EMOTIVE

PROJECT

Effectiveness of repeated MOTivational InterVention to reduce ethanol intake during prEgnancy

PROTOCOL FOR A CLUSTER RANDOMIZED CONTROLLED TRIAL

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Study design:

This is a collaborative study developed by different health and research institutions. The group is composed by BCNatal (Barcelona Center for Maternal Fetal and Neonatal Medicine, *Hospital Sant Joan de Déu*), *Grupo de investigación Infancia y Entorno* (GRIE), Psychiatry Service of *Hospital Clinic de Barcelona* and the Health Department of Catalunya and ASSIR (*Centre d'Atenció a la Salut Sexual I Reproductiva*) of Baix Llobregat.

This is a cluster randomized simple masking controlled trial evaluating the effectiveness of repeated motivational interview (MI) during pregnancy on prevalence of ethanol intake, together with its effects on offspring neurodevelopment.

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: Maternal age at recruitment at least 18 years old, speak Spanish fluently, women controlling their pregnancy in Baix Llobregat Center, who will attend their delivery in Hospital Sant Joan de Déu and Parc Sanitari Sant Joan de Déu, viable singleton and non-malformed fetus, coursing first trimester of gestation.

Exclusion criteria: Women not willing to participate in the study, multiple gestations, perinatal infections, fetal anomalies including chromosomal abnormalities or structural malformations detected by ultrasound, uncontrolled or/and severe maternal chronic disease, language barriers, impossibility to obtain the sample (hair length shorter than 9 centimeters and/or discolored hair), and premature rupture of membranes.

Interventions and procedures

For the experimental group, the intervention consists in a MI program during prenatal care visits. MI will be received at least one time each trimester of pregnancy.
For the control group, usual prenatal care attention will be given, but they will be directly asked sign a consent form.

Intervention: Motivational interview

The MI is integrated in a structure theoretical mark. This method is a person-centered counseling style that increases the intrinsic motivation of the patient to behavioral changes through spirit, acceptance, compassion and evocation. Furthermore, it is a low-cost methodology, and any professional or individual could have been capacitated. Since the motivational interview is a good cost benefit intervention, it is a potential and suitable tool to implement in a healthcare public program.

Professionals whose attend prenatal care visits at centers allocated to give MI will receive previous capacitation (15 hours) dictated by a multidisciplinary expert group who are dedicated several years to MI training and addiction disabilities. This training group is composed by a psyquiatrist and a psychologist from *Addictions Unit of Psychatry Department of Clínic Hospital of Barcelona*

Prenatal procedures:

All participants will be followed-up during the pregnancy applying following procedures:

- Questionnaires to evaluate sociodemographic, health and habits background. This questionnaire will be answered during the first trimester of pregnancy.
- SCL-90 (Symptom Checklist): In order to evaluate mental health. This questionnaire will be filled during the first trimester of pregnancy.
- AUDIT-C (Assessment of the Alcohol use disorders identification test): To evaluate ethanol intake. This questionnaire will be filled during first trimester of pregnancy and also up to 7 days after delivery.
- Fetal neurosonography: To evaluate fetal neurodevelopment and brain structure at 28 and 32 weeks of gestation through transabdominal and transvaginal exploration using a General Electric Voluson E10 sonograph (GE Medical Systems, Zipf, Austria).
- Biological samples: Samples will be collected at the moment of delivery to obtain to different biomarkers :
    - Ethylglucuronide (EtG) on mother`s hair: In order to evaluate chronic ethanol intake.
    - Phosphatidilethanol (PEtH) on dried cordblood spot: In order to evaluate ethanol intake during last 3 weeks prior delivery.

Postnatal procedures:

After both groups (the experimental and control) have delivery, a postnatal follow-up to participants (mothers and children) will be given:

- Edinburgh postnatal depression scale (EPDS): This scale evaluates the presence of post-natal depression or anxiety. This questionnaire will be performed to mothers at 6 months from delivery.
- ASQ-3 (Ages and Stages Questionnaires): This parent-report questionnaire could be applied since first month until 5 years and a half of life. It includes 30 questions organized in 5 areas of develop (communication, gross motor, fine motor, problems-solving and adaptative skills). It will applicate at 6 and 12 months of age.
- Infant Behavior Questionnaire Revised (IBQ-R): This questionnaire is a parent-report measure of infant temperament. It will performed at 12 months from delivery.
- Bayley- III test: This test evaluate mental and motor development and also children behavior between 1 month to 42 months of age. It will be performed at 18 months of age.
- Canadian Guidelines for Diagnosis of FASD: It will be evaluated by a pediatrician at 18 months of age regarding the diagnostic criteria of FAS and FASD of Canadian Guidelines.

Sample size

Assuming a prevalence of ethanol consumption in our environment of at least 40% in the control group and about 25% (or less) in the intervention group. Thus, about 240 of prenatally exposed children will be followed up in their postnatal period. According to previous experience cohort studies, we may assume a maximum of 30% of loss during their ambulatory control. Regarding this estimate, 168 children will complete their follow up. This sample size can ensure a 90% of potency to detect differences of prevalence between both groups, with a signification of 5%.

Values were corrected regarding number of clusters (n= 8) and intraclass correlation coefficient. Intraclass correlation coefficient was estimated regarding the prevalence of ethanol intake among groups.

Randomization and intervention

Under a sequential rollout, 8 clusters (primary care centers from a geographic location of Barcelona; Baix Llobregat) were randomly allocated according to a random number generator with a fixed seed, using R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/, to incorporate a MI program into existing prenatal care visits (intervention group) or usual intervention (control group). The allocation was performed by a statician. Midwives from centers allocated to perform MI were trained by an expert team. Participants enrolment was performed by midwives of both groups (interventional and control group). This is a simple masking study, it means that participants will not aware of the allocation and intervention.

Outcomes

The primary outcome of the study is to demonstrate the effectiveness of repetitive MI to reduce alcohol intake. This will be measured by the presence of ethanol intake biomarkers (EtG in mother's hair and Peth in cordblood).

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 among groups using t-test and expressed as mean and standard deviation (SD), while not normally distributed variables will be compared 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 counts (n) and proportions (%).For categorical variables Fisher exact test or Chi-squared test are used. Regarding demographic data (age, sex, body mass index (BMI), etc.); continuous variables will be presented as mean and SD, or median and IQR, according to their distribution, and categorical variables as percentages (%).

For the main outcome, differences in prevalence of ethanol intake between 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 Ratio for ethanol intake adjusting by demographic characteristics. Data will be analyzed using R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ and GraphPad Prism version 8.1.2, GraphPad Software, San Diego, California USA, www.graphpad.com.