# INVASIVE

## INFLUENCE OF PRENATAL COUNSELING IN INVASIVE TESTING

PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL


Raigam J. Martinez-Portilla

Fernanda Paz y Miño

Montse Pauta

Antoni Borrell

*Hospital Clinic of Barcelona / University of Barcelona*



Study Number: IRN2019/03/0001

Human Subjects Review Approval: HCB/2019/0788


September 15th, 2019

Study design:

This is a randomized open-label controlled trial evaluating the impact of an extra 15-minute prenatal counseling before the first trimester combined screening test for Down's syndrome, on the women's attitudes and preferences towards having an invasive testing as the first line option for screening of chromosomal abnormalities.

Data will be collected by the study-site manager and stored in an electronic data-capture database. The coordinator of the study and the statistician will witness the accuracy of the data at the beginning, middle, and end of the study (on-site audit). Data will be captured in a paper form basis and then captured into the electronic database.

Participants

Inclusion criteria: any pregnant woman of at least 18 years old, attending the first trimester combined screening test for chromosomal abnormalities (between 11+0 and 13+6 weeks' gestation). The exclusion criteria: women not willing to participate in the study, women without an answer in the question regarding which prenatal test would they choose (main outcome), or women with no sufficient knowledge of Spanish or Catalan to be able to read and understand the questionnaire.

Intervention and procedures

For the experimental group, the intervention will consist of an extra 15-minute prenatal counseling before their first trimester scan. This intervention will require an explanation of all screening techniques for chromosomal abnormalities, including the first trimester combined test, cfDNA testing, invasive testing, and no screening at all. The intervention will be given by a single maternal-fetal medicine specialist who will explain all pros and cons of all given methods, giving also time to solve any question the woman may have. After the intervention (counseling), all participants will be asked to fill a questionnaire of twenty-one question regarding their knowledge, attitude and preferences about prenatal testing.

For the control group, women will not be given an extra 15-minute counseling (no intervention), but will be directly asked to fill the questionnaire about their knowledge, attitude and preferences about prenatal testing.

Sample size

Sample size calculation has been made using an independent two-sample proportions likelihood-ratio test. We expect a 10% of women willing to have an invasive procedure as a first line test for aneuploidies in the control group, and a 25% difference to those in the experimental group that are given an extra 15-minute prenatal counseling, this yields a sample of 42 women per arm with a total of 84 subjects using a Type I error of 0.0501 and a power of 80% by a two-sided test.

Randomization and intervention

Participants will be randomized using an interactive Web-response system assigning patients in a 1:1 ratio to receive the extra counseling before first trimester assessment (intervention group) or nothing (control group). The allocation will be performed by the study manager. The maternal-fetal medicine specialist will be in charge of the participant's enrolment and will also perform the intervention to the corresponding randomized group. This is an open-label study which means that the specialist and women will be aware of the allocation and intervention every time.

Follow-up after the intervention

After both groups (the experimental and control) have filled the questionnaire, the routine prenatal care will be given according to our hospital's guidelines, which consists of a first trimester ultrasound scan, and the subsequent risk calculation for trisomy 21 and 18 with the use of the first trimester combined test. In case of risk greater than 1/250, an invasive diagnostic test will be offered. For risks between 1/250 and 1/1,000 a complementary first trimester genetic sonogram using secondary markers (nasal bone, tricuspid regurgitation, and ductus venosus) will be offered to re-calculate the risk for Down's syndrome. For women with Down's risk greater than 1/1000, no further evaluations will be offered.

Questionnaire

The questionnaire consists of twenty-one questions assessing the knowledge, preferences and attitude towards prenatal testing in the first trimester of pregnancy. The questionnaire will be divided in two parts.

The first fourteen questions consist of demographic characteristics and obstetrics history, such as age, ethnicity, study level, marital status, religion, salary, employment, parity, previous miscarriages, previous terminations of pregnancy, previous congenital defects, pregnancy search time in months, type of conception, and who had provided any type of previous information about prenatal screening/testing. Women will be asked to select only one option for each question. All questions will have the possibility to answer as "Prefer not to answer". The second part of que questionnaire will assess the preferences and attitudes towards prenatal testing; women will be asked to choose only one option for each question. The following questions will be included in the second part of the questionnaire: What influences you the most about prenatal testing? Who influenced you the most about prenatal testing? Would you like to choose your prenatal test? Which prenatal test would you choose? What is your opinion about termination? All questions include an "I don't know answer". The two final questions will ask the following, "What information regarding the results of prenatal testing is more important for you?" and "What is most important for you about prenatal testing?". Women will be asked to score the first question from 1 to 5, meaning 1 the least important and 5 the most important, and from 1 to 6 in the same manner for the second question. These two questions will be assessed as means, where the question with the highest mean represents what is most important for the patient.

Outcomes

The primary outcome of the study is the desire to choose an invasive diagnostic testing as the first option of screening for chromosomal abnormalities. This will be measured in the questionnaire by asking the question: which prenatal test would you choose if given the opportunity? Women will be asked to choose only one answer between first trimester combined test, cell-free DNA, invasive testing.

Statistical analysis

Analysis will be conducted by intention-to-treat. Missing data for the main outcome will be handled by complete-data analysis because women without an answer on the main outcome will be excluded. All analyses will be divided by groups (control vs experimental group). Continuous data will be assessed for normality using the Kolmogorov-Smirnoff test. Normally distributed variables will be compared using t-test and expressed as mean and standard deviation (SD), while not normally distributed variables will be analyzed using the Mann-Whitney-U test and expressed as medians and interquartile range (IQR). Quantitative variables will be

compared using $X^2$ test and expressed as numbers (n) and proportions (%). For the main outcome, preferences for prenatal testing among groups will be analyzed using absolute risk increase defined as the incidence of the outcome in the experimental group minus the incidence in the control group. The absolute risk increase will be depicted in a forest plot. A multivariate logistic regression will be performed to determine the Odds for choosing an invasive testing adjusting by demographic characteristics and previous counseling. Data will be analyzed using STATA v.15.3 for Mac (Texas College Station) and GraphPad Prism version 8.1.2 for Mac, GraphPad Software, San Diego, California USA, www.graphpad.com.