A COMPARISON FOR THE MATERNAL AND PERINATAL OUTCOME BETWEEN METFORMIN AND INSULIN IN THE TREATMENT OF GESTATIONAL DIABETES MELLITUS

BY:

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LIST OF ABBREVIATIONS

1HPG	One hour post-prandial glucose
2HPP	Two hour post-prandial
ADA	American Diabetic Association
AFI	Amniotic Fluid Index
ANC	Antenatal Care
ANOVA	Analysis Of Variance
AMP	Adenosine monophosphate
BD	twice a day
BMI	Body Mass Index
BSP	Blood sugar profile
CI	Confident Interval
CPG	Clinical Practice Guideline
CBS	Capillary blood sugar
CTEV	Congenital talipes equino varus
DM	Diabetes Mellitus
FBG	Fasting blood Glucose
GDM	Gestational Diabetes Mellitus
HPT	Hypertension
HPG	Hour postprandial glucose
IADPSG	International association of Diabetes and Pregnancy Study Groups
IUPAC	International Union of Pure and Applied Chemistry

IUGR	Intrauterine growth restriction
IOM	Institute of medicine
LGA	Large gestational age
LFT	Liver function test
MNT	Medical Nutrition Therapy
OGTT	Oral Glucose Tolerance Test
OHA	Oral Hypoglycaemic Agent
OD	once daily
OM	once on morning
ON	once on night
OR	Odd ratio
PCOS	Polycystic Ovarian Syndrome
PE	Preclampsia
PPROM	Preterm premature rupture of membrane
POG	Period of gestation
POA	Period of Amenorrhoe
PIH	Pregnancy induce hypertension
RCT	Randomized Control Trials
RP	Renal profile
RDS	Respiratory distress syndrome
SD	Standard Deviation
SHBG	Sex hormone binding globulin
S.C	Subcutenous injection

SAH	Subarachnoid haemorrhage
SPSS	Software package statistical Analysis
TDS	Three times daily
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization
WMD	Weight mean difference
USA	United State of America

ABSTRACT

Background: Diabetes mellitus (DM) is an important complication of pregnancy which may carry adverse effects on both mother and fetus. While insulin is effective in controlling high blood glucose levels, otherwise resistant to diet and exercise management, several factors hinder its usage. Metformin has been found to be a convenient, cheap, effective and safe hypoglycaemic agent in some countries. It is possible that metformin will have similar beneficial effects among Malaysian pregnant women.

Aim: The main aim of this study was to determine that metformin is an effective treatment for glycaemic control in the gestational diabetes mellitus (GDM) population in Malaysia as compared to insulin. It is also to assess the safety of these treatments by evaluating the maternal and fetal outcomes in GDM patients treated either with metformin or insulin.

Methodology: A prospective, open label, randomized controlled study involving 99 pregnant women recruited between 12 – 32 weeks gestation, diagnosed with GDM. Patients were randomized to be either in the insulin group (n=48) or metformin group (n=51). Participants were followed-up throughout their pregnancy with a 2-weekly BSP monitoring till date of delivery. Mother and perinatal outcomes were followed-up till mother and baby were discharged from the ward postnatally. Both laboratory and clinical data were recorded and analyzed.

Results: 98% and 95% of participants in the metformin and insulin groups respectively completed the study. The primary outcomes in comparing the differences of capillary blood glucose (BSP) levels between metformin group and insulin group shown that there is no significance difference between metformin group and insulin group at all different treatment periods.

Maternal weight gains between both groups were no significantly different- at 8.8kg (±4.27) in metformin group to the 8.8kg (±3.43) insulin group ($p > 0.950$). The rates of maternal hypertension complications did not differ significantly between the two groups. Higher reported cases of urinary tract infection (UTI) in metformin group as in 30% while only 6.5% in the insulin group ($p=0.003$).

Average birth weight in the metformin group [3.1kg (±0.26)] is similar to the insulin group [3.0kg (±0.48)]. No significance difference in neonatal morbidity; hypoglycemia, hyperbilirubinaemia or respiratory disorder, was observed between metformin and insulin group.

Conclusion: Efficacy of metformin therapy was similar to insulin in giving good optimum glycaemic control in GDM women in Malaysia and carries similar low risk in term of maternal and perinatal outcomes. However, more studies with larger sample numbers, wider sample population are needed to collaborate these findings.

ABSTRAK

Latar Belakang: Kencing manis ketika mengandung adalah suatu penyakit yang sangat lazim berlaku dan membawa impak kesan negatif kepada ibu dan bayi dalam kandungan. Walaupun insulin merupakan ubat yang sangat efektif bagi pengawalan kencing manis, terdapat beberapa perkara yang menghindar penggunaannya. Sebaliknya, metformin adalah ubat kencing manis yang didapati lebih murah, efektif, pengguna mesra dan selamat dikalangan negara-negara tertentu. Diharapkan metformin akan memberi kebaikan yang sama dalam pengawalan kencing manis dalam golongan ibu-ibu hamil di Malaysia.

Tujuan: Tujuan utama kajian ini adalah untuk membuktikan bahawa metformin adalah efektif dalam pengawalan gula dalam darah yang optimum dalam golongan wanita hamil berkencing manis di Malaysia seperti ubat insulin. Ia juga bertujuan untuk memastikan keselamatan ubat dengan mengkaji komplikasi-komplikasi keatas ibu dan bayi pesakit kencing manis yang menerima rawatan metformin atau insulin.

Kaedah: Ini adalah RCT melibatkan 99 orang wanita hamil yang berpenyakit kencing manis, direkrut diantara 12-32 minggu mengandung. Mereka secara rawak ditempatkan samaada dalam kumpulan insulin (n=48) atau kumpulan metformin (n=51). Ujian gula dalam darah dibuat setiap dua minggu sekali sepanjang proses mengandung sehingga tempoh bersalin. Data mengenai

bacaan ujian darah, komplikasi-komplikasi yang dihadapi oleh pesakit atau bayi dikumpul dan dikaji.

Keputusan: 98% dan 95% wanita dalam kumpulan metformin dan insulin telah disusuli sehingga tamat kajian. Keputusan utama telah membuktikan bahawa tidak ada perbezaan ketara diantara kumpulan metformin dan insulin dari segi pengawalan gula dalam darah (BSP) bagi pesakit berkencing manis ketika mengandung.

Keputusan sampingan adalah peningkatan berat badan wanita mengandung diantara kedua-dua kumpulan adalah antara 8.8kg (±4.4) dalam kumpulan metformin berbanding dengan 8.8kg (±3.43) dalam kumpulan insulin ($p>0.950$). Ini bermakna tidak ada perbezaan diantara kedua-dua kumpulan.

Kes penyakit darah tinggi dan komplikasinya diantara insulin dan metformin kumpulan adalah sama. Kes jangkitan infeksi pundi kencing (UTI) lebih tinggi dalam kumpulan metformin (30%) berbanding insulin (6.5%) ($p<0.003$)

Purata berat bayi dalam kumpulan metformin [3.1kg (±0.26)] sama dengan kumpulan insulin [3.0kg (±0.48)]. Tidak ada perbezaan dalam kes-kes komplikasi keatas bayi seperti gula rendah, jaundice atau masalah pernafasan.

Kesimpulan: Rawatan metformin adalah sama dengan rawatan insulin dalam memberi kawalan gula dalam darah yang optimum dikalangan wanita menghidap kencing manis ketika mengandung di Malaysia. Ia juga membantu mengawal komplikasi-komplikasi kencing manis bagi ibu dan bayi sama seperti insulin.

Walaubagaimanapun, adalah disarankan lebih banyak kajian dibuat dengan jumlah peserta yang lebih ramai dan melibatkan kawasan kajian yang lebih besar bagi menyokong kajian ini.

1) INTRODUCTION

1.1) OVERVIEW OF THE STUDY

Gestational diabetes mellitus (GDM) is defined as “glucose intolerance with onset or first recognition during pregnancy (Metzger BE and Couston DR, 1998). These criteria for the diagnosis were initially established more than 40 years ago and, with minor modifications, remain in use today. GDM is a very strong risk factor for the development of type 2 diabetes (T2DM) in later life. Published studies have shown that after GDM, 35-60% of women develop type 2 diabetes within 10 years (Metzger BE et al, 2007).

Several theories were proposed to explain why the rates of GDM and T2DM were found higher in Asian population:-

- Genetic studies of GDM and T2DM have demonstrated several shared gene loci (Petry C et al, 2010). Ethnic differences in gene loci associated with T2DM have been demonstrated between Thai and Caucasian women supporting the above theory.

- The number of low birth weight babies is concentrated in two regions of the developing world: Asia and Africa. 72% of low birth weight infants in developing countries are born in Asia. 22% are born in Africa. There are more than 1 million infants born with low birth weight in China and nearly 8 million in India (UNICEF, 2004). In 1992, Hales and Barker proposed the model of the “thrifty phenotype,” suggesting that intrauterine growth retardation (IUGR) and low birth weight can lead to insulin resistance and

decreased beta cell mass, thus predisposing to T2DM later in life (Hales and Barker, 1992).

The prevalence of diabetes in Peninsular Malaysia as reported in the 1st National Health and Morbidity Survey in 1986 was at 6.3%. National Obstetric Registry (2009) data shows there were 136856 deliveries in the 14 state hospitals in Malaysia. The incidence of diabetes in pregnancy is 9.9% in which majority is GDM 11,848 (8.6%) and 1009 (0.74%) is preexisting diabetes mellitus (DM). A local study in Negeri Sembilan has reported a high prevalence for GDM, which is 18.3% (Idris N et al, 2009). Therefore, it is prudent that GDM is diagnosed and appropriate treatment and monitoring instituted.

During pregnancy, an increase in insulin resistance occurs due to the effect of pregnancy hormones. Euglycaemia is achieved by compensating increase insulin secretion. As the increase in insulin resistance is greatest in 3rd trimester, screening of GDM is recommended around 24-28 weeks. In Malaysia, we advocate high risk pregnancy screening. Patients were considered to be risk-factor positive if any of the following is present as per recommended by Malaysia Clinical Practice guidelines (CPG) May 2009.

- age 25 years and above
- previous macrosomic baby with birth weight 4.0kg or more

- previous unexplained still birth
- previous baby with congenital abnormally
- recurrent miscarriages (3 or more)
- previous pregnancy with gestational diabetes mellitus
- history of DM in first degree relatives
- Body mass index (BMI) >27kg/meter square

In Hospital Tuanku Jaafar Seremban, oral Glucose Tolerance Test (OGTT) was done for these groups of people as per recommended by Malaysia CPG - Management of T2DM Third Edition (2004) using the value of ≥5.6mmol/L for 0-hour and ≥7.8mmol/L for 2-hour blood glucose level. In this study, the targets capillary fasting glucose < 5.3mmol/L and/or 2-hour postprandial glucose of <6.7mmol/L: as per recommended by The Fifth International Workshop-Conference on Gestational Diabetes (2007) were used.

Overt DM during pregnancy is associated with significantly increased risks of complications to the pregnancy, adverse perinatal outcomes and a long term risk of diabetes in both mother and offspring as demonstrated in the HAPO study (Coustan DR, 2004, Dabelea D et al, 2000). First-line therapy is dietary modification and moderate exercise. However pharmacotherapy is indicated if

maternal hyperglycaemia remains persistence and insulin has traditionally been the gold standard drug of choice.

Subcutaneous insulin therapy has been the mainstay treatment of women with gestational diabetes not controlled by diet modification and has been shown to improve perinatal outcomes (Crowther CA et al, 2005). However, women who begin insulin therapy require intense education and instruction to ensure the safe administration of insulin. Use of insulin is also associated with the risk of hypoglycaemia and weight gain. Insulin treatment is costlier and the administration is difficult and inconvenient.

The use of safe and effective oral agents may offer advantages over insulin. They are easier to administer, non-invasive and therefore user-friendly. Oral metformin is a logical option for women with GDM. Metformin was first described in scientific literature in 1922, but only made available worldwide in Britain (1958), Canada (1972) and USA (1994). Historically, some of the earliest reports of the use of metformin during pregnancy have come from South Africa, where it has been used since the late 1970s for women with both T2DM and GDM (Coetzee EJ and Jackson WPU 1979, 1980, 1984, 1985).

In Hospital Tuanku Jaafar, metformin has been used in combine with insulin in patient with GDM and T2DM with extreme high dose of insulin per day. It improves insulin sensitivity, probably by activating AMP kinase, thus enhances

peripheral glucose uptakes, improves insulin binding to the insulin receptor and reduces absorption of glucose in gastrointestinal tract.

Since then, multiple small studies have been done to explore the effectiveness of metformin in improving fertility in patient with polycystic ovarian syndrome (PCOS) such as studies done by (Tang T in 2010 and Palomba S in 2009) that look at the improvement of early pregnancy and reduction of 1st trimester miscarriage in PCOS patient on metformin through out pregnancy. No obvious adverse effect or cases of tetratogenicity were reported in these studies.

Since then, many other studies have been done on metformin for the treatment of GDM (Goh JE 2011, Rai L 2009, Balani J 2009). A recent systematic review and meta analysis (Jaya SD et al, 2010) involving six studies comprising 1388 subjects were analyzed. It has shown no significant differences were found in maternal fasting (weighted mean difference [WMD], 1.31; 95% confidence interval [CI], 0.81–3.43) or postprandial (WMD, 0.80; 95% CI, –3.26 to 4.87) glycaemic control. Use of OHA was not associated with risk of neonatal hypoglycaemia (odds ratio [OR], 1.59; 95% CI, 0.70–3.62), increased birth weight (WMD, 56.11; 95% CI, –42.62 to 154.84), incidence of caesarean section (OR, 0.91; 95% CI, –0.68 to 1.22), or incidence of large-for-gestational-age babies (OR, 1.01; 95% CI, 0.61–1.68). Other outcomes in which no significant differences were found between treatments were admission to neonatal intensive care units, neonatal respiratory distress and birth injuries, and incidence of small-

for-gestational-age babies, preterm births, intrauterine foetal death, congenital abnormalities and maternal hypoglycaemia. The review concludes that OHA are credible and safe alternatives to insulin for the first-line treatment of GDM. In selected cases, these agents may be used as adjunctive treatments to insulin in the management of gestational diabetes.

Metformin used in pregnancy remains controversial. To our knowledge, only small, randomized trials addressing this question have been reported to date (Jaya SD 2010, Rowan JA 2008, Glueck CJ 2004, Hague WM 2003). Reported outcomes of its use during pregnancy have been favourable and promising. However, more randomized trials studies are recommended to support these promising outcomes, thus the reason of this study. Also previous studies have not been done in Asian community. By doing this study, we will be able to provide the Asian population data to support the safety and effectiveness of the drug in treatment of GDM in pregnancy. This will hopefully allows future pregnant mother with GDM will have another option treatment that is practical, convenience and safe.

1.2) NULL HYPOTHESIS

- Glycaemic control will be equally control with metformin therapy as with insulin therapy in GDM patient in Malaysia
- Maternal outcome and perinatal outcome complication is similar in metformin therapy as with insulin therapy

1.3) JUSTIFICATION OF THE STUDY

Several studies have been done in countries like United States of America (USA), Australia, Canada and India have shown metformin as an effective treatment of GDM as to insulin. However, there is no published data on the use of metformin in pregnancy for glycaemic control in Malaysia. Thus, to collect local data regarding the perinatal and maternal outcome of GDM on metformin treatment in compare to insulin treatment cannot be overemphasized. Hopefully in the future, mother with GDM will have the options in the treatment of GDM that is more convenience, easier, simple and practical.

2) LITERATURE REVIEW

2.1) DIABETES MELLITUS (DM)

The World Health Organization (WHO) defines diabetes mellitus as a metabolic disorder of multiple aetiology characterized by, chronic hyperglycaemia with disturbance of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (WHO, 1999). This classification was used in this study.

The American Diabetes Association (ADA) categorized DM into four clinical classes:

Type 1 diabetes (results from β-cell destruction, usually leading to absolute insulin deficiency)

- Type 2 diabetes (results from a progressive insulin secretary defect on the background of insulin resistance)
- Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation)
- GDM (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (Diabetes Care, 2012)

Another method for classifying diabetes in pregnancy is the White classification. There are two main groups; GDM (class A) and pre-gestational diabetes (classes B-T). In this classification, the class A diabetes is further sub-divided into two as follows:

- Class A1: gestational diabetes; diet-controlled
- Class A2: gestational diabetes; medication-controlled

Pre-gestational diabetes, or classes B to T is sub-classified as follows:

- Class B: onset at age 20 or older or with duration of less than 10 years
- Class C: onset at age 10-19 or duration of 10–19 years
- Class D: onset before age 10 or duration greater than 20 years
- Class E: overt diabetes mellitus with calcified pelvic vessels
- Class F: diabetic nephropathy
- Class R: proliferative retinopathy
- Class RF: retinopathy and nephropathy
- Class H: ischemic heart disease
- Class T: prior kidney transplant

2.2) GESTATIONAL DIABETES MELLITUS (GDM)

GDM is defined as carbohydrate intolerance that begins or is first recognized during pregnancy (WHO, 1999). It is a well-known complication of pregnancy but its prevalence varies greatly due to differences in screening programmes and diagnostic criteria. GDM complicates about 5% of pregnancies with long-term risk