IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 11 Ver. III (Nov. 2017), PP 74-87
www.iosrjournals.org

Clinical Study of Infant of Diabetic Mother, Clinical Profile And Immediate Outcome in Peri-Natal Period –

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I. Introduction

Aims

1. To study the incidence of infant of diabetic mother in Niloufer hospital from July 2000 to August 2001.
2. To Study the clinical profile of infants of diabetic mothers.
3. To study outcome during Perinatal period who are born under different conditions.

Review Of Literature

Pregnancy in woman with diabetes mellitus:

The doctoral thesis of Heinrich Gottleib Bennewitz of Berlin published in 1824 presents the first case of what was probably insulin-dependent diabetes in pregnancy. The first case was reported in Berlin. Bennewitz describes Frederica Pape, a 22 year old woman, who after several successful pregnancies, was admitted to the Berlin Informatory at 36 weeks gestation with polydipsia and polyuria, classics symptom of diabetes. In 1880, J. Matthews Duncan reported 22 cases of diabetes complicating pregnancy in 15 Women. Thirteen fetal deaths occurred in 19 pregnancies, and nine of the women died within one year of pregnancy. He identified the two important causes of perinatal loss, namely stillbirths and macrosomia[2].In 1915, Elliott Joslin reported 7 cases of Diabetes complicating pregnancy between 1905 and 1915. Four maternal deaths were observed among the seven cases of which two died from ketoacidosis and one from tuberculosis. Only one surviving infant was observed in seven cases. The other six resulted in four stillbirths, one neonatal death, and one pregnancy termination[2]. Delee in 1913 stressed that pregnancy should be terminated if complicated by diabetes, as the maternal and fetal risks were too great[2].

Discovery of insulin:

In 1921, Frederick Banting and his collaborators, physiologist JJR Macleod, biochemist James Collip, and medical student Charles Best isolated insulin. With the discovery of insulin quality of life and life expectancy dramatically improved in-patients with diabetes mellitus could survive pregnancy[2]. In 1928, Delee stated that "Owing to the introduction of insulin and to advance in our knowledge of diabetics, the treatment of diabetes complicating pregnancy has undergone a complete revolution[2]," Dr. Priscilla White in 1928 at Joslin Clinic noted that excellent glucose control was essential to fetal welfare and suggested that high glucose content of placental blood was probably associated with excessive fetal growth. She advised team approach with "Close and persistent supervision" of both Obstetrician and Pediatrician.

Diabetic embryopathy:

More than a hundred years ago, the association between maternal diabetes mellitus and congenital anomalies was first made. Prior to the discovery of insulin, the outlook for the successful pregnancy outcome in woman with diabetes was extremely bleak. Following the introduction of insulin therapy, both maternal as well as fatal morbidity and mortality began to decline. Diabetes mellitus is one of the most common maternal illnesses that result in anomalous offspring. The frequency of major congenital anomalies has been estimated at 6% to 10%, which represent a two-to Threefold increase over the frequency in the general population. Congenital malformations in the offspring of diabetic mothers account for approximately 40% of perinatal deaths among this group of infants[3]. Khoury and colleagues evaluated the patterns of birth defects associated with diabetic embryopathy by analyzing 4929 infants with major defects. The predictive value was greatest for the combination of vertebral and cardiovascular anomalies [3].

Clinically, there is great diversity seen in the types of malformations associated with infants of diabetic mother. They are skeletal like caudal regression, Neural tube defects, Anencephaly, and Microrcephaly. Cardiac like transposition of the great Vessels, Ventricular septal defects, Coarctation of the aorta. Renal anomalies like Hydonephrosis, Renal agenesis, and ureteral duplication. Gastrointestinal likes duodenal atresia, Anorectal atresia, small left colon syndrome and others like single umbilical artery. Kucera has reported an increased rate of urologic anomalies among the fetuses of diabetes mothers[3].

Investigators have demonstrated a direct relationship between the tare of congenital heart disease in IDDM and the increasing degree of vascular complications and with the severity and duration of maternal diabetes . A relatively recent report from the Joslin center performed between 1984 and 1987 also found no relationship between risk for major malformations and white class of the duration of diabetes; however, these findings do not negate the importance of the assessment of diabetic Vasculopathy prior to conception for other pregnancy management purposes[6].
Various studies have suggested that good metabolic control early in pregnancy, specifically during the period of organogeneses, may be able to reduce the number of structural defects .

In 1979, Pedersen and Pedersen-molested compared two populations hospitalized diabetic patients. One group of women were controlled prior to pregnancy, were, as the other group was not controlled until pregnancy occurred. The rate of malformation was significantly reduced from 14.1% to 7.4% of infants whose mothers were controlled prior to pregnancy. Congenital malformations continue to be the major cause of perinatal morbidity and mortality in pregnancies complicated by diabetes mellitus. Although tremendous strides have been made in our understanding of the etiologic factors that contribute to the development of these malformations the precise mechanism involved have yet to be precisely elucidated. Well0-controlled diabetic women still have an increased risk of major malformation above that for the non-diabetic population. However, diabetic patients risk for major malformation can be kept to a minimum by careful attention to first trimester metabolic control.

Evidence has been accumulating that the incidence of neural tube defects could be reduced by folic acid dietary supplementation. In the treatment group of 429 patients, there were only three neural tube defects (0.7%), where as 24 of 510 (4.7%) of the control patients had recurrences. This was a highly statistically significant reduction in risk[9 10]. The incidence of neural tube defect among infants of diabetic mothers is several times that in the non-diabetic population. In a series from the Joslin Clinic, the incidence of neural tube defect was found to be 19.5.per 1000. This is an approximately 10/fold increase in risk over a non-diabetic population[6,11].

Screening of congenital anomalies in diabetic pregnancies:

The ability of meternal serum alpha-fetoprotein screening to help detect cases of neural tube defect led to the inclusion in the care of women with diabetes. At any gestational age the maternal serum values for diabetics of alpha-fetoprotein ten to be lower than the corresponding values for non-diabetics. To standardize these values, 0.8 should divide the result of the screen in a diabetic woman[12].

Reece at al correlated meternal serum alpha-fetoprotein values and glycohemoglobin, he found that poor metabolic control resulted in lower levels of maternal serum alpha-fetoprotein[13]. Group of Danish investigators suggested that ultra sound examinations performed during the first trimester among diabetic gravidas showed evidence of delayed embryonic growth. They compared the gestational age discrepancies between first trimester ultra sound examinations and last menstrual period dating for 99 diabetic women and 105 non-diabetic patients they found that a disproportionate number of fetuses of the diabetic women were smaller than expected for dates. They further suggested that the fetuses with the most pronounced growth lag were those that were destined to have major congenital malformations and/or were from women with poor first trimester metabolic control[14].

Fetal surveilance in the pregnancy complicated by diabetes mellitus:

Antepartum fetal surveillance is made easy be glucose monitoring as outpatient basis. Other test such as nonstress test, oxytocin challenge test, fetal heart rate monitoring labor and fetal biophysical profile will reduce the complications during labors[15]. Delivery should be delayed until fetal maturation has taken place, provided that the patient's diabetes is well controlled and that Antepartum surveillance remains normal. In practice, elective induction of labor usually is often planned at 38-40 weeks in well-controlled patients. If however, the cervix is unfavorable at 38 weeks and fetal size believed to be in the normal range, delivery is not undertaken simply because of meternal diabetes. Patients with vascular disease are delivered prior to term only if hypertension worsens of fetal growth retardation mandates early delivery[16].

Before elective delivery prior to 39 weeks, an amniocenteses is often performed to document fetal pulmonary maturity. Beyond 39 weeks it is rarely performed. The lecithin/sphingomyel in (L/S) ratio should be >=2.0. When antepatrtum testing suggests fetal compromise, delivery must be considered. When the L/S ratio is immature, the decision to proceed with delivery should be based on confirmation of deteriorating fetal condition. Delivery by cesarean section usually is favored when fetal distress is suggested. If patient reaches 38 weeks gestation with mature lung profile and is at significant risk for intrauterine growth retardation, elective cesarean should be performed[16,17].

Methods of screening for and diagnosing of gestational diabetes:

It is clear that pregnancies in women with pre existing diabetes more often end in perinatal death than do pregnancies in the general population, and that perinatal mortality rates in such diabetic pregnancies are directly proportional to the degree of maternal hyperglycemia during the third trimester[18]. The likelihood of delivering a large baby was also directly proportional to the plasma glucose response to a glucose challenge. A number of other studies have demonstrated that fetal macrosomia could be prevented by maternal insulin treatment[19,20,21].

Lavin et al observed that the simplest screening test for gestational diabetes is the taking of a history. Traditional historic risk factors such as presence of a family history of diabetes, a previous perinatal loss, or the previous birth of a macrocosmic baby clearly identify individuals at increased risk for gestational diabetes in their current pregnancies. A population based study by Coustan et al showed that gestational diabetes increases with age[23].

In the original study of O' Sullivan et al, a venous whole blodd glucose threshold of 130 mg/dl was found to have a sensitivity of 79% and a specificity of 87%. This study was unique in that all patients underwent both the screening test and the diagnostic glucose tolerance test so that gestational diabetes was ascertained throughout the population. It became necessary to modify the O'Sullivan plasma rather than whole blodd measurement, O' Sullivan et al used the Somogyi-Nelson method of glucose analysis, which measured approximately 5 mg/dl of reducing substances other than glucose. Modern enzyimatic methods, glucose oxides and hexokinase, are specific for glucose and thus yield slightly lower results. The 130-mg/dl threshold proposed by O' Sullivan et al would be equivalent to 142 mg/dl using these current approaches. When O' Sullivan et al originally devised the 50-g 1-hour screening test, it was administered without regard to the time of the last meal[24,25].

The diagnosis of gestational diabetes may be made by an oral or intravenous glucose tolerance test. The intravenous glucose tolerance test is the more reproducible of the two, but the oral test has gained favor because it is more convenient for the patient and more nearly approximates the normal route by which nutrients are ingested, bringing in to play gastric as well as pancreatic harmones. It should be noted that nutrient intake is not normally in the form of pure glucose, and the oral glucose tolerance test should be considered a provocative test rather than a parallel of glucose excursions during the course of normal daily life. The amount of glucose customarily used for the challenge varies in different parts of the world, and ranges from 50 to 75-100 g to a dose based on body weight. In 1979, the National Diabetes Data Group (NDDG) proposed the following derived values for venous plasma or serun[26].

Fasting	105 mg/dl
1 hour	190 mg/dl
2 hours	165 mg/dl
3 hours	145 mg/dl

As with the original criteria listed earlier, patients whose 100-g oral glucose tolerance tests meet or exceed at least two of these thresholds are diagnosed as having gestational diabetes. The American Diabetes Association and the American College of obstetrician and Gynecologists have accepted the NDDG criteria has been accepted by the American Diabetes Association and American College of Obstetrician and Gynecologists[27].

Metabolic changes in gestational diabetes:

The main components interact and influence the pathogenesis of gestational diabetes: beta cells, responsible for providing the insulin that in turn directs how the body metabolizes glucose; and the two insulinsensitive tissues, the liver and the muscles, which play critical roles in the maintenance of normal glucose homeostasis. First, the beta cell must have impairment in insulin secretion, although this need not be in absolute terms. Second, the insulinsensitive tissues, namely the liver and muscle, must be resistant to the effect of the insulin. A hyperinuinematic state and a decrease in insulin characterize pregnancy sensitivity[28].

Management of gestational diabetes:

Diet therapy means caloric restriction. It is well accepted that diet should include 50% carbohydrates, mainly composed of complex carbohydrates with an emphasis on reduced intake of simple sugars because of their high absorption rate. The complx high-fiber diet will delay gastrointestinal absorption and may improve they delay in gastric emptying in response to different types of glucose, resulting in different levels of glycemia[29].

In a retrospective study of gestational diabetic mothers, Langer et al used fasting plasma glucose <97 mg/dl (5.3 mmol/dl) as a threshold for insulin initiation in 471 patients with gestational diabetic mothers. Four factors believed to be associated with infants large for gestational age were evaluated: Fasting Plasma Glucose (FPG), overall glycemic control, maternal weight, and treatment regimen. They found that when glycemic control was optimized, the key factors related to large infants were FPG and treatment modality. In the low-FPG group (<5.3 mmol/L) diet therapy achieved an incidence of 5.3% LGA. When insulin therapy was used to optimize control, an incidence of 3.5% LGA was found. Patients in the mid-FPG group (5.3 to 5.8 mmol/L or 96 to 105 mg/dl) had a higher increased rate of LG (28.6%) for diet-treated versus insulin-treated obese women. Finally, treatment with insulin resulted in a similar incidence of LGA within all FPG groups. He concluded that FPG>95 mg/dl (5.3 mmol/L) can be the basis for initiation of insulin treatment in GDM subjects with optimization of glycemic control as the goal[30].

In order to assess the insulin dose required that would cause normoglycemia or any glucose-related morbidity associated with pregnancy, it is important to obtain accurate and reliable glucose data[31].

The insulin algorithm should always be synchronized with patient's meal patterns. The insulin dose should be calculated based on current weight at initiation of therapy prescribing 0.7 U insulin per kilogram of body weight. Human insulin should be administered to all patients and divided into three injections[32]. This injection should be administered about 20 minutes before breakfast[33]. The macrosomic infant has been described by Pedersen's theory. It is a glucose-driven theory that maternal hyperglycemia will cause fetal hyper-insulinemia, which in turn results in accelerated growth and fetal macrosomia[34].

In gestational diabetic patients, adverse outcome will either be a macrosomic or a growth-retarded infant. Langer et al found that when the mean blood glucose is greater than 105 mg/dl (mean 114 mg/dl), the incidence of large infants will increase from 9% to 24%. In contrast, when the mean blood glucose is less than 87 mg/dl, the incidence of large infants will show a marked decrease to 3%. The second and point is the small baby, the growth-retarded infant. They have as many problems as the large infants. This outcome is almost the exact opposite of what occurs with large infants. When the mean blood glucose is >87 mg/dl, the rate of small babies approximates 10%. In contrast, when the mean blood glucose is lower than 87 mg/dl, the rate of small for gestational age infants (SGA) is approximately 23% with a threefold higher risk for developing small infants in comparison with the higher blood glucose group. Thus, Langer et al concluded "we can achieve 3% macrosomia at the cost of 23% SGA or we can compromise by keeping the patient at 95 mg/dl" [35].

Coustan and imarah proposed an approach, with the administration of insulin on a prophylactic basis to all diabetic patients without exception. Their study resulted in a reduction in the rat of macrosomia, operative delivery, and birth trauma. The view that tight control can improve pregnancy outcome was also demonstrated in pregestational diabetes by several authors[20,36].

There is mother and child associated with the diagnosis of GMD. For example, for the mother, there is a higher risk of hypertension, preeclampsia, urinary tract infections, cesarean section, and future diabetes; for the child, there is a higher risk of macrosomia, hypoglycemia, hyperbilirubinemia, hypocalcemia, erythrocytosis, birth trauma, and future obesity. 50% of cases of gestational diabetes appear in women without any known risk factor for GDM. In view of the documented improvement in adverse outcome by appropriate treatment, universal screening for GDM for all pregnant women seems appropriate. The goals include forth at the Third International Gestational Diabetes Workshop/Conference include early diagnosis with standard guidelines[32].

This impact on mother and child and the documented success in decreasing fetal and neonatal losses, it is important that the "disease" be diagnosed and treated at the earliest possible point of intervention[38].

Metabolic changes in gestational diabetes:

Dietary strategy is the mainstay of therapy for the gestational diabetic women. The optimal dietary prescription would be the diet that provides the caloric and nutrient needs to sustain pregnancy but does not cause postprandial hyperglycemia[39]. A team management approach toward the diabetic mother including medical, high-risk obstetric, endocrinologic, nurse educator, and neonatology consultation have improved prenatal care to the point at which the associated perinatal complications with diabetes have been significantly reduced[40].

Diabetic nephropathy is characterized by macroproteinuria (dipstick positive, >300-500 mg in 24 hours), hypertension, retinopathy, declining glomerular filtration and azotemia[41].

Large for gestational age infants:

Despite an improvement in the management of diabetic pregnancies, the incidences of macrosomia seems essentially unchanged. In 1985, spellacy et al studied retrospectively 33,000 live births and reported that 1.7% of them were considered macrosomic (birth weight>=4500 g). In that study, single high-risk factors for

macrosomia were morbid obesity (10%), insulin dependent diabetes (9.2%), gestational diabetes (6.4%), obesity (5.6%), and postmaturity (15.4%)[42,43].

Other investigators have definded macrosomia differently (birth weight>=4000 g or weight above the 90th percentile for gestational age). The incidence of women and about 26% in women with diabetes. Irrespective of the definition of macrosomia, there is agreement that this condition carries significant risks for perinatal morbidity[44].

Most macrosomia infants are born of non-diabetic mothers. Other factors associated with fetal macrosomia are multiparty, Previous delivery of a macrosomic infant, and excessive weight gain during pregnancy. The large size of a macrosomic infant is due to greater size of the viscera caused by an increase not only in cell number but also in cell size. In the IDM, it has been elegantly demonstrated that this is due to the effects of insulin and not to the excess of available substrate[45,46].

In 1954, Pederson proposed that maternal hyperglycemia produced fetal hyperglycemia, hyperinsulinemia and that the later by unclear mechanisms simulated fetal growth[47]. Tight maternal serum glucose control during weeks 20 to 30 of gestation can decrease the incidence of fetal macrosomia; however, good glycemic control during the third trimester may not have similar effect. Poor intrauterine growth can be seen in 3% to 7% of non-diabetic pregnancies and up to 20% of diabetic pregnancies[35].

Macrosomia is associated with protracted labor, shoulder dystocia, perinatal asphyxia and skeletal and nerve injuries. Considering the high incidence of perinatal complications, the elevated rate of caesarean deliveries (47%) is not surprising. A condition unique to macrosomic IDMs often ignored is hypertropic cardiomyopathy. As consequence of fetal insulin stimulation, an increase in myocardial nuclei, cell number and fiber occur. Septal hypertrophy with decreased left ventricular function and left ventricular outflow obstruction are common and may explain the fact that a large number of IDMs without congenital heart disease show sings suggestive of heart failure. Hypoglycemia is known to occur in 47% of macrosomic and in about 20% of nonmacrosomic infants of diabetic mothers. Hypocalcemia, hypomagnesemia, hyperbilirubinemia and polycythemia also affect macrosomic infants, but at rates comparable with that of nonmacrosomic infants of diabetic mothers[48].

Small for gestational Age infants

Nonchromosomal malformations are often associated with fetal growth retardation. Abnormalities in cell replication and reduction in the number of cells result in a pattern of impaired fetal growth that is early in onset and symmetric in distribution[49]. Longer et al divided 334 GDM patients who experienced tight metabolic control into three groups according to their fasting mean blood glucose. Twenty percent of 79 patients who had average blood glucose < 86 mg/dl delivered small for gestational age infants which was twice as common as in those women in the 87 to 104 mg/dl>105 mg/dl serum glucose categories. Further more in small for gestational age fetuses, levels of total amino acids, branched chain aminoacids, lysine and serine are below normal values[35,36].

Pulmonary Development

Clinical observations in human have clearly documented that hyperglycemia and hyperinsulinemia are involved in the delay of pulmonary maturation observed in diabetic pregnanceis[51]. In 1975, Smith et el, using monolayers of cultured cells from fetal lungs, demonstrated that insulin stimulates H3 choline incorporation into Phosphotidy1 choline (Lectihin). More significantly these investigators noted that when insulin was added to cultures with cortisol present, steroid-enchanced lecithin synthesis was abolished[52]. Hyperglycemia per se did not alter de novo lecithin synthesis, suggesting that it is hypernsulinism that is primarly responsible for inhibition of surfactant synthesis[47]. Smith has postulated that insulin interferes with the normal timing of glucocorticoid-induced pulmonary maturation in the fetus. Apparently cortisol acts on pulmonary fibroblasts to induce syntheses of fibroblast-pneumocyte factor, which than acts on type-II cells to stimulate phospholipid synthesis[47]. Derangement in intermediary glucose metabolism caused by hyperinsulinemia may also impair surfactant synthesis. Stubbs and Stubbs[53].

In a series of 805 infants of diabetic mothers delivered over a 10-year period, Robert et al found the corrected risk for respiratory distress syndrome(RDS) to be nearly six times that of infants of nondiabetic mothers[54]. In wel-controlled diabetic women delivered at term, the incidence of RDS is not higher that that observed in the general population[55].

The use of standard fetal lung maturity values of lecithin spingomyelin ratio>=2.0, phsophotidy1 – glycerol concentration2.5%, and amniotic fluid optical density at 650mm>=0.150 were recently evaluated by Kjos et al. These investigations reported that each test had 100% sensitivity in identifying the surfactant-deficient RDS and 100% negative predictive value in identifying the absence of disease. It thus appears that aggressive control of maternal diabetes, judicious use of amniotic fluid pulmonary maturity tests, antepartum

biological surveillance with avoidance of unnecessary premature or surgical deliveries should result in no more than 5%to 10% of cases of respiratory distress of other origin, such as transient tacypnea of new born hypertrophic cardiomyopathy, meconium aspiration, and Polycythemia[17].

Hypoglycemia

In most cases, blood glucose levels decrease during the first 2 hours of life and then start to rise and stabilize. Because it is not unusual to observe a single low blood glucose value, the diagnosis of hypoglycemia should be based on two consecutive values taken no more than 30 minutes apart[56]. During the first 3 days of life hypoglycemia is defined by a serum (or plasma) glucose value less than 35 mg/dl (1.7mM/L) for full term and less that 25mg/dl (1.4mM/L) for prematurely born infants. Beyond the second day of life, serum levels below 40mg/dl (2.2mM/L) are considered abnormal[57]. Blood glucose levels measured with chromogen strips are on the average 10% lower than those obtained by the standard glucose oxidase method. Comparative studies have shown that chemstrip readings correlate with 90% of serum glucose levels <35mg/dl and with 95% of these above 35mg/dl[58].

Recently, it has been suggested that maternal control during later part of pregnancy and maternal glucose levels during labour and delivery greatly influence the frequency and severity of hypoglycemia[59]. Infant of diabetic mother (IDM) exhipiting hypoglycemia has elevated cord C-peptide and free insulin levels at birth[60].

Nelson RL et al studied the metabolic control of gestational diabetes mellitus. All the mothers were screened for gestational diabetes at 24 to 48 weeks of gestation with glucose tolerance test. Diet therapy and insulin therapy were instituted when appropriate, the risk of congenital malformations, macrosomia and hypoglycemia can be reduced to that of normal pregnancy[61].

A1 Najashi et al studied 355 diabetic women at King Fahd Hospital. He divided patients into three groups according to the mean glucose levels during the pregnancy. Good control was defined as a mean glucose level of less that 120mg/dl(Group-A); moderate control as a mean plasma glucose level between 102-140 mg/dl (Group – B); Group – B); and poor control as a mean plasma glucose level in excess of 140 mg/dl (Goup – C). The results showed higher antenatal neonatal complications in moderate and poorly controlled diabetic women. The overall complication rate being 5times higher than poorly controlled diabetic as compared to well controlled diabetes[72]. Hawthorne G et al studied the outcome of gestational diabetes and compared than with non-diabetic pregnancy. 169 patients were studied with established diabetes and 61 patients with gestational diabetes. The perinatal morality was 8.2/1000 in women with established diabetes and viable fetal loss (sum of perinatal mortality rate, neonatal mortality rate and infant loss) was 41/1000. The perinatal mortality in women with gestational glucose intolerance was 49.2/1000 and fetal loss 82/100. Perinatal mortality in the background population was 11.6/1000. Fetal malformation rate was 17.3 for established diabetes, 9.8%for gestational diabetes and 2.2% for normal population. Fetal abnormality remains the gestational glucose intolreance[63].

Johnstone FD et al studied the prevalence and type of glucose intolerance in pregnancy and the effect of different types of perinatal morality and fetal size. He studied 731 women over a period of 16 months. He classified them into established diabetes and gestational diabetes. Of the 731 cases 22% were established diabetes and 43% of gestational diabetes and 25% as impaired glucose tolerance. Overall 50% of cases were treated with insulin. Established diabetes had perinatal mortality rate nearly four times greater than non-diabetes and for gestational diabetes. Unexplained deaths were particularly common both in established diabetes and in gestational diabetes. Cases with impaired glucose tolerance had no-still birth of minimal perinatal loss compared with controls. Heavier babies were seen in all case groups compared with controls[64].

Hod M et al studied the prevalence of congenital anomalies and neonatal complications in the offspring of diabetic mothers. The study group consisted of 878 gestational diabetic women, 132 pre-gestational diabetic women, and 380 healthy pregnant women who served as controls, Major congenital anomalies between 1.80 and 6.82%, neonatal complications, such as macrosomia (5.6 -25 %), hypoglycemia (0.9 – 7.8 %), Hyperbilirubinemia (8.2 – 16.7 %), Polycythemia (3.8 – 13.3%), hypocalcemia (2.7 – 5.5%) were observed in the study population. He concluded that despite meticulous maternal glucose control neonatal complications could not be entirely eliminated[65].

In the following Indian study Ranade AY, Merchant RH, Bajaj RT, did a prospective study of 50 infants of diabetic mothers, 40% were large, 44% appropriate and 16% small for gestational age, 36% were preterm, 24% of the mothers were managed by dietary modification, 62% received insulin, 10% were treated with oral hypoglycemia agents while 4% did not receive any treatment as they were diagnosed postpartum, 58% deliveries, 6% were delivered by forceps and 2% by vacuum. Sixty four percent were infants of gestational diabetic (IGDM) and 36 % of preconceptional diabetic mother (IPDM). Hypoglycemia was documented in 50% Polycythemia in 20%, birth asphyxia in 18 % respectively distress syndrome and hypocalcemia in 14% each, transient tachypnea of the newborn in 12%, Hyperbilirubinemia in 8%, congenital anomalies in 4 % and cardiomyopathy, birth trauma and meconium aspiration in 2% each. The overall mortality was 20%[66].

In 1991, Deorari AK, Singh M Studied perinatal outcome of two hundred and sixty three diabetic mothers. Two hundred and twenty five infants were born to gestational diabetic mother (IGDM) and 38%

infants to mother with established diabetes mellitus (IDM), In IGDM group, 34 babies (15%) were preterm and 45 (20%) were low birth weight. 38 babies (17%) were large-for-dates and 14 (6.2%) were small-for dates. Out of all babies, hypoglycemia occurred in 43 (16%), birth asphyxia in 24 (9%) and respiratory distress in 21 (8%). Perinatal mortality rate was 40/1000 live births in the gestational diabetic group[67].

In 1992, Singh M studied 2248 infants born at All India Institute of Medical Sciences Hospital, New Delhi over a period of 15 months. They were screened for hypoglycemia. Hypoglycemia was diagnosed in 107 babies (4.8%). Preterm babies had three times increased risk (12.8%) as compared to term babies (3.6%). Small-for-dates and large-for-dates infants were at increased risk of manifesting hypoglycemia (7 and 10 times respectively) as compared to the appropriate for dates (AFD) babies (2.7%). Of the hypoglycemic babies 2/3 (67.38) had one or more risk factors such as birth asphyxia (24.28), diabetic mothers (23.8%), respiratory distress (13.9%) and septicemia (11.6%)[68].

II. Materials And Methods

1. All babies born to mothers with gestational diabetes and having regular antenatal checkups at NILOUFER HOSPITAL and cases refereed from peripheral centers in 24 hours for a period of one year were included in the study.
2. The mothers of these infants had been screened as follows during the antenatal period.

(i) Fasting Blood Suger .105 mg/dl
(ii) Post Prandial Blood Suger. 140ml/dl

Glucose tolerance test is done to confirm gestational diabetes. A fasting early morning sample for blood for blood sugar is taken and 100 gram of glucose is given orally. Blood and Urine samples are taken at 1 hr, 2 hrs, and 3 hrs and estimated for sugars.

Plasma

Cut off Values:	Fasting	-	105 mg/dl
	At 1 hour	-	190 mg/dl
	At 2 hour	-	165 mg/dl
	At 3 hour	-	145 mg/dl

If any two values are abnormal or any value is greater than 200 mg/dl then they were considered diagnostic of gestational diabetes[69]. The method used for estimating blood glucose was Glucose-Oxidase method.

3. Mother's antenatal history was recorded and relevant investigations such as hemoglobin, urine culture ultrasound abdomen was recorded. Pregnancy induced hypertension was diagnosed if the systolic blood pressure was more than 90 mmHg. Hydpertension prior to conception was diagnosed if blood pressure was above 140/90 mm Hg before pregnancy[70]. Anemia was diagnosed if hemoglobin less than 11.5 g /dl[71]. Urinary tract infection was diagnosed if urine microscopy showed more than 5 WBC/high power than 100000 colonies per ml of urine[72].
4. The lengh, weight and head circumferences of infants were measured and gestational assessment was done using modified Ballard's scoring system[73]. Detailed clinical examination was done to diagnose congential malformations.
5. The infants were screened for hypoglycemia using Dextrostix and confirmed by caplillary method at 1,2,3,6,12,24,26 and 48 hours. If hypoglycemia was detected i.e. serum glucose less than 40 mg/dl[74].

Then 2 ml of 10% dextrose solution was given as bolus infusion followed by intravenous glucose drip delivering 6 mg/kg min of glucose. Blood glucose levels were monitored every six hours if found to have hypoglycemia, then bolus infusion was repeated and glucose stepped up by 2 mg/kg/min. If hypoglycemia persisted then glucose was increased to a maximum of 14 mg/kg/min following which if refractory to glucose, steroids were given. Once serum glucose was maintained for 24 hours and the infant has no hypoglycemia then glucose was stepped down by 2mg/kg/min every 6 hours with strict glucose monitoring.

6. Infants at risk for septicemia were screened with band neutrophil rotia; micro-ESR>15mn after one hour, then diagnosis of sepsis was made and antibiotics were started after taking blood culture[75].
7. Monitoring was done to identify hypocalcemia i.e., serum calcium less than 8mg%[76].
8. Polycythemia was detected if venous heamatocrit was >/65% at 12 hours of life[77] and partial exchange was done using saline or plasma.
9. Hyperbilirubinemia was diagnosed as per Maisels chart and phototherapy was instituted[78].
10. Chest x-ray was done to diagnose pneumonia whenever warranted. Echocardiography was done to confirm congenital heart disease when suspected.

11. Hematological investigations such as hemoglobin total count, platelet count and peripheral smears were taken.
12. All the above data was fed into computer database and statistical analysis was done using Epi-info program.

III. Results

Table 1: Incidence:

Total No. of Deliveries	No. of IDM Babies	Percentage
10055	20	0.198

Table 2: Sex Distribution:

Sex	Total No. of IDM Babies	Percentage
Male	14	70
Female	0	30

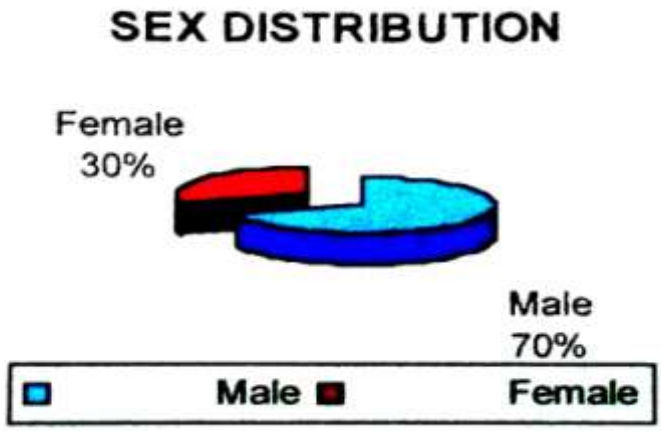


Table 3:

Population characteristics:

	Mean	Range
Birth Weight (grams)	3387.20 ± 521.06	1550 --- 4565
Gestational Age (Weeks)	38.71 ± 1.03	37 --- 42

Table 4: Birth Weight & Gestational Age:

	No. of IDM (n=20)	Percentage
1. S G A	4	20
2. A G A	10	50
3. L G A	6	30

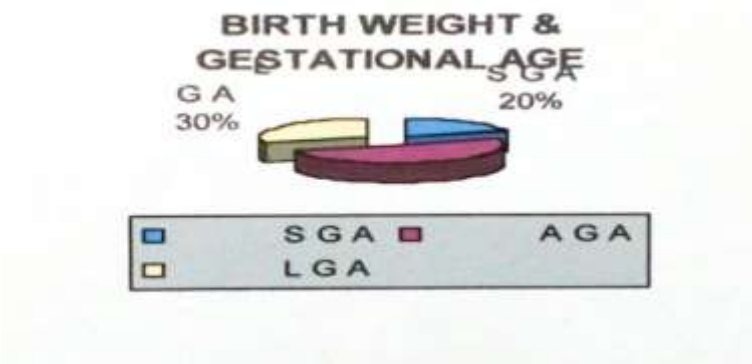


Table 5:

Birth weight & hypoglycemia:

	S G A (n=4)	**A G A (n=10)**	**L G A (n=6)**
Hyperglycemia	2 (50%)	6 (60%)	5 (83.3%)
Euglycemia	2 (50%)	4 (40%)	1 (16.7%)

P-value < .00000002 -- Significant

table 6: type of diabetic control & hypoglycemia:

Hypoglycemia (n=13)	**Diet Control (n=8)**	**Percentage**	**Insulin Control (n=11)**	**Percentage**
Symptomatic Hypoglycemia (n=6)	1	12.5	5	45.45
Asymptomatic Hypoglycemia (n=7)	1	13	5	45.45
Euglycemia (n=7)	6	75	1	9.10

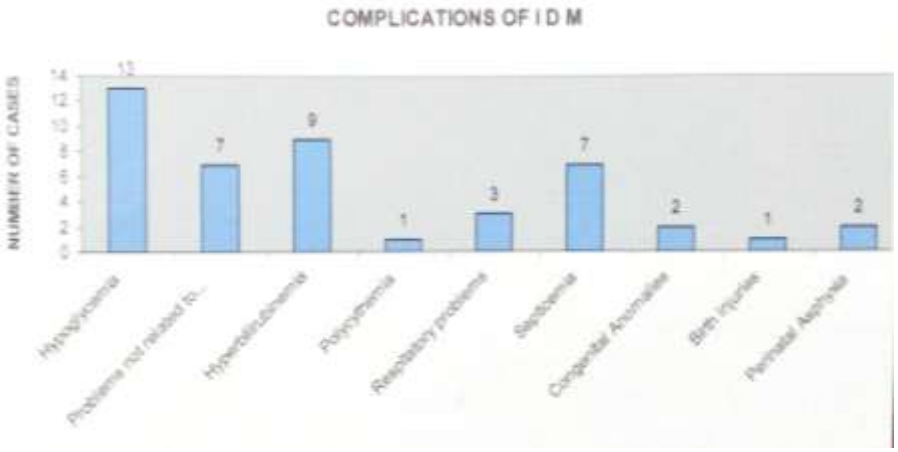
P-value – 0.08808416 -- Not Significant

Table 7: Complications Of Idm (N=20):

TYPE	**TOTAL NO.**	**PERCENTAGE**	**TOTAL PERCENTAGE**
Hypoglycemia	13	---	65
a) Isolated Hypoglycemia	6	30	
b) Hypoglycemia with other problems *	7	35	
Problems not related with Hypoglycemia	7	---	35
Hyperbilirubine mia	9	---	45
Polycythemia	1	---	5
Respiratory Problems (Pneumonia, MAS, TTNB)	3	15	
Septicemia	7	35	
Cpongenital Anomalies (CHD, DOWNS)	2	10	
Birth Injuries (erbs, facial)	1	5	
Perinatal Asphyxia	2	10	

***** Sepsis, Pneumonia, Hyperbilirubinemia

Table 7:



Type Of Complication

Table 8: Duration Of I. V. Fluids For Control Of Hypoglycemia:

Days	No. of Hypoglycemia Infants (n=13)	Percentage
1	8	61.50
2	3	23
3	0	0
4	1	7.60
>= 5	0	0

IV. Observations

During the study period from AUGUST 2000 to JULY 2001 the incidence of diabetic mothers among admitted babies is 0.198% Sex distribution showed 14 males (70%) and 6 females. The birth weight ranged between 1550-4565 g with a mean weight of 3387.20 g, SD 527.06.The gestational age ranged between 37-42 weeks of with a mean weight of 38.71.Caesarean section was mode of delivery in 80% of the admitted babies and 20% were delivered by spontaneous vaginal delivery. 10 babies were appropriate for gestational age, 6 were large for gestational age and 4 were small for gestational in two of these mothers had associated pregnancy induced hypertension. Hypoglycemia was seen in 13 babies, 83.3% of large for gestational age babies, 50% of the small for gestational age babies and 60% of appropriate for gestational age babies had hypoglycemia. Of the 7-euglycemic infants, 4 were appropriate for gestational age (40%). Asymptomatic hyperglycemia was seen in 6%(46.15%) out of 18 babies. Three of the euglycemic infants were born to mothers who where controlled by insulin during pregnancy. Eleven infants had mothers on insulin therapy. Eight of the infants were hypoglycemic and had EUGLYCEMIA.

Hypoglycemia 65%, Hyperbilirubinemia (45%) and Polycythemia (5%) were the three major complications noticed.

Infants had problems related to maternal diabetes 35% had problems related to hypoglycemia, respiratory problems was 15% (transient tacypnea, meconium aspiration). Septicemia was seen in 35% congenital anomalies 10% perinatal asphyxia and Birth injury in 10%. Septicemia was noticed in 15% of niloufer hospital and 65% in GMH, Koti Hyderabad in the present study.12 out of 13 babies who had hypoglycemia were given intravenous dextrose. 11 babies required 2 days or less of intravenous fluids. Two infants did not respond to intravenous glucose of upto 14mg/kg/min, therefore considered refractory hypoglycemia and responded to steroids. The mean glucose requirements were 9.2mg/kg/min. Polycythemia was seen in only 1 baby.None of the infants had hyaline membrane disease. None of the babies developed acute renal failure or nercotizing enterocolitis. Two infants with congenital anomalies died. The cause of death was not attributable to diabetes.

V. Discussion

The morbidity of infants born to diabetic mothers has been progressively decreasing owing to the tight glycemia control during pregnancy[31,35].

The risk of neonatal morbidity is directly related to the degree of control of maternal diabetes during pregnancy[61].

The incidence of infants born to diabetic mothers in the present study was 0.198%. The total number of infants born to diabetic mothers included in the study was 20.

The comparative incidence of infants born to diabetic mothers during pregnancy from other studies varies from 0.48 to 3% [67,79,80].

In the present study 6 were female babies and 14 were babies. Sex distribution showed a male predominance.

The birth weight showed a range between 1550 – 4565gms. This included small for gestational age, appropriate for gestational age and large for gestational age babies.

Neonatal macrosomia is a result of fetal hyperinsulinaemia due to maternal hyperglycemia[46,82]. Large for gestational age babies are at increased risk for developing perinatal asphyxia, shoulder dystocia, sketetal and nerve injuries [47].

In the present study, large for gestational babies was 30%. Other studies have shown an incidence ranging between 1.7% to 26%[43,44,62,67.]

Al Nagashi SS observed a high incidence of large for gestational age babies. In his study, only 30% of mothers were well-controlled diabetes[62].

Improved glycemic control has shown to reduce the incidence of macrosomia in infants born to diabetic mothers 81. The risk for developing large for gestational age infants is 20% more in gestational diabetes with poor glycemic control. Tight glycemic control during 20-30 weeks gestation can decrease the incidence of fetal macrosomia[35].

In the present study, 83.5% of large gestational age babies had hypoglycemia. Others have reported an incidence of 23-38%[35,87].

Large for gestational babies are 10 times at risk for developing hypoglycemia as compared to appropriate for gestational age babies[61.68].

Birth injury is common in large for gestational age babies. This is a result of shoulder dystocia[82,88]. An incidence of 2% has been reported by Ranade et al[66]. In the present study there was one case of facial palsy.

There were multiple mechanisms associated with development of small for gestational age infants. Reduction in cell size and number, fetal hyperglycemia, impaired fetal growth and associated vascular disease[47].

Small for gestational age infants account for 4 of the diabetic infants in the present study (20%). Other studies have observed an incidence ranging between 6.2% to 20% [35,67]. 2 out of 4 (50%) small gestational age infants had hypoglycemia in the present study.

2 out of 13 small for gestational infants in the present study had mother with associated pregnancy induced hypertension.

50% of the infants in our study were appropriate for gestational age . Other studies have observed a range between 36-77% [67,87]. In the present study, the incidence of hypoglycemia was 65%. Among these 7 infants had other associated problems with hypoglycemia and 6 had isolated hypoglycemia. Normal incidence of hypoglycemia in healthy term neonates accounts for 0.22-11.4%[68,84,85].

Among the infants born to diabetic mothers, the incidence of hypoglycemia has been reported as 0.90-7.8% [61,68]. Ranade et al has reported an incidence of 50%[66].

Asymptomatic hypoglycemia I was seen in 6 out of 13 babies. Two infants had refractory hypoglycemia , which was not associated with any other complications such as sepsis and polycythemia. Both these infants were symptomatic and they required steroids to control hypoglycemia .Of the two, one infants was large for gestational age and one was appropriate for gestational age. 40% babies were seen to be Euglycemic in the present study. The incidence of hypoglycemia is less in infants born to gestational diabetic mothers as compared to insulin dependent diabetic mothers[66].

The difference in incidence of hypoglycemia between infants whose mothers were on insulin and those mothers who where on diet control was not significant. (P-value 0.08808). Hyperbilirubinium was the 2nd most common problem in our study. It is accounted for 45%. Hyperbililrubinemia is due to increased erythropoietin, hyperinsulinaemia, decreased red cell life span because of deformed red cell membrane and increased glycosylation. Other studies have observed a range between 8- 16%[66,67,87]. Exchange transfusion was done in two babies during the study. Polycythemia was seen in 1 (1%) out of 20 babies in our study and required partial exchange transfusion. Other studies an incidence between 11-20%.

Other studies showed a range between 6-24% for large for gestational age babies[90,91] and an incidence of 15% for small for gestational age babies[91]. Respiratory problems were present in 3 out of 20 babies. This included transient tachpypnea of newborn, pneumonia and meconium aspiration. There was no infant who had Hyaline membrane disease in our study.

A similar incidence of Respiratory problems has been reported by Gabbe et al[89]. Other studies have shown a higher incidence of respiratory problems. The reasons being both term and preterm babies were included in the studies[66,67,87]. 7 out of 20 babies had culture proven sepsis. 3 babies had associated as hypoglycemia. For the purpose of analysis, this has been including as hypoglycemia with other problems. Risk of major malformations can be minimized by careful attention to first trimester metabolic control 8. The incidence of neural tube defects ranged between 3.5 – 4.6%[66,67,87]. The incidence of neural tube defects is 10 times more in infants born to diabetic mothers than in the general population[6,11]. Other factors are hyperglycemia and hyperinsulinaemia during pregnancy[47,48].

Congenital anomalies were seen in 2 out of 20 babies in the present study. They were ventricular septal defect (1 case), Microphallus and UDT. Perinatal asphyxia occurs due to maternal hypertension with resultant reduction in placental blood flow. Premature labor fetal macrosomia and maternal hyperglycemia with 6-8 hours preceding delivery are also implicated[88]. In our study, Perinatal; asphyxia was seen in 2 infants.

None of the infants in our study developed acute renal failure of narcotizing entercolitis.

VI. Conclusion

40% OF Appropriate for gestational age infants were Euglycemic.

46.2% of the hypoglycemia were asymptomatic. Therefore strict glucose monitoring is essential to defect asymptomatic hypoglycemia. Large for gestational age accounted for 30%of the total infants.

Large for gestational age infants had increased frequency of hypoglycemia and Polycythemia. Thus they need to be monitored to detect both these problems. One of the baby died during the study and 95% of perinatal outcome was noted.

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Dr. A. Yashowanth Rao Clinical Study of Infant of Diabetic Mother, Clinical Profile And Immediate Outcome in Peri-Natal Period –." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.11 (2017): 74-87.