Statistical analysis plan for the INDAO randomized controlled trial

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Document outline

1. The INDAO trial: Review of principal aspects

a. Objectives and design

The INDAO trial is a randomized multicenter non-inferiority trial conducted between 2012 and 2016 in France in 13 centers. Its principal objective is test whether oral glyburide is not inferior to subcutaneous insulin for prevention of perinatal complications in women with gestational diabetes mellitus (GDM).

The secondary objectives are to compare glyburide 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.

b. Outcome

i. Primary outcome

The primary outcome 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

ii. Secondary outcomes

<u>Maternal criteria:</u>

- 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 (Appendix 18.2)

<u>Neonatal criteria:</u>

- 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
  - Birth weight index: Birth weight (g)/ Size cm3 X100
  - pH <7, lactate, base deficit >10, measured using cord blood
  - Rate of neonatal mortality
  - Rate of transfer to pediatrics or neonatal intensive care

<u>Other criteria:</u>

- Number of prenatal obstetric visits
- Number of diabetology appointments

- Number of days spent in hospital during pregnancy

2. Flow chart

Flow chart of the study will be drawn according to the Consort general recommendations.

3. Analysis

a. Descriptive analysis

The characteristics of the women at the time of randomization will be described separately for the two groups (glyburide and insulin) by providing mean and IQR for quantitative variables and number and percentages for qualitative variables.
No statistical test will be done to compare because of the randomization (a priori, the null hypothesis is always true). However, variables with a substantial difference between groups will be identified for further adjustment.

b. Analysis of the primary outcome

Primary outcome will be analyzed in providing the difference between the rates in the two groups and its 95% CI. Noninferiority will be demonstrated if the upper bound of the 95% CI is smaller than the pre-specified threshold of 7%.
Analyses and estimations will be adjusted for centers to take into account the multicenter nature of the trial.
The analysis of the primary outcome will be conducted on a "per protocol" (PP) basis as usual in non inferiority trials. Indeed, this analysis is the most conservative if there is a difference between the two treatments.
Women who were switched from glyburide to insulin during the trial will be excluded because they received a mix of both treatments. The compared groups will thus consist of two groups of women who follow the treatment that was initially assigned to them until delivery:
Complementary analyses will be done with the 3 components of the composite criterion with the same way to provide the results: 95%CI of the difference.
Additional sensitivity analyses will be done on an "intention to treat" (ITT) basis in which women remain in their initial group or by including women switched to the insulin group in a modified per protocol analysis.

c. Secondary outcomes

The secondary outcomes results will be considered as exploratory and as a way to comment or explain the results on the primary outcome.
The comparisons between groups will be adjusted for centers and made as superiority comparisons.
No corrections for multiple tests will be made.

d. Satisfaction questionnaire

The results of this questionnaire will be analyzed in the same way as the secondary outcome.

e. Management of missing data for the primary outcome

The protocol stipulates sensitivity analyses may be undertaken to evaluate the influence of missing data or lost to follow up.
Since there are very few lost to follow up and no missing data on primary outcome among women followed up, only complete-case method will be used.