrauterine fetal growth retardation. (43)

Inositol:

Giugliano et al performed a review aiming at discussing options to prevent Gestational Diabetes Mellitus especially the role of the dietary inositol supplement. Inositol is a cyclitol found naturally in animal and plant cells, exists in 9 stereo isomeric forms, Myo-inositol (MI) is the predominant isomer and related to vitamin B. Abnormalities in Myo- Inositol [MI] metabolism have been linked to Insulin Resistance and increased Gestational Diabetes Mellitus adverse outcomes, the deficiency of intracellular Myo Inositol is seen in primary sites of diabetic complications. Myo Inositol deficiency leads to decreased synthesis of phosphatidylinositol (PI) and altered its metabolism, which in turn results in affection of the nerve tissue of diabetic experimental animals. The rate of inositol excretion increases remarkably as diabetes progresses, the urinary excretion of inositol was found to be directly related to the underlying Insulin Resistance.

High rate of Myo Inositol lost in the urine reduces its blood values, which reduces the intracellular d-chiro-inositol (DCI) in insulin receptors of different organs. Thus, the insulin signal transduction decreases and this results in Insulin Resistance. It appears possible that Myo Inositol or d-chiro-inositol [DCI] supplementation in insulin-resistant patients may help in preventing Gestational Diabetes Mellitus. The impact of inositol administration on the Insulin Resistance has been proven in vivo in restoring spontaneous ovarian function in patients with Poly cystic ovarian syndrome. Myo Inositol therapy has corrected all the abnormal hormonal parameters: decreased Luteinizing Hormone, Follicle Stimulating Hormone, testosterone levels, and increased sex hormone binding globulin [SHBG], estrogens and progesterone levels. Insulin peripheral sensitivity had improved as reflected by reduced Homeostasis Model Assessment of Insulin Resistance [HOMA-IR] index, decreased blood pressure BP, reduced triglycerides, increased High Density Lipids and decrease in total cholesterol and Low Density Lipids.

Recently, some authors studied the effect of pre-conceptional inositol supplementation on the Gestational Diabetes Mellitus onset. Corrado et al proved the decrease in Fasting Plasma Glucose and insulin in Gestational Diabetes Mellitus patients treated by 4 g Myo-inositol daily, following that D'Anna et al published the first report about the impact of Myo-Inositol on Gestational Diabetes Mellitus incidence in Poly Cystic Ovarian Syndrome infertile women. The authors have shown that 98 patients with anovulatory and hyperinsulinemic Polycystic ovarian syndrome became pregnant after MI therapy plus folic acid, or metformin. The incidence of Gestational Diabetes Mellitus was 17% vs. 54%; $P<0.001$, showing a double risk of gestational diabetes mellitus In the control group compared to the MI group. The same authors enrolled 220 pregnant in a prospective, randomized, placebo-controlled study, 110 patients treated with 2 g Myo Inositol plus 0.2 mg folic acid twice daily (treated group) and 110 patients treated from the end of the first trimester with0.2mg folic acid twice daily only (control group) through the whole pregnancy.

The prevalence of Gestational Diabetes Mellitus was significantly reduced in the treated group (6 vs. 15%) and a reduction of 65% in the risk for Gestational Diabetes Mellitus (Odds Ratio0.35; CI 95%0, 13-0, 96) was reported, fetal macrosomia was significantly reduced ($P<0.007$), reduced glycaemia at basal ($P<0.001$) and in the first hour ($P<0.02$), reduced fetal weight at delivery ($P<0.01$) in the treated group. Matarelli et al performed a prospective, randomized, double-

blinded, placebo-enrolled 84 non-obese singleton pregnant women with a high Fasting Plasma Glucose in the first or early second trimester, randomized to receive either MI or placebo, the treated group had a significantly lower incidence of abnormal Oral Glucose Tolerance Test [OGTT] (71 vs. 6%; OR 0.12, CI 95% 0.03-0.5).Basal,1 and 2 hour glycemic control were significantly lower in the Myo Inositol group (P<0.001, <0.04, 0.06, respectively).Also, postnatal hypoglycemia was significantly lower in MI group (0 vs 26%, Odds Ratio:0.05, CI 95% 0.003-0.849). The above three studies verified the effect of MI in reducing the incidence of Gestational Diabetes Mellitus. (41)

2.5.3. Counseling:

Lifestyle counseling in pregnant women at high risk of gestational diabetes mellitus was introduced by Ritta and colleagues as a new preventive intervention for both gestational diabetes mellitus and large-for-gestational-age newborns. They performed an Randomized Controlled Trials in Finland, distributed among 14 regions. 2,271 patients were recruited and screened with OGTT at week's 8 to 12 gestation with one or more risk factors for Gestational Diabetes Mellitus. The intervention was basically an individualized intensified counseling on physical activity, diet, and weight gain at five antenatal visits. The primary outcome was incidence of gestational diabetes mellitus and newborns' birth weight adjusted for gestational age. Other outcomes included increased weight in mothers and the need for insulin therapy during gestation. The authors concluded that lifestyle counseling was very effective in reducing the newborns' birth weight while less beneficial in the prevention of gestational diabetes mellitus.
The authors had chosen the cluster randomization in order to remove any possibility of contamination between the study groups, which might arise if the randomization was involving the participants or medical facilities alone. The inclusion criteria are If the pregnant women presented with any of these risk factors, Body mass index >25kg/m2, history of Gestational Diabetes Mellitus or impaired glucose tolerance test or neonatal macrosomia occurring in previous pregnancies, presence of diabetes mellitus type1 or 2 in any family member, maternal age more than 40 years, the exclusion criteria are abnormal Glucose Tolerance test at 8-12 weeks gestation, pre-pregnant type1 or 2 diabetes mellitus, inability to speak Finnish.

Patients with age group less than18 years, multiple pregnancies, physical restriction preventing activity, substance abuse, treatment or clinical history of for psychiatric illness. Recruitment of patients started between weeks 8 and 12 of pregnancy, from 1 October and December 31, 2008. The trial was finalized at the end of the year 2009, when all participants had delivered. The intervention started at weeks 8 to 12 gestation and continued till week 37.They initiated the intervention from the first clinic visit to gynaecology unit. Gestational weight gain recommendations were addressed thoroughly and graphs concerning the ideal weight values were obtained when reviewing the patient's chart at the out-patient clinic visit, the initial exercise counseling was carried out at weeks 8 to 12 gestation, while the counseling regarding dietary advice was initiated at weeks 16 to 18 gestation period.

Exercise counseling was at 4 visits and dietary counseling at 3 consequent out-patient visits. When oral glucose tolerance test was significantly impaired at weeks 26 to 28 gestation, patients were advised to visit diabetes specialists in other specialized health facilities. The aim of physical activity counseling was to increase leisure time physical activity to a minimum of 800

Metabolic Equivalent of Task (MET) MET minutes/week of moderate-intensity exercise. The aim of dietary intervention was to allow the patients to achieve a balanced diet such as less than 10% saturated fat, polyunsaturated fat of about 5 to10%, total fat around 25-30%, less than 10% of the total energy intake should be saccharose of total energy intake, and 25-35g/day fiber. Women were advised and encouraged to increase the dietary intake berries, fruits, and several vegetable to reach a minimum of 5 portions(400g)/day, high fibre bread (>6g fibre /100g), fat-free or low-fat milk and milk products and of meat and meat products, to eat fish at least twice/week, to use moderate amounts of soft table spreads on bread, oil-based salad dressing in salad, and oil in cooking and baking, to encourage the consumption of seldom little amounts of foods rich in fat or high carbohydrates containing portions. Women in the control arm received usual care.

The 2 important outcomes of the study were the number of patients with Gestational Diabetes Mellitus diagnosed on the basis of oral glucose tolerance test at 26-28 weeks gestation, called maternal outcome. The neonatal birth-weight had been adjusted to match the age of gestation; this was described as neonatal outcome. Utilizing the homeostasis model assessment insulin resistance (HOMA-IR), the levels of blood glucose were obtained and the degree of insulin resistance was calculated as fasting insulin level x fasting plasma glucose level /22.5. Blood samples were collected at 8 to 12 weeks gestation and 26-28 weeks gestation. Newborns' outcomes recorded include sex of the newborn, macrosomia, large and small-for-gestational-age infants, the exact age of gestation at the time of labour, newborns' weight standard deviation scoring system, crown-heel length score, ponderal index and the measurements of the newborn's head circumference. Secondary outcomes obtained are gestational weight gain, the necessity for using oral hypoglycemic medications or insulin therapy started from weeks 26 to 28 gestation, post-partum growth and development of the newborn's weight, Data collection regarding exercise and dietary intervention were performed through validated questionnaires set at 8 to 12, 26-28, and 36-37 weeks gestation.

Assessment of free-time exercise was achieved through a reliable and valid report written by the patient at start, 26 to 28 weeks gestation, and 36 to 37 weeks gestation. Pre-pregnancy exercise was assessed at baseline and throughout clinic visits. Dietary assessment was performed by utilizing questionnaires, containing 181 food related items, started at baseline, between weeks 26 to 28 weeks gestation, and ending at 36 to 37 weeks gestation. At first, patients were questioned about the dietary habits in one month before pregnancy. Adherence to the recommendations required that women participants should achieve the target of more than 800 Metabolic Equivalent of Task MET minutes /week at weeks 36 to 37 gestation and the body mass index must be in the acceptable range. Adverse effects were reported at specific interviews within 4 visits to the medical facility and include; headache, severe contractions, blood loss, nausea, vertigo, lassitude or fatigue, aches and pain, chest discomfort, and calf muscle cramps and pain. Statistically, the intention to treat approach was used. 95% CI for RR, numerical values and percentages were recorded for the different variables, standard deviation, together with the means. The establishment of the incidence of gestational diabetes mellitus and neonatal macrosomia necessitated involving only women who showed high degree of adherence to the intervention. The total number of women who were screened was 2,271, out of these, 520 were randomized to the intervention arm and representing 22.9% of cases. On the other hand, 496 women were randomized to the placebo arm. 23.6% of the participants in the intervention group and 31.3% of the participants in the usual care group had an abnormal Oral Glucose Tolerance Test result at

baseline and were excluded. The final number of participants in the analyses was 219 (89% of participants receiving allocated intervention) and were regarded as the intervention arm of the study. The number of women who received allocated intervention in the routine care arm was 180, representing 91.8% of cases.

The proportion of women fulfilling the inclusion criteria was comparable in the two groups.
The age of 30 years was found to be the average age for most of the participants. The percentage of the primi-gravidae in the intervention group was 47% and around 41% in the routine care group. Average Body Mass Index prior to conception was estimated to be 26 kg/m2 in the intervention and e to achieve 4 out of 5 goals set by the authors regarding dietary intervention. The rate of high education was seen more in the intervention arm (26.8%), compared to 20.6% in the routine care group. The two most prevalent risk factors were overweight and family history of diabetes. The authors reported similar rates of impaired glucose tolerance in the intervention as well as the routine care arms, mainly at baseline and at 26 to 28 weeks gestation.

No differences were reported between the two groups regarding the rate of Gestational Diabetes Mellitus, total increase in weight, incidence of pre-eclampsia, and the utilization of diabetes medications. Regarding the infants, 54% of boys in the intervention arm while 43% in the routine care arm. In both groups, the proportion of gestational age was about the same. The mean birth weight of babies was found less in the intervention arm, compared to the routine care arm (3,532 g vs. 659 g, p was 0.035).The proportion of large-for-gestational-age infants was lower in the intervention group (12.1%) than in the usual care group (19.7%, p=0.042), the results persisted the same after adjusting for individualized-level covariates (p=0.043).The proportion of macrosomia, crown-heel length, crown-heel length SD score, small-for-gestational-age, ponderal index, or head circumference were similar in the two groups. Women in the intervention group had a minimal decrease in the moderate activity Metabolic Equivalent of Task (MET) minutes, compared to patients in the routine care group at baseline until weeks 26 to 28 gestation (95% CI-37 to 219, p=0.17). The intervention group showed a reduction in the intake of saturated fatty acids starting from baseline till 26 to 28 weeks gestation compared to the routine care group. The intervention group decreased the consumption of saccharose (95% CI-1.16 to -0. 03, p=0.04) compared to usual care group at 26-28 weeks gestation.

The intervention arm decreased the consumption of saturated fatty acids, beginning from baseline to weeks 36 to 37 gestation, in comparison with the routine care group (95% CI-1.12 to -0.15, p=0.01) and showed an increase in the consumption of dietary fibers (95%CI 0.30-3.35, P=0.019) and polyunsaturated fatty acids (95%CI0.16-0.57, P<0.001). The incidence of Gestational Diabetes Mellitus was lower in those women who showed good adherence in the in the intervention group compared to routine care group (27.3% vs 33%). The rate of large-for-gestational-age infants was lower in the intervention group compared to the routine care arm (7.3% vs. 19.5%). At weeks 32 to 34 gestation, headache was found in 41.5% in the intervention arm compared to 56.5% in the routine care arm, p= 0019, but otherwise all the adverse effects were similar in both groups. The study examined the impact of lifestyle counseling in the primary prevention of Gestational Diabetes Mellitus among women with at least one risk factor of Gestational Diabetes Mellitus. Utilizing a cluster-randomized controlled design, lifestyle counseling was beneficial in controlling the proportion of large-for-gestational-age newborns, though the result for Gestational Diabetes Mellitus was inconclusive.

The intervention group had achieved 4 goals out of the 5 diet- related goals, including consumption of high fibers, saturated and polyunsaturated fatty acids, and saccharose. A minimally decreased physical exercise Metabolic Equivalent of Task (MET) minutes at weeks 26 to 28 gestation was more pronounced in the exercise arm versus the routine care arm. Adherence to lifestyle recommendations by pregnant women had resulted in lower incidence of Gestational Diabetes Mellitus and large-for gestational age. Previous studies had looked into Gestational Diabetes Mellitus with regards to cut-off values for initiating treatment or setting measures to prevent weight gain during Gestational Diabetes Mellitus.

The number of patients already excluded from the study in view of impaired oral glucose tolerance test at weeks 8 to 12 gestation was extremely high, amounted to 23.6% in the intervention arm versus 31.3% in the routine care arm. This can explain the huge drop in the expected study population. The proposed recruitment time was delayed by 6 months, due to some personal issues involving the participants. Lifestyle counseling including dietary measures, exercise, and issues related to weight gain during pregnancy was shown to affect the blood glucose and insulin sensitivity positively and hence may influence the newborns' birth weight favorably. Three small clinical trials demonstrated the reduction in additional gain in weight, Gestational Diabetes Mellitus and large-for-gestational-age when utilizing supervised physical activity training and diet- related intervention. In those studies, low Glycemic Index provided meals were found to reduce the newborn birth-weight by 446 g.

According to the authors, the observed changes regarding diet- related problems at weeks 36 to 37 gestation could provide the explanation of the differences between these groups in the birth-weight of the newborns. The explanation of the inconclusive results regarding the prevention of gestational diabetes mellitus in this study was due to the relatively shorter period since the starting of the diet counseling sessions, which were initiated only at weeks 16 to 18 gestational weeks. The investigation of Gestational Diabetes Mellitus was performed between 26 to 28 gestation weeks. Thus, the time lapse was too short to influence a positive impact on pregnancy adverse effects. The adherence of women to the lifestyle goals is of paramount importance in achieving a positive impact on the primary outcomes.

The adherence was defined as the achievement of 4 out of 5 goals related to dietary recommendations, exercise-related goals, and weight gain intervention aims. The authors suggested that the achievement of all the aims of the three interventions was the key for lowering the risk of both large-for-gestational-age and Gestational Diabetes Mellitus. The risk group status of the women may explain the negative impact of the intervention on the prevention of Gestational Diabetes Mellitus, as women with at least one GDM risk factor were recruited and the majority had been reported to have low risk potential for having Gestational Diabetes Mellitus. The results of the study could have been quite different if high risk groups, such as obese women and those with past history of Gestational Diabetes Mellitus required insulin therapy were included. In the intervention arm, no complications or premature delivery were reported. The authors believed that the counseling procedure was practical and can be better applicable if carried out at the obstetric units other than been performed by the paramedics and nursing staff.
Limitations considered by the authors comprised the lack of last trimestric checking of maternal blood glucose levels; therefore the assessment of maternal endpoints just prior to delivery was

not performed. There was a significant correlation between the high rate of birth-weight and the chronic maternal hyperglycemia during the whole stages of pregnancy. So, the increase in birth weight was regarded as a predictor of high maternal blood glucose. The results revealed a positive impact of lifestyle counseling in minimizing the birth weight of the newborns in patients with high risk of developing Gestational Diabetes Mellitus. As well, they demonstrated clearly a positive behavioral change. There was no evidence in the prevention of Gestational Diabetes Mellitus in women to have diabetes at around 26 to 28 gestation weeks as it was explained earlier. The results of the study were very encouraging and signified the importance of counseling on exercise, dietary measures, and issues related to maternal weight gain in the obstetric facilities, particularly for patients considered at high risk of developing Gestational Diabetes Mellitus, and in preventing the incidence of large-for-gestational-age newborns and its consequences. (57)

2.6. Impact of treatment on gestational diabetes mellitus:

Treatment targets should be set in order to guarantee adequate control of gestational diabetes mellitus, similar to those used in patients with pre Gestational Diabetes Mellitus. Patients with Gestational Diabetes Mellitus need to be told about the importance of adequate control of the blood glucose in reducing large-for-gestational-age, birth trauma and its adverse effects to the mother and newborn, assisted labour or caesarean delivery, neonatal hypoglycemia, and perinatal mortality. These gestational diabetes mellitus patients should receive adequate knowledge regarding the positive impact of dietary measures, maintaining ideal weight, and physical activity on the prevention of gestational diabetes, the gestational diabetes mellitus high chances to have macrosomic baby, which may contribute to high incidence of birth trauma, assisted labour and caesarean delivery among women with this condition, gestational diabetes mellitus adequate control of maternal blood glucose during delivery and early introduction of feeding to the newborn soon after delivery, with the aim of minimizing the risk of hypoglycemia, the need for admission to neonatal intensive care unit in view of early neonatal complications, the high probability of the newborn developing diabetes mellitus and overweight in near future.

Patients with this condition gestational diabetes mellitus must be encouraged to select their carbohydrates from sources rich in low glycemic index, fish oil and plant protein. Balanced diet comprising monosaturated and polyunsaturated fat should be advised. In women with Body Mass Index higher than 27kg/m2 prior to pregnancy, an effort has to be exerted to decrease the caloric intake to 25kcal/kg or even lower. Patients should perform a 30 minutes moderate physical activity per day. In case of modification in the lifestyle, dietary measures, and physical activity did not meet the glycemic goal within the first two weeks, the patients should start anti-diabetic therapy immediately.-Patients with gestational diabetes mellitus in which the ultrasound shows large-for-gestational-age fetus, anti-diabetic should be initiated at the earliest possible. The treatment comprises human insulin, insulin rapid-acting analogues, insulin detemir, glibenclamide or metformin. (46). In 2008, an RCT was performed studying the relation between maternal glucose and fetal growth using metformin and glibenclamide. Treatment starting with oral therapy but often involving insulin as add on to maintain good glycaemic profile was found

equally effective as insulin therapy alone, but did not show superiority over insulin alone regarding acute outcomes of pregnancy.

The Hyperglycemia and Pregnancy Outcome study demonstrated the strong relation between maternal Fasting Plasma Glucose and Oral Glucose Tolerance Test with birth weight above the 90th percentile, infant adiposity conferred a strong linear relationship with maternal glucose. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) results did not show specific target that should be considered in the diagnosis of Gestational Diabetes Mellitus. Many previous studies have had shown the direct association between maternal hyperglycemia and intrauterine fetal growth. Two randomized controlled trials were conducted with a view to study the impact of screening methods, diagnostic tools, and the management of Gestational Diabetes Mellitus. The positive pregnancy outcome had been demonstrated by the Australian Carbohydrate Intolerance Study in pregnant women when using insulin therapy to treat the condition gestational diabetes mellitus, with significant reduction in the incidence of large-for-gestational-age, maternal weight in large proportion of participants.

Several studies demonstrated the need for insulin therapy in about one third of patients who were started on glibenclamide and metformin; those who needed supplementation of insulin were having high levels of Fasting Plasma Glucose. Pregnancy outcomes were found similar in the metformin group and in those who started insulin initially. This was reported by Rowan and colleagues, 46% of those on metformin needed insulin supplementation in order to meet targets. Women in the metformin group tend to show less weight gain in comparison with the insulin group. These studies reported very low rate of complications in those who reached levels lower than the intended therapeutic goals. The minimal risk of adverse effects was reported with Fasting Plasma Glucose below 4.9 mmol/l and when the 2-h post prandial glucose lies between 5.9 to 6.4 mmol/l.

The mentioned target levels correspond to the high incidence of maternal complications, especially LGA, high fetal c- peptide, high fetal fat above the 90th percentile. These parameters were observed to exceed those of the HAPO trial by more than 1.75 times. The rate of fetal macrosomia was 16.2% in HAPO population, while 22% in Australian Carbohydrate Intolerance Study In Pregnant Women (ACHOIS—NEJM , 1995), and 14.5% in the Maternal Fetal Medicine Units [MFMU] usual care groups. The beneficial effects derived from the MFMU, ACHOIS, and HAPO trials were very evident from the study of hyperglycemia in pregnant women who did not receive any treatment (HAPO). In MFMU trial, the study population used insulin in about 8% of these gestational diabetes mellitus patients, compared to 20% in ACHOIS trial. In all these trials the control group received treatment in view of high blood glucose, ethically no trial can be accepted if not diagnosing or treating the condition gestational diabetes mellitus in the control group except in women with the mildest levels of blood glucose levels.

Both National Institute for Health and Care Excellence [NICE] and Australian Carbohydrate Intolerance Study In Pregnant Women (ACHOIS) use the same diagnostic target at 2-hours (7.8 mmol/l), while Maternal Fetal Medicine Units [MFMU] trial used different diagnostic criteria. 93% of women in Australian Carbohydrate Intolerance Study In Pregnant Women trial screened with Oral Glucose Tolerance Test without considering the risk factors (unlike NICE). Despite the diagnosis of Gestational Diabetes Mellitus, 16% of the population represents high prevalence

rate, data has shown better outcomes with modest dietary and lifestyle modifications. Insulin was used in 8% of women in Maternal Fetal Medicine Units [MFMU] MFMU trial and in 20% of those with gestational diabetes mellitus in Australian Carbohydrate Intolerance Study In Pregnant Women ACHOIS study. So, it appears clearly that a large proportion of patients required only dietary, lifestyle modifications and blood glucose monitoring alone, with a positive impact on newborn weight and maternal weight gain.

Moderate evidence from 3 Randomized Controlled Trials demonstrated less pre-eclampsia with treatment. Two RCTs showed no difference, while two extensive randomized controlled trials reported little gain in weight in the treatment group. One such trial showed lower BMI with treatment at delivery but with insufficient evidence. No evidence was shown for long-term maternal outcomes (type 2 diabetes, obesity, and hypertension). No sufficient evidence for birth trauma due to low quality studies, 2 randomized controlled trials demonstrated similar incidence in birth trauma in the two groups. Only one study reported fewer incidences in the treatment group. Shoulder dystopia was seen less in the treatment group as had been verified by moderate evidence. Randomized controlled trials showed inconclusive results with regards to fracture of the clavicle and nerve injury. The incidence of birth weight >4 kg, exact birth weight, neonatal macrosomia were all studied, and the researchers were able to show less incidence of all these parameters in the treatment group. The grade of evidence for neonatal macrosomia was moderate. These trial studies showed no difference in Hyperbilirubinemia, but the cohort studies reported significant reduction in cases with treatment. Perinatal death showed no differences, though the incidence of pregnancy adverse outcomes was found significantly reduced accounting to less than 0.5%.

Apgar score showed differences at 1minute but not at 5 minutes in many studies. Infants had been followed for 7 to 11 years in a randomized controlled trial. The authors concluded that the incidence of type 2 diabetes mellitus or Insulin Glucose Tolerance was found similar in infants of mothers with Gestational Diabetes Mellitus and normal pregnant women. Maternal depression and anxiety were assessed by one randomized controlled study initially at around 6 weeks following enrollment, and another assessment was performed following 90 days post-delivery, no differences in anxiety among all groups were seen. Incidence of depression was found less in the in the intervention 90 days after labour. No difference was observed in 4 randomized controlled trials with regards to small-for-gestational -age neonates, neonatal hypo glycaemia, and no statistical heterogeneity. Two cohort studies reported inconsistent results, possibly due to lack of a universal definition of hypoglycemia and several studies used different screening protocols for hypo-glycaemia. There was no difference in the number of admissions to neonatal intensive care unit. One trial showed the highest trend for admission to NICU in the treatment arm compared to placebo.

Two randomized controlled trials reported high rate of prenatal visits among the intervention group. Results were inconclusive, as was shown by randomized controlled Trials regarding induction of labour, cesarean delivery, and unplanned cesarean delivery. There were major differences found in the rate of pre-eclampsia, macrosomia, and shoulder dystocia. The majority of these outcomes were detected in women without evidence of Gestational Diabetes Mellitus, so the weight of the pregnant women, as well as the gain in weight during pregnancy plays an important role in in the predisposition to these outcomes, especially in those with this condition.

It has been suggested that glycaemia confers a minimal risk for neonatal macrosomia, and this contribution was found to be around 1.7%. The pre-eclampsia events occur in 3 – 5% of pregnancies, the risk conferred by gestational diabetes mellitus probably small, the study showed treatment benefit. One study evaluated the incidence of anxiety state and maternal depressive illness through subgroup analysis of large randomized controlled trials. The conclusion was the incidence of anxiety at about 40 days following enrolment and at 90 days post-delivery was similar in both groups. The incidence of depression was found lower at 90 days post-delivery in those treated for Gestational Diabetes Mellitus.

A follow- up for 3 – 5 years post diagnosis of Gestational Diabetes Mellitus reported that women were more concerned about the implications of the condition gestational diabetes mellitus and its negative impact on their bodies, therefore, they reported poorly about their offspring's health compared to those without Gestational Diabetes Mellitus. In 2 randomized controlled trials, follow-up of infants of patients with gestational diabetes mellitus failed to establish a positive impact of treatment on the metabolic abnormalities of the offspring. This was shown by the IDEAL trial (Investigation of Dietary Advice and Lifestyle for women with borderline gestational diabetes mellitus). It was an RCT, assessing the impact of treatment on pregnant women with mild impaired glycaemia. In conclusion, treatment of mild gestational diabetes mellitus was beneficial and supported by evidence, especially pre-eclampsia, macrosomia, large-for-gestational-age infants, and shoulder dystocia, though the risk attributed to gestational diabetes mellitus is low. Recent research did not report an impact of treatment of gestational diabetes mellitus on neonatal hypo glycaemia or future metabolic problems. RCTs found no harm from the treatment of gestational diabetes mellitus, except for adding little burden on the health system. (49)

The American College of Obstetricians (ACOG) urged the Agency for Healthcare Research and Quality (AHRQ) to conduct an evidence report through the Evidence-based Practice Center program (EPC) with a view to examine the literature on specific aspects of the management of gestational diabetes mellitus. The prevalence of gestational diabetes mellitus is increasing remarkably, both globally and in the U.S. due to the sedentary lifestyle and obesity. In order to limit the adverse neonatal outcomes and improve maternal wellbeing, ACOG developed clinical recommendations for the management of gestational diabetes mellitus.

The guidelines advocate the importance of glucose control to reduce the risk of macrosomia and its related complications. When lifestyle and dietary measures fail to control gestational diabetes mellitus, medications needed to start, insulin is the traditional antidiabetic for the treatment of this condition , but now glyburide and metformin are in common use though are not approved by FDA. There is limited evidence to compare the efficacy and safety of oral therapy and insulin therapy for patients with gestational diabetes mellitus. The Cochrane Collaboration conducted a systematic review of RCTs comparing the effects of alternative management regimen in women with impaired glucose tolerance and gestational diabetes mellitus. The analysis included three trials studying women with impaired glucose tolerance, no significant difference was seen regarding cesarean delivery rates, neonatal ICU admissions, or large-for-gestational age infants among women with impaired glucose tolerance receiving intensive insulin therapy, compared to those receiving dietary advice alone. ACOG recommends cesarean delivery if the fetal weight is

4,500 g or greater. There are emerging risk factors like homocysteine and glutamic acid decarboxylase (GAD) antibodies.

A systematic review regarding evidence on labor and postpartum management of gestational diabetes mellitus is paramount for the clinical guidelines, so providing the healthcare professionals with knowledge needed for provision of evidenced-based, quality care to meet the high demand of the increasing prevalence of condition. Evidenced-based practice will result in promoting treatment effectiveness, improving labor management, better evaluation of risk factors for future diabetes in women with gestational diabetes mellitus, and effective postpartum screening for type 2 diabetes. (51) Several studies demonstrated the positive impact of treatment on minimizing the rate of complications. An RCT had been conducted by the Australian Carbohydrate Intolerance Study on women with Gestational Diabetes Mellitus. They randomized them into intervention group and controlled group. The primary fetal outcomes were Death, bone fracture, shoulder dystocia, and nerve palsy. Caesarean section and induction of labour define the primary outcome in women with Gestational Diabetes Mellitus. Perinatal complications was lower in the treatment group (Relative Risk 0.33; 95% CI, 0.14 to 0.75), though the rate of cesarean section was similar in both groups, induction of labor was higher in the treatment group (RR=1.36; 95%CI, 1.15 to 1.62), the study showed that treatment of gestational diabetes mellitus improves fetal outcomes.

The timing of glucose testing favors checking Fasting Plasma Glucose and Post Prandial Glucose, but not the pre-prandial testing which is linked with high level of A1C, large-for-gestational-age infants, and high prevalence of cesarean sections. The first- line treatment option for gestational diabetes mellitus patients is dietary modification, known as medical nutritional therapy. This should be carried out through involvement of the nutritionist and must consider the cultural background of the patient. Certain programs advocate strategies, like carb counting with snacks and meal related dietary advice. Changes related to diet should be tailored to meet patients' discretion, amount of weight gain, and blood glucose checking. Moderate exercise has a major role to play in the management of gestational diabetes mellitus. Despite the importance of medical nutritional therapy and exercise in the management of gestational diabetes mellitus, being safe, cheap, and practical, their influence on patient- related complications was not been shown in good randomized controlled trials. Drug therapy should be considered when medical nutritional therapy fails to control blood glucose, there is lack of expected weight gain, and if the patient continues to be hungry all the time. The ADA defines target Fasting Plasma Glucose as< 5.1 mmo/l and two-hour Post Prandial Glucose as <6.7 mmol/l. Regular insulin is the most commonly used form, but now lispro, detemir and as part insulin are becoming the preferred forms, especially after the approval of FDA (class B drugs in pregnancy).Expert opinion suggested starting insulin therapy in a dose of 0.7 units/kg, given bid and the pre pregnancy weight need to be considered.

Glyburide is effective and safe during pregnancy as evidenced by several prospective and retrospective studies, some authorities disagree with the above claiming that it crosses the placenta. Likewise, metformin is another oral option that can be used during pregnancy as shown by Metformin in Gestational Diabetes (MiG) trial, but crossing the placenta is an issue for some authorities (FDA). Fetal surveillance involves valid screening tests for the detection of fetal malformations, assessment of fetal well-being and sonographic evaluation for large-for-

gestational- age infants. The American Diabetes Association recommendations include; early detection of fetal malformations in patients with Gestational Diabetes Mellitus, through effective screening tests, especially women with high blood glucose levels in pre-pregnancy period for congenital anomalies in women with gestational diabetes mellitus who presented with an element of preexisting hyperglycemia. Such patients might have undiscovered pre-gestational diabetes and are at higher risk of fetal congenital malformation, possibly related to the prolonged exposure to high blood glucose during organogenesis.

The frequency of antenatal follow-up depends on the metabolic control, type of treatment regimen received by the patient, and the existence of other risk factors. ACOG recommends that women with gestational diabetes mellitus who are on insulin or who have poor glycemic profile should be monitored in antenatal visits similar to those with pre-gestational diabetes. This involves twice-weekly testing, with amniotic fluid assessment starting early in the third trimester. Patients with this condition on specific diet not only require active glucose management in labor, but blood glucose should be checked on admission, and those on therapy need to be monitored hourly and should receive variable intravenous insulin infusions with dextrose. Best practice regarding timing and method of delivery in patients with gestational diabetes mellitus depends on expert opinion, as there are no conclusive results and reliable database. An RCT showed the comparison of outcomes between elective delivery (induction at 38 weeks' gestation) and elective cesarean delivery with expectant management to 42 weeks. Early delivery was associated with less incidence of large-for-gestational-age, but no changes were observed regarding incidence of nerve injuries, neonatal hypoglycemia, or skeletal abnormalities. Majority of physicians prefer delivery before 39 weeks' gestation, so amniocentesis is needed as assessment tool for fetal lung maturity. Most women with gestational diabetes mellitus do not need insulin post-delivery. Around 50% of women with this condition are at high risk for developing diabetes within 5 to 10 years, also they have higher risk of earlier gestational diabetes mellitus in the subsequent pregnancies. Therefore, continuous testing and screening for DM 2 is warranted and lifestyle modifications set by the Diabetes Prevention Program should be encouraged (breastfeeding, 150 minutes per week at least of moderate intensity physical activity, and dietary measures to ensure weight loss). (51) Janet A and colleagues conducted an RCT on women with Gestational Diabetes Mellitus (Metformin Induced Glucose trial) comparing the use of metformin therapy versus insulin treatment in those two groups. The study was performed in ten Women's Hospital in New Zealand and Australia. Inclusion criteria include women between 18 and 45 years, diagnosed to have gestational diabetes mellitus based on Australian Diabetes in Pregnancy Society (ADIPS), women with singleton pregnancy in the period between twenty and thirty-three weeks of gestation, started insulin therapy according to hospital's protocol, and had more than one reading of fasting plasma glucose level exceeding 5.4 mmol/l and one 2-hour postprandial blood glucose above 6.7 mmol/l, advice about diet and exercise was provided.

The following points were regarded as exclusion criteria which include: pre-Gestational Diabetes Mellitus, if metformin cannot be used as a treatment option to metformin, congenital malformations, pregnancy-induced hypertension, pre-eclampsia, intrauterine growth retardation, and premature rupture of the membranes. Randomization was done according to site and gestational age. Australian Diabetes in Pregnancy Society ADIPS blood glucose targets were applied for all sites. Women received medications from their local pharmacies; metformin was started at a dose of 500 mg once or twice daily with food and increased over a period of two

weeks to achieve the therapeutic goal to reach a maximum of 2500mg/day. If targets were reached with metformin alone, then insulin was added. Liver and renal impairment or sepsis were the indicators to stop metformin, as well as fetal growth restriction.
Patient's characteristics were recorded at enrollment. Fasting blood samples were tested to assess the chemical panel (liver and renal function, glucose, A1C, lipids), glucose was measured by a hexokinase method. Blood glucose was checked by women at home using a MediSense meter and the measurements were analyzed through software and recorded in the database. Another plasma glucose sample was taken at 36 or 37 gestation weeks for re-checking. At delivery, complications, indications for urgent interventions, type of delivery, and fetal outcomes were all reported. Blood sample was taken from cord and kept in EDTA – treated tubes and in simple plain tubes. Around 10 minutes post collection, the samples were processed. The coefficients of variation of insulin concentration were 1.8% at 175mU per liter, 2% at 330 pmol per liter, and 4.8% at 38 pmol per liter.

The primary outcome of the study was a composite of neonatal complications reflecting adverse effects of fetal exposure to high maternal blood glucose. Complications include neonatal hypoglycemia, Respiratory Distress Syndrome requiring additional ventilator support and oxygen therapy to overcome the existing hypoxia, positive pressure ventilation is needed, either continuous or intermittent, depending on the status of the newborn. Ventilator support is required especially within the first post-deliver day. In order to avoid neonatal hypoglycemia, continuous monitoring of the blood glucose is advised, especially soon after birth for continuous 2 hours. Prior to feeding, the blood glucose needs to be checked. Continuous monitoring should continue till the blood glucose remains constant at 2.6 mmol/l or higher maternal hypertension was diagnosed based on the Australian guidelines. A customized calculator was used to measure birth weight percentiles, adjusted to infant gender, phase of pregnancy, height of the patient, maternal weight during the first trimester of pregnancy, ethnic group, and parity. A trained staff performed the following neonatal measurements within 48 hours after birth; crown-heel length, crown-rump length, head circumference, chest circumference, abdominal circumference, mid-upper-arm circumference, triceps skin-fold thickness, and sub scapular skin-fold thickness.

Consent was obtained from the participants. Adverse outcomes were delivered to a special committee responsible for data monitoring and safety. Adverse effects related to medications and pregnancy outcomes were reported at each antenatal visit. Serious adverse outcomes were observed such as congenital anomalies and fatal events, life threatening, resulted in serious disability or incapacity, required prolonged hospitalization or required major interventions. Neonatal complications as well include; admission to a level 2 or 3 NICU, length of stay in NICU, and the diagnosis at discharge from the hospital. The lowest value of scalp or cord blood pH was reported. The following are the secondary outcomes of the study and include; neonatal and maternal weight, degree of maternal blood glucose control, gestational hypertension , post-partum Oral Glucose Tolerance Test performed to the mother at 42 to 60 days, and acceptance of management by the mother.

The estimated frequency of the primary outcome prior to study was 30%. The proposed rates for hypoglycemia was 14%, 5% for respiratory distress, 5% for phototherapy, 1.5% for birth trauma, < 1% for Apgar score below 7, and 15% for preterm delivery. The primary objective of the study was to rule out an increase in the outcome in the metformin arm.751 women enrolled in the study

between October 2002 and November 2006.The final analysis included 363 women in the metformin group and 370 in the insulin group. Intention –to –treat concept was adopted. In 168 patients with gestational diabetes mellitus on metformin (46.3%), supplemental insulin was added in order to optimize blood glucose level. 27 patients discontinued metformin therapy prior to labour (7.4%). 7 patients in the metformin group had to stop the drug in view of the severe abdominal discomfort, another 5 patients stopped the drug on their own, but 4 women were told to stop metformin by some healthcare providers. The doses of metformin were reduced in 32 women (8.8%) due to gastrointestinal upset. The average dose of metformin was 2.5 g/ day, median dose of supplemental insulin was 42 units, being lower than the dose in the insulin alone arm (50 units). Supplemental insulin was initiated at a median of 20.4 days in the metformin arm. The primary outcome regarding neonatal complications was similar in both groups (32% in the metformin group and 32.2% in the insulin group, p= 0.95), severe hypoglycemia was lower in the metformin group (p=0.008), preterm delivery (<37 weeks) was seen more in the metformin arm (p=0.04). In both groups, one pre-term delivery was reported and that was exactly prior to week 32.

There was one reported case of perinatal loss in the insulin group, the mother had poor glycemic control evidenced by A1C of 10.2%, postmortem examination revealed Budd-Chiari syndrome, the iatrogenic preterm birth was similar in both groups, though the spontaneous preterm births were more common in the metformin group. At delivery, similar gestational age was seen in the metformin-treated arm and the insulin group (38.3 Vs. 38.5 weeks) respectively, with p value of 0.02. The neonatal anthropometric measures and umbilical cord insulin levels were similar in both groups, metformin arm showed low levels of 2h Post Prandial Glucose compared with the insulin group, and the rates of maternal hypertensive complications were similar in the two groups.

Acceptability of treatment was assessed by questionnaire in the postpartum period, 76.6% of women in the metformin group would choose metformin in the future pregnancies, while 27.2% of women who received insulin therapy agreed to choose their treatment in the future in the form of insulin, p value was less than 0.001. Women who received metformin therapy (59%) found the oral formulation was the best and simplest portion of the management when compared to insulin group (35.3%, p<0.001). Very few cases around 10.5% opined the most difficult side of the management was the ingestion of the oral form compared to those who received insulin (27.2%),P<0.001.Women who required supplemental insulin were having higher BMI and blood glucose levels than those treated with metformin alone. There were no more iatrogenic preterm births or complications in the metformin group reflecting the safety of the drug during pregnancy. In a cohort of women with Gestational Diabetes Mellitus who received insulin therapy or glibenclamide, the rate of premature labour was 13% in those treated with insulin, compared with 12% in the glibenclamide arm. 46.3% of women started on metformin required additional insulin for better control.

In a randomized clinical trial involving 404 women with gestational diabetes mellitus comparing glyburide and insulin therapy, researchers have found no differences between the insulin group and the glibenclamide regarding blood glucose levels and the rate of complications. Further analysis revealed 20% of the glyburide group changed to insulin, but so far no available study comparing metformin with glyburide. Study did not reveal any differences in the rate of neonatal

complications between women who received metformin alone and those demanded additional insulin therapy. The authors considered the performance of the trial within the routine clinical practice and involvement of a variety of women with gestational diabetes mellitus a positive point added to the strength of the trial. The open-label treatment [An open-label trial or open trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered] in the study was regarded as weakness. The 95% CI for Relative Risk regarding fetal adverse effects did not prove higher risk more than 10% in the metformin-treated group. The non-inferiority of metformin to insulin therapy was verified by this study (RR 1; 95% CI 0.89- 1.12). In a study involving patients with polycystic ovary syndrome, all of them received metformin.

126 babies of these patients were followed for 18 months. The authors concluded that metformin alone or with supplemental insulin was found to be a safe, effective, and more popular treatment for gestational diabetes mellitus in women who fulfill the criteria for its use. (53) Landon et al studied pregnant patients suffering from subtle gestational diabetes mellitus and another Australian study, which involved cases with established Gestational Diabetes Mellitus. In the two studies, the authors concluded that there was a definite relation between high blood glucose levels in subjects during pregnancy and high neonatal mortality and adverse effects. Studies on primary newborn birth weight results have had demonstrated that treating patients with gestational diabetes mellitus was of great benefit on newborns' birth weight. Hyperglycemia and Adverse Pregnancy Outcome-HAPO study did not find substantial variations among patients in the routine care and intervention arms with regards to the rate of large-for-gestational-age, the net gain in weight during the whole pregnancy period, newborns' ponderal index, and head circumference measurements.

In a randomized, placebo-controlled, double blind study, performed on 257 women with PCOS, aged 18- 42 years, randomized to either metformin or placebo, no significant reduction in the incidence of gestational diabetes mellitus was observed. A prospective study done on 98 pregnant women with Poly Cystic Ovarian Syndrome who received metformin in a dose of 1700-3000 mg/day, initiated before conception and continued up to 37 weeks of gestation, compared to 110 normal pregnant controls. A significant reduction in gestational diabetes mellitus and gestational hypertension was demonstrated. (37) Metformin improves many metabolic defects of poly cystic ovarian syndrome [PCOS]. Thus, its use before and throughout pregnancy may have beneficial effects on early pregnancy loss and the development of gestational diabetes mellitus.
In a case controlled study on 197 women with poly cystic ovarian syndrome [PCOS] conducted within 3 years, intervention group received metformin throughout pregnancy, the controls stopped metformin after the first trimester.

A significant reduction in the incidence gestational diabetes mellitus was shown in the study group. Another case-controlled study was conducted on 137 women with PCOS demonstrated a significant reduction in the incidence of gestational diabetes mellitus and early pregnancy loss in the group continued to use metformin throughout pregnancy. (38) A prospective clinical trial concluded that metformin use in pregnant women with abnormal GTT and history of recurrent abortions reduced the incidence of first trimester abortions and the development of gestational diabetes mellitus .(43) In a prospective cohort study on 360 non-diabetic PCOS patients.200 women received metformin 1- 2 g/day throughout pregnancy while the remaining 160 controls

discontinued metformin .The study showed a significant reduction in the incidence of gestational diabetes mellitus in the intervention group(43).Metformin use in women with Poly Cystic Ovarian Syndrome contributes to weight reduction in obese subjects which might result in decreased incidence of diabetes mellitus and gestational diabetes mellitus. Based on the above data, metformin therapy in patients with polycystic ovary syndrome showed favorable effect on the prevention of gestational diabetes among this important group. In our review, obesity was seen in 88% of pregnant citizens with Gestational Diabetes Mellitus while 62% of pregnant expatriates were found obese.

Weight loss through physical activity before and during pregnancy was associated with a significant reduction in the risk of developing Gestational Diabetes Mellitus.

Methodology

An audit of risk factors for Gestational Diabetes Mellitus was designed through reviewing 50 medical records of patients diagnosed to have gestational diabetes mellitus. The study was conducted with a study population with a mixture of citizens (Qatari) and expatriates (non-Qatari). The study was conducted at Hamad Medical Corporation -Alkhor Hospital, State of Qatar.

3.1. Data Collection

Retrospective study was carried for the 50 patients who attended both outpatients department and inpatients ward of the obstetrics and gynaecology unit. The data collected included risk factors for gestational diabetes mellitus. They are personal history of impaired Glucose Tolerance Test and gestational diabetes mellitus in a previous pregnancy. Patients belonging to high risk ethnic group for diabetes type 2, especially South or East Asians, family history of diabetes among first degree relatives, pre-pregnancy weight > 110% of ideal body weight or BMI > 30 kg/m2, significant weight gain in early adulthood and between pregnancies or excessive gestational weight, maternal age > 25 years of age, previous delivery of a baby >4.1 kg, previous unexplained perinatal loss or birth of a malformed infant, medical condition or setting associated with development of diabetes, such as metabolic syndrome, polycystic ovary syndrome (PCOS), current use of steroids, and hypertension.

Data was analyzed using various statistical tools and techniques, percentages and averages in excel sheet, graphs and tables. The Inclusion criterion involves pregnant women between the ages of 18- 40 years, pregnant women who met the diagnostic criteria for the diagnosis of gestational diabetes mellitus. The exclusion criteria involves patients known to have pre gestational diabetes mellitus were excluded. The patients are managed by obstetricians, diabetologists, endocrinologists, dietitians, diabetes educators (diabetes team), and if necessary, ophthalmologists. The potential opportunities for gestational diabetes mellitus prevention were studied through an extensive literature review including most of the studies pertinent to the topic.

3.2. Diagnosis:

Initially 50 gram of oral glucose load is administered to the patients without consideration to the time elapsed since the last meal and plasma glucose is measured one hour later. A venous sample is used and at one- hour if the blood glucose is equal or more than 130 mg/dl (7.2 mmol/l) then the patient will undergo a two-hour oral Glucose Tolerance Test. [OGTT]. Screening for gestational diabetes mellitus is performed at Al Khor hospital at 24- 28 weeks of gestation. Based on Fasting Plasma Glucose level of 5.1mmol/l or more and a 2h Post Prandial Glucose level of 8.5 mmol/l or more on a 75 g GTT. If any of the above thresholds is met, the diagnosis of gestational diabetes mellitus is established

3.3. Statistical Analysis

Analysis was performed on the data collected based on the following parameters. They are

1. Demographics-Qatari Vs Expats

2. Age of the patients-greater than 25
3. Nationality
4. Ethnicity-Asians Vs Non -Asians
5. Past Medical History:
    a. GDM
    b. Hypertension
    c. PCOS
    d. Family History of GDM
6. Past Obstetric History-Large Baby, Unexplained Perinatal Loss, Fetal Malformation
7. Body Mass Index-greater than 30 Kg/m2
8. Treatment Regimen:
    a. Diet Alone
    b. Metformin
    c. Metformin +Insulin
    d. Insulin

1. Results reveal :

a. Demographics-

Table:1 –Demographic Details of patients

Category	No	Percentage
Qatari	16	32%
Non-Qatari	34	68%
Asians	36	72%
Non-Asians	14	28%
Age > 25 Years	42	84%

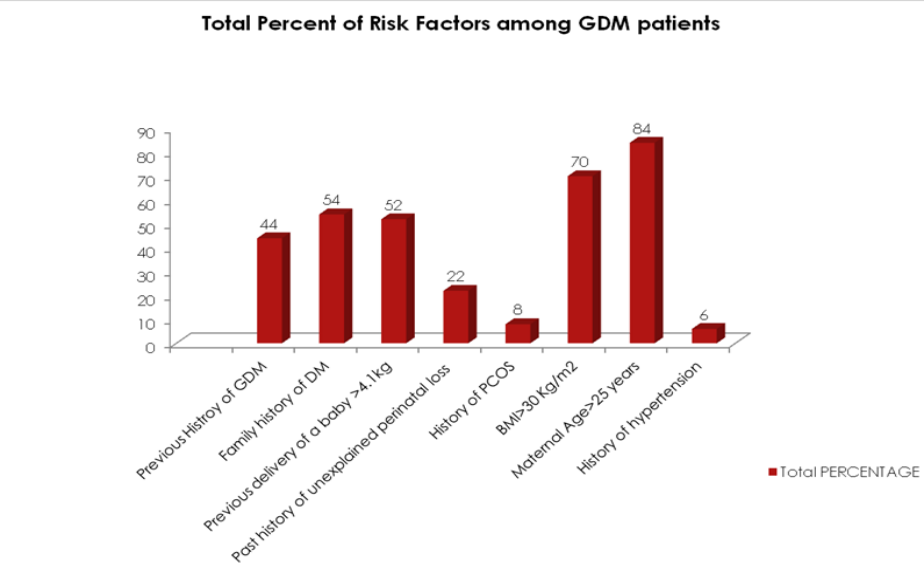
b. Age factor: 42 patients (84%) were > 25 years, 14 (88%) were citizens and 28 (82%) were expatriates.
c. Nationality: 16 patients (32%) were citizens, 34 patients (68%) were expatriates.
d. Ethnicity**:** Asians were 36 patients (72%) and Non-Asians accounted for 14 patients (28%)
e. Past medical history: Past medical history included the following parameters:
    1. Gestational diabetes mellitus -22 patients (44%), 8 (50%) were citizens, 14 (41%) were expatriates
    2. Hypertension: 3 patients (6%), 2 (13%) were citizens and 1 (3%) was expatriate
    3. Polycystic ovary syndrome (PCOS): 4 patients (8%), 3 (19%) were citizens and 1(3%) was expatriate
    4. Family history of Gestational Diabetes Mellitus: 27 patients (54%), 11 (69%) were citizens and 16 (47%) were expatriates
f. Past obstetric history: Past Obstetric history included the following parameters for analysis.
    1. Large baby (> 4.1 kg): 26 patients (52%) , 10 (63%) were citizens and 16 (47%) were expatriates

2. Unexplained perinatal loss or fetal malformation: 11 patients (22%), 6 (38%) were citizens and 5 (15%) were expatriates
3. BMI > 30 kg/m2: 35 patients (70%), 14 (88%) were citizens and 21 (62%) were expatriates

Table 2: Risk Factors

				Qatari		Non-qatari	
No	Risk factor	No	Percentage	No	Percentage	No	Percentage
1	Previous H/ O of gestational diabetes mellitus	22	44%	8	50%	14	41%
2	Family history of DMC first degree	27	54%	11	69%	16	47%
3	BMI>30 Kg/m^2	35	70%	14	88%	21	62%
4	Maternal Age>25 years	42	84%	14	88%	28	82%
5	Previous delivery of a baby >4.1kg	26	52%	10	63%	16	47%
6	Past history of unexplained perinatal loss of fetal malformation.	11	22%	6	38%	5	15%
7	H /O of PCOS	4	8%	3	19%	1	3%
8	H/ O of Hypertension	3	6%	2	13%	1	3%

Figure 1: Total Percent of Risk Factors among GDM patients:

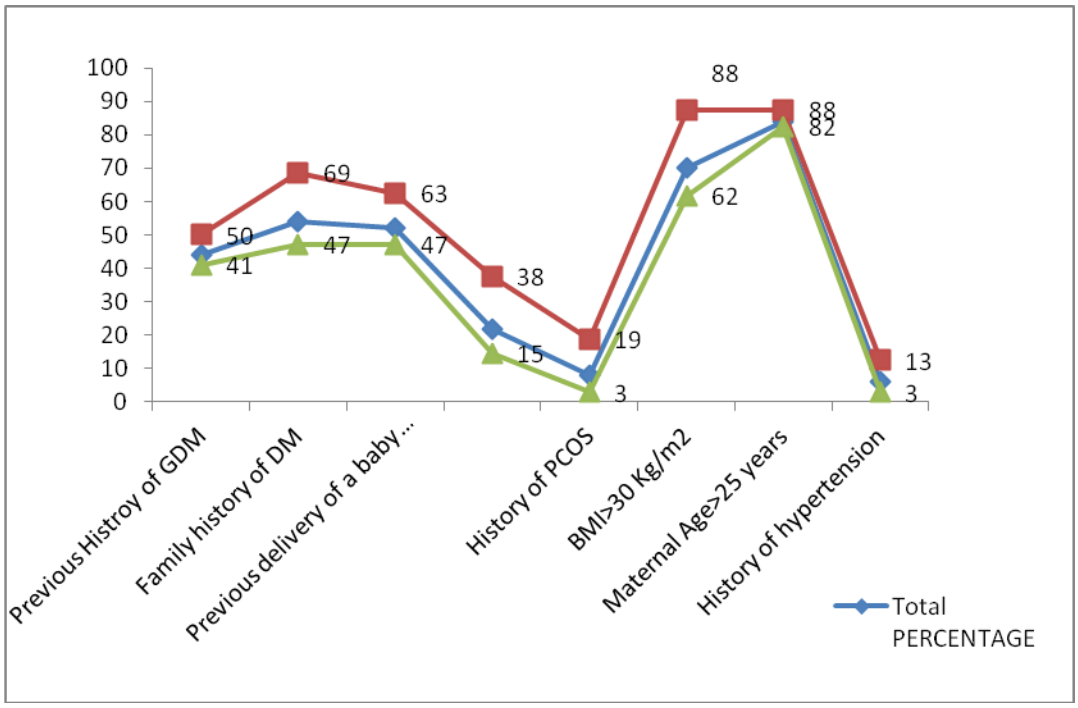


g. Treatment regimen: The treatment regimen included Diet, Metformin, Metformin with Insulin, Insulin.
    1. Diet only-9 patients (18%),
    2. Metformin: 15 patients (30%)
    3. Metformin + insulin- 20 patients (40%)
    4. Insulin only: 6 patients (12%)

Table 3: Treatment Regimen:

Treatment	No	Percentage
Diet only	9	18%
Metformin only	15	30%
Metformin+Insulin	20	40%
Insulin only	6	12%

Figure 2: Total percentages of various parameters for GDM



Blood glucose data were not available for many patients as they have already been diagnosed and referred to the hospital. According to ADA screening criteria all patients need to be screened for gestational diabetes mellitus. According to NICE 23 patients (46%) should be considered for screening. 18 patients (36%) with 1 risk factor. 22 patients (44%) with 2 risk factors.8 patients (16%) with > 2 risk factors. Missing data includes Blood glucose and Physical activity data, as this was not a standard of care among these patients.

4. Discussion

The study population represents a diversity of multi-ethnic groups similar to that seen in all gulf countries. Almost 70% of the population in the State of Qatar were expatriates and have migrated from different parts of the world for work purpose. Citizens (Qatari) represent the remaining third. In this audit, most of the known risk factors for gestational diabetes mellitus were shown among the study population. Interestingly, BMI>30 kg/m2 was seen in about 70% of the total cases and in 88% of the Qatari group. This is not surprising, because of the sedentary lifestyle and the dietary habits among those people, as high carbohydrate diet constitutes the main portion of the meal. Similar trend is also seen in all other gulf countries without exception. Obesity is growing very rapidly and becomes a trend in this part of the world, explaining the high prevalence of diabetes mellitus type 2 and constituting a major risk factor for gestational diabetes mellitus as well. In my review of these patients, maternal age > 25 years was the most prevalent risk factor for gestational diabetes mellitus as it was shown in 42 patients (84%), and interestingly, 88% of the citizens were > 25 years of age.

Polycystic ovary syndrome being an important risk factor for gestational diabetes mellitus was detected in 4 patients (8%) and mostly among the citizens.

4.1. Preventive measures identified:

From the data, there are certain risk factors that can be modified and might be of a great help in preventing gestational diabetes mellitus and hence improving both fetal and maternal outcomes. The 3 main risk factors that can be influenced are:

- Obesity.
- Polycystic ovary syndrome (PCOS).
- Old maternal age.

4.1.1. Maternal age:

According to analysis, increased maternal age was found to be the most prevalent risk factor for Gestational Diabetes Mellitus as was seen in 42 patients (84%). 88% of the citizens were at maternal age between 30-40 years, while the expatriate women were relatively younger. Terence T et al performed a systematic- review aiming to study the relationship between age and the risk of Gestational Diabetes Mellitus, they studied the prevalence of Gestational Diabetes Mellitus from 1998 to 2001. The maternal ages were categorized between <20 years and >40 years. 16,383 women were managed in this period, 15,827 (96.6%) women continued their pregnancy beyond the first trimester. The youngest cohort was 2% while the oldest was 3.9%.

The prevalence of Gestational Diabetes Mellitus was 1.3% among the youngest cohort and was 31.9% among the oldest cohort ($p<0.001$).The authors concluded that at age 25 years and more the incidence of gestational diabetes mellitus showed a dramatic rise. This agreed with the ADA guideline. So, the age > 25 years was regarded as an important predictive factor for gestational

diabetes mellitus risk. (55) The audit regarding maternal age agrees with the finding of Terence T et al and the American Diabetes Association. There should be more focus on this important risk factor. Measures have to be created in order to address this issue. Effective health education programmes need to be established at different levels of the healthcare system. Primary health care facilities are the first health access to most of the patients, so setting structured health education programmes about the advanced maternal age and the risk of gestational diabetes are highly needed. At hospital levels, pre conceptional counseling and educational sessions by health care providers and educators will have a positive impact on the prevention of Gestational Diabetes Mellitus.

Another effective educational tool is the media, being the most accessible tool for most of the people. In our community, the problem of maternal age is under estimated and often overlooked by many professionals.

4.1.2. Dietary advice:

The primary goal of the dietary advice is to prevent maternal hyperglycemia and reduce insulin resistance. Women with the low glycemic index (GI) diets were found to have the least risk of having large-for-gestational- age infants. Babies born to mothers on low GI diet were lighter than those born to mothers on high GI diet. The influence of low GI diet on gestational diabetes mellitus prevention was evidenced by the significantly lower maternal fasting blood glucose levels. Diet counseling encouraging less carbohydrate intake was linked to fewer incidences of Gestational Diabetes Mellitus and was found to be helpful in preventing the risk of obesity.

4.1.3. Medications:

Metformin:

Metformin is well known to restore ovulation and reduce the rate of abortions in Poly Cystic Ovarian Syndrome patients. Several researchers showed that metformin protects pancreatic beta cell's reserve and reduces the high insulin secretion triggered by the chronic insulin resistance leading to decreased incidence of gestational diabetes mellitus and good glycemic profile throughout pregnancy when given pre-conceptionally in patients with Poly Cystic Ovarian Syndrome.

Inositol:

Is a cyclitol presents in animal and plant cells. Myo-inositol (MI) is the predominant isomer, when deficient in insulin target tissues could reduce insulin signal transduction and therefor leads to insulin resistance. Corrado et al reported a low fasting glucose and insulin in gestational diabetes mellitus patients treated by 4 g MI daily. 98 anovulatory and hyperinsulinemic Poly Cystic Ovarian Syndrome [PCOS] non diabetic patients were randomized to MI plus folic acid throughout pregnancy and metformin. There was a significant reduction in the incidence of gestational diabetes mellitus (17% versus 54%; $P<0.001$), with a double risk of gestational diabetes mellitus in the control group (Odds Ratio: 2.4; CI 95% 1.3-4.4) compared to the MI group. Another study on 220 patients demonstrated the benefit of MI plus folic acid

supplementation in the prevention of gestational diabetes mellitus compared with the control (6 versus 15%), and a reduction of 65% of the risk for gestational diabetes mellitus (OR 0.35; CI 95% 0, 13-0, 96). The above review has shown new and promising insights on the prevention of gestational diabetes mellitus, especially the use of Myo-inositol evidenced by many studies. (41)
In review of these 50 cases of gestational diabetes mellitus, polycystic ovary syndrome (PCOS) was seen in 4 cases. There is enough evidence to prove that metformin use before and throughout pregnancy plays a significant role in both fertility and gestational diabetes mellitus prevention.

4.1.3. Counseling:

It has been suggested that high proportion of women were excluded due to abnormal OGTT at the 8-12 weeks gestation (23.6% in the intervention arm versus 31.3% in the routine care group).So, the study population showed less influence on the Gestational Diabetes Mellitus risk. The initiation of the dietary measures were at week's16 to 18 gestation and the measurements of gestational diabetes mellitus was at 26-28 weeks gestation, so the time was too short to have significant influence on the dietary habits and the development of gestational diabetes mellitus.
The reason to justify the negative impact of lifestyle counseling on the prevention of gestational diabetes mellitus was the selection of low risk women for the development of gestational diabetes mellitus in the study instead of the high risk category, which could have resulted in different outcome. (57) The above study should not preclude the need for effective lifestyle counseling in women during pregnancy in the prevention of gestational diabetes mellitus risk in high risk women. The above mentioned reasons should be considered meticulously in future research.

5. Conclusion

The review showed that the most prevailing risk factors for the development of Gestational Diabetes Mellitus include; maternal age > 25 years, BMI > 30kg/m2, and history of diabetes mellitus among first-degree relatives. Based on the extensive literature review, the following represent the potential opportunities for the prevention of gestational diabetes mellitus and include:

- Pre-pregnancy and early pregnancy physical activity and
- Dietary advice.

Both have a positive impact on insulin resistance and hence on the prevention of gestational diabetes mellitus, but the non-compliance of some patients may be regarded as a limiting factor. C-Metformin therapy prior to and throughout pregnancy in Poly Cystic Ovarian Syndrome women has a positive impact on the beta cell reserve, leading to the delay or prevention of gestational diabetes mellitus. Inositol therapy has been shown to improve insulin sensitivity and reproductive parameters, so regarded as an effective option for the prevention of gestational diabetes mellitus.

Effective lifestyle counseling including diet, physical activity, and weight gain in maternity care for women at risk for gestational diabetes mellitus was found beneficial for reducing large-for-gestation-age newborns and the incidence of gestational diabetes mellitus in adherent pregnant women. Further studies are recommended especially on debatable issues like screening methods for gestational diabetes mellitus and the role of counseling in the prevention of Gestational Diabetes Mellitus.

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