Essai randomisé contrôlé multicentrique de non infériorité

Protocole INDAO

Glyburide versus insulin for the prevention of perinatal complications of gestational diabetes: a pragmatic, non-inferiority, randomized trial

INDAO Protocol

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1 INTRODUCTION

In patients presenting gestational diabetes, therapeutic management comprising diet management, blood sugar monitoring, and, if necessary, insulin therapy is associated with decreased neonatal complications. Although of proven efficacy, insulin treatment has various drawbacks, notably in terms of implementation and adherence. An alternative is the use of oral antidiabetics, particularly sulfonylureas like glyburide. Although the data comparing glyburide and insulin in treatment of gestational diabetes show similar control of maternal blood glucose and a comparable rate of neonatal complications, most countries do not recommend glyburide in the treatment of gestational diabetes. This is mainly because of methodological weaknesses in existing studies: insufficient power to demonstrate a lack of between-treatment difference in the rate of neonatal complications in the only valid randomized trial, moderate quality with heterogeneous criteria, and biases inherent to observational studies.

2 SCIENTIFIC RATIONALE AND GENERAL DESCRIPTION OF THE RESEARCH

2.1 Definition of gestational diabetes and screening modalities

The World Health Organization (WHO) defines gestational diabetes as impaired glucose tolerance leading to hyperglycemia of variable severity that occurs or is first diagnosed during pregnancy, regardless of the treatment needed and post-partum progression. The estimated prevalence of gestational diabetes is between 2.2% and 8.8% of pregnancies [1], depending on the populations studied and the screening criteria used. In France, the Audipog network reports an estimated prevalence of 4% to 5% [2]. Gestational diabetes has been increasing in prevalence for some years, probably because of changes in the eating habits of patients, increased maternal mean age at pregnancy, and increased body mass index (BMI). The main risk factors are overweight, age, ethnic origin, first-degree family history of type 2 diabetes, history of gestational diabetes or of macrosomia, and polycystic ovary syndrome. Uncontrolled hyperglycemia is a source of well-known maternal and fetal complications, both short- and long-term [3].

There are currently 2 methods of diagnosing gestational diabetes between 24 and 28 weeks of gestation: the two-step **O'Sullivan test** (detection by blood glucose measurement one hour after ingestion of 50 g of glucose) [4] then diagnosis of hyperglycemia by means of a 100-g oral glucose tolerance test (OGTT) over 3 hours) [5]; and the one-step **WHO test** (75-g OGTT over 2 hours) [6]. A single study [3] has investigated the relations between maternal-fetal morbidity and blood glucose, after screening by 75-g OGTT. This method has the advantage of greater safety, reduced time till treatment, and better adherence because of one-step screening and diagnosis. This is why the International Association of Diabetes Pregnancy Study Group (IADPS) has proposed, as diagnostic criteria of gestational diabetes between 24 and 28 weeks of gestation, a fasting blood glucose ≥ 0.92 g/L (5.1 mmol/L) and/or blood glucose ≥ 1.80 g/L (10.0 mmol/L) 1 hour after a 75-g oral glucose challenge and/or blood glucose ≥ 1.53 g/L (8.5 mmol/L) 2 hours after glucose challenge, these values being associated with a 1.75-fold increase in the risk of macrosomia and fetal hyperinsulinism [7]. These criteria have just been included in the 2010 recommendations (in press) for screening for gestational diabetes in French clinical practice.

Once gestational diabetes is diagnosed, treatment usually comprises dietary management plus either self-monitoring of fasting blood glucose and postprandial blood glucose 10 days later or self-monitoring of blood glucose 4 times/day. However, approximately 20% to 30% of patients need treatment on top of dietary management alone. In France, the only drug treatment used is subcutaneous insulin. So, approximately 1% to 2% of all pregnant women have gestational diabetes requiring insulin treatment, ie, 8 000 to 16 000 per year in France.

2.2 Neonatal complications associated with gestational diabetes

In 2008, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [3] revealed a continuum between maternal blood glucose during pregnancy and perinatal risks. Fasting blood glucose and blood glucose 1 hour and 2 hours after a 75-g oral glucose challenge were positively and linearly associated with the risk of macrosomia, neonatal hypoglycemia, shoulder dystocia, and neonatal hyperbilirubinemia. It was also shown that these risks were increased even for blood glucose considered normal in pregnant women (fasting blood glucose <0.95 g/L).

2.3 Proven value of the treatment of gestational diabetes

In patients with gestational diabetes, therapeutic management, dietary management, blood sugar monitoring, and, if necessary, insulin therapy are associated with a decrease in neonatal complications [8-14]. Two randomized trials comparing active treatment of gestational diabetes with usual pregnancy follow-up showed a decrease in maternal-fetal morbidity in the interventional group [8, 12].

The first trial [8] included 1000 women at between 24 and 34 weeks of gestation with blood glucose >1.40 g/L (7.8 mmol/L) after 50 g of glucose, with fasting blood glucose <1.40 g/L (7.8 mmol/L) after 75-g OGTT, and blood glucose between 1.40 g/L and 2 g/L (7.8 mmol/L and 11 mmol/L) at 2 h. The patients of the control group and the medical team were unaware of blood glucose levels. The intervention group had dietary management adapted to weight before pregnancy, to weight gain during pregnancy, and to usual diet plus self-monitoring of capillary blood glucose 4 times/day. The blood glucose targets were fasting blood glucose between 0.63 g/L (3.5 mmol/L) and 0.99 g/L (5.5 mmol/L), preprandial blood glucose <0.99 g/L (5.5 mmol/L), and postprandial blood glucose <1.26 g/L (7 mmol/L) at 2 h. The insulin treatment was started if 2 fasting or postprandial blood glucose values exceeded the targets or if 1 postprandial blood glucose value was >1.62 g/L (9 mmol/L) over a 15-day monitoring period. Twenty per cent of patients in the intervention group were given insulin. The composite endpoint, combining perinatal death, shoulder dystocia, fracture of an upper limb, and paralysis of the plexus brachial, was significantly decreased in the intervention group compared with the "usual treatment" group (4% vs 1%, $p<0.05$); the rates of macrosomia and birth weight >90th percentile for gestational age were also significantly decreased in the intervention group (10% vs 21% and 13% vs 22%, $p<0.001$).

The second trial [12], the aim of which was to evaluate the efficacy of active treatment of moderate gestational diabetes, included 958 women at between 24 and 30 weeks of gestation with blood glucose of between 1.35 and 2.00 g/L (7.5 mmol/L and 11 mmol/L) 1 h after 50 g of glucose and a 100-g OGTT with fasting blood glucose <0.95 g/L (5.3 mmol/L), and at least 2 abnormal blood glucose values at 1 h, 2 h or 3 h (>1.80 g/L [10 mmol/L] at 1 h; 1.55 g/L [8.6 mmol/L] at 2 h; 1.40 g/L [7.7 mmol/L] at 3 h). The women were randomized to the intervention group or to the control (usual treatment) group. The treatment of the intervention group comprised dietary management, monitoring of fasting blood glucose and of postprandial glucose at 2 h, and insulin therapy if the targets were not reached. The blood glucose targets were a fasting blood glucose <0.95 g/L (5.3 mmol/L) and postprandial glucose at 2 h <1.20 g/L (6.7 mmol/L). There was no between-group difference in the composite endpoint combining neonatal death, hyperbilirubinemia, hypoglycemia, hyperinsulinism, and neonatal trauma (32.4% and 37% in the intervention and control groups, respectively; $p=0.14$). In the intervention group, there were significant decreases in the frequency of macrosomia (5.9% versus 14.3%), children of birth weight >90th percentile (7.1% versus 14.5%), and shoulder dystocia (1.5% versus 4.0%).

Active treatment comprising dietary management, blood glucose self-monitoring, and insulin treatment, if necessary, is therefore beneficial in the treatment of gestational diabetes.

2.4 Insulin therapy

Insulin therapy is currently the reference therapeutic strategy used to manage gestational diabetes when blood glucose targets are not achieved by dietary management alone. One of insulin's advantages is that, because of its high molecular weight (6000 Da), it does not cross the placental barrier and so in theory there are no fetal or neonatal side effects.

Although of proven efficacy [8, 12], insulin treatment has several drawbacks. It is inconvenient as it generally requires 4 and sometimes 5 subcutaneous injections a day. It also requires appropriate training on how to perform injections and on capillary blood glucose monitoring 4 to 6 times a day. There is often a need for endocrinologists to adjust the treatment with, if necessary, short hospitalization. And, lastly, insulin treatment is expensive, because of the restrictions related to its use, and involves a risk of maternal hypoglycemia.

2.5 Oral antidiabetics and glyburide

Alternatives to oral antidiabetics have been envisaged for some years. Although they cross the placenta, biguanides (Metformin®) have no long-term effects on the fetus, but they are effective on blood sugar balance in only 54% of cases, meaning that they are of little value as an alternative to insulin therapy [15]. Sulfonylureas, like glyburide, are the other drug class of choice.

Pharmacology of glyburide

Drug class: sulfonylurea, oral antidiabetic (ATC code: A10BB01; A: alimentary tract and metabolism).

Glyburide is a second-generation sulfonylurea with a short half-life which is completely metabolized by the liver into 3 inactive metabolites that are eliminated in bile (60%) and by the kidneys (40%). Its half-life of elimination is on average 4 hours [16]. Glyburide induces a sharp drop in blood glucose by stimulating insulin

release by the pancreas, an effect that is dependent on the presence of active β cells in the pancreatic islets. Sulfonylureas act on the potassium and calcium channels, which leads to depolarization of cells and release of insulin by the β cells of the pancreas. Insulin secretion abolishes liver production of glucose, which is a major factor of high fasting blood glucose [17, 18].

Administration of glyburide to a diabetic patient enhances the postprandial insulinotropic response and so lowers postprandial blood glucose. After oral administration, glyburide is strongly absorbed (98%). Peak plasma concentration is reached in 2 to 6 hours. Food intake alters neither the rate nor the percentage of absorption.

Hepatic insufficiency decreases glyburide metabolism and so greatly slows its elimination. Biliary excretion of metabolites increases in cases of renal insufficiency in proportion to the severity of renal impairment. Renal insufficiency does not affect the elimination of glyburide as long as creatinine clearance remains above 30 mL/min.

An in vitro model of placental perfusion has shown that, in contrast to other sulfonylureas, the passage of glyburide across the placenta, from the maternal circulation to the fetal circulation, is insignificant, even if the maternal glyburide concentration is increased 100-fold compared with the therapeutic level used [19, 20]. This is in part explained by glyburide's very high plasma protein binding (99.8%), short plasma half-life, and rapid elimination [20]. Langer et al [21] confirmed these data in a randomized trial. Chromatographic analysis showed there was no glyburide in the cord blood of newborns. Also, in 12 randomly selected cases of mother and child, glyburide was undetectable in the cord blood of the newborn, whereas its concentration was between 50 and 150 ng/mL in the mother. A recent pharmacological review of the potential value of glyburide in the treatment of gestational diabetes supports these pharmacological data [22]. However, an in vivo pharmacological study shows that, in term pregnancies, there is maternal-fetal transfer of glyburide across the placenta, but also shows, after studies of glyburide concentrations, that glyburide can be used safely up to a dose of 20 mg/day [23].

- Teratogenicity

To date, no teratogenicity has been reported in animal studies. Here are the data on glyburide updated in June 2011 by the Centre de Référence des Agents Tératogènes (CRAT):

- Malformations

Published data on pregnant women exposed to glyburide during the first trimester are scarce, but no malformation has been recorded to date. Glyburide is not teratogenic in animal studies.

- Fetal and neonatal effects

Published data on the second and third trimesters are numerous and no particular neonatal effect has been noted in newborns. These data essentially concern gestational diabetes.

- Treatment of pregnant women

If the specialists managing the patient deem it relevant, the use of glyburide can therefore be envisaged, particularly during the second and third trimesters. When treatment continues to term, neonatal blood glucose will be monitored on principle.

- Discovery of pregnancy during treatment

Reassure the patient regarding the risk of malformation associated with glyburide (meaning that glyburide does not increase the baseline 2% to 3% risk of malformation in any pregnancy. The discovery of pregnancy in a diabetic woman calls for appropriate multidisciplinary management.

2.6 Results of studies of glyburide

Observational studies

Nonrandomized retrospective or prospective studies comparing the effects of insulin and glyburide in the treatment of the gestational diabetes (Table 1) show that glyburide is effective in achieving glycemic control, with a nonsignificant between-group difference in fasting and postprandial blood glucose. Only the study by Jacobson et al shows that fasting and postprandial blood glucose targets were reached more often in the glyburide group than in the insulin group (86% versus 63% $p<0.001$), including after adjustment for body mass index, ethnicity, fasting blood glucose, and gestational age at diagnosis. In this study by Jacobson et al, which is the largest numerically, glyburide was not significantly associated with a risk of macrosomia, birth weight >90th percentile for gestational age, hypoglycemia, or hyperbilirubinemia, compared with insulin.

Table 1. Observational studies comparing insulin and glyburide

	Fines 2003 [24]	Gilson 2003 [25]	Yogev 2004 [26]	Chmait 2004 [27]	Conway 2004 [28]	Jacobson 2005 [29]	Rochon 2006 [30]	Ramos 2007 [31]
Study	Prosp	Retro	Retro	Prosp	Retro	Retro	Prosp	Retro
No. of glyburide patients	40	15	25	56	63	236	80	44
No. of insulin patients	44	30	30	-	-	268	21	78
No. of insulin patients after failure of glyburide	-	-	-	13	12	-	-	-
Failure of glyburide	-	-	-	18.8%	12%	12%	21%	16%
Maternal blood glucose target	NS	NS	NS	NS	NS	P<0.01 Gl: 86% Ins: 63%	NS	NS
Macrosomia	NS	NS	-	NS	NS	NS	NS	NS
Birth weight >90th percentile	-	-	-	-	-	NS	-	NS
Neonatal hypoglycemia	-	-	-	-	-	NS	-	P<0.01 Gl: 34% Ins: 14%
Hyperbilirubinemia	-	-	-	NS	-	NS		-
Maternal hypoglycemia	-	-	P=0.009 Gl: 28% Ins: 63%	-	-	P<0.01 Gl: 20% Ins: 8%	-	NS

Retro: retrospective studies Prosp: prospective studies Gl: glyburide Ins: insulin
NS: not significant; - not available

Randomized clinical trials

Five randomized controlled trials comparing glyburide and insulin in the treatment of gestational diabetes have been conducted. Their results are summarized in Table 2.

The trial by Langer et al in 2000 [21] in 404 patients showed that in 96% of cases glyburide alone achieved exactly the same glycemic control as insulin (average blood glucose during treatment 105 mg/dL±16 mg/dL and 105 mg/dL±18 mg/dL for glyburide and insulin, respectively). Although the frequency of neonatal complications (macrosomia, birth weight ≥ 90th percentile for gestational age, neonatal hypoglycemia, and hyperbilirubinemia) was slightly higher in the glyburide group than in the insulin group, the between-group differences were not significant. The incidence of maternal hypoglycemia was significantly decreased in the glyburide group (2% versus 20%). However, some authors [32-34] have pointed out the lack of power of this study [21]. The main outcome was maternal blood sugar balance and the number of subjects included did not enable demonstration of large differences between insulin and glyburide in the rate of neonatal complications. A smaller, but clinically important difference could have been demonstrated with more subjects.

Four other trials [35-38], albeit subject to methodological criticisms and including a limited number of patients (23, 51, 97, 68, respectively), have since yielded similar results on glycemic control. Neonatal morbidity criteria were not always reported in these studies (Table 2). Also, the calculation of the number of subjects needed and the main outcome were not always specified. Two trials [36, 38] reported a statistically higher frequency of macrosomia in the glyburide group than in the insulin group and 2 trials did not report this parameter [35, 37]. The frequency of children of birth weight >90th percentile for gestational age was reported in only 2 trials [36, 38], one of which reported a higher frequency in the glyburide group [36] and the other [38] found no difference between glyburide and insulin. Two trials [36, 38] reported a statistically higher frequency of neonatal hypoglycemia in the glyburide group than in the insulin group (33.3% versus 3.7% and 25% versus 2.78%, respectively), one trial found no between-group difference [37], and one did not report this parameter [35].

Langer et al [21] reported no between-group difference in hyperbilirubinemia, but this parameter was not reported in the other studies.

Table 2. Randomized trial comparing insulin and glyburide

	Langer 2000 [21]	Bertini 2005 [36]	Silva 2007 [38]	Anjalakshi 2007 [35]	Ogunyemi 2007 [37]
No. of glyburide patients	201	24	32	10	48
No. of insulin patients	203	27	36	13	49
Failure of glyburide	4%	20.8%	18.75%	0%	6.25%
Maternal fasting and postprandial blood glucose	NS	NS	NS	NS	NS
Macrosomia	NS	P<0.01 Gl: 16% Ins: 0%	P=0.02 Gl: 15.62% Ins: 0%	-	-
Birth weight >90th percentile	NS	P<0.01 Gl: 25% Ins 3.7%	NS	-	-
Neonatal hypoglycemia	NS	P=0.06 Gl: 33.3% Ins: 3.7%	P=0.01 Gl: 25% Ins: 2.78%	-	NS
Hyperbilirubinemia	NS	-	-	-	-
Maternal hypoglycemia	P=0.03 Gl: 2% Ins: 20%	NS	-	NS	-

Gl: glyburide Ins: insulin

NS: not significant -: not available

Meta-analyses

In their 2008 meta-analysis [33], Moretti et al compared glyburide and insulin in 9 studies, one randomized [21], 4 prospective [25, 27, 39, 40] and 4 retrospective [24, 28-30], with a total of 745 women treated with glyburide and 637 treated with insulin, from 24 weeks of gestation. Moretti et al concluded that there was no difference between the 2 treatments in terms of the risk of macrosomia (OR: 1.07; 95% CI 0.78-1.47), the frequency of birth weight ≥90th percentile for gestational age (OR: 1.04; 95% CI 0.75-1.43), the rate of transfer to the neonatal unit (OR: 0.95; 95% CI 0.43-2.09), or neonatal hypoglycemia (OR: 1.24; 95% CI 0.91-1.69). The effect of treatment on maternal blood glucose control was not analyzed because this parameter was reported in only 3 studies. One of the limitations of this meta-analysis is the combination of retrospective and prospective analyses, which in theory reduces the probability of detecting a difference, even though neonatal outcomes seem to be homogeneous in the studies.

A literature review of the risks and benefits of oral antidiabetics compared with insulin therapy by Nicholson et al in 2009 [34] included in part the previous studies: 3 randomized studies comparing treatment by glyburide and insulin (n=478) [21, 35, 36], a randomized study comparing insulin and metformin (n=751) [15], and 5 observational studies (n=831) [26-30]. There was no between-group difference in blood glucose targets. The fetal or maternal prognosis was comparable with glyburide and metformin compared with insulin. Data analysis of the 3 studies comparing insulin and glyburide indicated no significant difference in birth weight.

Lastly, a recent meta-analysis of all randomized trials comparing oral antidiabetics and insulin [41] included 6 trials, 4 of which [21, 35, 37, 38] compared glyburide and insulin. This meta-analysis in 1388 patients found no between-group difference in fasting (OR: 1.31; 95% CI 0.81-1.43) or postprandial (OR: 0.80; 95% CI 3.26-4.87) blood glucose control. The use of oral antidiabetics was not associated with the risk of neonatal hypoglycemia (OR: 1.59; 95% CI 0.70-3.62) or with the risk of birth weight >90th percentile for gestational age (OR: 1.01; 95% CI 0.61-1.68). However, while the trials included met the CONSORT criteria, the authors pointed out that not all trials reported neonatal variables of interest, so this meta-analysis had insufficient power to detect any differences in neonatal complications between the 2 treatments.

2.7 Description of the study population

The study population will comprise pregnant women who develop gestational diabetes between 24 and 34 weeks of gestation. Only singleton pregnancies will be included as the screening thresholds for gestational diabetes for twin pregnancies are unknown. Patients with diabetes prior to pregnancy, patients diagnosed with diabetes before 24 weeks of gestation, and patients with an initial diagnosis of diabetes with a fasting blood

glucose >1.26 g/L are considered to have type 2 diabetes and will not be included in the study as they require urgent insulin treatment.

2.8 What INDAO adds to published trials

Although the existing data show that glyburide and insulin achieve similar maternal blood glucose control, without significant increase in maternal or neonatal adverse effects, most countries, including France (RPC [clinical practice guidelines], in press 2010), do not recommend first-line use of glyburide in the treatment of gestational diabetes. The data are considered insufficient, mainly because of methodological weaknesses: small study populations in most randomized trials without a clearly defined hypothesis and without calculation of the number of subjects needed [35-38], lack of power to demonstrate no between-treatment difference in the rate of neonatal complications in the only valid randomized trial [21] and in the meta-analyses [33, 41], studies of average quality with heterogeneity in reported criteria, small study populations, and biases inherent to observational studies [24-30, 39, 40].

INDAO is the first large-scale multicenter trial with well-defined goals in terms of blood glucose, designed methodologically to demonstrate glyburide's noninferiority with respect to insulin in terms of neonatal complications. The main outcome is a criterion combining morbidity criteria reflecting fetal hyperinsulinism and hence the effect of exposure to maternal hyperglycemia.

Anticipated benefits

Oral glyburide in not inferior to subcutaneous insulin in treating women with gestational diabetes who need therapy other than dietary management, notably in terms of the frequency of neonatal complications, and can be offered first line because it is easy to use. Less training is needed for one or 2 oral doses per day than for subcutaneous injections of insulin, with potentially better adherence and fewer appointments. The only real risk associated with glyburide is treatment failure, defined by failure to achieve blood glucose targets at the maximum dose, resulting therefore in a treatment switch to insulin. Trials have estimated this risk as between 4% and 20.8% [21, 36-38]. Each year, approximately 16 000 women in France develop gestational diabetes and could benefit from first-line glyburide.

2.9 Trial length and feasibility

Our study will require 450 women per group (see section 10.2 for the calculation of the number of subjects needed). Because an estimated 1.5% of pregnant women with gestational diabetes require drug treatment, 60 000 pregnant women will be necessary. Assuming that one in 2 women will agree to randomization, we need a population of 120 000 pregnant women. As all participating maternity units manage about 40 000 deliveries a year, recruitment can be achieved in 3 years.

2.10 Assumption

We assumed that glyburide is not inferior to insulin in treating gestational diabetes.

2.11 Primary objective

To test whether oral glyburide is not inferior to subcutaneous insulin in terms of perinatal complications in treating pregnant women with gestational diabetes requiring treatment other than dietary management.

2.12 Secondary objectives

The secondary objectives of the INDAO trial are to demonstrate the noninferiority of glyburide compared with insulin in terms of maternal blood sugar balance, rate of cesarean section, rate of premature delivery, perinatal mortality rate, rate of neonatal and maternal trauma associated with delivery, rate of respiratory distress, number of prenatal visits, number of days of hospitalization. Maternal satisfaction regarding the 2 drugs will be evaluated.

2.13 Primary outcome

The primary outcome (see also section 5.1) is a composite criterion of neonatal complications associated with gestational diabetes. Each component reflects the potential adverse effects of exposure to maternal hyperglycemia and hence of fetal hyperinsulinism. The components selected for this composite criterion are:

- fetal macrosomia (>4000g) or birth weight >90th percentile for gestational age
- neonatal hypoglycemia
- neonatal hyperbilirubinemia

2.14 Secondary outcomes

The secondary outcomes (see section 5.1) include maternal criteria (blood sugar balance, conditions of delivery, satisfaction) and neonatal criteria.

2.15 Methodology

INDAO is a clinical, noninferiority, multicenter, open, randomized, balanced trial.

2.16 Experimental plan – practical considerations

Study procedure

The patients will be recruited among women with gestational diabetes diagnosed by hyperglycemia (75 g of oral glucose), with fasting blood glucose ≥0.92 g/L (5.1 mmol/L) and <1.26 g/L (7 mmol/L) and/or blood glucose at 1 h and 2 h after 75 g of glucose ≥1.80 g/L (10 mmol/L) and ≥1.53 g/L (8.5 mmol/L), respectively, or after 50 g of glucose with blood glucose at 1 h >1.3 g/L (7.2 mmol/L) followed by hyperglycemia (100 g of oral glucose), with fasting blood glucose >0.95 g/L (5.1 mmol/L) and <1.26 g/L (7 mmol/L) and/or blood glucose at 1 h, 2 h and 3 h >1.8 g/L (10 mmol/L), 1.55 g/L (8.6 mmol/L) and 1.40 g/L (7.8 mmol/L), respectively (2 abnormal values).

The WHO 75-g OGTT will be favored as it is recommended in the French 2010 RPC (clinical practice guidelines) for gestational diabetes. However, the 2 screening tests will be possible to enable new practices to be integrated into some maternity units and so as not to limit patient recruitment in departments where the O' Sullivan test is still used for screening. As the inclusion criterion is failure to achieve blood glucose targets after 10 days of dietary management and the randomization will be done afterwards, the patients will be comparable regardless of the screening test used.

The women will initially be treated by dietary management adapted to their individual needs evaluated by means of an interview. Dietary intake will be 35 kcal/kg for non-obese patients, divided into 3 meals and 2 snacks, with approximately 40% to 45% of calories provided by carbohydrates, 20% by proteins, and 30-40% by fats. Dietary intake will be 25 kcal/kg in obese patients defined by a BMI >30 kg/m^2. This diet will be combined with encouragement to do exercise equivalent to 30 min of walking 3 to 5 times per week, if the patient's obstetrical condition allows. The patients will be educated concerning self-monitoring of blood glucose using glucose meters, which should have a searchable memory and comply with standard ISO 15197. During the diet, monitoring will be set up as a function of the centers: self-monitoring of capillary blood glucose (4 times/day) or, after 10 days, fasting blood glucose and blood glucose 2 h after a meal.

Patients eligible for randomization between the 2 treatments will be those whose blood glucose target is not reached, ie, those for whom at least 2 abnormal blood glucose values are recorded in one week: fasting blood glucose ≥0.95 g/L and/or postprandial blood glucose at 2 h ≥1.20 g/L after 10 days of well-conducted dietary management. In cases where there is an unusual departure from the diet, the blood glucose value following the meal in question will not be taken into account.

Prior to the study, the patients will be informed about it and its procedures, and their written consent will be collected.

The randomization between glyburide and insulin will be performed in each center, by the obstetrician or the diabetologist, depending on the center's organization, using the randomization module of the application CleanWEB® (Telemedicine Technologies). The patient will be managed by the diabetologist and the obstetrician in terms of treatment initiation, education, and monitoring of treatment and of capillary blood glucose.

The insulin and glyburide regimens will be adapted as a function of the patients' blood glucose profiles and the centers' habits regarding insulin therapy. In the 2 groups, a protocol for drug dose adjustment as a function of capillary blood glucose will be given to the patient, who will adapt the doses by performing 4 capillary blood glucose measurements per day: fasting in the morning and 2 hours after each meal. These blood glucose values will be entered in a monitoring notebook and will be available in the memory card readers. If the blood glucose targets are not achieved after a diet associated with maximum doses of glyburide over 1 week, the treatment will be replaced by insulin. If the diabetes is balanced and there are no complications, there will be no need to change obstetrical management. If gestational diabetes is unbalanced or has an effect on the fetus, delivery will be induced, taking into account the risk-benefit ratio.

In the framework of their usual treatment, the newborns will have a routine pediatric examination at birth, with measurement of weight, body length, and cranial circumference, and in the first 3 days of life. They will also undergo routine monitoring of capillary blood glucose and screening for jaundice.

Patient follow-up

Timeline and content of visits

Randomization and treatment initiation will be done in hospital or in the outpatient department, depending on the center's organization, at which time the obstetrician or diabetologist will collect the mother's consent. An appointment will be made with a diabetologist one week after randomization, and then at least every 2 weeks, and then, when the blood glucose target is reached and stable, every month until delivery, all this within the framework of the usual follow-up of pregnant women with gestational diabetes. Between these appointments, the patients can themselves increase the dose, as a function of capillary blood glucose readings, in line with the dose adjustment protocol given to the patient at the first appointment. Between these appointments, the patients in each center can, should they wish, have a telephone appointment or an email exchange if they have questions or doubts.

At each visit, capillary blood glucose values in the monitoring notebook or in the memory card reader will be analyzed. If the target is not reached, the diabetologist will increase the dose. In the event of hypoglycemia (<0.6 g/L) or symptomatic hypoglycemia, doses will be decreased to the level below. The content of these visits will not differ from that of the usual appointments for management of patients with gestational diabetes in the participating maternity units. At these appointments, checks will be made for the presence of side effects or adverse events.

Clinical follow-up of patients will be noted by the clinical research technician and/or the investigator in the electronic case report form (e-CRF) provided for the purpose. Also noted will be pregnancy characteristics, gestational age at diagnosis, and the dose of insulin or glyburide. At birth and in the days afterwards, the following will be recorded:

- gestational age at delivery
- method of delivery

and, if the informed parents do not refuse:

- the child's birth weight, body length, and cranial circumference
- pH and/or cord blood lactate at birth
- 5-minute APGAR score
- all endpoints
- any reasons for discontinuation or change of treatment

Monitoring of newborns

Monitoring will be identical to that generally recommended for the newborns of diabetic mothers:

- Weighing of children from birth
- Measurements: body length and cranial circumference
- Plotting of birth weight on growth curves [42]
- Early and frequent feeding from birth: breastfeeding and/or bottle feeding from 30 min of life and every 2 h or 3 h.
- Measurement of capillary blood glucose before the first breastfeed, then before the second meal, then every 3 hours; before feeding for asymptomatic newborns. Capillary blood glucose must be measured using a reader adapted to the characteristics of the newborn. Hypoglycemia must be checked by sending a blood sample collected in a fluoropolymer tube to the laboratory.
- The presence of abnormal clinical signs is an indication for blood glucose measurement whenever these signs are observed.
- If 2 consecutive capillary blood glucose values are between 45 mg/dL and 54 mg/dL (2.5 mmol/L and 3 mmol/L), measurements can be made every 6 hours and stopped after 24 hours if the blood glucose values are normal and if the newborn is feeding normally.
- Hypoglycemia will be corrected in accordance with the local protocol.
- Jaundice will screened for in accordance with the local protocol and its severity will be assessed using a bilirubin meter and/or a blood bilirubin test. The indications for phototherapy will be drawn up using the blood bilirubin curves usually applied in the department concerned, as a function of gestational age, term of delivery, and birth weight. This monitoring will not differ from that of infants born to mothers with gestational diabetes.

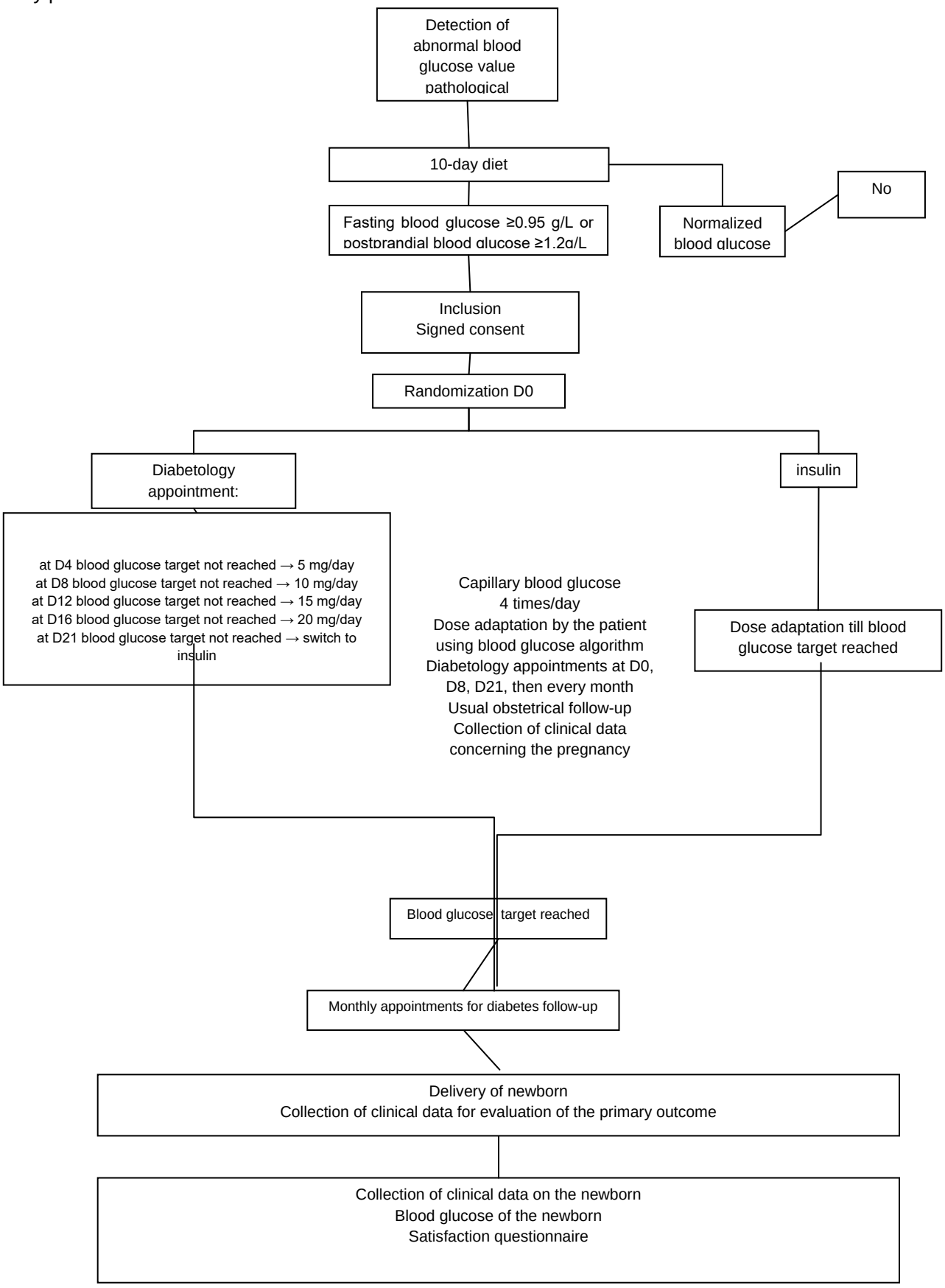
Procedures, examinations, and samples collected at visits

In patients included in the trial, apart from randomization and allocation of insulin or glyburide, no specific procedure and no additional examination will be done for research purposes.

Study sites

The INDAO trial will essentially be conducted during appointments. An outpatient visit will be possible at some centers at initiation of treatment or when the diabetes is difficult to balance in the framework of usual follow-up.

Study procedure



Length of participation of study participants

The participation of patients in the INDAO trial will extend from inclusion, after failure of dietary management, and treatment initiation until the patient's child is discharged from the maternity unit or from the neonatal unit.

Study timetable for each patient

Day	Appointment Abnormal blood glucose values after testing	Appointment or outpatient visit after 10-day diet Fasting blood glucose ≥0.95 g/L or postprandial blood glucose ≥1.2 g/L after 10-day diet D0	Monitoring by email or telephone if desired D4	Appointment 1 week after randomization D8	Monitoring by email or telephone if desired D12 and D16	Appointment at least every 15 days D21	Birth	Post-partum
Information	×	×			×			
Inclusion criteria		×						
Consent		×						
Inclusion and randomization		×						
Genotyping CYP2C9*3		×						
Satisfaction questionnaire								×
Adverse events			×	×	×	×	×	×
Insulin or glyburide		×		×		×		
Primary outcome							×	×

2.17 Steps taken to minimize bias

2.17.1 Randomization

Treatments will be allocated by means of centralized balanced randomization (randomization module of the application CleanWEB®, Telemedicine Technologies). The randomization list (insulin versus glyburide) will be drawn up by the statistician Mrs Armelle Arnoux of the Paris Sud clinical research unit, using reference software (eg, NQuery Advisor®), after agreement by the study scientific director. The randomization will be stratified by center and by blocks of random size. After the patient signs the consent form, the investigator will record the inclusion data in the e-CRF (CleanWEB®, Telemedicine Technologies), which will enable access to the CleanWEB® randomization module. A single number will be attributed to each patient. The use of this e-CRF directly accessible via the Internet will facilitate the interaction between the maternity units, the participating diabetology departments, and the various study participants.

Subjects who subsequently drop out will keep their inclusion number, if given one, and new subjects will always receive a new inclusion number. The patients will therefore be identified by an alphanumeric code in the form of "center number (3 characters) – center inclusion number (3 characters) - initials of the name and first name (1 and 1 characters)."

2.17.2 Blinding and methods used for its maintenance and code break procedure

The 2 treatments have different routes of administration and so blinding will not be used.

2.18 Dosage and mode of administration of the experimental drug

Glyburide will initially be taken in a single oral dose of 2.5 mg/day before breakfast. Dose increases will be incremental as a function of blood glucose values up to a maximum total dose of 20 mg/day, until blood glucose targets are reached (fasting blood glucose <0.95 g/L and postprandial blood glucose at 2 h <1.20 g/L). An algorithm for dose adaptation depending on capillary blood glucose values will be given to the patient at the instruction session. In the event of at least 2 abnormal values (fasting blood glucose ≥0.95 g/L and/or postprandial blood glucose at 2 h ≥1.20 g/L), the dose will be increased by the patient at D4 to 5 mg in the morning. At D8, the patient will have a review appointment with the diabetologist. If there are still 2 abnormal values, the dose will be increased to 5 mg in the morning and 5 mg in the evening before dinner. At D12, if there are still 2 abnormal values, the patient will increase the dose to 10 mg in the morning and 5 mg in the evening, up to a maximum dose of 10 mg in the morning and 10 mg in the evening at D16. If there is a deviation from the usual diet, the blood glucose value following the meal in question will not be taken into account.
The patient will have a diabetology appointment on D21: switch to insulin if the blood glucose targets are not reached. The patient can use monitoring by telephone or by email at D4, D12 and D16 or if she experiences side effects between appointments. In cases of symptomatic hypoglycemia or of blood glucose <0.6 g/L, the glyburide dose will be decreased or returned to the previous level. Treatment will be continued until delivery.

2.19 Description of the experimental drug

Glyburide

Glyburide is marketed as Daonil® scored 5 mg tablets by Sanofi-Aventis France, which has the marketing authorization. Treatments will be labeled by the Clinical Trials Unit of the Agence Générale des Equipements et Produits de Santé (AGEPS; medicines and healthcare products regulatory agency) with the regulatory texts for drugs used in clinical trials. Removable labels will be attached to the boxes, to ensure the traceability of dispensing.

2.20 Description of the reference drug

Insulin

The protocol will be adapted as a function of the department's usual practice. As the insulin will be used as per the marketing authorization indications and in the framework of usual follow-up, it will not be supplied by the sponsor but rather will be bought in the community pharmacy.

2.21 Experimental drug accountability procedures

The clinical research assistant representing the study sponsor will check management of stocks when conducting on-site monitoring visits. The study drugs will be kept in a safe, reserved access site. The contents of the different drug packages will not be mixed.
For each patient, all information on the administration of the treatment received (date, time, dose) will be noted in the paper records and in the e-CRF and in the dispensing follow-up notebook. The investigator undertakes to deliver these products only to patients participating in the study and agrees to return to the sponsor, at the end of the study, all original packaging, whether empty or containing unused drugs, in accordance with the instructions of the study monitor. It is also agreed that the investigator will neither deliver these drugs to sites nor keep them at sites other than those agreed with the sponsor.

2.22 Duration of the research

Patients with gestational diabetes requiring drug treatment will be included between 24 and 34 weeks of gestation. They will take part from inclusion and treatment initiation until their child is discharged from the maternity unit or the neonatal unit, ie, a maximum of 24 weeks. The total duration of the study will be 3.5 years (3 years of recruitment and 24 weeks of follow-up).

2.23 Rules for temporary or definitive withdrawal

2.23.1 Interruption of participation in the research

Patients can end their participation in the research if they so wish at any time and for any reason, or as decided by the investigator. This will in no way alter the quality of their subsequent healthcare.

Procedures for follow-up of drop-outs

All drop-outs should be documented and the investigator should indicate the reason for drop-out. For patients lost to follow-up, the CRF should be completed up to the last visit. The investigator will make every possible effort to contact the patient and to establish the reason for her withdrawal from the trial and her state of health.

Consequences of drop-outs

The patients who drop out will not be re-included in the study and their treatment numbers will not be re-used. These patients will be followed up in the maternity unit outside the protocol.

Lost to follow-up

The risk of patients lost to follow-up is very low because there is a small probability that a woman treated for gestational diabetes will give birth in another maternity unit. The investigator will make every possible effort to obtain news about the patient.

2.23.2 Discontinuation of all or part of the research

Only unanticipated serious adverse events in the glyburide arm of the study will be a reason to stop the research. As glyburide is well known and used in diabetic patients, the likelihood of this happening is low.

3 SELECTION OF RESEARCH PARTICIPANTS

3.1 Inclusion criteria

The eligibility criteria are:

- Pregnant woman
- Aged 18 to 45
- Diagnosis of gestational diabetes between 24 and 34 weeks of gestation, by either:
  - 75-g OGTT

Fasting blood glucose ≥0.92 g/L (5.1 mmol/L) and <1.26 g/L (7 mmol/L) and/or blood glucose at 1 h and 2 h after 75 g of glucose ≥1.80 g/L (10 mmol/L) and ≥1.53 g/L (8.5 mmol/L), respectively, or

  - 50-g OGTT

Blood glucose at 1 h >1.30 g/L (7.2 mmol/L) followed by 100-g OGTT with fasting blood glucose >0.95 g/L (5.1 mmol/L) and <1.26 g/L (7 mmol/L) and/or blood glucose at 1 h, 2 h and 3 h >1.8 g/L (10 mmol/L),1.55 g/L (8.6 mmol/L) and 1.40 g/L (7.8 mmol/L), respectively (2 abnormal values).

- Complete, 10-day dietary management: treatment by dietary management adapted to the woman's individual needs evaluated at a dietary interview. Dietary intake will be 35 kcal/kg for non-obese patients, divided into 3 meals and 2 snacks, with approximately 40% to 45% of calories provided by carbohydrates, 20% by proteins, and 30% to 40% by fats. Dietary intake will be 25 kcal/kg in obese patients defined by a BMI >30 kg/m^2. This diet will be combined with encouragement to do exercise equivalent to 30 min of walking 3 to 5 times per week, if the patient's obstetrical condition allows. The patients will be instructed concerning self-monitoring of blood glucose using glucose meters, which should have a searchable memory and comply with standard ISO 15197. During the diet, monitoring will be set up as a function of the centers: self-monitoring of capillary blood glucose (4 times/day) or, after 10 days, fasting blood glucose and blood glucose 2 h after a meal.

The patients included are

- Eligible patients with blood glucose targets not reached, ie, those for whom at least 2 abnormal blood glucose values were noted after 10 days of well-conducted dietary management: fasting blood glucose ≥0.95 g/L and/or postprandial blood glucose at 2 h ≥1.20 g/L.

3.2 Non-inclusion criteria

- Multiple pregnancy
- Chronic hypertension
- Preeclampsia
- Proven renal insufficiency
- Proven hepatic insufficiency
- Long-term corticosteroid treatment
- Suspected sulfonylurea allergy
- Diabetes prior to pregnancy
- Abnormal value in screening for gestational diabetes before 24 weeks of gestation
- Fasting blood glucose ≥1.26 g/L at initial diagnosis of diabetes

- The need, in addition to glyburide, for a drug treatment that is contraindicated or inadvisable
- Poor understanding of the French language
- No social security coverage

3.3 Exclusion criteria

The discovery in a patient included of a non-inclusion criterion during the study will lead to the exclusion of the patient.

3.4 Simultaneous participation in other research, exclusion period

Patients cannot take part in other research during their participation, except for the ancillary studies described in section 10.

4 TREATMENTS ADMINISTERED

4.1 Treatments necessary for the research

4.1.1 Experimental treatment (glyburide)

Nature of the treatment

Glyburide is available as scored 5 mg tablets (Daonil®) from Sanofi Aventis. It is authorized in France for the treatment of type 2 diabetes. The information leaflet is given in Appendix 18.5.

Modes of administration

Glyburide: The oral dose of glyburide will initially be 2.5 mg/day before breakfast and will be increased incrementally as a function of blood glucose values up to a maximum of 20 mg/day until blood glucose targets are reached (fasting blood glucose <0.95 g/L and postprandial blood glucose at 2 h <1.20 g/L). An algorithm for dose adaptation depending on capillary blood glucose values will be given to the patient at the instruction session. In the event of at least 2 abnormal values (fasting blood glucose ≥0.95 g/L and/or postprandial blood glucose at 2 h ≥1.20 g/L), the dose will be increased by the patient at D4 to 5 mg in the morning. At D8, the patient will have a review appointment with the diabetologist. If there are still 2 abnormal values, the dose will be increased to 5 mg in the morning and 5 mg in the evening before dinner. At D12, if there are still 2 abnormal values, the patient will increase the dose to 10 mg in the morning and 5 mg in the evening, up to a maximum dose of 10 mg in the morning and 10 mg in the evening at D16. If there is a deviation from the usual diet, the blood glucose value following the meal in question will not be taken into account. The patient will have a diabetology appointment on D21: switch to insulin if the blood glucose targets are not reached. The patient can use monitoring by telephone or by email at D4, D12 and D16 or if she experiences side effects between appointments. In cases of symptomatic hypoglycemia or of blood glucose <0.6 g/L, the glyburide dose will be decreased or returned to the previous level. Treatment will be continued until delivery.

Authorized and prohibited drugs and treatments

Contraindicated:

Miconazole (systemic route, oral gel)

Not recommended:

- Phenylbutazone (for all dosage forms, including topical)
- Alcohol

Require precautions for use:

- Beta-blockers
- Fluconazole
- Clarithromycin, erythromycin

In all cases, the alternative treatment will be insulin.

4.1.2 Reference treatment (insulin)

Nature of the treatment

The insulin treatment regimen will be adapted as a function of each department's usual practice and according to capillary blood glucose values within the framework of the patient's usual treatment.

4.2 Methods for monitoring adherence to treatment

Treatment will be noted in a monitoring notebook. Capillary blood glucose values will available in this notebook and also in the memory card reader. At appointments, the diabetologist and/or obstetrician can check adherence to treatment using the monitoring notebook, which will be produced by the Paris Sud clinical research unit. Each sheet will be in duplicate, the copy being for subsequent data entry by the clinical research

technician. This notebook will be kept by the patient. At each appointment, the investigator will collect the completed duplicate sheets and will give them to the clinical research technician, who will then enter the data.

4.3 Provision of the experimental drug

Glyburide 5 mg:

Labeling:

Treatment will be labeled by the Clinical Trials Unit of the Agence Générale des Equipements et Produits de Santé (AGEPS) with the regulatory texts for drugs used in clinical trials. Removable labels will be attached to the boxes, to ensure the traceability of dispensing.

Supply and restocking

At the start of the study, the AGEPS will supply the treatment (Daonil®) to the pharmacies of the participating centers. An initial stock of treatment units will be made available as a function of the number of potential patients. If necessary, AGEPS will restock at the request of the participating centers' pharmacies.

Monitoring of dispensing

A notebook for monitoring the dispensing of treatment will be made available for the study in each pharmacy and will be completed by the clinical research assistant.

Insulin:

Dispensing:

The boxes of insulin will be dispensed in accordance with their marketing authorization by community pharmacies or by the pharmacies of the participating centers.

4.4 Treatment discontinuation procedure

4.4.1 Criteria and methods for treatment discontinuation or patient exclusion

Glyburide will be stopped and replaced by insulin if it fails.

Glyburide will be replaced by insulin if it fails to achieve blood glucose targets (at least 2 abnormal blood glucose values: fasting blood glucose ≥0.95 g/L and/or postprandial blood glucose at 2 h ≥1.20 g/L) for one week at the maximum dose of 20 mg/day. The patients will remain in the study.

4.4.2 Data collection methods and timetable

The decision to stop treatment can be taken at an appointment for blood glucose monitoring or at an obstetrical appointment.

Procedures for follow-up of drop-outs

All drop-outs should be documented and the investigator should indicate the reason for drop-out. For patients lost to follow-up, the CRF should be completed up to the last visit. The investigator will make every possible effort to contact the patient and to establish the reason for her withdrawal from the trial and her state of health.

Consequence of drop-outs

Patients who drop out will not be re-included in the study and their treatment numbers will not be re-used. These patients will be followed up in the maternity unit outside the protocol.

4.4.3 Modalities for replacement of drop-outs, if necessary

When a patient's glyburide treatment is discontinued, it will be replaced by insulin, as treatment of gestational diabetes is considered necessary. Follow-up of these patients in the study will continue.

4.4.4 Modalities of follow-up of drop-outs

Patients who drop out will be followed up in the department, outside the protocol. In cases where there is a change of treatment, follow-up of such patients will continue in the research.

6.4.5 Recording of refusals and exclusions

Patients who refuse randomization and patients who are excluded by their characteristics will also be recorded (registry).

4.5 Integration of INDAO in the management of patients with gestational diabetes

When the blood glucose target is not reached after 10 days of well-conducted dietary management, the reference treatment is subcutaneous insulin. The INDAO protocol proposes to test glyburide, a treatment of type 2 diabetes outside pregnancy, in this indication.

Inclusion in INDAO in no way changes the usual treatment of patients with gestational diabetes. The intervention consists of treatment with glyburide (experimental drug) or with insulin (according to the recommendations for management of gestational diabetes), but the treatment frequency, type of appointment, blood glucose monitoring, monitoring of pregnancy, delivery and monitoring of newborns are the same regardless of the treatment group generated by randomization. The study results in no change in the usual treatment for the end of pregnancy.

5 EVALUATION OF EFFICACY

5.1 Parameters for evaluation of efficacy

5.1.1 Primary outcome

The primary outcome is a composite criterion comprising neonatal complications associated with gestational diabetes. Each parameter reflects the potential adverse effects of exposure to maternal hyperglycemia and hence of fetal hyperinsulinism. The parameters selected for this composite criterion are fetal macrosomia or birth weight >90th percentile for gestational age, neonatal hypoglycemia, and neonatal hyperbilirubinemia.

- Macrosomia is defined as birth weight >4000 g or birth weight >90th percentile for gestational age. The birth weight percentiles are those of published growth curves [42].
- Hypoglycemia will be taken into account in the analysis for a blood glucose value <36 mg/dL
-
- (<2 mmol/L) after 2 h of life or a value <45 mg/dL (2.5 mmol/L) associated with clinical signs suggestive of hypoglycemia and resolved by glucose administration. Hypoglycemia detected using a blood glucose test strip will be confirmed by a laboratory assay of a blood sample collected in a fluoropolymer tube. The presence of abnormal clinical signs is an indication for measurement of blood glucose whenever these clinical signs are observed.
- The blood glucose value in the 1st hour of life before the 1st breastfeed will be collected as information but will not be taken into consideration in defining hypoglycemia, as the norm for this value is unknown. This value will, however, be compared between the 2 groups.
- Hyperbilirubinemia will be taken into account in the analysis if a treatment is initiated with phototherapy or by other therapeutic means and if no pathological cause of jaundice is found (ABO incompatibility, G6PD deficiency, hematoma, other). Its frequency will be compared in the 2 groups.

5.1.2 Secondary outcomes

Maternal criteria:

- Maternal blood sugar balance evaluated using the average fasting blood glucose and postprandial blood glucose between diagnosis and delivery
- Number of episodes of maternal hypoglycemia defined by blood glucose <0.6 mg/dL and/or a clinical episode
- Rate of failure of glyburide (number of patients requiring insulin after maximum doses of glyburide)
- Rate of cesarean section
- Rate of premature delivery
- Rate of 3rd and 4th degree perineal tears
- Maternal satisfaction evaluated using a questionnaire

Neonatal criteria:

- Rate of neonatal trauma associated with delivery (shoulder dystocia, fracture, bone trauma, elongation of the brachial plexus)
- Rate of respiratory distress: need for respiratory support and/or oxygen therapy beyond 2 hours of life
- Other neonatal criteria

  Ponderal index: Birth weight (g)/ Size cm^3 X100

  pH <7, lactate, base deficit >10, measured using cord blood

  Rate of neonatal mortality

  Rate of transfer to pediatrics or neonatal intensive care

Other criteria

- Number of prenatal obstetric visits
- Number of diabetology appointments
- Number of days spent in hospital pre- and postnatally

5.2 Methods and timetable for the measurement, recording, and analysis of parameters for evaluation of efficacy

All study outcomes and data will be recorded using the CleanWEB® e-CRF. Data on the children will be collected if the previously informed parents voice no opposition. This CRF will be used by the investigator or the clinical research technician to record the follow-up of patients at appointments. Data recorded will include pregnancy characteristics, gestational age at diagnosis, dose of insulin or of glyburide, gestational age at delivery, method of delivery, birth weight, pH at birth, 5-minute APGAR score, and all endpoints as well as the reasons for any discontinuation or change of treatment.
A paper notebook (duplicate pages) will be used to record the patient's treatment (insulin or glyburide) and the doses received. The data collected at follow-up appointments with the diabetologist and data recorded by the pediatrician at birth will be entered in a paper CRF. The clinical trial technician will subsequently enter these data in the e-CRF.

6 ASSESSMENT OF SAFETY

6.1 Description of parameters of safety assessment

6.1.1 Adverse event

Any untoward medical occurrence that may present in a person taking part in biomedical research, whether or not it has a causal relationship with the product used in the research.

6.1.2 Adverse reaction

Any noxious and unintended response to an experimental drug, whatever the dose administered.

6.1.3 Serious adverse event or effect

Any adverse event or effect of a drug, irrespective of the dose administered, that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

6.1.4 Unexpected adverse reaction to an experimental drug

An adverse reaction the nature, severity, or progression of which is inconsistent with the summary of product characteristics, when the drug is authorized, or with the investigator brochure, when it is not authorized.

6.1.5 New finding

Any new safety finding that could lead to reassessment of the risk-benefit ratio of the research or of the experimental drug, or which could be sufficient to envisage changes in the administration of the experimental drug or in the conduct of the research.

6.2 Adverse reactions to treatment

Expected adverse reactions associated with glyburide:
- Metabolic and nutritional disorders:
  - Hypoglycemia: skin and subcutaneous tissue disorders
  - Mucocutaneous eruptions: pruritus, urticaria, maculopapular
  - Some cases of photosensitization have been reported
- Immune system disorders:
  - Manifestations of hypersensitivity, such as bronchospasm, hypotension, or even shock.
- Gastrointestinal disorders:
  - Nausea, diarrhea, epigastric pain
- Hepatobiliary disorders:
  - Increased liver enzymes with the possibility of cytolytic or cholestatic hepatitis requiring treatment discontinuation. Can progress to life-threatening liver failure
- Blood and lymph system disorders:
  - Blood disorders generally reversible on treatment discontinuation:
    - Hypereosinophilia, leukopenia, moderate or severe thrombocytopenia that presents as purpura
    - More rarely: agranulocytosis, hemolytic anemia, medullary aplasia, and pancytopenia
- Investigations:
  - Hyponatremia (isolated cases)
  - Occasional moderate increases in blood urea and creatinine

- Eye disorders:
  - Transient visual disturbances such as blurred vision or visual accommodation disturbances, especially at the start of treatment, with or without blood glucose variation

Expected adverse reactions associated with insulin therapy:

- Hypoglycemia is the most frequent adverse reaction during insulin therapy of the diabetic patient. Severe hypoglycemia can lead to loss of consciousness and, in extreme cases, death. Hypoglycemia can result from excess insulin and other factors, such as food intake and energy expenditure. No frequency of onset of hypoglycemia can be presented.
- Local allergy is frequent (1/100 to <1/10). Redness, edema, and itching can occur at the injection site.
- Systemic allergy, which is very rare (<1/10 000) but potentially more serious, corresponds to generalized allergy to insulin. It can lead to generalized eruption over the whole body, dyspnea, wheezing, drop in blood pressure, fast heartbeat, or sweating. Severe generalized allergy can be life-threatening. The rare cases of severe allergy to Humulin® must be treated immediately. A change of insulin or desensitization may be necessary.
- Lipodystrophy at the injection site is infrequent (1/1000 to <1/100).

6.3 Methods and timetable for measuring, recording, and analyzing safety assessment parameters – Study committees

Steering committee

This committee will comprise the clinicians who initiated the project, the biostatistician in charge of the project, the clinical research unit representative appointed for this research, and the department of clinical research and development representative. It will define the general research organization and procedures and will coordinate data. It will initially determine the methodology and, during the research, will decide how to deal with unforeseen situations and will monitor the research, in terms of safety and adverse events, in particular.

Scientific committee

This committee will comprise those who helped draw up and write the protocol. It will be consulted during the trial to take stock of progress and for analysis of the results.

Independent monitoring committee

This committee will comprise a group of experts who supervise the clinical trial data concerning the safety of patients and the efficacy of treatment. Notably, the committee will be in charge of monitoring any severe adverse effects that occur. The committee can recommend discontinuation of the trial following evaluation of the results. It can also decide to stop the trial for reasons of patient safety, inefficacy compared with the reference treatment, or a clinical benefit much greater than that of the reference treatment. This independent committee will meet periodically to assess progress, safety data, and determinant events in terms of efficacy. It will comprise Prof François Goffinet, gynecologist-obstetrician at the Port Royal maternity unit, Dr Vincent Gadjos, pediatrician at the Hôpital Antoine Béclère, and Dr Eric Pussard, pharmacologist, at the Hôpital Bicêtre.

6.4 Adverse event reporting

Non-serious adverse events:

Any non-serious adverse event (see definition above) observed during or after the research should be noted in the CRF in the section provided for the purpose. A single event should be reported per item. The event can correspond to a symptom, diagnosis, or the result of a complementary examination deemed significant. All clinical or laboratory data that help describe the event in question should be recorded.

Serious adverse events:

The investigator must immediately notify the sponsor, the Paris public hospital system, of any serious adverse events as defined above. The investigator completes the serious adverse events form (of the study CRF) and faxes it (no. 01 44 84 17 99) to the clinical research and development department within 48 hours (after, if possible, an immediate telephone call [01 44 84 17 23] in cases of death or life-threatening condition). The investigator must also inform the clinical research unit in charge of the research of any serious adverse events.

For each serious adverse event, the investigator must give an opinion on the causal relationship of the event with the experimental drug (glyburide), with insulin, or with any other treatments. For the initial declaration, the time available may be insufficient to obtain information regarding the description and evaluation of an

adverse event. Should the death of a participant occur during the research, the investigator will send the sponsor all additional information requested (hospital report, autopsy findings, etc.).

The sponsor must be informed of any new finding in the research or in the context of the research, provided by the research itself or from the scientific literature.

- Reporting of serious adverse events to the health authorities

The pharmacovigilance unit of the clinical research and development department will report serious adverse events to the health authorities, after evaluation of their seriousness, the causal relationship with the experimental drug, with insulin, and with any other treatments, and the unexpected nature of the adverse events. The sponsor will notify the appropriate health authorities of any suspected unexpected serious adverse event within the legally stipulated timeframe. Any safety data or new finding that could significantly affect the evaluation of the risk-benefit ratio of the experimental drug, or of the research, or which could lead to changes concerning the administration of the drug or the conduct of the research, will be sent by the sponsor to the appropriate health authorities, the ethics committee, and the study investigators.

6.5 Modalities and duration of follow-up of patients after adverse events

Any patient presenting an adverse event must be followed up until the event is resolved or stabilized.

- If the event is not serious, progress will be noted on the corresponding page of the CRF in the section provided for the purpose.
- If the event is serious, a serious adverse event follow-up report will be sent to the clinical research and development department.

7 STATISTICS

7.1 Data analysis

Data will be entered progressively as the trial advances, overseen by the investigator, using CleanWEB® software. The statistical analysis will be done using STATA (College Station, TX USA). Methodological and statistical aspects will be managed by the Epidemiology of Reproduction and Child Development team at the Epidemiology and Population Health research center (Inserm Unit 1018), under the responsibility of Jean Bouyer.

The glyburide group will be compared with the insulin group in terms of the patients' demographic, obstetrical, and medical characteristics. The glyburide and insulin groups will be compared in terms of the composite endpoint (primary study outcome) by calculating the confidence interval of the percentage difference between the 2 groups. It will be concluded that glyburide treatment is not inferior to insulin therapy if this confidence interval does not contain the value 7%, which has been selected as the limit of equivalence.

If, despite randomization, the 2 groups are unbalanced for one or more demographic, obstetrical, or medical variables, an adjustment will be made by logistic regression [44]. All tests and confidence intervals will be done with a 5% risk of error.

The usual recommendations for a clinical trial are an intention to treat analysis [45]. However, for a noninferiority trial this type of analysis can reduce the apparent deviation between the treatments and so incorrectly indicate noninferiority. A per protocol analysis is therefore recommended. Both analyses will be done because they yield complementary information. More weight will be given to the per protocol analysis. The results will be all the more convincing if the results of the 2 types of analysis agree.

It was decided not to perform interim statistical analyses because this would require an increase in the number of subjects included.

7.2 Planned number of people to be included in the research

The number of subjects needed was calculated using the primary outcome. The frequency of neonatal complications was estimated using literature data [33, 34, 41] on women presenting gestational diabetes treated with insulin as well as local data from maternity units over an 18-month period. The estimated frequency was approximately 18%.

The aim was to show that glyburide treatment was not less effective than insulin therapy, which is equivalent to determining a maximum difference that can be tolerated to conclude that the new treatment (glyburide) is not less effective than the reference treatment (insulin). This difference must be small enough to have no clinical significance.

To calculate the number of subjects needed, we set this difference at 7%, ie, glyburide treatment is not considered to be less effective than insulin therapy if the frequency of the composite endpoint does not exceed

25% with glyburide (when it is 18% with insulin). To guarantee a power of 80% (with a 5% threshold of significance), we therefore need 372 subjects per group. In considering that about 20% of the patients treated with glyburide will not reach the defined blood glucose targets and will be switched to insulin, 450 subjects per group will be necessary.

The estimated percentage of pregnant women with gestational diabetes who require drug treatment is 1.5%, so 60 000 pregnant women will be necessary. Assuming that one in 2 women will agree to randomization, we need a population of 120 000 pregnant women. Given that the participating maternity units manage about 40 000 deliveries per year, recruitment should be complete in 3 years.

The distribution of subjects per center is not fixed and will depend on recruitment, which is a function of the number of pregnant women followed up and the real percentage of acceptance of the trial by the patients. The only restriction is the balance between the groups in each center, which is ensured by the fact that the randomization is stratified by center.

7.3 Missing data

If necessary, the characteristics of patients lost to follow-up will be studied and compared with those of the patients who are followed up. A sensitivity analysis will be used to determine to what extent the results of the study may have been influenced by this lack of information.

In cases of missing data, the analysis will be done using the classic complete-case method, ie, by considering only subjects without missing data. Multiple imputation methods can also be used as an analysis of sensitivity as, even if the methodology is under development, the assumptions of these methods are less strong than those of the complete-case analysis.

7.4 Choice of patients to be included in the analysis

The per protocol analysis will only include patients who followed the treatment allocated to them by randomization. Patients who switched to insulin from glyburide because the latter was ineffective will be excluded from the per protocol analysis. The characteristics of the patients excluded from the per protocol analysis will be clearly described. The intention to treat analysis will be used to study the 2 groups of patients as defined by the randomization.

7.5 Transcription of data in the case report form

An e-CRF will be configured for this study by Laure Coutard, the data manager of the Paris-Sud Clinical Research Unit, in collaboration with the investigator/coordinator and the biostatistician. The data will be recorded:

- Directly in the e-CRF for data relating to inclusion, which allow the randomization of patients
- In paper documents (in duplicate), which will constitute the source medical data and which the clinical research technician will subsequently enter in the e-CRF:
  - The patient monitoring records of the treatment initially allocated by randomization (insulin or glyburide) and the doses received
  - The data collected at the follow-up appointment with the diabetologist
  - The data collected by the pediatrician at birth

All information required by the protocol must be noted in the CRF along with the investigator's explanation of any missing data. The data, whether laboratory or clinical, must be transferred into the CRF as they are recorded.

Patient anonymity will be ensured by the use of a code number and the patient's initials on all documents necessary to the research, or by using appropriate means to erase named data on copies of source documents intended for documentation of the research.

8 ETHICAL CONSIDERATIONS

The sponsor is defined by the French law no. 2004-806 of 9 August 2004 and is the Paris public hospital system. Regulatory considerations will be taken care of by the Department of Clinical Research and Development.

Before starting the research, each investigator will provide the research sponsor's representative with a signed curriculum vitae bearing his or her French Medical Association registration number.

8.1 Application to AFSSAPS for authorization

To start the research, the clinical research units as sponsor must apply for authorization from AFSSAPS, the competent authority as defined in Public Health Code article L. 1123-12, which gives its opinion regarding the safety of this biomedical research involving human subjects, notably in terms of the safety and quality of the medicinal products used during the research in accordance with, where necessary, the references/norms in force, the conditions for their use, and the safety of the human subjects in terms of the procedures and methods used, as well as the planned modalities for follow-up of the subjects.

8.2 Submission of the protocol to the ethics committee

In accordance with article L.1123-6 of the Public Health Code, the research protocol must be submitted by the sponsor to an ethics committee, the opinion of which is conveyed to the competent authority by the sponsor before the research starts.

9 DECLARATION TO THE FRENCH DATA PROTECTION AUTHORITY

Under French law, before the research starts the French Data Protection Authority (CNIL) must be sent the computer file used to collect personal data for the research. In January 2006, the CNIL established a reference methodology specific to the processing of personal data in the context of biomedical research, as defined by law no. 2004-806 of 9 August 2004, because it comes within the scope of article L.1121-1 et seq. of the Public Health Code.

This methodology enables a simplified notification procedure when the nature of the data collected in the research is compatible with the list drawn up by the CNIL in its reference document.

9.1 Information note and informed consent

Written consent will be collected from every woman who participates in the research before any procedure required by the research is performed. The study obstetrician or diabetologist will inform patients beforehand about the study. After a period of reflection, the patients' consent will be collected by the study obstetrician or diabetologist at an appointment or at an outpatient visit, before initiation of treatment. Parents who do not object to the collection of data on their child will be informed thereof beforehand.

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12 ALGORITHM FOR ADAPTATION OF DAONIL® DOSES GIVEN TO THE PATIENT AT APPOINTMENTS

PRESCRIPTION AND ADAPTATION OF DAONIL
DIABETIC PREGNANT WOMAN
Capillary blood glucose measurements in the fasting state and 2 h after each meal
OBJECTIVE: Blood glucose: in fasting state: below 0.95 g/L
2 hours after each meal: below 1.20 g/L

Starting treatment with Daonil® 5 mg: ½ tablet/day
Doses will then be adjusted every 4 days for 21 days:
- on the 4th day by you, and on the 8th day by the diabetologist,
- on 12th and 16th days by you, and on the 21st day by the diabetologist.

- If in the 4 days following treatment initiation 2 or more blood glucose readings are above target values (>0.95 g/L fasting blood glucose or >1.20 g/L 2 hours after a meal), on the 5th day, ie, on ……., increase Daonil® to 1 tablet/day, ie, 5 mg.

Diabetology appointment scheduled for 8 days after the start of treatment, ie, on:…….
New prescription: Daonil® 5 mg: Morning:……tablets Evening:……tablets

- If in the 4 days following treatment adjustment by the diabetologist 2 or more blood glucose readings are above target values (>0.95 g/L fasting blood glucose or plus de 1.20 g/L 2 hours after a meal), the next day, ie, on:……., increase Daonil® to:
1 tablet/day if the previous dose was ½ tablet/day
2 tablets/day (1 tablet in the morning and 1 tablet in the evening) if **the previous dose was 1 tablet/day**
3 tablets/day (2 tablets in the morning and 1 tablet in the evening) if **the previous dose was 2 tablets/day**

- If in the next 4 days 2 or more blood glucose readings are above target values (>0.95 g/L fasting blood glucose or >1.20 g/L 2 hours after a meal), the next day, ie, on:……, increase Daonil® to:
1 tablet/day if the previous dose was ½ tablet/day
2 tablets/day (1 tablet in the morning and 1 tablet in the evening) if **the previous dose was 1 tablet/day**
3 tablets/day (2 tablets in the morning and 1 tablet in the evening) if **the previous dose was 2 tablets/day**
4 tablets/day (2 tablets in the morning and in the evening) if the previous dose was 3 tablets/day

- If there is a deviation from the usual diet, do not take into account the blood glucose value following the meal in question.
- In cases of hypoglycemia (<0.70 g/L with malaise, or <0.60 g/L), decrease Daonil® to the previous dose the next day.

Diabetology appointment scheduled in 21 days, ie, on:…….
Name of prescriber: …… Signature and stamp:

13 SATISFACTION QUESTIONNAIRE

Glyburide versus insulin in the treatment of gestational diabetes after failure of dietary management: INDAO trial

SATISFACTION QUESTIONNAIRE

Patient's identification code _ _ - _ _ _ _ - _ _

Date questionnaire completed _ _ - _ _ - _ _ _ _
DD-MM-YYYY

Madam,
You have just taken part in a research study designed to show that treatment with Daonil® is not less effective than insulin in terms of maternal and fetal complications in the treatment of gestational diabetes resistant to dietary management alone. We would like to know what you think about this treatment.

For each question, please tick the appropriate box.

A. EASE OF TREATMENT

1) How many times did you forget your treatment?

- ☐ Never
- ☐ <1 time a week
- ☐ 1 to 3 times a week
- ☐ 4 to 6 times a week
- ☐ >6 times a week

2) Which treatment would you take for a new pregnancy?

- ☐ Insulin (subcutaneous injection)
- ☐ Daonil® (oral tablets)
- ☐ I'm not bothered

3) What was the simplest part of the treatment?

- ☐ Blood glucose monitoring (capillary blood glucose)
- ☐ Dietary monitoring
- ☐ Taking the treatment

4) What was the hardest part of the treatment?

- ☐ Blood glucose monitoring (capillary blood glucose)
- ☐ Dietary monitoring
- ☐ Taking the treatment

B. ADVERSE REACTIONS TO TREATMENT

1)Did you experience symptoms of hypoglycemia (malaise, feeling of weakness) during your treatment?

- ☐ No
- ☐ Yes

2)Overall, how severe were the unpleasant symptoms caused by the treatment that you experienced?

Tick the box that best describes your experience
(0=No symptoms…. 10=Extremely unpleasant symptoms)
(The more unpleasant the symptoms, the higher the score)

□-□-□-□-□-□-□-□-□-□-□
0 1 2 3 4 5 6 7 8 9 10

C. OVERALL SATISFACTION

Overall, are you satisfied with your treatment?

- ☐ Not at all
- ☐ Fairly
- ☐ Moderately
- ☐ Very
- ☐ Extremely

D. TO BE COMPLETED ONLY BY PATIENTS WHO RECEIVED DAONIL® AND THEN INSULIN

1) For a subsequent pregnancy, would you wish to receive:

- ☐ Daonil® and then, if necessary, insulin again
- ☐ Insulin straight away

2) Does the change of treatment worry you?

- ☐ No
- ☐ Yes

14 REPORTING NONINFERIORITY AND EQUIVALENCE (CONSORT)

From JAMA, 2006

Table. Checklist of Items for Reporting Noninferiority or Equivalence Trials (Additions or Modifications to the CONSORT Checklist are Shown in Italics)

Paper Section and Topic	Item Number	Descriptor (Adapted for Noninferiority or Equivalence Trials)
Title and abstract	1*	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned"), *specifying that the trial is a noninferiority or equivalence trial.*
Introduction		
Background	2*	Scientific background and explanation of rationale, *including the rationale for using a noninferiority or equivalence design*.
Methods		
Participants	3*	Eligibility criteria for participants *(detailing whether participants in the noninferiority or equivalence trial are similar to those in any trial[s] that established efficacy of the reference treatment)* and the settings and locations where the data were collected.
Interventions	4*	Precise details of the interventions intended for each group, *detailing whether the reference treatment in the noninferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy,* and how and when they were actually administered.
Objectives	5*	Specific objectives and hypotheses, *including the hypothesis concerning noninferiority or equivalence.*
Outcomes	6*	Clearly defined primary and secondary outcome measures, *detailing whether the outcomes in the noninferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment* and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).
Sample size	7*	How sample size was determined, *detailing whether it was calculated using a noninferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.* When applicable, explanation of any interim analyses and stopping rules *(and whether related to a noninferiority or equivalence hypothesis).*
Randomization		
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated.
Statistical methods	12*	Statistical methods used to compare groups for primary outcome(s), *specifying whether a 1- or 2-sided confidence interval approach was used*. Methods for additional analyses, such as subgroup analyses and adjusted analyses.
Results		
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the trial protocol, and analyzed for the primary outcome. Describe protocol deviations from trial as planned, together with reasons.
Recruitment	14	Dates defining the periods of recruitment and follow-up.
Baseline data	15	Baseline demographic and clinical characteristics of each group.
Numbers analyzed	16*	Number of participants (denominator) in each group included in each analysis and whether *"intention-to-treat" and/or alternative analyses were conducted*. State the results in absolute numbers when feasible (eg, 10/20, not 50%).
Outcomes and estimation	17*	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval). *For the outcome(s) for which noninferiority or equivalence is hypothesized, a figure showing confidence intervals and margins of equivalence may be useful.*
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.
Adverse events	19	All important adverse events or side effects in each intervention group.
Comment		
Interpretation	20*	Interpretation of the results, taking into account the *noninferiority or equivalence hypothesis and any other* trial hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.
Generalizability	21	Generalizability (external validity) of the trial findings.
Overall evidence	22	General interpretation of the results in the context of current evidence.

*Expansion of corresponding item on CONSORT checklist.[2,3]

15 CLASSIFICATION OF SERIOUS ADVERSE EVENTS

Classification of adverse events in biomedical research on a drug or related product
Classification of serious adverse events in biomedical research (Art. R. 1123-54 of the Public Health Code)
Comparison of Insulin and DAOnil in the treatment of gestational diabetes
Randomized, controlled, multicenter, noninferiority trial (INDAO) - P110104

DO NOT NOTIFY THE SPONSOR BY FAX (do not complete the serious adverse events form), <u>but</u> note on the adverse events pages of the CRF		The investigator SHOULD NOTIFY the sponsor WITHOUT DELAY (by faxing the serious adverse events form to 01 44 84 17 99) and enter the information on the adverse events pages of the CRF	
Other events	Expected non-serious adverse events Known to be related to: au experimental drug of the research	Expected serious adverse events known to be related to the experimental drug	Unexpected serious adverse events
EVENTS THAT MAY BE SERIOUS but are not associated with the experimental drugs or the research procedures: Description: Everything that is in accord with the natural progression of the disease -Pregnancy-related complications:* -Scheduled hospitalizations for examinations in the framework of usual follow-up Usually observed during pregnancy: nausea, esophagitis due to reflux or vomiting, anemia, bacteriuria, nephritic colitis, cramp, cystitis, cytomegalovirus, lower back pain, pelvic pain, perineal pain, maternal fever, viral hepatitis, genital herpes, herpes during pregnancy, polyhydramnios, sexually transmitted infection, ovarian cyst, listeriosis, acute lymphangitis, mycoplasma, aseptic necrobiosis, parodontitis, parvovirus**,** postterm pregnancy, cesarean section, cervical tear, perineal tear, instrumental delivery, forceps, metrorrhagia - Fetal complications: macrosomia, shoulder dystocia, neonatal hyperbilirubinemia, fracture of the upper limb, brachial plexus paralysis	Description: **DAONIL 5 mg** Mother - Metabolic and nutritional disorders: *According to CTCAE V4 0 criteria - Hypoglycemia: <3 - **Mucocutaneous eruptions**: pruritus, urticaria, maculopapular. **<3** - **Some** cases of photosensitization have been reported **- Immune system disorders**: •Signs of hypersensitivity such as bronchospasm **<3** - **Gastrointestinal disorders**: •Nausea, diarrhea, epigastric pain. **<3** **- Hepatobiliary disorders**: •Increased liver enzymes **<3** **- Blood disorders** generally reversible on treatment discontinuation - **Hypereosinophilia,** leuko-penia, thrombocytopenia **<3** - **Hyponatremia** (isolated cases). - Occasional moderate increases in blood urea and creatinine <3 **- Eye disorders**: Transient visual disturbances such as blurred vision or visual accommodation disturbances, especially at the start of treatment, with or without blood glucose variation **<3** - **General disorders**: Antabuse effect when alcohol ingested with meals **<3** Newborn: Hypoglycemia **<3** moderate	Description: **<u>DAONIL 5 mg</u>** Mother * According to CTCAE V4 0 criteria - Hypoglycemia ≥3 - Hypotension or even shock ≥3 - **Hepatobiliary disorders**: •cytolytic or cholestatic hepatitis requiring discontinuation of treatment. These can progress to life-threatening liver failure **≥3** - **Hypereosinophilia:** leukopenia, thrombocytopenia **≥3** - Thrombocytopenia≥3 **-- More rarely**: agranulocytosis, hemolytic anemia, medullary aplasia, and pancytopenia **≥3** **-- Exceptionally**, allergic, cutaneous, or visceral vascularitis that can be life-threatening **≥3** Other: Unbalanced diabetes in the mother (hospitalization) . Newborn: - Neonatal hypoglycemia **≥3** -Prenatal death -Death	This column will be completed progressively as reported by the investigators Report all events meeting one of the criteria of severity* noted below, except for those identified in the other columns *Criteria of severity: in **<u>mother / newborn</u>** 1- Death 2- Life-threatening 3- Requires inpatient hospitalization or prolongation of existing hospitalization 4- Lasting sequelae 5- Anomaly or congenital malformation 6- Event deemed serious by the investigator (specify reason)