Comparison of the Effect of Glycemic Control on the Incidence of Fetal Macrosomia and Large for Gestational Age in Gestational Diabetes Mellitus Patients; A Systematic Review

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Abstract

Background: Gestational diabetes mellitus (GDM) can be managed with blood glucose control management, which includes a healthy lifestyle, insulin therapy, and oral anti-diabetic drug (OAD) medications when needed. Sub-optimally or poorly managed GD Mmay lead to arisk of complications, one of which is an abnormal growth in the fetus. This study aimed to compare the effect of blood glucose control management on the incidence of fetal macrosomia and large for gestational age (LGA) births in patients with GDM. **Methods**: This systematic review study obtained data from formerly published studies from the Science Direct database. The article search method used the characteristics of PICO (Population, Intervention, Comparison, Outcome) and compiled using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) method. **Conclusion:** The use of medical nutrition therapy (MNT) and exercise in the therapeutic regimen, as well as routine monitoring of glycemic levels are very important to control the patient's glycemic level. The use of metformin can increase the success of therapy due to reduced levels of LGA and macrosomia in GDM patients.

Keywords: *diabetic pregnancy, glycemic control, macrosomia, large for gestational age, diabetes control, diabetic therapy*

Introduction

Diabetes is the most common metabolic disease that occurs during pregnancy.[1] Diabetes in pregnancy that is not managed optimally can cause morbidity in both mother and baby. A cohort systematic study showed that pregnant women with hyperglycemia had a greater risk of complications during delivery, particularly macrosomia in the newborn and preeclampsia in the mother.[2] The incidence of macrosomia in GDM with poor glycemic control is 40%.[3]

According to 2013 WHO classification, hyperglycemia first detected during pregnancy must be categorized into 1) Pregestational diabetes, which can be determined by the same criteria as diabetes in nonpregnant persons; and 2) Gestational diabetes mellitus, which is diabetes diagnosed in the second or third trimester of pregnancy that did not exist before gestation.[4] GDM therapy consists of two regimens:

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1) Non-pharmacological (medical nutrition therapy/ MNT/diet and exercise), and 2) Pharmacological (insulin).[5] This study aims to find out and analyze the comparison of the effect of blood glucose control management on the incidence of macrosomia and large for gestational age in patients with gestational diabetes.

Materials and Methods

The material used in this study is the result of studies and analyses that have been carried out about the effect of blood glucose control management on the incidence of fetal macrosomia and large for gestational age in patients with gestational diabetes mellitus. Articles that have been collected are managed using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) method. All articles were identified, screened, assessed for theireligibility, and included in the review.

A complete Science Direct search was done to obtain secondary data from articles published that included the search term containing gestational diabetes AND macrosomia AND (diet OR insulin OR metformin OR glyburide OR treatment) in their title and abstract. Boolean Operators including OR/AND were used. The keywords used are entered together into the electronic database search engine using advanced search, then selected using the PRISMA flow according to the inclusion and exclusion criteria that have been set. Articles are selected quickly by using the find word feature of the Google Chrome browser to find keywords.Types of studies that meet the inclusion criteria are quantitative studies that can be cross-sectional, cohorts,or clinical trials.This study focused on published articles papers from 2016 to 2020. Seventeen articles were selected in total. The chosen papers were published from 2016 to 2020.

Results and Discussion

Seventeen quantitative research studies have been identified by search (Au *et al*., 2016; Kanai *et al*., 2016; Shi *et al*., 2016; Silva *et al*., 2016; Bogdanet *et al*., 2017; Bianchi *et al*., 2018; Eid *et al*., 2018; Huhtala *et al*., 2018; Khin *et al*., 2018; Zamstein *et al*., 2018; Zygula *et al*., 2018; Lu *et al*., 2019; Manoharan *et al*., 2019; Meghelli *et al*., 2019; Kapustin *et al*., 2020; Pazzagli *et al*., 2020; Penager *et al*., 2020). Data extracted can be seen in **Table 1**. This study was conducted at one or more institutions from various countries, with the research subjects being patients with GDM who received MNT (medical nutrition therapy), exercise, insulin, and/or OAD (oral anti-diabetic drugs).All studies contain evidence of anti-hyperglycemic therapy and related outcomes of macrosomia or LGA outputs from GDM patients.

GDM Therapy Used in Research

GDM therapy primarily consisted of low glycemic index dietary modification.[6] In several studies, patients received dietary recommendations from nutritionists.[7,8]According to the recommendations of the American Diabetes Association (ADA), insulin therapy is then given when the glycemic target cannot be achieved only with dietary modifications, MNT, and lifestyle changes[6,9], namely if fasting blood glucose (FBG)> 92 mg/dl or 1 hour. Post-prandial (PP)blood glucose > 130 mg/dl in at least 20% of measurements in a week.8

Table 1. Journal Summary Matrix

No	Author, Year of Publication, Type of Study	Sample	Therapy Used	LGA Outcome	Macrosomia Outcome
1	Au et al. 2016, cross-sectional	67 single term babies born to GDM patients between September - October 2010 at the Royal Prince Alfred Hospital, Sydney, Australia	MNTandexercise (n = 38) MNT, exercise, insulin (n = 29)	MNTandexercise 5% (n = 2) MNT, exercise, and insulin 10% (n = 3)	N/A
2	Kanai et al. 2016, cohort	38 patients with mild GDM according to IADPSG criteria between 2009 - 2010 at Tsukuba University Hospital, Japan	Without therapy (n = 38)	Without therapy26.3%	Without therapy2.6%
3	Shi et al. 2016, retrospective cohort	488 GDM patients aged 21-44 years who were treated by the associate Department of Clinical Nutrition and Obstetrics of the China-Japan Friendship Hospitalbetween 2008-2012	MNT (n = 307) [With insulin 20.25% (n = 63)] WithoutMNT (n = 181) [With insulin 42.54% (n = 77)]	N/A	MNT 9.77% (n = 30) WithoutMNT 27.62% (n = 50)
4	Silva et al. 2016, retrospective cohort	705 GDM patients in general maternity hospitalsbetween July 2010 - August 2014	MNT + exercise 41.6% MNT + exercise + metformin 35.5% MNT + exercise + insulin 15% MNT + exercise + metformin + insulin 7.9%	MNT + exercise 26.31% (n = 30) MNT + exercise + metformin 28.07% (n = 32) MNT + exercise + insulin 26.31% (n = 30) MNT + exercise + metformin + insulin 19.29% (n = 22)	1.9% (n = 13)
5	Bogdanet et al. 2017, retrospective cohort	1319 GDM patients according to IADPSG criteria between 2009 - 2014 from the ATLANTIC DIP database	MNT + exercise (n = 567) MNT + exercise + insulin (n = 752)	MNT + exercise 12.5% (n = 71/566) MNT + exercise + insulin 19.7% (n = 143/727)	MNT + exercise 12.7% (n = 72/565) MNT + exercise + insulin 22.2% (n = 165/744)
6	Bianchi et al. 2018, retrospective cohort	1198 pregnant womenwere referred to the diabetes clinic at The University Hospital of Pisa from January 2010 - March 2015 for GDM screening	MNT + exercise 67% MNT + exercise + insulin 33%	No differences were observed	No differences were observed
7	Eid et al. 2018, RCT	250 GDM patients at Alglaa Teaching Hospital antenatal clinic from March 2016 - June 2017	MNT + exercise + insulin (n = 113) MNT + exercise + metformin (n = 116)	MNT + exercise + insulin 15.5% (n = 18) MNT + exercise + metformin 11.5% (n = 13)	MNT + exercise + insulin 5.2% (n = 6) MNT + exercise + metformin 2.8% (n = 3)
8	Huhtala et al. 2018, RCT	319 GDM patients at Turku University Hospital, Turku, Finland, from June 2006 - December 2010, 216 of whom were randomized to receive insulin or metformin therapy	MNT (n = 103) MNT + insulin (n = 107) MNT + metformin (n = 109)	MNT 11.7% (n = 12) MNT + insulin 15.9% (n = 17) MNT + metformin 14.3% (n = 15)	MNT 4.9% (n = 5) MNT + insulin 0.9% (n = 1) MNT + metformin 4.6% (n = 5)
9	Khin et al. 2018, retrospective cohort	138 GDM patients on diet and metformin therapy in a UK district hospital, from January 2009 - December 2012	MNT + exercise + metformin (n = 61) MNT + exercise + metformin + insulin (n = 77)	MNT + exercise + metformin 6.5% MNT + exercise + metformin + insulin 13% (n = 10)	MNT + exercise + metformin 3.8% (n = 2) MNT + exercise + metformin + insulin 5.2%

Cont... **Table 1. Journal Summary Matrix**

10	Zamstein et al. 2018, population-based cohort	10184 GDM patients with singleton pregnancies who gave birth at a tertiary referral hospital from 1991-2014 59 GDM patients from January 2011 - January 2013	MNT + exercise (n = 9460) MNT + exercise + insulin/OAD (n = 724)	MNT + exercise 11% MNT + exercise + insulin/ OAD 18%	MNT + exercise 10% MNT + exercise + insulin/OAD 13.3%
11	Zygula et al. 2018, cohort	59 GDM patients from January 2011 - January 2013	MNT (n = 44) Insulin (n = 15)	N/A	MNT 0% Insulin 13%
12	Lu et al. 2019, case-control retrospective	68 GDM patients who delivered at term at People's Hospital of North Jiangsu Province from January 2017 - June 2017	MNT (n = 56) Insulin (n = 12)	N/A	MNT 16.1% (n = 9) Insulin 16.7% (n = 2)
13	Manoharan et al. 2019, cross-sectional	40 primi gravida GDM patients on insulin therapy in the South Indian Tamil population	MNT + insulin (n = 40)	MNT + insulin 17.5% (n = 7)	N/A
14	Meghelli et al. 2019, retrospective cohort	121 singleton gestational diabetes mellitus patients with BMI before gestation> 40 kg/m2 from January 1996 - December 2014	MNT (n = 56) MNT + insulin 52.9% (n = 63)	MNT 35.2% (n = 19) MNT + insulin 29.5% (n = 18)	N/A
15	Kapustin et al. 2020, longitudinal prospective	40 GDM patients according to IADPSG criteria	MNT (n = 20) Insulin (n = 20)	N/A	MNT 20% (n = 4) Insulin 35% (n = 7)
16	Pazzagli et al. 2020, cohort	2467 GDM patients in Sweden from 2012-2016 who had recently received insulin or metformin therapy at 2nd or 3rd trimester	Insulin 88% (n = 2182) Metformin 7.6% (n = 187) Insulin + metformin 4.3% (n = 107)	N/A	Insulin 20% (n = 436/2182) Metformin 9.7% (n = 18/187) Insulin + metformin 21.7% (n = 23/107)
17	Penager et al. 2020, case-control retrospective	113 cases of birth in singleton gestational GDM patients with complicated macrosomia (only 81 data on therapy)	MNT76%, MNT + insulin 24% (n = 26) [Insulin wasmore used in macrosomia group than in normal control group]	N/A	N/A

In several other studies, metformin is used as the first line when glycemic control cannot be achieved with MNT and physical activity alone.[10] If the glycemic control target remains unattainable with the maximal dose of metformin (2,5 g), the patient is then advised to take insulin therapy. In some cases of severe GDM, insulin can be given immediately, without having to use metformin first. GDM is considered severe if the fetal abdominal circumference exceeds the 90th percentile, the patient'sFBG> 100 mg/dl, and the 1 hour-PP blood glucose level>140 mg/dl.[11]

Shi *et al*. in 2016 used MNT guidelines published by the Chinese Diabetes Society and the China Medicine Doctors Association Nutrition Doctor Specialized Committee. MNT is regulated based on the patient's body type before pregnancy, gestational age at diagnosis of GDM, weight gain during pregnancy, blood pressure, and lipid levels. MNT regulates food types and measures recommended intakes to ensure a balanced intake of the necessary nutrients, especially those with a low glycemic index. MNT also provides mealtime recommendations based on routine blood glucose monitoring data. MNT recommends small but frequent meals, to reduce the glycemic load at each meal, and suggests postprandial exercise.[7]

Suggestions for postprandial exercise include walking for 10 minutes a few days a week and gradually adding 5-10 minutes of exercise each day. For the majority of patients, the goal is to walk for 30 minutes most days of the week. Patients are also

advised to add more time to their daily physical activities. This exercise is recommended not to be done excessively, and only in a light form.[12]

Effect of GDM Therapy on Glycemic Control

Data on glycemic control are only available in a few articles. Au *et al*. in 2016 found that good glycemic control was achieved in most of the subjects, with 56 of 62 (90%) patients meeting the control targets. All patients in this study used MNT and exercise, while those who had not reached the target with both were given insulin in their regimen. Both groups showed the same results on the results of glycemic control.[6]

However, in another study, it was found that in patients on insulin therapy, patients with excess body weight, and/or BMI>30 kg/m^2, glycemic control was only sub-optimal, and HbA1C values were higher. This was subsequently associated with higher levels of LGA and macrosomia in patients receiving insulin therapy, compared to those receiving MNT alone.[9] This phenomenon was also found in a study by Penager *et al.* in 2020, who found that poor glycemic control was found three times more in the group with macrosomia, whereas in this group higher insulin use was also foundcompared to the control group without macrosomia.[13]The use of a combination of metformin and insulin, was found to increase the average score of glycemic control when compared to insulin alone.[10]

In another study, the use of metformin in MNT and exercise regimens also showed good results in GDM control and was shown to reduce unwanted neonatal outcomes.[11] This result is quite different from the study by Huhtala *et al.* in 2018, which found that patients who were given a combination of MNT and metformin with MNT and insulin did not show different results on glycemic control.[14]

Comparison of Macrosomia Incidence in Various Therapies

Of the seventeen studies analyzed, only twelve had data regarding the number of incidences of macrosomia. Of these, only eleven studies contained more than one group of therapeutic modalities so that they could be compared.Ten studiessuggested an association between insulin use and a higher incidence of macrosomia.[9,10,12,13,15,16,17,18] Three studies found this phenomenon in patients treated with insulin alone[16,17,18] and two studies found this phenomenon in patients receiving MNT, exercise, and insulin.[9,12]

When viewed by percentage, the average macrosomia level was found to be highest in the group without MNT, which was 27.62%[7] and was followed by the metformin and insulin combination group with 21.7%.[19] Other moderately high results were found in the insulin-only group, with a mean of 21% (range 13-35%).[16,17,18] The results obtained indicate a relationship between insulin use and high levels of macrosomia.This can be explained by the existence ofa therapy protocol that insulin will only be given or added to the therapeutic regimen if a patient is not able to achieve good glycemic control with lifestyle modification alone. The results also demonstrate the importance of using lifestyle modifications that accompany insulin therapy, compared to the use of insulin alone.

Different results were obtained in a study by Huhtala *et al*. in 2018, who found that the incidence of macrosomia was found to be higher in patients with MNT alone, although the incidence of LGA was more common in the use of MNT and insulin.The different results obtained could be explained by the excellent glycemic control achieved in both groups. There were no differences in maternal weight before and after therapy, as well as other baseline characteristics. The variation in glucose levels in this study was very small, leading to the outcome differences between the two groups were not significant.

Data regarding therapeutic modalities associated with the lowest levels of macrosomia were only obtained in ten studies.Four studies found the lowest levels of macrosomia in the group with MNT alone[7,16,17,18], two studies found this phenomenon in groups with MNT and exercise.[9,15], and two other studies found this phenomenon in the group with MNT, exercise, and metformin.[12,10]. The rest of the studies found this phenomenon in the group treated with metformin alone[19]and MNT and insulin.[14] Most of the studies that contain data regarding the lowest levels of macrosomia (6 out of 10) found that the use of lifestyle modification as the first line in the GDM therapy protocol was able to reduce the level of macrosomia. The absence of additional therapy also implies that the patient's glycemic balance is achieved, resulting in a lower macrosomia outcome.This phenomenon can prove that the GDM therapy protocol that has been applied has good and appropriate outcomes as expected.

In terms of percentage, the average macrosomia level was found to be the lowest in the MNT and insulin therapy group, which was 0,9%. This study showed excellent glycemic control in all groups of therapeutic modalities so that even though insulin was used, the macrosomia level was still very low.[14] The percentage of the smallest macrosomia level was then followed by the group without any therapy with 2,6%. However, this may be influenced by the severity of GDM in the study sample which was still mild.[20]The next four treatment regimens had additional metformin as a treatment modality. MNT, exercise, and metformin occupy the third-lowest percentage level, with an average of 3,3%% (range 2,8-3,8%)[10,12];MNT and metformin group with a percentage of only 4,6%[14]; followed by the MNT, exercise, metformin, and insulin group with 5,2%[10]; and metformin therapy alone with a macrosomia incidence of 9,7%.[9]This phenomenon can support the idea of using metformin in the treatment regimen before insulin is given.

Comparison of LGA Incidence in Various Therapies

LGA is defined as neonate weight > P90 according to gestational age and sex.[6] Of the seventeen studies, only nine have data related to the number of LGA incidents. Among these, there were only eight studies that contained more than one therapeutic modality group that can be compared.Six studies found a link between insulin use and a higher incidence of LGA. Three of them found this phenomenon in patients with MNT, exercise, and insulin.[6,9,12]Different results were obtained in the study by Silva *et al*. in 2016, who found that the incidence of LGA was higher in patients with MNT, exercise, and metformin therapy, compared to patients treated with lifestyle modification alone, lifestyle modification and insulin, or lifestyle modification with a combination of insulin and metformin.[11] The incidence of LGA is also seen to have a fairly large percentage in the group with MNT therapy alone in Meghelli *et al.* 2019, which is 35.2%. However, this may occur due to the sample of this study which is GDM patients with obesity. Obesity is an independent risk factor for macrosomia, so its effect is synergistic with GDM in aggravating LGA in infant patients. This study implies that optimal therapy is important to minimize the risk of macrosomia.[21]

All studies containing outcomes in the form of LGA and macrosomia have synergistic results, except in the study by Huhtala *et al* in 2018, which found differences in the treatment group which gave more incidences of outcomes. This study found a higher incidence of LGA in the MNT and insulin groups, which was 15,9% of the total sample, while the incidence of macrosomia was higher in the group of patients treated with insulin alone, which was 4,9% of the total sample.[14]

Manoharan *et al*. in 2019 found that the LGA outcome in patients receiving MNT and insulin was 17,5%.[22]Another study also found that mild GDM patients without therapy found the incidence of LGA of 26,3%.[20]

Data on therapeutic modalities associated with the lowest LGA levels were obtained in eight studies. Three of them found this phenomenon in the group with MNT and exercise.[6,9,15] Two studies found this phenomenon in groups with MNT, exercise, and metformin.[10,12]The rest of the studies found this phenomenon in the MNT, exercise, metformin, and insulin therapy group[11]; MNT alone[14] and MNT and insulin.[21] When viewed from the percentage of LGAincidence, therapeutic modalities with the best outcomes are the MNT and exercise group, with a range of 5-13%, and an average of only 10%.[6,9,15]

The next three treatment groups with the best outcomes used metformin in their treatment regimen. MNT and metformin are the therapeutic modalities with the second smallest percentage, which is only 14,3%[14]; followed by the group receiving MNT, exercise, and metformin with an average of 15,36% (range 6,5-28,07%)[10,11,12]; and the MNT, exercise, metformin, and insulin groups with an average of 16,15% (range 13-19,29%).[10,11]Further research is needed on the safety of using metformin in GDM patients.

Conclusion and Acknowledgement

In conclusion, the use of MNT and exercise in the therapeutic regimen, as well as routine monitoring of glycemic levels are very important to control the patient's glycemic level. The use of metformin can increase the success of therapy due to reduced levels of LGA and macrosomia in GDM patients. Therefore, glycemic control with MNT, exercise, and administration of metformin or insulin optimally as indicated, is very important to reduce undesirable GDM outcomes, especially macrosomia and LGA.

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Abbreviation

1) ADA — American Diabetes Association

2) FBG – Fasting Blood Glucose

3) GDM – Gestational Diabetes Mellitus

4) IADPSG – I*nternational Association of the Diabetes and Pregnancy Study Groups*

5) LGA – Large for Gestational Age

6) MNT – Medical Nutrition Therapy

7) N/A – Not Available

8) OAD – Oral Anti-Diabetic Drug

9) PICO – Population, Intervention, Comparison, Outcome

10) PP – Post-Prandial

11) PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analysis

12) RCT – Randomized Controlled Trial

13) WHO – World Health Organization

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