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A Study on Drug Utilization Pattern, Efficiency of Monotherapy and Combinational Therapy in Gestational Diabetes Mellitus and Its Complications in a Tertiary Care Teaching Hospital

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Keywords: GDM, drug utilization pattern, DDD, monotherapy, combinational therapy, complications.

ABSTRACT

Aim: To study the anti-diabetic usage pattern in gestational diabetes mellitus, as per WHO-MLEM and NLEM 2021 and to observe the efficiency of monotherapy and combinational therapy of anti-diabetic drugs in GDM and its complications. **Methodology:** A prospective cross-sectional observational study (2021-2022) was conducted at the Department of Obstetrics and Gynaecology, GCMC, Chidambaram. Demographic details such as age, gender, chief complaints, past medication history, obstetric history, information on Fasting Blood Sugar (FBS), Randomized Blood Sugar (RBS), and Post Prandial Blood Sugar (PPBS) and therapeutic management were collected from the case sheets. The collected data will be analyzed using statistical tools. **Results:** Among a total of 80 patients enrolled, majority belongs to age group of 26-30 years. Along with GDM, a maximum of patients had gestational hypertension followed by hypothyroidism and anaemia. During hospital stay, patients were prescribed with metformin, human actrapid, human mixtard, and human monotard as monotherapy based on NLEM 2021 and WHO. Among combinational therapy, 50% of patients were treated with metformin + human actrapid + human mixture. After delivery, 53 babies were alive and 4 babies were dead. Complications of GDM were gestational hypertension, undergoing early preterm, obesity, fetal distress, excessive birth weight and baby death. **Conclusion:** From this study, we have observed that metformin, insulin and combinational therapy were prescribed for patients whose blood sugar levels were below 150 mg/dl, between 150-190 mg/dl and above 200mg/dl respectively. It is also concluded that the treatment pattern (monotherapy, combinational therapy) was chosen based on the blood sugar level.

INTRODUCTION:

Gestational diabetes mellitus (GDM) is the most common medical complication that occurs during pregnancy. Gestational diabetes mellitus is defined as carbohydrate intolerance that is developed or diagnosed for the first time and is associated with adverse outcomes in the mother and baby[1]. GDM usually develops at the end of the II trimester as a result of the body's inability to make and use all the insulin it needs during the gestational period[2]. There are enormous changes in reported prevalence estimates for GD in India, varying from less than 4% to nearly 18%. The overall prevalence is approximately 7%, higher in urban vs rural areas, among older age groups, and among higher socioeconomic status (SES) groups[3]. The symptoms of GDM are weight loss, polyuria, polydipsia fatigue, nausea, and vomiting, blurred vision. During pregnancy, GDM usually results from β-cell dysfunction along with chronic insulin resistance[4]. The dysfunction of beta cells results from inadequate glucose sensing to stimulate insulin secretion therefore elevated glucose concentrations prevail[5]. Chronic insulin resistance leads to insufficient plasma translocation of glucose transporter 4 (responsible for bringing glucose into cells to use as energy)**.** During GDM, the rate of glucose uptake which is stimulated by insulin is reduced by 54% when compared with normal pregnancy[4]. The first line treatment in GDM is dietary therapy, together with weight management and physical activity. It has been suggested that lifestyle modification alone is sufficient to control blood glucose in 70%-85% of the women that were diagnosed with GDM[6]. When treatment targets are not achieved by dietary means, then insulin and oral antidiabetic agents are required. Human insulin lowers blood glucose by increasing peripheral glucose uptake, especially by fat and skeletal muscle tissue. It also decreases blood glucose by inhibiting glycogenolysis, gluconeogenesis production, lipolysis, and proteolysis. The action of an antihyperglycemic agent is to decrease hepatic glucose production and the intestinal absorption of glucose and increase peripheral glucose uptake and utilization[7]. Maternal complications of GDM are Polyhydramnios, Preterm birth, Kidney infection (pyelonephritis), Problems with labour, Caesarean birth risks, and Damage to your retinas. Fetal complications of GDM are Erb's palsy, Fetal demise, Enlarged pancreas, liver or heart, Lifelong risk of obesity, high BP and Diabetes, Skeletal and limb abnormalities, Abnormal growth patterns- being large or small, or growth restricted during development[8]. Drug utilization pattern as defined by WHO in 1977 is an important tool in marketing, distribution, prescription and analysing the use of drugs in a society with special emphasis on medical consequences, social consequence, economic consequence[9]. For the comparison of drug

utilization, defined daily dose (DDD) serves as an important role and it is an internationally accepted tool. The assumed average maintenance dose per day for a drug used for its main indication in adults is called defined daily dose[10]. The goal of the project is to study on drug utilization pattern of GDM and to compare the efficiency of monotherapy and combinational therapy in gestational diabetes mellitus and its complications.

MATERIALS AND METHODS:

Ethical clearance: This prospective study was approved by Institutional Human Ethics Committee, Number: IHEC/873/2022 and permitted by Member Secretary, Institutional Human Ethics Committee, Government Cuddalore Medical College & Hospital (RMMCH), Annamalai University. The registration number of IEC is EC/NEW/INST/2020/1249.

Study site: Department of obstetrics and gynaecology, Government Cuddalore Medical College Hospital (RMMCH), 1200 bedded multi-speciality tertiary care teaching hospital, Annamalai University, Chidambaram, Tamil Nadu. **Study type:** A prospective cross-sectional observational study. **Study period:** 6 Months (Nov 2021- April 2022). **Study tools:** Data collection form. **Sources of data:** The data required for the study was collected from the case sheets (In-patients) and personal interactions with patients**.**

Study recruitment:

The study method involves the enrolment of patients based on inclusion and exclusion criteria. **Inclusion criteria:** Patients who are admitted in OG department with GDM. Patients who are willing to participate in the study. Patients with age group between 18-45 years. **Exclusion criteria:** Patients with mental disorders. Outpatients. Patients who are not willing to participate in this study. Patients above 45 years.

Study procedure:

The study period was conducted for 6 months (Nov 2021- April 2022). Selection of subjects based on inclusion and exclusion criteria. Prior to starting the study, an informed consent form was obtained from patients. The data collection form is designed to collect all the details like In-patients' number, name, age, chief complaints, obstetric history, marital status, menstrual history, lab investigation, abdominal scan report, diagnosis and therapeutic management. The present study was carried out among the patients visiting the inpatient department under the department of O&G, Government Cuddalore medical college &

Hospital (RMMCH). From the lab report, collection of biochemical profiles such as fasting blood sugar (FBS), randomized blood sugar (RBS), and postprandial blood sugar (PPBS) were collected. Patient counseling was provided. Neonatal health was checked using the APGAR score. The net result of treatment was recorded and tabulated. The results were interpreted based on the data collected during the treatment course. The conclusion is drawn from the study. Submission of report. Collected data will be stored in the department library for future reference in the form of a thesis book. **Data analysis:** The data gathered were recorded using Microsoft Excel and analyzed using relevant statistical tools to provide significant results.

RESULTS AND DISCUSSION:

In this study, we have endeavored to study the drug utilization pattern and efficiency of monotherapy and combinational therapy in GDM and its complications on inpatients of Rajah Muthiah medical college and Hospital, Chidambaram. Metformin and glimepiride are the most recommended oral anti-diabetic agents by many professions for the treatment of GDM. Thus, WHO recommends a 'watchful waiting' and insulin in case where the blood sugar level is above 146 mg/dl (7.0 mmol/L)**.**

DEMOGRAPHIC DATA:

Based on inclusion and exclusion criteria, a total of 80 patients were enrolled in the study.

TABLE 1: MEAN AND SD FOR AGE, WEIGHT, NO. OF DAYS DRUG USED, CO-MORBIDITIES OF METFORMIN, INSULIN, METFORMIN + INSULIN

CRITERIA		METFORMIN (MONOTHERAPY)	INSULIN (MONOTHERAPY)	MET+INSULIN (COMBINATIONAL THERAPY)
AGE	MEAN	29.35	30.29	29.12
	S. D	5.54	5.85	3.90
	MEAN+S. D	29.54±5.54	30.29±5.85	29.12±3.90
WEIGHT	MEAN	68.92	74.05	73.43
	S. D	9.98	8.60	7.61
	MEAN+S. D	68.92±9.98	74.05±8.60	73.43±7.61
NO. OF DAYS DRUG USED	MEAN+S. D	5.95±1.76	8.04±2.0	8.12±2.34
CO-MORBIDITIES	GHTN n (%)	16(40)	9(37.50)	5(31.25)
	HYPOTHYROIDISM n (%)	15(37.50)	4(16.67)	7(43.75)
	ANEAMIA n (%)	3(7.5)	3(12.50)	-
	UPPER RESPIRATORY INFECTION n (%)	4(10)	1(4.16)	1(6.25)

The majority of patients enrolled in the study belong to age group of 26-30 years (35%). 80 patients were enrolled out of which majority (40%) of patients were in the weight range of 70-8 kgs. In this study, 8 patients stayed in the hospital for a longer duration (11-15 days). After enrolment of subjects, it was found that the maximum percentage of patients (35%) were in the gestational age of 36-38 weeks.

Along with GDM, a maximum percentage of patients (40%) had gestational hypertension followed by 34.67% had hypothyroidism, 8% had anaemia, 8% had upper respiratory tract infection, 5.33% had fetal distress, 4% had covid positive.

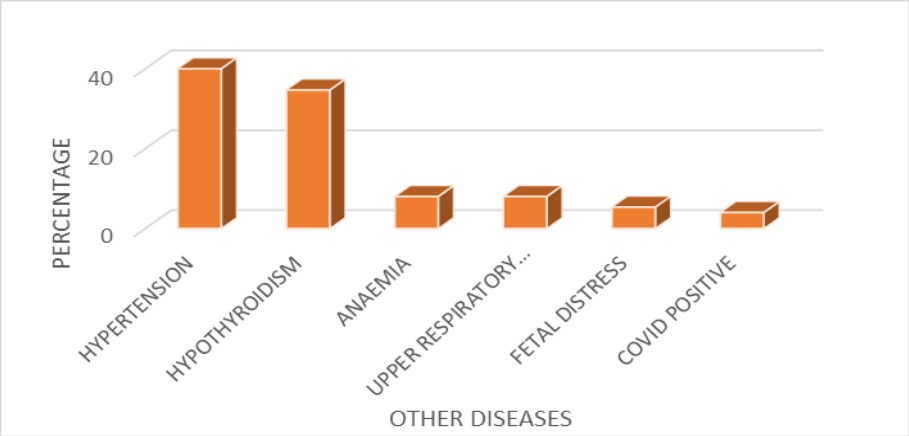

FIGURE 1: OTHER DISEASES ALONG WITH GESTATIONAL DIABETES MELLITUS

In this study, it was observed that maximum percentage of patients (42.50%) were diagnosed with GDM mostly in the first trimester itself.

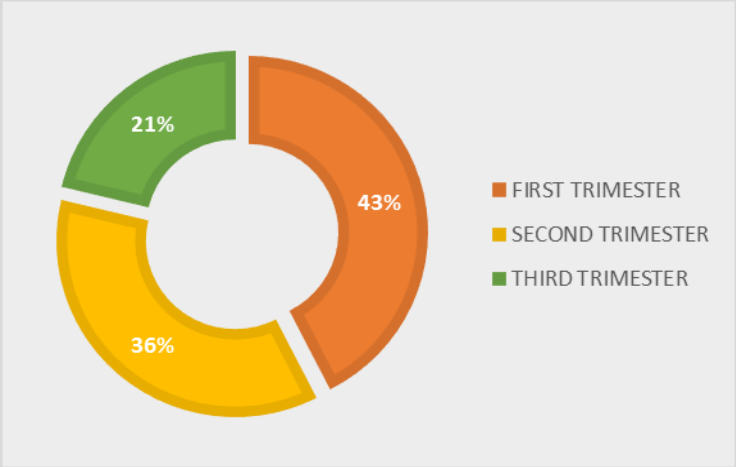

FIGURE 2: PIE CHART REPRESENTING TRIMESTER AT WHICH GDM DIAGNOSED

THERAPEUTIC REGIMEN:

Gestational hypertension was treated with labetalol (40%), anaemia was treated with iron sucrose and folic acid (8%), hypothyroid was treated with levothyroxine (26.67%) and thyroxine (6.67%), and upper respiratory tract infection was treated with azithromycin (10.67%).

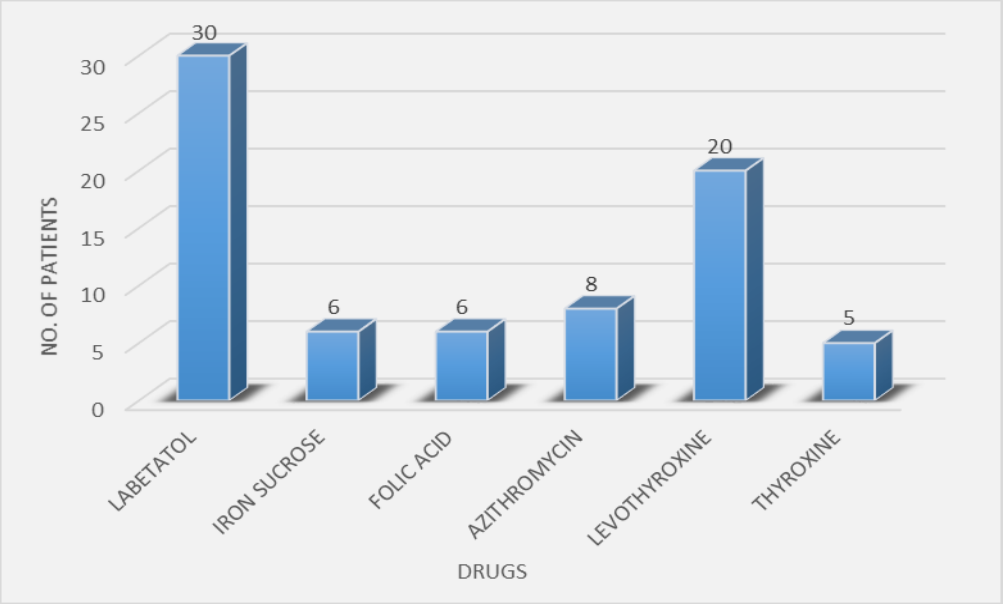

FIGURE 3: DRUGS PRESCRIBED FOR OTHER DISEASES BASED ON NLEM 2021 AND WHO

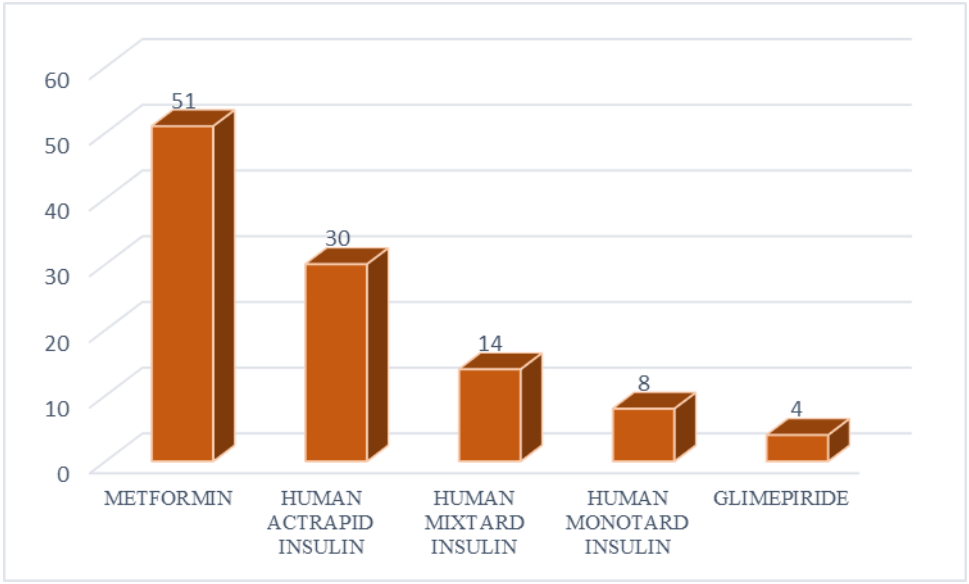

FIGURE 4: NUMBER OF DRUGS PRESCRIBED DURING TRIMESTER BASED ON NLEM 2021 AND WHO

In this study total of 80 patients, maximum number of patients (51) were prescribed with metformin, 30 patients were prescribed with Human actrapid, 14 patients were prescribed Human mixtard, 8 patients were prescribed with Human monotard and 4 patients were prescribed with glimepiride during the trimester period based on NLEM 2021 and WHO.

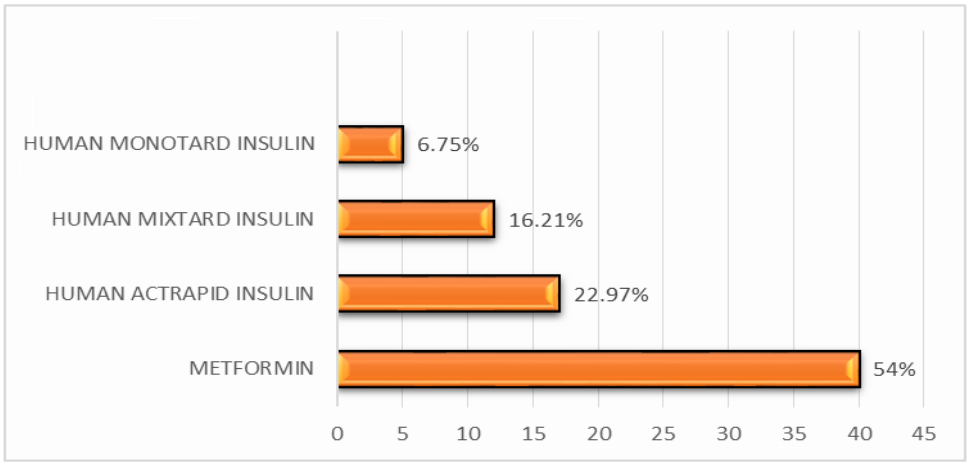

FIGURE 5: BAR GRAPH REPRESENTING MONOTHERAPY OF ANTI-DIABETIC DRUGS BASED ON NLEM 2021 AND WHO

During the stay in the hospital, 40 patients were prescribed metformin, 17 patients were prescribed human actrapid, 12 patients were prescribed human mixtard, 5 patients were prescribed human monitor based on NLEM 2021 and WHO.

In this study, 16 patients received combinational therapy out of which 50% of patients were treated with metformin + human actrapid + human mixtard.

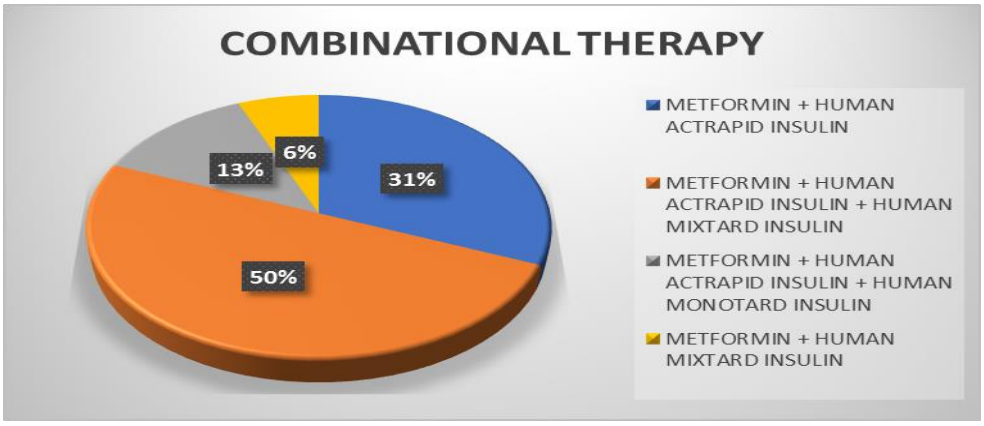

FIGURE 6: BAR GRAPH REPRESENTING COMBINATIONAL THERAPY OF ANTI-DIABETIC DRUGS

In this study, we observed that maximum number of doses and frequencies of the drugs used as follows:

TABLE 2: DOSES AND FREQUENCIES OF DRUGS GIVEN AS MONOTHERAPY AND COMBINATIONAL THERAPY

DRUGS	DOSES		FREQUENCY	
	MONOTHERAPY	COMBINATIONAL THERAPY	MONOTHERAPY	COMBINATIONAL THERAPY
METFORMIN	500 mg	500 mg	BD	BD
HUMAN ACTRAPID	8 U	8U	BD	BD
HUMAN MIXTARD	8U	8U	BD	BD
HUMAN MONOTARD	6U	4U	BD	OD

OUTCOMES:

Women with GDM have a higher risk of LSCS. In this study, 18.33% of patients had undergone normal delivery, 51.67% of patients had undergone emergency LSCS, 25% of patients had undergone labor abnormal with preterm and 5% had spontaneous abortion.

After delivery 53 babies were alive and 4 babies were dead.

Neonatal health was determined using APGAR score. In this study, the maximum APGAR score at one minute and at five minutes was in the range of 6-9.

TABLE 3: APGAR SCORE OF NEONATES

S.NO	APGAR SCORE	METFORMIN		INSULIN		MET+INS	
		ONE MINUTE	FIVE MINUTES	ONE MINUTE	FIVE MINUTES	ONE MINUTE	FIVE MINUTES
1	0-3	3	-	2	1	3	-
2	4-6	6	3	4	3	2	1
3	7-9	22	26	8	9	7	10

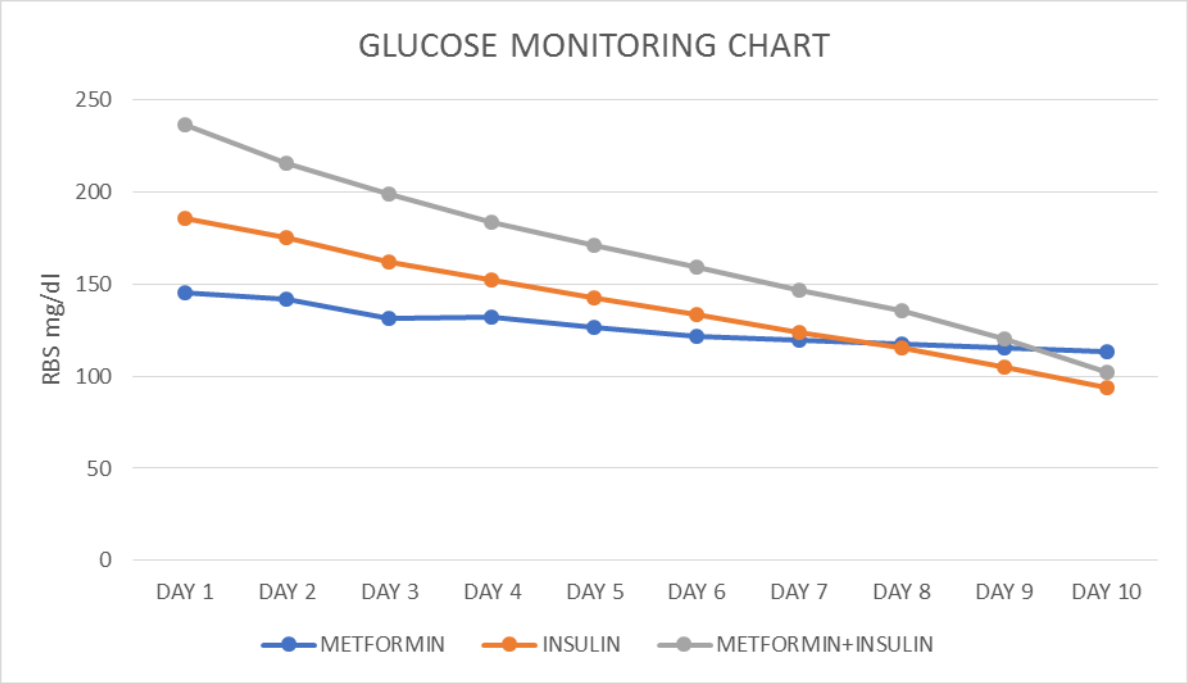

FIGURE 7: GLUCOSE MONITORING OF METFORMIN, INSULIN, METFORMIN + INSULIN

From this study, we examined that metformin had prescribed for patients whose blood sugar level were below 150 mg/dl, insulin for those who had blood sugar level between 150-190 mg/dl and combinational therapy were recommended for patients whose blood sugar level were above 200mg/dl. Complications of GDM were gestational hypertension (32%), undergone early preterm (16%), obesity (12%), fetal distress (7%), excessive birth weight (17%), baby death (4%), polyhydromnios (5%), oligohydromnios (7%).

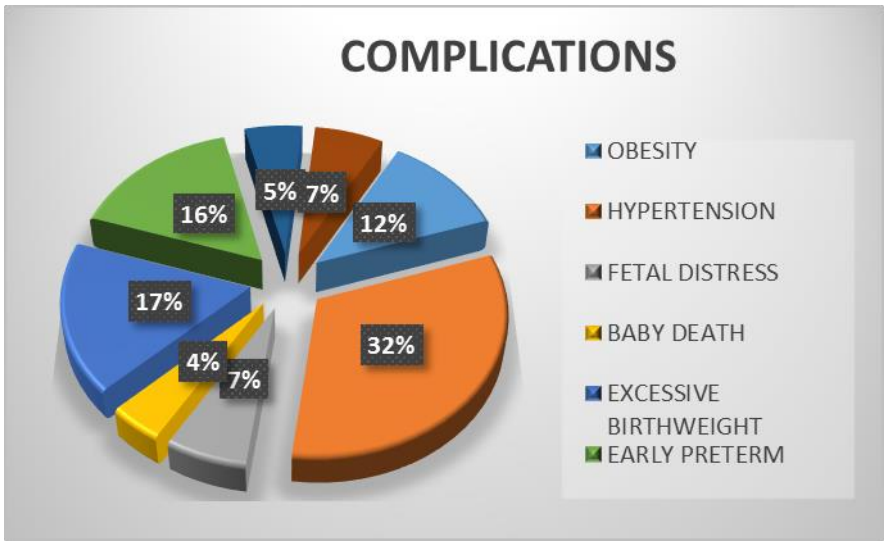

FIGURE 8: COMPLICATIONS DUE TO GDM

DEFINED DAILY DOSE

DEFINED DAILY DOSE FOR METFORMIN:

Number of patients prescribed with metformin in monotherapy and combinational therapy = 56

Number of amounts of drug administered in a given period for 56 patients = 288000 mg = 288 g

DDD (WHO) = 2 g

Number of days = 336 days

Number of beds = 56 beds

$$\text{Occupancy index} = \frac{\text{Total in patients service days for a period X 100}}{\text{Total bed count X number of days in the period}}$$

= 3.33

$$\text{DDD/100 beds} = \frac{\text{Number of amounts of drug administered in a period X 100}}{\text{DDD X Number of days X Number of beds X occupancy index}}$$

$$= \frac{288 \text{ X } 100}{2\text{X}6\text{X}56\text{X}3.33}$$

DDD/100 beds = 12.87 g/100 beds for metformin.

DEFINED DAILY DOSE FOR HUMAN INSULIN:

Number of patients prescribed with human insulin analogs in monotherapy and combinational therapy = 40

Number of units of insulin administered in a given period = 11260 units

DDD (WHO) = 40 units

Number of days = 400 days

Number of beds = 40 beds

Occupancy index = 5.55

DDD/100 beds = $\frac{11260 \text{ X } 100}{40\text{X}10\text{X}40\text{X}5.55}$

DDD/100 beds = 12.68 g/100 beds for human insulin analogs.

TABLE 4: INDICATES ATC CODE AND DDD/100 BEDS OF ANTIDIABETIC DRUGS

ATC CODE	DRUG	WHO DDD	OCCUPANCY INDEX	DDD/100 beds
A10BA02	METFORMIN	2 g	3.33	12.87 g/100 beds
A10AB01	HUMAN INSULIN ANALOUGES	40U	5.55	12.68 g/100 beds

TABLE 5: COMPARISON OF LENGTH OF STAY IN MONO AND COMBINATIONAL TREATED GROUP

TREATMENT GROUP		N	LENGTH OF STAY (DAYS)		
			MEAN	S. D	RANGE
MONOTHERAPY	METFORMIN	40	6.14	1.98	4-8
	INSULIN	24	9.27	2.29	7-11
COMBINATIONAL THERAPY		16	9.34	2.41	8-12

TABLE 6: COMPARISON OF RBS LEVELS IN MONO AND COMBINATIONAL TREATED GROUP

TREATMENT GROUP		RBS LEVEL mg/dl (DURING ADMISSION-Mean)	RBS LEVEL mg/dl (DURING DISCHARGE-Mean)
MONOTHERAPY	METFORMIN	145.35	113.55
	INSULIN	185.62	93.54
COMBINATIONAL THERAPY		236.12	102.06

CONCLUSION:

In summary, we have presented the effectiveness of monotherapy and combinational therapy in gestational diabetes mellitus and also the drug utilization pattern in GDM patients. In our study, out of 80 patients, 40 patients received metformin as monotherapy, 24 received insulin as monotherapy and 16 patients received combinational therapy (metformin+insulin). The drug use pattern for other diseases along with GDM is as follows: Hypertension- Labetalol, Anaemia- Folic acid and Iron sucrose, Hypothyroidism- Levothyroxine and Thyroxine, Upper respiratory tract infection- Azithromycin. Common complications of GDM that were observed are preterm delivery, excessive birth weight, fetal distress, fetal demise, maternal obesity, hypertension, maternal hypoglycemia, and fetal hypoglycemia. In this study, we estimated the effectiveness between monotherapy and combinational therapy by calculating the mean random blood sugar level, cost of drugs and length of stay. For uncontrolled diabetes (above 200 mg/dl) combinational therapy is recommended as it is more effective but it has a risk of hypoglycaemic so, it cannot be given for controlled diabetes. For controlled diabetes, monotherapy is recommended. The findings of this study suggest that metformin monotherapy may be equally effective in achieving glycaemic targets in the management of diabetes in pregnancy. Cost analysis showed the cost burden of anti-diabetic drugs: which has been greatly reduced by the PMJAY scheme by the Central Government of India.

ETHICAL CLEARANCE:

This prospective study was approved by Institutional Human Ethics Committee, Number: IHEC/873/2022 and permitted by Member Secretary, Institutional Human Ethics Committee,

Government Cuddalore Medical College & Hospital (RMMCH), Annamalai University. The registration number of IEC is EC/NEW/INST/2020/1249. Patient Informed Consent forms were obtained since human participants were involved in this investigation.

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AUTHOR CONTRIBUTION:

Conceptualization and methodology including data collection: Mahalakshmi S, Harini V, Madhusudhan S, Latha K; Writing - original draft preparation and literature search: Mahalakshmi S, Harini V; Writing – Review and Supervision: Madhusudhan S. The final manuscript has been read and approved by all the authors.

CONFLICT OF INTEREST:

The authors affirm that the publishing of this paper is free of conflict of interest.

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