FETAL BRAIN CARE

Therapies for brain neurodevelopment in fetal growth restriction

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Setting: BCNatal | Fetal Medicine Research Center (Hospital Clínic and Hospital Sant Joan de Déu), Barcelona, Spain

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Study title: FetalBrainCare

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Center: BCNatal (Hospital Clínic de Barcelona - Hospital Sant Joan de Déu)
Promotor: IDIBAPS (Institut d'Investigacions Biomèdiques August Pi i Sunyer)

INTRODUCTION

We are writing to you to invite you to participate in the clinical trial (FetalBrainCare). This study is carried out jointly with other centers in Spain (Hospital Clínic de Barcelona, Hospital Sant Joan de Déu, Hospital Sant Pau, Hospital Can Ruti, Hospital del Mar y Hospital Dexeus-Quirón). It has been approved by the Clinical Research Ethics Committee of each center in accordance with current legislation (Law 14/2007 on biomedical research). It is our intention that you receive correct and sufficient information so that you can decide whether or not to participate in this study. For this reason, read this information sheet carefully and we will clarify any doubts that may arise. In addition, you can consult with the people you deem appropriate.

VOLUNTARY PARTICIPATION

You should know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw your consent at any time without altering your relationship with your doctor or causing any harm to your treatment.

GENERAL DESCRIPTION OF THE STUDY

We offer you the possibility of participating in this study because we have detected in the ultrasound of the third trimester of pregnancy that your baby has an intrauterine growth restriction

(IUGR). IURG is a complication that appears during pregnancy and consists of a decrease in the growth of the baby, generally secondary to a malfunction of the placenta. The malfunction of the placenta means that the placenta does not get enough blood, which means that the baby receives less nutrients affecting both its growth and the correct development of the organs, with a more important effect on the brain and the heart.

WHY ARE WE CONDUCTING THIS STUDY?

Nowadays, there is no treatment that has been shown to cure the alteration of the placenta, as well as to protect the brain and the heart from the lack of nutrients. Increasing the maternal intake of certain nutrients with protective effects on the development of the brain and the heart could constitute a fundamental pillar for the prevention of complications in these babies. In this way, with this study we want to demonstrate that with a maternal supplementation with docohexaenoic acid (DHA) and lactoferrin with fetuses diagnosed with IUGR, we are able to improve brain and cardiac development.

HOW DOES THE STUDY WORK?

We need to include a total of 304 pregnant women with the finding of an IUGR in the fetus to evaluate whether the supplementation of maternal nutrition with DHA and lactoferrin protects neurological and cardiac development in these babies. If you agree to participate, it will be determined randomly if you fall into the group of patients which will receive the supplementation (1000mf of lactoferrin + 1000mf od DHA daily orally) or if you fall into the placebo group (similar presentation to that used in the treatment group, but without containing DHA or lactoferrin). You are just as likely to receive the supplementation as placebo. Neither you nor the medical personnel treating you will know if you are in the supplementation group or the placebo group. This is the only way to answer the question of whether this treatment is really helpful in patients like you.

WHAT DO I HAVE TO DO IF I DECIDE TO PARTICIPATE IN THE STUDY?

You will take the supplementation/placebo every day from the start of the study (24-32.6 weeks) until the 37th week of pregnancy. At the beginning of the study, a maternal blood sample will be collected in addition to the usual clinical follow-up in a random subgroup of 100 women. This subgroup of patients will be randomly selected. Subsequently, you will follow the usual follow-up proposed by your medical center (medical appointments, ultrasounds, blood and urine tests and blood pressure measurement). However, during the follow-up of the pregnancy, additional examinations will be carried out aimed at evaluating in a very specific way the neurological and cardiovascular development of the baby. For this propose, a neurosonography (ultrasound evaluation aimed at evaluating neurological development) and an echocardiography

(ultrasound evaluation aimed at evaluating cardiac development) will be scheduled at Hospital Clínic or at Hospital Sant Joan de Déu at the time of inclusion in the study and during pregnancy monitoring. Additionally, an MRI will be performed to be able to asses neurological development very precisely at BCNatal around 34 weeks of gestation. In addition, both at the start of the study and at 36 weeks of gestation, you will be given questionnaires you should fill out in order to assess your lifestyle and stress level. You will be able to give birth in your center of origin. In the same subgroup of 100 patients, a sample of umbilical cord blood and maternal blood will be collected at the time of delivery. After delivery, medical data about you and your baby will be collected In addition, the baby's neurodevelopment will be closely monitored, both at the center of origin and at Hospital Clinic or Hospital Sant Joan de Déu. At 6 and 24 months of life, a neurodevelopmental assessment will be carried out by applying a functional test called the Bayley III test. The same day that this test is performed, the baby's blood pressure will be determined. During the pregnancy and postnatal follow-up, you will be contacted by telephone by the Speech Acquisitions and Perception Group of the Universitat Pompeu Fabra in order to expand the neurodevelopmental assessment of the baby. A specific consent form will be signed in case you decide to expand this study.

Apart from completing the study visits and activities, you must also notify any adverse event that happens to you or changes in the medication. Except in an emergency, you cannot modify the medication you are taking or take other medications or "medicinal plants" without first consulting with the study doctor.

BENEFITS AND RISKS DERIVED FROM YOUR PARTICIPATION IN THE STUDY

The main Benefit expected from this study is to objectify an improvement, especially in the brain development in babies who have suffered IUGR during fetal life. However, it is possible that any benefit will be obtained for your health or for your child for you participation in this study, either due to lack of efficacy of the supplements under study or due to taking placebo. If during the course of this study definitive data are obtained on the usefulness or otherwise of the treatment, you will be informed so that you can make the decision you deem appropriate about it.

Both DHA and lactoferrin are considered dietary supplements according to the Spanish Agency for Medicines and Medical Devices (AEMPS). Both substances at the proposed doses have been shown to be safe without presenting adverse or undesirable effects. There is prior information in humans on the safety of DHA during pregnancy and lactation. In the case of lactoferrin, information on safety in pregnancy and lactation comes from animal studies. Even the administration of these substances at higher doses that those proposed in this study have been used for other problems without evidence of significant undesirable effects, although some patients and at very high doses have presented gastrointestinal discomfort (stomach or intestinal

discomfort, diarrhea and constipation) and some episodes of skin rash. In this case, you can contact you doctor to assess these discomforts and whether or not to continue the treatment.

In addition, no risk is expected from the tests performed during the study. Both obstetric ultrasound and Tesla MRI have proven to be safe and not harmful, which is why today they are routine tests in obstetric monitoring when indicated.

INSURANCE

If you suffer any damage from participating in the study, all means will be made available to remedy it. In addition, the promoter has contracted a Civil Liability Insurance according to current legislation that covers any eventuality, providing compensation in case of impairment of your heath or injuries that may occur in relation to your participation in the study, provided that these are not consequence of the disease itself.

WHAT HAPPENS WITH THE INFORMATON WE COLLECT?

The Hospital Clínic, with Tax Identification Code 0802070C, as responsible for the processing of you data, informs you that the treatment, communication and transfer of personal data of all participants will comply with the EU Regulation 2016/679 of the European Parliament and the Council of April 27th 2016 regarding the protection of natural persons with reference to the processing of personal data and the free circulation of data and to the Organic Law 3/2018 of December 5th on Protection of Personal Data and Guarantee of digital rights.

Data collected for this study will be identified only by a code, so any information identifying the participants will be included. Only the study investigators and his collaborators with specific permission will be able to relate your data collected in the study with your medical history.

Your identity will not be available to any other person except for a medical emergency or legal requirement. The health authorities, the Research Ethics Committee and personnel authorized by the study promoter will have access to your personal information, when necessary to verify data and study procedures, but always maintaining confidentiality in accordance with current legislation.

Only coded data Will be transferred to third parties and other countries, which in no case will contain information that can directly identify the participant (such as name and surname, initials, address, social security number, etc.). In case this transfer occurs, it would be for the same purpose as described in the study and guaranteeing confidentiality.

If a transfer of encrypted data is made outside the EU, either to entities related to the hospital center where you participate, to service providers or researchers who collaborate with your doctor, your data will be protected by safeguards such as contracts or other mechanisms established by the data protection authorities.

In addition to the rights that the previous legislations already contemplated (access, modification, opposition and data cancellation, deletion in the new Regulation) you can now also limit the processing of data that are incorrect, request a copy or request that data to be transferred to a third party (portability). To exercise these rights, or if you want to know more about confidentiality. You should contact the main researcher of the study or the Data Protection Delegate or the Hospital Clínic de Barcelona through protecciodades@clinic.cat. You have also the right to contact the Data Protection Agency if you are not satisfied.

Data already collected cannot be delete even if you leave the study to ensure the validity of the research and to comply with legal duties and drug authorization requirements. But no new data will be collected if you decide to stop participating.

The researcher and the sponsor are obliged to keep the data collected for the study for at least 5 years after its completion. Subsequently, the personal information will only be kept by the center for the care or your health and by the sponsor for other scientific research purposes if the patient has given its consent to do so, and if this is permitted by law and applicable ethical requirements.

ECONOMIC COMPENSATION

You will not be charged for your participation in the study and for the study drugs. You will not receive any financial compensation for your participation in this study.

WHAT WILL BE DONE WITH THE BLOOD SAMPLES?

At the time of inclusion in the study, a maternal blood sample will be drawn in order to determine baseline levels of DHA and lactoferrin as well as angiogenic factors and certain cytokines. At the time of delivery, another sample of maternal blood will be taken to evaluate the levels of DHA and lactoferrin achieved at the end of the study, the angiogenic factors and the level of certain cytokines. Blood will also be collected from the umbilical cord to be able to evaluate the levels of DHA and lactoferrin in the baby's blood, without having to directly prick the baby. These samples are biological samples for which all assumptions will be met in accordance with the Biomedical Research Lay 14/2007 and RD 1716/2011 of November 18th, which establishes the basic requirements for authorization and operation of the biobanks for biomedical research purposes and the treatment of biological samples of human origin. By signing this document, you agree the use of the samples collected for the purposes of this study.

The simples will be kept stored in the Biobank-IDIBAPS of Maternal-Fetal Medicine at Hospital Clínic until they are used for the purposes of this study. Once completed, the remaining samples will be Destroyer, unless you sign a specific consent form in order to be stored and used in future research (this will be provided separately).

A code will be used to identify your samples and no data that could reveal your identity will be used. Only the study doctor and his collaborators will be able to associate the samples with you.

The data derived from the use of these samples will be treated in the same way as the rest of the data obtained during this study.

The transfer of biological samples for this study is free and voluntary. This means that you will not have rights to possible commercial benefits of the findings that could be derived from de results of biomedical research.

If relevant information is obtained that could affect you or your family members health, you will be notified. If it is necessary to contact you, the data that appears in your medical history will be used. However, your right to not receive that information will be respected. In that case, you have to check the specific box found on the consent form.

OTHER RELEVANT INFORMATION

Any new information regarding the treatment used in the study that may affect your willingness to participate or that is discovered during your participation, will be communicated to you by your doctor as soon as possible.

If you decide to withdraw your consent to participate in this study, no new data will be added to the database and you can demand the destruction of all identifiable samples previously retained to avoid further analysis.

You should also know that you can be excluded form the study if the promoter and/or the study investigators consider it appropriate, either for safety reasons, for any adverse event that occurs and is considered to be related to your participation in the study or because they consider that you are not complying with established procedures. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study.

By signing the attached consent form, you agree to comply with the study procedures that have been set forth to you.

Participant consent form sheet

Study tittle: FetalBrainCare

Version 6 (November 2022)

I, *(name and surname of the participant)* _____

- I have read the informational sheet given to me about the study.
- I have been able to ask questions about the study.
- I have received enough information about the study.
- I have spoken with: (name of researcher) _____
- I understand that my participation is voluntary.
- I understand that I can withdraw from the study:
    - Whenever I want.
    - Without having to explain anything.
    - Without this affecting my medical care.
- In accordance with the EU Regulation 2016/679 of the European Parliament and the Council of April 27th 2016 regarding the protection of natural persons with reference to the processing of personal data and the free circulation of data and to the Organic Law 3/2018 of December 5th on Protection of Personal Data and Guarantee of digital rights, I declare to have been informed of the existence of storage of processing of personal data, of the purpose of the collection of that data and of the recipients of the information.

Given this information that the Data Controller has given to me, and having understood it, I offer my consent to the treatment of:

☐ My personal data to carry out the research project.

☐ My personal data to carry out research projects related to the present or in the same research area.

I freely give my consent to participate in the study.

Signature of participant

Date: ____/____/____

Signature of researcher

Date: ____/____/____

I would like to be informed about any information derived from the research that may be relevant to my health:

☐ YES ☐ NO

I would like to be contacted by Pompeu Fabra University to complete the postnatal neurological follow-up:

☐ YES ☐ NO

Signature of participant	Signature of researcher
Date: ____/____/____	Date: ____/____/____