Project Title: A randomized pilot study evaluating combination DPP4 inhibitor sitagliptin plus biguanide metformin compared to metformin monotherapy or placebo on glycemic and metabolic abnormalities in women with a recent history of gestational diabetes mellitus

Principal Investigators: Karen Elkind-Hirsch, M.Sc., PhD
Martha Paterson, M.D.

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Address Woman's Health Research Department
Woman's Metabolic Health Center
100 Woman's Way
Baton Rouge, LA 70817

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A randomized pilot study evaluating combination dipeptidyl peptidase IV (DPP4) inhibitor sitagliptin plus biguanide metformin compared to metformin monotherapy or placebo on glycemic and metabolic abnormalities in women with a recent history of gestational diabetes mellitus

Project Overview/Summary

The objective of the present proposal is to compare the clinical, endocrine and metabolic effects of therapy with combination sitagliptin and metformin to metformin monotherapy and placebo in former GDM women with prediabetic hyperglycemia. Sitagliptin is an oral dipeptidyl peptidase IV (DPP-4) inhibitor whose mechanism of action is to prolong the duration of blood glucagon-like peptide (GLP-1) levels by inhibiting its degradation and thereby augmenting insulin secretion This study will serve as a pilot investigation to open perspectives for future studies combining anti-diabetic drugs with different mechanisms of action in women with a history of GDM for whom standard treatment with metformin is less effective.

Primary Objective:

- To assess the effects of sitagliptin plus metformin therapy compared to metformin monotherapy and placebo on pancreatic beta cell (β-cell) compensatory function and glycemic parameters in former GDM women with prediabetic hyperglycemia who are at high risk of developing Type 2 diabetes (DM2). Our findings focus on delineating which medication(s) show the best promise for slowing or arresting the β-cell dysfunction and increased risk of developing diabetes in women with recent GDM.

Secondary Objective(s)

- To analyze the impact of sitagliptin + metformin therapy compared to metformin alone and placebo in improving select cardiometabolic markers (lipid fractions and blood pressure) in at-risk prior GDM women with prediabetic hyperglycemia.

Study Background and Rationale

Gestational diabetes mellitus (GDM) is one of the most frequent metabolic disorders occurring during pregnancy that complicates both the course of pregnancy and the delivery, and also has significant implications for the future health of the mother.[1, 2] Although the precise definition of GDM remains unclear, it is widely assumed to be an early manifestation of type 2 diabetes (DM2) resulting from insulin resistance and inadequate insulin secretion associated with overweight and obesity, and the diabetogenic effects of placental hormones.[3-5]

Insulin resistance and beta cell dysfunction are the main pathophysiological factors of GDM just as they are for diabetes outside of pregnancy.[6-7] There may be a finite level of pancreatic “beta cell reserve” that is further depleted with recurring GDM. It is possible that recurrent episodes of heightened insulin resistance, such as with recurrent pregnancy, place

high demands on the pancreas and contribute to an eventual decline in beta cell function that leads to type 2 diabetes (DM2) in high-risk individuals. After an index pregnancy with gestational diabetes, GDM recurs in 30-84% of subsequent pregnancies.[8-10] Gestational diabetes is also a strong risk factor for the development of DM2 at a later stage of life in previous GDM woman. Among all the risk factors of diabetes mellitus, the experience of gestational diabetes is the strongest one. The incidence of various forms of diabetes in this group balances from 10 to 60% over a period from 2 to 10 years. Russell et al [11] found that 36% of GDM women had some degree of persistent abnormal glucose tolerance when tested at any time postpartum. Recently, Nelson et al [12] found that 8.9% of patients tested immediately postpartum had DM2, another 31.3% had other glucose metabolism abnormalities; only 55.8% had normal 2-hour glucose tolerance tests.

Most, but not all women with a history of GDM have falling β-cell compensation for chronic insulin resistance during the first 5–10 years after the index pregnancy. In this setting, two general factors influence the risk of diabetes. The first is the level of metabolic deterioration that is present during and soon after pregnancy. In general, women with the highest glucose levels (*e.g.* impaired glucose or impaired A1C after pregnancy) are closest to diabetes and require relatively little deterioration to "cross the line" to that diagnosis. They are clearly prime targets for aggressive measures to prevent additional deterioration to diabetes. The second general factor that influences diabetes risk is the rate of deterioration. Rising glucose is a clinical indicator of deterioration. Hyperglycemia ensues when insulin secretion fails to compensate for the degree of insulin resistance. Defects in insulin secretion have been reported following a 75 g oral glucose load with a diminished response at 30 and 60 minutes in previous GDM women of European origin.[13] Among pharmacological interventions for the non-pregnant population, thiazolidinediones have the largest impact on diabetes risk reduction—in the range of 55–70% compared with placebo.[14,15] Interventions such as metformin or acarbose that primarily lower glucose produce smaller risk reductions (25–33%) and provide less evidence for slowing of rates of progression in general.[16,17] However, in the DPP,[18] metformin had a particularly strong effect to reduce diabetes risk or delay its onset in women with a history of GDM.

Whether pharmacological therapy should be prescribed for diabetes prevention is an open question given that waiting to add drug therapy until diabetes develops can arrest β-cell decline, albeit at a lower level of β-cell function than when medications are used for prevention.[19] Studies are needed for optimal postpartum and long-term health of women who have had GDM. Considerable recent evidence suggests that incretin-based therapies may be useful for the prevention of DM2. Whereas native GLP-1 has a very short half-life, continuous infusion of GLP-1 improves first and second-phase insulin secretion suggesting that early GLP-1 therapy may preserve ß-cell function in subjects with IGT or mild DM2. Incretin mimetics and inhibitors of the protease dipeptidyl peptidase (DPP)-4 use the anti-diabetic properties of the

incretin hormone, glucagon-like peptide (GLP)-1[20] hormone to not only augment glucose-induced insulin secretion in a highly glucose-dependent manner,[21] thus preventing GLP-1 alone from provoking hypoglycemia. Additional beneficial effects of GLP-1 on endocrine pancreatic islets are that it 1) supports the synthesis of proinsulin to replenish insulin stores in β-cells; 2) reduces the rate of β-cell apoptosis when islets are incubated in a toxic environment (glucotoxicity, lipotoxicity, cytotoxic cytokines); and 3) promotes differentiation of precursor cells with the ability to develop into β-cells and proliferation of β-cell lines, and in whole animals (rodent studies), this leads to an increased β-cell mass within a few days or weeks [20,22]. Furthermore, GLP-1 can lower glucagon concentrations, i.e., induce α-cells to respond again to the inhibitory action of hyperglycemia, while leaving the counterregulatory glucagon responses undisturbed, as in the case of hypoglycemia.[21,23] Additional activities of GLP-1 are the deceleration of gastric emptying, [24] which slows the entry of nutrients into the circulation after meals, a reduction in appetite, and earlier induction of satiety, [25] leading to weight reduction with chronic exposure.[26] Inhibition of DPP-4 increases the concentration of GLP-1 and may potentially delay disease progression in GDM considering the ß-cell function improvement in DM2 and ß-cell mass shown to increase in animal models. This study will examine if combination sitagliptin-plus metformin is more effective than metformin alone or placebo in improving metabolic parameters, specifically the impact on β-cell function, in at-risk women with a recent history of GDM and prediabetic hyperglycemia.

Rationale

The diagnosis of GDM identifies young women with abnormalities in pancreatic beta cell function that worsens over time, leading to diabetes. Weight loss and medications that mitigate impairments in insulin secretion show the best promise for delaying or preventing DM2, the dominant form of diabetes that develops after GDM.

The Primary Aims of this study are to determine whether administration of combination sitagliptin plus metformin will be more effective compared with metformin alone or placebo in:

- Improving ß-cell compensatory function by enhancing insulin release after an oral glucose load and thus improve or delay a decline in glucose tolerance estimated by the disposition index defined as the product of insulin action (Matsuda index) and insulin secretion (insulinogenic index) derived from the OGTT (SI_{OGTT} x Δinsulin30–0 min to glucose30–0 min).
- Improving markers of insulin sensitivity and secretion after an oral glucose load as measured by the Matsuda index and early insulin response adjusted for insulin sensitivity (insulinogenic index/HOMA-IR),
- Correcting glucose control as evaluated by fasting and 2 hour glucose levels after an OGTT.

Metformin failure in this patient population is associated with ß-cell dysfunction. We propose that combination sitagliptin plus metformin treatment will be superior to metformin monotherapy or placebo treatment in improving pancreatic ß-cell response resulting in a greater improvement in β-cell compensatory function which reflects a shift away from impaired glucose tolerance and DM2.

Secondary Aims

We will further examine whether the addition of sitagliptin to metformin therapy is more beneficial than metformin alone or placebo in altering the development or progression of select cardiometabolic risk factors as measured by changes in:

- plasma lipid fractions
- blood pressure
- anthropometric parameters, including body mass index [BMI], absolute body weight, waist circumference, waist: hip ratio, waist-height ratio

Direct comparison to metformin monotherapy is not expected to yield significantly differential weight loss or reduced central body weight in favor of combination sitagliptin plus metformin treatment given that both metformin and DPP-inhibitors are generally weight neutral. Given the short interval of treatment (12 weeks at full dose), no significant differences between placebo treatment and medical intervention on anthropometric measures or body fat distribution is anticipated.

Study Design

Design

Parallel 3 treatment group, single-blinded prospective, randomized, outpatient drug efficacy trial

Subjects

Women who are $\geq$ 18 years to 42 years of age with a recent history of GDM in the previous 12 months (diagnosis of GDM using Carpenter-Coustan criteria according to Fifth International Workshop—Conference on Gestational Diabetes Mellitus in the index pregnancy), meet all inclusion/exclusion and shown to have postpartum metabolic abnormalities will be offered participation in the study. It is inclusive of only those patients with previous GDM that require pharmacological intervention added to diet and exercise. Subjects will be recruited using flyers distributed in the obstetric clinics and pathology laboratory associated with Woman's Hospital. Participants will give written informed consent for participation in the IRB-approved study. All subjects will undergo a verbal screen, and if they are eligible and sign a medical release form, their prenatal records will be obtained to confirm their pregnancy history. A formal two hour Oral Glucose Tolerance test (OGTT) will be performed using a 75 gram oral glucose load. Patients will be eligible for randomization if they have impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both (IFG/IGT) by OGTT.

Inclusion Criteria

- Females ≥18 years to 42 years of age who experienced GDM during recent (within 12 months) pregnancy with prediabetic hyperglycemia determined by an oral glucose tolerance test (OGTT) with 75 g glucose postpartum. Study subjects will be inclusive of prior GDM women with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both (IFG/IGT) postpartum.
- Written consent for participation in the study

Exclusion Criteria

- Cholestasis during the past pregnancy
- Any hepatic diseases in the past (viral hepatitis, toxic hepatic damage, jaundice of unknown etiology)
- Serum AST and/or ALT level exceeding more than twice normal lab values
- Presence of hypersensitivity to sitagliptin or other DPP-4 inhibitor
- Current use of metformin, thiazolidinediones, GLP-1 receptor agonists, DPP-4 inhibitors, or weight loss medications (prescription or OTC)
- Prior use of medication to treat diabetes except gestational diabetes
- Use of drugs known to exacerbate glucose tolerance
- History of diabetes or prior use of medications to treat diabetes except GDM
- Renal impairment (e.g., serum creatinine levels ≥1.4 mg/dL for women and eGFR less than 60 mL/minute/1.73 m^2
- Pregnancy planned during the coming 6 months
- Currently lactating
- Patient not willing to use adequate contraception during study period (unless sterilized)

Method

All study patients will undergo the following clinical, metabolic and laboratory evaluations before and during treatment. A full physical examination will be performed including measurement of body mass index (BMI), waist and hip circumference (WHR), and vital signs (blood pressure, respiration and temperature) at the initial and final study visit. The total body adiposity (total fatness), defined as the accumulation of body fat without regard to regional distribution, will be expressed as BMI and calculated as weight (kg)/ height (m) ^{2}, whereas the waist-to-hip girth ratio (WHR) is a measure of body fat distribution. Height will be measured to the nearest centimeter and weight measured by a sliding weight balance to the nearest 0.1 kg. Waist circumference will be measured at the minimum circumference between the rib cage and iliac crest (in centimeters) and hip circumference at the level of the largest circumference around the buttocks. The circumference measurements will be taken in the

upright position using a 15-mm width flexible metric tape held close to the body but not tight enough to indent the skin.

All patients will randomly be assigned to one of 3 medication treatment groups-– either sitagliptin-metformin (50 mg/1000 mg BID), metformin (1000 mg BID) or placebo (1 pill/BID); all subjects will be allocated to one of these 3 groups based on computer-generated random numbers using a block randomization method. The pharmacy will "single-blind" all the treatment arms to the physicians and clinical coordinators by filling prescription containers with 1 of 3 medications- A) sitagliptin -metformin, B) metformin and C)placebo and dispensing open-label tablets to study patients in blinded coded (A,B,C) bottles. Oral glucose tolerance tests (OGTTs) with glucose (G) and insulin (I) measured at 0, 30, 60, and 120 after glucose load to assess diabetes, fasting (FBG) and mean blood glucose (MBG) concentrations, insulin resistance and pancreatic ß-cell function will be performed prior to randomization and at 12-14 weeks after full study medications are reached. Mean blood glucose (MBG) concentrations will be calculated by summing glucose values obtained at 0,30,60 and 120 minutes during the OGTT and dividing by 4. Baseline blood samples will also be analyzed for lipid profiles, TSH,liver enzymes creatinine with eGFR, and quantitative ßhCG levels. A negative serum pregnancy test is a prerequisite for commencing treatment. . All patients will meet with the registered dietician and receive postpartum lifestyle (diet and exercise) plans. At study completion, all medications will be stopped and subjects will be allowed to continue or given a prescription for other medications if needed. (See Flow charts 1 & 2)

Treatment

Eligible patients will be randomized to one of three treatment groups; either sitagliptin-metformin (50 mg/1000 mg BID), metformin (1000 mg BID), or placebo. For all patients taking metformin only, the initial oral dose will be 1000 mg Q.D. (with dinner) for 2-3 weeks and then increased to an oral dose of 1000 mg BID (breakfast and dinner) to reduce side effects. Patients assigned to combined therapy will be started on oral sitagliptin-metformin (50 mg/1000 mg) Q.D. (with dinner) for 2-3 weeks. They then will be increased to an oral dose of sitagliptin-metformin (50 mg/1000 mg) BID (breakfast and dinner). For placebo, the same regimen for other 2 treatments will be followed with patients starting with one pill in evening for 2-3 weeks, followed by one pill twice a day. All patients will receive the same counseling concerning the benefits of lifestyle modification through diet and exercise. The patients will be also encouraged to increase daily exercise (such as walking, using stairs), although this will not be formally assessed. The participants will receive further encouragement to adhere to the regime during follow-up phone calls. Side effects of the treatment and reason for any withdrawals from the study will be recorded. (See Figures 1 & 2).

Assessment of insulin sensitivity and secretion

Indexes of insulin sensitivity and secretion using the serum glucose and insulin concentrations obtained in the fasting state and during the 2hr OGTT with INS will be computed

by several measures previously validated in women. Fasting and glucose-stimulated insulin sensitivity will be estimated by homeostasis model assessment of insulin sensitivity (HOMA-IR) and by Matsuda's insulin sensitivity index [SI_{OGTT}]. [27,28] Early pancreatic β-cell response will be estimated as the insulinogenic index (IGI) derived from the ratio of the increment of insulin to that of glucose 30 minutes after a glucose load (insulin 30 min − insulin 0 min/glucose 30 min − glucose 0 min) corrected for by the relative level of insulin resistance (IGI/HOMA-IR).[29] An estimation of β-cell compensatory function will be calculated as the index of insulin secretion factored by insulin resistance (ΔINS/ΔPG 30 x Matsuda insulin index) during the OGTT.[30]

Collateral Research

Several other endpoints will be assessed at each study visit. Baseline blood samples will also be collected for measurement of lipid profiles (cholesterol, HDL and LDL cholesterol, and triglycerides), TSH, and liver enzymes (AST/ALT). Dyslipidemia is defined as the presence of at least one of the mentioned lipid parameters abnormalities.

Weight, height, BMI, waist circumference (WC), body fat distribution (waist/hip ratio [WHR] and waist/height ratio (WHtR), and blood pressure (BP) will also be determined.

The safety criteria will include incidence and intensity of adverse events, withdrawals because of adverse events, physical exams, vital signs and laboratory parameters

Concomitant Medications and Therapy

None of the patients will be allowed to take medications likely to influence metabolic profiles except thyroid supplementation. The following medications cannot be used immediately prior to or concomitant with the treatment therapy; drugs known to affect gastrointestinal motility, lipid lowering agents (statins), other medications known to affect carbohydrate metabolism (glucocorticoids, anabolic steroids) or anti-diabetes medications (metformin, thiazolidinediones, GLP-1 receptor agonists, pramlintide; DPP4 inhibitors) or weight reducing agents. Vitamins and topical medications can continue to be used. Use of IUD and hormonal contraceptives are also permitted.

Safety Measures

This protocol and the associated Informed Consent as well as any addenda or amendments, must be reviewed and approved by the Woman's Hospital Foundation Institutional Review Board (WHIRB) review committee prior to the start of the study. All revisions to this Protocol are considered "protocol amendments" these must be approved in advance, in writing, by the WHIRB. Every patient will have given her written informed consent prior to participating in the study. Prior to participation in this trial, each subject will have an opportunity to ask questions and will sign (and date) a written Informed Consent, which must be witnessed. The signed consent forms will be filed with the investigator's study charts for

each subject. Any subject may voluntarily withdraw from the study at any time without prejudicing treatment.

Patients starting all oral therapies will be advised that they may have minor gastrointestinal side effects. The most common side effects of metformin are diarrhea, nausea or vomiting, flatulence, indigestion, abdominal discomfort and rarely, a metallic taste in the mouth. These acute reversible adverse effects occur in 5–20% of patients treated with metformin. The symptoms are dose related and remit if the dose is reduced, sometimes an increase in the dose can later be tolerated. Taking the drug with or after food, and starting therapy with low dosages that may be increased slowly can minimize these. The dose can then be increased slowly at intervals of two weeks. Lactic acidosis is the biguanide-related adverse effect of most concern with an estimated incidence of less than 0.01 to 0.08 cases. Should a patient have lactic acidosis attributable to metformin, the drug can be removed by hemodialysis. Other contraindications to the use of metformin include concurrent liver disease and a previous history of lactic acidosis. Oral therapy will also be stopped if the blood lactate concentration is substantially increased by any illness. Oral therapy will be temporarily suspended for all major surgical procedures that involve restriction of fluid intake. Metformin and combined metformin plus DPP4 inhibitors are classified as United States Food and Drug Administration category B drugs (i.e., "no evidence of risk in humans"). This means that, while there is no evidence of teratogenesis or adverse fetal effects, insufficient data exist to state that harm does not occur. Metformin does cross the placenta, prompting a cautious approach to its use in pregnancy. There have been several published reports of the use of metformin during pregnancy, predominantly in women with insulin resistance and PCOS. Some clinicians routinely use metformin to treat diabetes in pregnant women. However, most experts believe that if medication is needed to control blood sugar during pregnancy, insulin is the drug of choice, not an oral antihyperglycemic agent. If patients become pregnant during the study, metformin will be stopped immediately.

For safety, all subjects who enter the study are evaluable. Subjects will be monitored for safety by assessment of adverse events, physical exams, vital signs and laboratory values. Continued patient safety assessment will be carried out and all adverse events documented and reported to the WHIRB. On each visit, compliance with treatment will be checked with questions about the side-effects and a subjective evaluation of the tolerability of the administered drug; the patients will also asked about incidental missed administrations.

Adverse Event Procedures

An adverse event is defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a pharmaceutical product, whether or not it is considered

related to that product. All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study drug will be recorded in the patient's record. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing illnesses will be recorded. Exacerbation of pre-existing illness may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication. Exacerbation of a pre-existing illness should be considered when a patient/subject requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the trial. Lack of or insufficient clinical response, benefit, efficacy, therapeutic effect, or pharmacologic action, will not be recorded as an adverse event. The investigator will make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy. In addition, clinically significant changes in physical examination findings and abnormal objective test findings (e.g., laboratory, x-ray, ECG) will also be recorded as adverse events. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

In order to avoid vague, ambiguous, or colloquial expressions, the adverse event term will be recorded using standard medical terminology rather than the subject's own words. Every attempt will be made to describe the adverse event in terms of a diagnosis. All related signs, symptoms and abnormal test results will be grouped together as a diagnosis if applicable and recorded as a single adverse event. All adverse events will be evaluated for intensity and causal relationship with use of the study medication. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event (i.e., study drug or other illness). Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator or his/her designated representative. Clinically significant changes, in the judgment of the investigator, in physical examination findings (abnormalities) will be recorded as adverse events. All subjects who have adverse events, whether or not the adverse events are considered associated with the use of the study medication, will be monitored until the adverse event resolves, stabilizes, or becomes chronic. The clinical course of the adverse event will be followed according to accepted standards of medical practice, even after the end of the observation period, until a satisfactory explanation for the adverse event is found or the investigator considers it medically justifiable to terminate follow-up.

SERIOUS ADVERSE EVENTS: A SERIOUS ADVERSE EVENT (SAE) IS ANY ADVERSE DRUG EXPERIENCE OCCURRING AT ANY DOSE THAT:

1. results in death;

2. is life-threatening (adverse drug experience that places the patient/subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death);

3. results in inpatient hospitalization or prolongation of existing hospitalization;

4. results in a persistent or significant disability/incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions); or

5. results in congenital anomaly/birth defect.

6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug experiences when, based upon appropriate medical judgment, they may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe pain); the event itself, however, may be of relatively minor medical significance (such as severe headache). By contrast, the term "serious" is used to describe an event based on an event outcome or actions usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. The collection of serious adverse event information will begin at the signing of informed consent and continue through 30 days after administration of the last dose of study medication. Regardless of the above criteria, any additional adverse experiences which an investigator considers serious should be immediately reported. If an SAE occurs, the investigator should initiate appropriate support procedures.

All serious adverse events regardless of treatment group or suspected relationship to study drug must be reported to MedWatch in an expedited manner. The investigator will determine expectedness by referring to the most current version of the Investigator's Brochure in conjunction with any sponsor-generated IND Safety Reports. Since the trial is being conducted under a physician's IND, Drs. Paterson and Elkind-Hirsch are responsible for submitting all IND Safety Reports to the Food and Drug Administration (FDA). The FDA 3500A Form with built-in instructions will be downloaded at: http://www.fda.gov/medwatch/getforms.htm. They will also be reported immediately to the Woman's Hospital Foundation Institutional Review Board at (225) 924-8516 and Woman's Health Research Institute at (225) 231-5275. After submitting an expedited MedWatch 3500A report to the FDA, a courtesy copy will be sent by fax to NovoNordisk. NovoNordisk Safety personnel may fax a follow-up form to the study site to request additional information or clarification of information that was included on the FDA 3500A Report. Queries that address medical issues must be signed by a medically qualified (MD, DO) principal or sub-investigator.

In cases where the investigator learns of the SAE after its occurrence and resolution, the time and circumstances of the event will be recorded. The reporting requirements will still be followed.

Any serious adverse event or death will be reported immediately independent of the circumstances or suspected cause if it occurs or comes to the attention of the investigator at any time during the study through the last follow-up visit required by the protocol or 30 days after the last administration of study drug, whichever comes later. Any serious adverse event occurring at any other time after completion of the study will be promptly reported if a causal relationship to study drug is suspected. The only exception to these reporting requirements are serious adverse events that occur during a pre-randomization/washout run-in period, during which placebo alone or no active study drug or no protocol-specified background drug is administered.

Discontinuations

The reason for a subject discontinuing from the study will be recorded in the patient chart. A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Withdrawal due to adverse event will be distinguished from withdrawal due to insufficient response according to the definition of adverse event noted earlier. The final evaluation required by the protocol will be performed at the time of study discontinuation. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up (if required) for such subjects, and document the course of the subject's condition. They will also to be reported to Woman's Hospital Foundation Institutional Review Board at (225) 924-8516 and Woman's Health Research Institute at (225) 231-5275.

Statistical Evaluation

A priori sample size analysis was performed using the online calculator provided by the Massachusetts General Hospital Mallinckrodt General Clinical Research Center (http://hedwig.mgh.harvard.edu/sample_size/size.html). The primary outcome is comparison in β-cell compensatory function between prior GDM women treated with sitagliptin-metformin, metformin or placebo using a Ss/Groups by repeated measures ANOVA in which the effects of drug intervention (12-14 weeks at full dose) between the 3 treatment groups will be analyzed Given there were no previous studies utilizing sitagliptin or combination treatment for previous GDM women, sample size analysis was based on the assumption that the smallest mean difference between treatment groups is 20% with an average SD of 12%; the sample size with a statistical power of 0.80 and two-sided P-value <0.05 is calculated to be 10 for each group. The study is designed to recruit 12 patients in each arm to ensure that the number of subjects completing the study as derived by the sample size calculation is met. Data will be analyzed on

the basis of intention to treat and also on completed treatment parameters where relevant. The intent-to-treat population (ITT) is defined as all randomized subjects who received one oral dose of medication starting from the evening of day 1. The evaluable population is defined as all randomized subjects who complete treatment through week 14- 16 (12-14 weeks full dose).

The primary outcome measure is β-cell compensatory function and secondary outcome measures include changes in insulin sensitivity and early pancreatic ß-cell response, glycemic parameters (fasting blood glucose [FBG] and 2 hour glucose after a 75-g OGTT), mean blood glucose (MBG), anthropometric parameters, blood pressure and lipid profiles. The normality of all variables will be checked using the Kolmogorov-Smirov test. When necessary, non-normally distributed data will be subjected to logarithmic or square-root transformation to obtain a normal distribution before group comparison. Direct and indirect estimates of insulin sensitivity and secretion (HOMA, SI_{OGTT}, IGI/HOMA and ß-cell compensatory), glycemic parameters (FBG, MBG, 2 hour post OGTT glucose level) anthropometric measurements (body weight, BMI), fat distribution (WC, WHR and WHtR), BP and lipid profiles will be considered as dependent variables. For all analyses, in which the measures are continuous, data from evaluable subjects will be submitted to a repeated-measures general linear model (SS/ Drug treatments x repeated measures ANOVA) including the arm of drug treatment as the between-subjects effect, and the visit (baseline and 16 wks.) as the within-subjects effect. To evaluate the differences in the response to each treatment over visits, the interaction effect will be calculated. Only where a statistically significant interaction effect is found ($P \leq 0.05$) will the contrast test applied to locate the differences between the 3 medication groups. Baseline comparisons between groups (intent-to treat population) will be made by one-way ANOVAs and post hoc comparisons performed with the Bonferroni-Dunn test to analyze the variation among the three groups if the ANOVA shows overall baseline differences were significant ($p<0.05$). Dysglycemia occurrence before and after different treatment will be compared with the McNemar test (complex chi square for paired data), which formally tests for a change between the observed proportions of k related samples. Results will be reported as mean +/- S.E.M unless otherwise noted. Calculations will be performed using SPSS for Windows (version 11.01, SPSS, Inc.; Chicago, Ill).

Additional Information

Woman's Hospital is one of the largest, not-for-profit women's specialty hospitals in the United States. The hospital's most valuable asset is its patient population. Woman's statistics of over 8400 births (2012), 75,000 pap smears, 47,000 mammograms, 300,000 lab tests, and 13,000 biopsies annually in a centralized location make it ideal for clinical research studies in women's health. The ethnic mix is about 60% Caucasian and 40% African American. In the calendar year of 2012, 704 patients with gestational diabetes delivered at Woman's hospital. The rate of GDM was 8.4% for the year 2012.

The Physician Office Building, which is on the hospital campus, offices approximately 65 private obstetrician-gynecologist offices that actively participate in Woman's Health Research Institute clinical trials and encourage patient participation. This study will utilize the research staff (nurses, physicians, PhD) of the Woman's Hospital Metabolic Health Clinic and Health Research Department for recruitment and patient consenting. The Woman's Hospital Pathology laboratory facility will be utilized for all metabolic and glucose tolerance testing. Study administrative work (IRB approval and updates) and statistical analyses will be done through the Woman's Health Research Department. The staff of the Woman's Metabolic Health Clinic will be used for all patient follow-up, medication instruction and medical care.

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