



CEREBRA

Working wonders for children
with brain conditions

FINAL PROGRESS REPORT FORM

**PREVENTING PRENATAL BRAIN DAMAGE
WITH NEW TOOLS FOR IMPROVED RISK
IDENTIFICATION AND THERAPY
(2020-2023)**

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1. GENERAL INFORMATION

PROJECT TITLE
PREVENTING PRENATAL BRAIN DAMAGE WITH NEW TOOLS FOR IMPROVED RISK IDENTIFICATION AND THERAPY
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2. BACKGROUND INFORMATION

Provide an introduction that reviews the context and rationale for your research.
<p>Prenatal life is a critical moment in human development that strongly determines future health. Even small changes in the delicate environment of the mother's womb can substantially deviate the normal development of the brain, heart, or other organs [1] [2]. This notion is particularly true for the developing brain, the most frail and delicate organ of the future human being [3].</p> <p>1. Human brain development in fetal and postnatal life.</p> <p>From the second trimester of pregnancy, millions of neurons are generated daily at the germinal matrix, an area situated at the center of the fetal brain. From there, they migrate towards the brain surface where they form the grey matter, the external brain layer where thinking and reasoning will take place later in life (Figure 1) [4]. Since the grey matter receives so many new neurons within a restricted volume, the fetal brain surface starts to fold, adopting the typical wrinkled appearance of the adult's brain. There, billions of neurons will establish connections between each other linking different brain areas. These connections will be crucial later in life. Thus, although the fetus is using the brain in a non-conscious and primitive fashion, the way the brain develops during the fetal stage will determine how it will work for the rest of its life [3].</p>

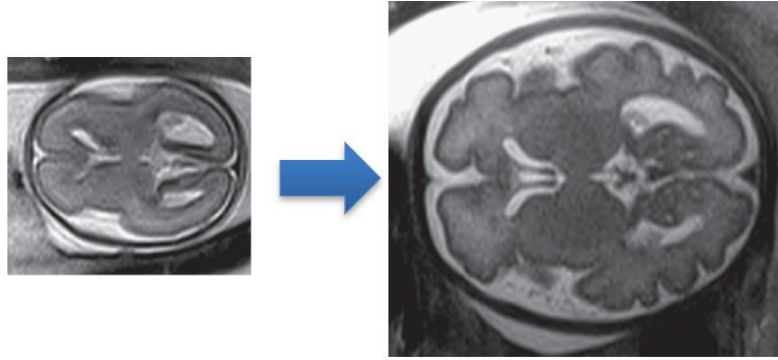


Figure 1. MRI of a fetal brain showing the evolution from 20 to 40 weeks' gestation. The external darker layer corresponds to grey matter.

This extremely complex process is governed by the information contained in our genes [5] but it is extremely influenced by the environment [3]. Thus, any change in the optimal environment during prenatal life might lead to significant deviations in brain functioning in the future. Early identification and prevention of these changes represents a huge opportunity to tackle neurodevelopmental problems from the moment they are generated.

2. Role of fetal life in the origin of neurodevelopmental disorders.

It has been estimated that one in ten children [6] will suffer neurodevelopmental delays and learning disabilities. In about two thirds of these, brain injury occurred before birth. In most instances, brain injury is so subtle that it goes unnoticed during pregnancy and first years of life. These cases are not associated with overt brain injury, but instead with brain reorganization, also called remodeling, and are often expressed as cognitive alterations, thus affecting behaviour (e.g., learning, memory), social relationships or neuromuscular function [7]–[10].

Brain growth is very dynamic and plastic in the beginning of life. While pregnancy is a highly susceptible period, there is a window of opportunity during the first years of life [11] to intervene and revert or substantially improve the consequences of fetal life on brain development. Thus, early identification and intervention may prevent neurodevelopmental problems that otherwise will not be detected until later in life, when interventions may be ineffective (Figure 2).

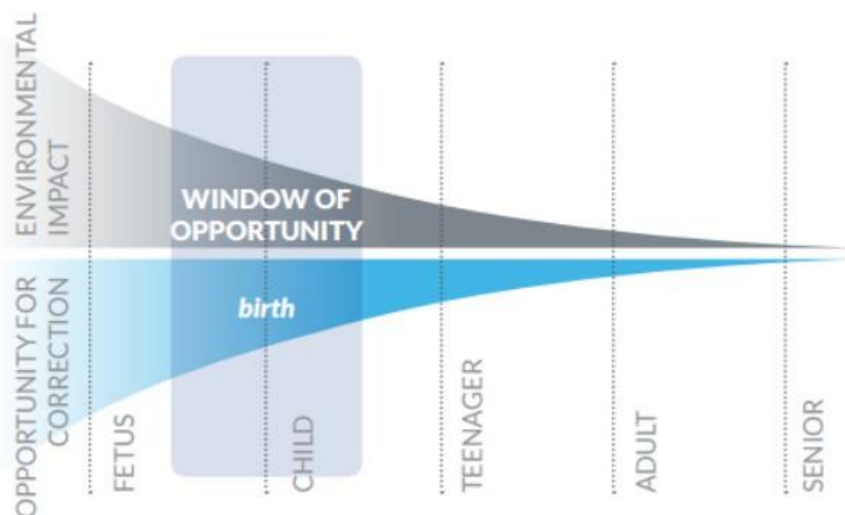


Figure 2. Importance of prenatal life and Fetal Medicine as a window of opportunity to prevent future diseases.

3. Why our research is important for families?

The current understanding and diagnosis of perinatal brain injury can only be improved through competitive and innovative research and a multidisciplinary approach to the problem. Our pioneering research looks at the fetus as a patient in order to address issues as early as possible with the aim of reducing the impact of fetal problems in neurodevelopment.

Our research focuses on identifying those conditions that pose a risk on the brain during pregnancy. In addition, we work to develop indicators (biomarkers) that help identifying babies at risk of developing neurodevelopmental disorders. Finally, we work on new interventions that aim at reducing the impact of pregnancy problems on brain development.

4. Most relevant causes of neurodevelopmental disorders of fetal origin

Most children with abnormal neurodevelopment suffer from differential brain reorganization processes due to exposure to suboptimal environments. The main classical causes of suboptimal neurodevelopment are prematurity and intrauterine growth restriction (IUGR) [12].

- ❖ In prematurity, the baby is exposed ahead of schedule to the “outer world” while the brain is still in a critical developmental phase.
- ❖ IUGR limits the nutritional support to the brain, thereby leading to differential brain development, favouring the growth of some areas with respect to others.

Over the last 10 years we have mainly focused on IUGR and also prematurity, as the most important models for understanding and preventing abnormal brain development.

However, there are other important disruptors of brain development in fetal life. Some are very obvious, such as tobacco and alcohol [13] [14]. Despite strong information campaigns, alcohol consumption remains a prevalent problem in developed societies. In addition, new evidences accumulate that show how pollution and environment may have strong impacts on fetal development [15] [16]. Finally, thanks to our recent research, we have identified how poor-quality nutrition or stress may be factors that influence brain development. In summary, aside from focusing on the traditional causes of abnormal fetal brain development we will also address new perspectives that open new opportunities to improve the quality of brain development from public health and citizen empowerment perspectives.

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3. PROGRAMME SUMMARY

ORIGINAL AIMS AND OBJECTIVES (AS GIVEN IN YOUR ORIGINAL PROPOSAL)

Main goals:

- (1) To improve our current understanding of the fetal conditions that will cause neurological damage later in life;
- (2) To develop new tools to better detect pregnancies/fetuses at high risk and;
- (3) To develop new intervention strategies, before or shortly-after birth, to minimize or prevent neurological problems.

Objectives of the Research Programme 2020-2023:

WP 1: **Advancing towards a better and more refined risk identification** of pregnancy complications; which aims to better understand fetal brain conditions that may cause neurological damage later in life.

WP 2: **Developing new imaging brain biomarkers to detect neurodevelopmental disorders of prenatal origin**; which aims to develop new tools to better detect pregnancies/fetuses at high risk to be affected by these conditions.

WP 3: **Preventing neurological damage by prenatal therapy**, aiming to test and evaluate different therapy strategies, applied before or shortly-after birth to minimize and prevent long-term neurological problems

WP 4: **Training new researchers**, an educational program to train a new generation of researchers in fetal medicine to continue promoting the participation of researchers in European doctoral and training programmes.

WP 5: **Dissemination - Actions for the society** to promote the participation of patients and public opinion and to achieve a greater impact of our research through dissemination to society.

HAVE YOUR AIMS AND OBJECTIVES CHANGED? IF SO, EXPLAIN IN WHAT WAY AND WHY

No, the aims and objectives have not changed.

SUMMARY OF OUTCOMES

WP 1: Advancing towards a better and more refined risk identification of pregnancy complications; which aims to better understand fetal brain conditions that may cause neurological damage later in life.

We have achieved all objectives planned for this WP1. The main outcomes of WP1 are:

- We identified **assisted reproductive technologies** as a risk factor for suboptimal neurodevelopment (Boutet et al. Hum Reprod 2022). Remarkably, fetuses conceived by in vitro fertilization after fresh embryo transfer have significant changes in fetal cortical development. These changes were more subtle in fetuses conceived after frozen embryo transfer. These findings provide the first evidence of the importance of mode of conception in neurodevelopment and highlights the importance of identifying the safest reproductive technique for offspring health.
- We have also identified **umbilical and fetal cerebral Doppler** as a useful tool to detect adverse outcomes in fetuses with severe growth restriction (Meler et al, BJOG 2023). Therefore, we provide evidence that Doppler evaluation of the umbilical and fetal brain circulation can accurately predict short-term adverse perinatal complications and serious adverse outcome in periviable small fetuses.
- We revealed **complement and coagulation cascades** as potential therapeutic targets for preventing severe preeclampsia (Youssef et al. Sci Reports 2021).
- We identified the **metabolomic fingerprint** of preeclampsia and fetal growth restriction (Youssef et al. Sci Reports 2021).
- We provided further evidence of the **long-term consequences of fetal growth restriction**, demonstrating less exercise capacity in adults born small (Crispi et al. JAMA Cardiology 2021, Vellve et al. Respiriology 2022).
- We **applied artificial intelligence** to integrate complex clinical-imaging-omics data and identified two different phenotypes of fetal growth restriction for a novel

classification of this condition (Miranda et al. iScience 2023). Interestingly, one of the phenotypes (with earlier onset, impaired placentation and lipogenic metabolic state) associated most of the neurological complications. Thus, applying such a novel classification might help to detect those cases at highest neurological risk.

- We have described the incidence of brain anomalies related with **open spina bifida** (Trigo et al. UOG 2022) and the longitudinal evolution in relation to prenatal repair (Trigo et al. AJOG MFMF 2023). We have found that half of fetuses that underwent prenatal repair have structural brain anomalies, mainly corpus callosum dysgenesis, and that prenatal repair does not have a negative impact in the evolution.

WP 2: Developing new imaging brain biomarkers to detect neurodevelopmental disorders of prenatal origin; which aims to develop new tools to better detect pregnancies/fetuses at high risk to be affected by these conditions.

We have successfully completed this WP2 by providing new prenatal brain imaging biomarkers:

- We have demonstrated that preeclampsia (with or without fetal growth restriction) present a differential fetal cortical development assessed by **neurosonography** which is similar to what has been described previously in small fetuses (Basso et al. UOG 2022). These results confirm that adverse prenatal conditions have an effect on fetal brain development and that neurosonography is a useful and affordable tool to demonstrate fetal brain anomalies.
- We have showed with **magnetic resonance** that fetuses with prenatal cytomegalovirus (CMV) infection and no evidence of severe brain lesions have an underdeveloped cortical maturation pattern compared to healthy fetuses taken as controls (Hawkins-Villarreal et al. UOG 2023; Hawkins-Villarreal et al. Front Med 2022). These results suggest that congenital CMV-infection even in non-severely affected fetuses, typically considered of good prognosis, could be related to altered brain cortical structure.
- We demonstrated that **neurosonography** is a sensitive tool to detect differences in cortical development in late-onset small fetuses. (Paules et al. UOG 2021). These results confirm previous evidences obtained by magnetic resonance imaging, but using a more affordable and available tool as ultrasound.
- We developed an **automated method based in artificial intelligence** using brain maturation as a surrogate to estimate gestational, which works better than the standard biometric parameters (Burgos-Artizzu et al. AJOG MFM). In addition, we have implemented a method to automatically delineate and measure key brain structures showing the potential of deep learning methods to delineate fetal head and brain structures and obtain automatic measures during routine fetal US examination (Coronado-Gutierrez et al. Fetal Diagn Ther 2023).
- We showed that fetuses with congenital heart disease have a smaller **corpus callosum**, specifically those with poorer brain oxygenation (Perez-Cruz et al. UOG 2021). These results highlight the importance of prenatal brain development in this group of fetuses at risk and that sonographic CC size could be a clinically feasible marker of abnormal white matter development in CHD.
- We propose a new set of measures corpus callosum-fastigium length and tectal length as potential biomarkers of altered prenatal brain development as it is reduced in growth restricted fetuses (Lip-Sosa et al. UOG 2023). These findings illustrate the potential value of midbrain measurements assessed on neurosonography as biomarkers for brain development in a high-risk population.

WP 3: Preventing neurological damages by prenatal therapy, aiming to test and evaluate different therapy strategies, applied before or shortly-after birth to minimize and prevent long-term neurological problems

This programme has encompassed important achievements on preventive strategies for neurological problems with several randomized clinical trials completed and ongoing. Strikingly, the IMPACT BCN trial has demonstrated that neurodevelopment can be improved by maternal lifestyle strategies and RATIO 37 study demonstrated that assessing fetal brain redistribution by ultrasound in third trimester may prevent important perinatal complications. In brief:

- Results from the **IMPACT BCN trial** were published and disseminated at the end of 2021 demonstrating that Mediterranean diet and stress reduction during pregnancy has a beneficial effect on fetal growth (Crovetto et al. JAMA 2021). In a recent subanalysis of the IMPACT trial data, we have identified maternal proinflammatory diet as a risk factor to develop maternal overweight and low-weight fetuses (Casas et al. Nutrients 2022). We also identified the risk factors for higher levels of maternal stress and anxiety (Pascal et al. J Clin Med 2023). More importantly, we have recently published a subanalysis of the trial demonstrating that maternal lifestyle interventions can improve fetal and infant's neurodevelopment (Crovetto et al. JAMA Network Open 2023; Nakaki et al. AJOG MFM 2023).
- In 2023, results from the **RATIO 37 study** were published and disseminated (Rial-Crestelo et al. Lancet 2024). The RATIO 37 is a randomized clinical trial study in 11,582 pregnancies demonstrating the utility of fetal brain Doppler ultrasound to neonatal complications including hypoxic brain events. Of note, fetal brain Doppler was the subject of the first CEREBRA grant to our group, back in 2006. This randomized study has demonstrated the clinical impact of these developments and will have a strong impact on clinical guidelines in the years to come.
- We have continued the recruitment for the **EMOTIVE project**, a randomized trial testing a motivational interview to reduce alcohol consumption during pregnancy with the aim to improve perinatal results. We have currently recruited 48% of the total sample size (n = 1051/ 2,184).
- **FETAL BRAIN CARE project** is a randomized double-blinded trial based on providing maternal supplementation with lactoferrin and docosahexaenoic acid (DHA) for severe IUGR pregnancies. We start recruitment in January 2023 and we have included 50 patients, without any secondary effect or negative effects in any of the randomized patients.
- In 2022, we started the **PE37 randomized trial** that aims to evaluate a strategy to screen all pregnant women close to term and identify those at high risk of preeclampsia and offer planned delivery. Preeclampsia is a well-known cause of poor child neurodevelopment, and preventing even a small proportion of its adverse consequences might be of benefit to large number of pregnant women, considering that this condition affects 2-5% of all pregnancies at term. This is a multicentre trial that has already recruited 5525 pregnancies from 11 centers in Spain, Poland, Belgium, India, Panama, Colombia, Chile and Czech Republic. We expect to complete the trial in 2026.

WP 4: Training, an educational program to train a new generation of researchers in fetal medicine to continue promoting the participation of researchers in European doctoral and training programmes.

Our group invests a great amount of effort to training and teaching in Maternal and Fetal Medicine through exceptional educational programs and we encourage our researchers to pursue outstanding doctoral studies with us and our European partners.

Several doctoral students of our research group have defended their thesis during the course of CEREBRA 2020-2023 Programme:

- Rosalia Pascal, 15th March 2024, with her thesis entitled "Impact of stress on pregnancy mental health", directed by Dr. Lola Gómez and Dr. Francesca Crovetto.
- David Coronado, 30th November 2023, with his thesis entitled "Deep Learning applied to medical image analysis" directed by Dr. Elisenda Bonet and Dr. Xavier Burgos.
- Laura Nogué, 28th November 2023, with her thesis entitled "New modalities to evaluate cardiovascular remodeling in fetuses with congenital heart defects" directed by Dr. Mar Bennasar and Dr. Olga Gómez
- Ayako Nakaki, 24th October 2023, with her thesis entitled "Impact of maternal lifestyle on fetal and maternal brain", directed by Francesca Crovetto and Prof. Eduard Gratacós.
- Kilian Vellvé, 17th March 2023, with his thesis entitled "Impact of Fetal Growth Restriction on lung development", directed by Dr. Francesca Crovetto, Dr. Fàtima Crispi and Prof. Jan Deprest.
- Ana Lisbeth Moreno, 16th November 2022, with her thesis entitled "Prediction of neonatal respiratory morbidity assessed by quantitative ultrasound lung texture analysis in specific populations of high-risk pregnancies", directed by Dr. Montserrat Palacio and Prof. Stefan Hansson.
- Ameth Hawkins Villarreal, 4th November 2022, with his thesis entitled "Assessment of prenatal imaging, fetal blood parameters, and new pharmacological interventions, in congenital cytomegalovirus infection", directed by Dr. Anna Goncá.
- Maria Laura Boutet, 26th October 2022, with her thesis entitled "Fetal programming in assisted reproductive technologies", directed by Dr. Gemma Casals and Prof. Stefan Hansson.
- Marta Rial, 16th June 2022, with her thesis entitled "Clinical impact of cerebroplacental ratio evaluation at third trimester of pregnancy in the general population" directed by Dr. Francesc Figueras and Prof. Stefan Hansson.
- Ximena Torres, 11th January 2022, with her thesis entitled "Evaluation of cardiac morphometry and function by advanced echocardiography in monochorionic twin pregnancies", directed by Dr. Josep María Martínez and Dr. Mar Bennasar.
- Talita Micheletti, 13th September 2021, her thesis is entitled "Development of a sealing system for iatrogenic preterm prelabor rupture of membranes after endoscopic fetal surgery", directed by Dr. Elisenda Eixarch and Prof. Jan Deprest.
- Iris Soveral Rodrigues da Silva Dias, 8th January 2021, Thesis entitled "Evaluation of left-sided congenital heart defects by advanced fetal echocardiography and cold blood biomarkers", directed by Dr. Olga Gómez and Dr. Fatima Crispi.
- Laura Guirado, 9th October 2020, her thesis is entitled "Cardiopatías con obstrucción del tracto de salida del ventrículo derecho: estudio del remodelado cardiovascular fetal mediante ecocardiografía", directed by Dr. Olga Gómez and Dr. Fátima Crispi.
- Lina Youssef, 30th January 2020, her thesis is entitled "Omics approach to characterize different phenotypes of preeclampsia and fetal growth restriction", directed by Dr. Fatima Crispi and Prof. Gratacós.

Fellow researchers are encouraged to participate in both national and international congresses; it is a valuable opportunity to disseminate their findings within the scientific community and to be aware of the latest breakthrough in the field. Further details can be found in the 'Dissemination of Results' section.

We support the professional development of our doctoral students. As an example, during CEREBRA 2020-2023 Programme, Maria Laura Boutet, Ana Moreno, Paz Ahumada and Lucas Trigo have had the opportunity to be additionally trained in University of Lund, Sweden, and University KU Leuven, Belgium. Moreover, Kilian Vellvé and Leticia Benitez have visited Oregon Health & Science University – Advance Imaging Research Center (AIRC), Portland, USA, and the Universitäts Klinikum of Düsseldorf, Düsseldorf, Germany, respectively.

Our research group meets weekly in a Journal Club via an on-line platform to share our progress in the different research projects and we have also invited national and international external speakers to present their work.

Finally, we keep our tight relationship with Fetal i+D Education, where our students can find several online courses in Spanish and English.

WP 5: Dissemination - Actions for the society to promote the participation of patients and public opinion and to achieve a greater impact of our research through dissemination to society.

Details on these aspects are outlined in the “Impact Statement”, “Public Involvement”, and “Dissemination of Results” sections. These sections cover our strategies and initiatives aimed at fostering engagement with patients and the wider community to amplify the reach and significance of our research outcomes.

KEY FINDINGS

- The use of Assisted Reproductive Technologies is associated with offspring’s suboptimal neurodevelopment that can be detected using neurosonography.
- Fetal neurosonography to assess cortical development and corpus callosum is a powerful tool to detect subtle fetal brain anomalies from the earliest stages of life.
- Application of Machine Learning in fetal brain ultrasound can improve its accuracy.
- Maternal lifestyle interventions during pregnancy, including a healthy anti-inflammatory diet or interventions for stress reduction, improve fetal growth and neurodevelopment.
- The use of fetal brain Doppler ultrasound in the third trimester prevents neonatal complications including hypoxic brain events.

IMPACT STATEMENT

The outcomes of our research throughout the duration of the CEREBRA 2020-2023 Programme have impacted in the scientific field, as well as, in health and social areas. The translation of these findings into tangible actions described below.

Scientific Impact

In 2024:

- Within the CEREBRA programme, we have published a total of 3 papers.
- The main scientific impact thus far is the clinical trial RATIO37 published in The Lancet has shown in 11,500 low-risk pregnant women that adding a Doppler study of fetal circulation in the last ultrasound can reduce by half the complications requiring admission to the neonatal intensive care unit for full-term babies.

In 2023:

- BCNatal-FMRC has published 63 papers in international journals in 2023 accumulating a total of 338,9 points of Impact Factor. Within the CEREBRA programme, we have published a total of 16 papers.
- The main scientific impact of the programme this year has been the publication of the IMPACT follow up in JAMA Network Open, in this study we assessed the effects of lifestyle interventions during pregnancy on infants. The results indicate that the children of women who followed a Mediterranean diet program in pregnancy during the IMPACT study show better neurodevelopment.

In 2022:

- BCNatal-FMRC has published 67 papers in international scientific journals in 2022 accumulating a total of 450.462 points of Impact Factor. Within the CEREBRA programme, we have published a total of 6 papers.
- The main scientific impact has been the publication of the IMPACT study in JAMA, the third top medical journal in the world. This study has shown for the first time that a non-pharmacological intervention during pregnancy, based either on a Mediterranean diet or a stress-reduction programme, reduced fetal growth restriction and other main complications of pregnancy. We have continued working on the analysis of the secondary data generated by the IMPACT study. We have published studies to better understand the mechanisms behind these benefits, for instance the anti-inflammatory properties of Mediterranean diet. In addition, we have finalized studies based on neurosonography, brain MRI and neurodevelopment based on Bayley-III at 2 years. These studies demonstrate that the interventions improved also fetal and infant neurodevelopment, which represent major scientific news. This is the first evidence from a randomized trial supporting the value of maternal lifestyle interventions on child neurodevelopment.

In 2021:

- BCNatal-FMRC has published 84 papers in international scientific journals accumulating a total of 561.724 points of Impact Factor. Within the CEREBRA programme we have published 17 papers and 1 public image database.
- The main scientific impact has been publishing the IMPACT study, which shows for the first time that a non-pharmacological intervention based on Mediterranean diet and mindfulness in pregnancy can improve fetal growth, these results have a several scientific implications; we now know that diet and mindfulness have a measurable impact on the health and well-being of future pregnancies.

In 2020:

- BCNatal-FMRC has published 72 papers international scientific journals accumulating a total of 386.6 points of Impact Factor. Within the CEREBRA programme we have published 6 papers and 1 public image database.
- The main scientific impact has been finishing the IMPACT study, which studies for the first time that a non-pharmacological intervention based on Mediterranean diet and mindfulness during pregnancy can improve fetal growth.
- We have also published very relevant results about COVID-19 infection during pregnancy, which provided data to optimize the healthcare advice and how to monitor pregnancies in relation to this infection.

- The programme has also had a high innovation component by developing two new systems for segmenting and plotting fetal brain ultrasound and resonance imaging, which substantially improve the ability to study the fetal brain.

Social Impact achieved or foreseen

In 2024

- We have showed in Rial et al. 2024 that adding a Doppler study to measure blood flow in the umbilical cord and brain in the last ultrasound examination in pregnancy can effectively reduce by half the complications requiring admission to the neonatal intensive care unit for full-term babies. Given that these complications may lead to neurological impairment, this study will be a game changer in perinatal control over the next years, with a foreseen impact in hundreds of thousands of pregnancies yearly.

In 2023

- We have shown in Crovetto et al. 2023 that children of women who adhered to a structured Mediterranean diet program during pregnancy exhibit better outcomes on brain neurodevelopment. These pioneering findings demonstrate for the first time that mothers' empowerment is one of the strongest tools to proactively contribute to the future health of their babies.

In 2022

- We have shown in Boutet et al. 2022 that assisted reproductive technologies (ATS) shows that infants conceived with these technologies are more prone to have impaired neurodevelopment. These results inform the general population potential risks in brain development of children conceived with ATS.
- Additionally, our study on fetal cortical development in preeclampsia published by Basso et al. 2022 has shown that this adverse condition during pregnancy predisposes the fetal brain to a poor development. These results warn medical professionals of potential complications in infant neurodevelopment in pregnant patients with preeclampsia.

In 2021

- We have successfully published the main publication for the IMPACT clinical trial, including over 1,200 pregnant women, and demonstrated that the Mediterranean diet and mindfulness can improve pregnancy and fetal growth. These results are very relevant because they will allow the implementation of new non-pharmacological strategies for improving fetal development.
- The program has also demonstrated that ultrasound, an affordable image that can be acquired in a standard room (bed-side), can be used to obtain similar information than those acquired with MRI to detect differences in brain cortical development. These results are relevant because they will allow cortical development assessment without the need of an MRI.

In 2020

- We have successfully completed the recruitment for the IMPACT clinical trial, including over 1,200 pregnant women, and demonstrated that the Mediterranean diet and mindfulness can improve pregnancy and fetal growth.
- These results are very relevant because they will allow the implementation of new non-pharmacological strategies for improving fetal development.
- We have included more than 3,000 pregnant women and fetuses taking into account the different research projects.

4. PLAIN ENGLISH SUMMARY

Please also provide a summary of the outcomes in lay/simple language (avoiding scientific jargon where possible) including an impact statement.

During the CEREBRA 2020-2023 Programme, significant advances have been made in understanding fetal brain development in pregnancy:

- Identification of assisted reproductive technologies as a risk factor for suboptimal brain development, revealing significant changes in fetal brain among fetuses conceived through in vitro fertilization.
- Using special ultrasound tests called umbilical and fetal cerebral Doppler can help us find potential problems in babies who are not growing properly in the womb. These tests allow us to check the blood flow to the baby's brain and umbilical cord, helping us identify any issues early on.
- We have discovered promising leads in preventing a serious condition called preeclampsia, one of the main causes of serious complications for the mother and neurological complications in the baby. By studying how certain parts of our body's immune and clotting systems work, we have identified areas where we might be able to develop new treatments to keep preeclampsia from becoming severe.
- We have looked closely at the chemicals and substances in the blood of pregnant women with preeclampsia and babies who are not growing well. This has given us a better understanding of the unique patterns, or "fingerprint," of these conditions, which could lead to improved ways of diagnosing and treating them in the future.
- We have demonstrated long-term consequences of fetal growth restriction, including reduced exercise capacity in adults born small.
- By analysing large amounts of data, artificial intelligence has helped us identifying different types of fetal growth restriction, which is a condition where babies do not grow as they should in the womb. This new classification system could revolutionize how we diagnose and treat this condition, ultimately improving outcomes for babies and mothers.
- Additionally, we've been studying babies with a condition called open spina bifida, where the spine does not form properly before birth. We've looked at how often these babies have problems with their brains and how these problems change over time.

We created new ways of looking at the brain in unborn babies to detect potential problems early. Overall, our work has opened up new possibilities for spotting potential brain issues in babies before they are born, giving doctors and parents a chance to take action early:

- We have found that babies whose mothers have preeclampsia, or those affected by a virus called cytomegalovirus before birth, have differences in how their brain's outer layer, called the cortex, grows. We have been able to see these differences using special imaging techniques like neurosonography and magnetic resonance imaging, which help us look inside the womb.
- Using artificial intelligence, we have developed a way to estimate gestational age and to map out different parts of the baby's brain during routine ultrasound scans. This automated method makes it easier and faster for doctors to spot any potential problems and provide the best care for both the baby and the mother.
- We have identified certain measurements in the brain, like the size of a structure called the corpus callosum and assessments of the midbrain, that could serve as early signs of changes in brain development before birth. These could be valuable indicators helping us identify and address any issues early on to give babies the best start in life.

Additionally, we focused on preventing brain damage through prenatal therapy, showcasing several completed and ongoing clinical trials aimed at minimizing and preventing long-term neurological problems. Our efforts centred on dissemination actions to promote the participation of patients and public opinion, ensuring a greater impact of research on society. We carried on various strategies and initiatives aimed at engaging patients and the wider

community to amplify the reach and significance of research outcomes.

We have made significant impacts in the scientific, health, and social domains, here is a summary of our key achievements:

- We now better understand how lifestyle choices and medical interventions during pregnancy influence the health of both mothers and babies. One of our key findings is the positive impact of following a Mediterranean diet during pregnancy on infant brain development. This discovery empowers mothers with valuable insights into supporting their babies' health from the womb.
- Additionally, our research has generated a breakthrough and has closed a story that we started thank to the support of Cerebra almost two decades ago. Our data from the largest international randomized trial to date have provided conclusive evidence on the effectiveness of incorporating brain Doppler studies into prenatal care. By measuring brain blood flow during pregnancy, we can identify potential complications in full-term babies early on and prevent serious brain-related problems.
- Moreover, our studies have shed light on the risks associated with certain pregnancies. We have uncovered how assisted reproductive technologies may affect infant brain development and how conditions like preeclampsia during pregnancy could also impact fetal brain development. These findings emphasize the importance of informed decision-making for expectant parents and heightened awareness among medical professionals.
- Through our ongoing efforts, we are committed to advancing knowledge in maternal and child health, providing evidence-based strategies to support healthy pregnancies and optimal outcomes for both mothers and babies.

5. PUBLIC INVOLVEMENT

Complete this section outlining patient and public involvement in this research. If there is no involvement, please explain why. Please, also comment on how have the research findings been made available/accessible to lay audiences?

Since the inception of our research initiatives, we have consistently considered the public viewpoints. Our research endeavors aligned with the highest standards in the field, leading us to evaluate the potential consequences and societal expectations of our findings.

We highly value the input from patients and their families, striving to enhance the impact and inclusivity of our results. Our goal was to create a patient experience that was as positive as possible. Consequently, our projects have adhered to the principles of Responsible Research and Innovation. For instance, we have actively sought the opinions of participants recruited in our clinical trials, such as in PE37 study. We prepared questionnaires and organized discussion groups aiming at comprehend their experiences and address concerns related to the interventions within the study.

Moreover, in regard to the IMPACT BCN study, we have organized educational sessions covering various aspects of pregnancy and our research such as mindfulness workshops and nutrition classes specifically designed for pregnant women. Subsequently, participants provided insights on ethical considerations, participation in the study, and general questions regarding project expectations. Their insights have been fundamental in refining our research protocols, facilitate information access, adjusting elements to reduce stress among the recruited participants, accommodate timelines, and identify concerns among pregnant participants.

Our commitment to transparency involved consistently keeping participants informed about the developments and findings of the study. We prioritize staying in touch with those involved in the research, providing them with timely updates on the project's results and fostering a collaborative and informed partnership with the recruited patients.

The accessibility of research findings to a general audience is addressed in “Results Dissemination” section.

6. PUBLICATIONS AND OTHER OUTPUTS

PUBLICATIONS RESULTING DIRECTLY FROM WORK OF THIS GRANT

Number of **published or in press** papers: 48

Rial-Crestelo M, Lubusky M, Parra-Cordero M, Krofta L, Kajdy A, Zohav E, Ferriols-Perez E, Cruz-Martinez R, Kacerovsky M, Scazzocchio E, Roubalova L, Socias P, Hašík L, Modzelewski J, Ashwal E, Castellá-Cesari J, Cruz-Lemini M, Gratacos E, Figueras F; RATIO37 Study Group. Term planned delivery based on fetal growth assessment with or without the cerebroplacental ratio in low-risk pregnancies (RATIO37): an international, multicentre, open-label, randomised controlled trial. *Lancet*. 2024 Feb 10;403(10426):545-553. DOI: 10.1016/S0140-6736(23)02228-6. **Published**

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Castro-Quintas Á, Eixarch E, Martin-Gonzalez NS, Daura-Corral M, Marques-Feixa L, Palma-Gudiel H, Rocavert-Barranco M, Miguel-Valero A, Monteserín-García JL, de la Fuente-Tomás L, Crispi F, Arias B, García-Portilla MP, Fañanás L. Diurnal cortisol throughout pregnancy and its association with maternal depressive symptoms and birth outcomes. *Psychoneuroendocrinology*. 2024 Mar;161:106930. DOI: 10.1016/j.psyneuen.2023.106930. **Published**

Crovetto F, Nakaki A, Arranz A, Borrás R, Vellvé K, Paules C, Boutet ML, Castro-Barquero S, Freitas T, Casas R, Martín-Asuero A, Oller Guzmán T, Morilla I, Martínez-Àran A, Camacho A, Pasqual M, Izquierdo Renau M, Pozo ÓJ, Gomez-Gomez A, Estruch R, Vieta E, Crispi F, Gratacós E. Effect of a Mediterranean Diet or Mindfulness-Based Stress Reduction During Pregnancy on Child Neurodevelopment: A Prespecified Analysis of the IMPACT BCN Randomized Clinical Trial. *JAMA Netw Open*. 2023 Aug 1;6(8):e2330255. DOI: 10.1001/jamanetworkopen.2023.30255. **Published**

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Lip-Sosa DL, Pérez-Cruz M, Ahumada-Droguett P, Ribas-Prats T, Puertollano M, García-Gómez MA, Mazarico E, Eixarch E, Escera C, Gómez-Roig MD. Corpus callosum-fastigium and tectal lengths in late-onset small fetuses. *Ultrasound Obstet Gynecol*. 2023 Aug;62(2):226-233. DOI: 10.1002/uog.26169. **Published**

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Lina Youssef, Jezid Miranda, Miquel Blasco, Cristina Paules, Francesca Crovetto, Marta Palomo, Sergi Torramade-Moix, Héctor García-Calderó, Olga Tura-Ceide, Ana Paula Dantas, Virginia Hernandez-Gea, Pol Herrero, Nuria Canela, Josep Maria Campistol, Joan Carles Garcia-Pagan, Maribel Diaz-Ricart, Eduard Gratacos, Fatima Crispi. Complement and coagulation cascades activation is the main pathophysiological pathway in early-onset severe preeclampsia revealed by maternal proteomics. *Sci Rep.* 2021. DOI: 10.1038/s41598-021-82733-z. **Published**

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Crovetto F, Crispi F, Llurba E, Pascal R, Larroya M, Trilla C, Camacho M, Medina C, Dobaño C, Gomez-Roig MD, Figueras F, Gratacos E; KidsCorona Pregnancy COVID-19 Group. Impact of Severe Acute Respiratory Syndrome Coronavirus 2 Infection on Pregnancy Outcomes: A Population-based Study. *Clin Infect Dis*. 2021. 16;73(10):1768-1775. DOI: 10.1093/cid/ciab104. **Published**

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Lina Youssef, Lena Erlandsson, Bo Åkerström, Jezid Miranda, Cristina Paules, Francesca Crovetto, Fatima Crispi, Eduard Gratacos, Stefan R Hansson. Hemopexin and α 1-microglobulin heme scavengers with differential involvement in preeclampsia and fetal growth restriction. *PLoS One*. 2020. DOI: 10.1371/journal.pone.0239030. **Published**

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Number of papers **in preparation or submitted**: -

OTHER OUTPUTS RESULTING DIRECTLY FROM WORK OF THIS GRANT

X Burgos-Artizzu, D Coronado-Gutierrez, B Valenzuela-Alcaraz, E Bonet-Carne, E Eixarch, F Crispi, E Gratacós. Fetal Planes DB: Common maternal-fetal ultrasound images. Dataset. 10.5281/zenodo.3904280 **Dataset**

OTHER PUBLICATIONS/OUTPUTS THAT HAVE BEEN FACILITATED OR SUPPORTED BY THIS GRANT

Please list any other publications or outputs that have been indirectly supported by this grant, indicating for publications whether they are in preparation, submitted, in press or published.

DISSEMINATION OF RESULTS

We have strived to enhance the impact of our research by effectively disseminating it to the broader community. Additionally, our commitment to promoting the importance of early-life research has gained media coverage, contributing to the broader understanding of our work. Our group's presence in numerous national and international media channels, coupled with active participation in impactful social events, shows our dedication encouraging patient involvement and engaging public opinion. Furthermore, our active participation in high-impact social events further consolidates our commitment to advancing the field.

Throughout the duration of the CEREBRA Programme 2020-2023 we have translated some of our results into clinical practice:

- In 2023, we have developed 6 new clinical guidelines and revised 15 existing clinical protocols with the aim of enhancing patient care within Obstetric and Neonatal wards.
- In 2022, our efforts resulted in the creation of 2 new and updated 14 more clinical guidelines for good practice—all referring to gestational complications.
- In 2021, we wrote and published 2 clinical guides.
- In 2020, we published a total of 16 clinical guidelines, including 3 specifically addressing COVID-19 and pregnancy. Additionally, we conducted webinars for healthcare professionals with over 20,000 attendees.

Our research has received significant coverage in the media on multiple occasions.

- In 2023, we have been echoed in multiple media channels. For example, the 1st edition Premios MERCO-Observatorio de Salud awarded Dr. Eduard Gratacós as the most renowned specialist in Gynecology and Obstetrics in Spain and it was covered by la Razón. Moreover, Catalunya press and el Diari de la Sanitat covered our studies on how Mediterranean diet and stress reduction during pregnancies improve infant neurodevelopment. Additionally, Mi bebé y yo journal published an article on interviewing Dr. Fàtima Crispi about the importance of diet in pregnancy to have healthy babies and practical recommendations to improve maternal nutrition. We have been awarded with V Manu Barrera grant and it was covered in our social media. The publication of the clinical trial RATIO37 in Lancet gathered some attention from the media and it was covered by national channels: La Voz de Galicia, Cadena SER and Las tardes de RNE de Lourdes Maldonado.

- In 2022, we have appeared multiple times in the media. To name a few, the national newspaper La Vanguardia published the award one of our senior researchers, Dr. Fàtima Crispi, for her contribution in Maternal and Fetal Medicine at Premios a la Investigación Fundación Jesús. The official website of Hospital Clínic reported our blood test to distinguish severe COVID-19 symptoms from preeclampsia during pregnancy. In addition, they advertised our workshop on the importance of preventing and detecting congenital CMV.
- In 2021, several researchers have been invited to Radio or TV programs, for instance, Dr. Eduard Gratacós who was invited on November 17th to a gathering in Radio 4 to talk about premature babies or Dr. Fàtima Crispi and Dr. Francesca Crovetto have been invited to a Press Conference in the regional TV of Catalonia to expose the results of the IMPACT study. More than 15 national media have echoed the information disseminated in the IMPACT Press conference.
- In 2020, We have participated in the KidsCorona initiative (www.kidscorona.org), a platform to understand COVID-19 in children and pregnancy. We lead the information about how COVID-19 affect pregnant women. Overall, the website oriented to the general public and the platform have generated more than 600 media (TV, press, radio) appearances and three different press releases.

Our researchers have actively participated in numerous events to disseminate our results to the general public.

- In 2023, Dr. Gratacós was invited to speak at One Birdcage Walk Conference in London on June 14th. The event, supported by CEREBRA, focused on ways to help children with complex needs and their families. It was addressed to parents, caregivers, professionals, and anyone interested in learning about research and efforts to improve the lives of these children and their families by reducing inequalities and promoting health and wellbeing.
- In 2022, Dr. Francesc Figueras participated in the 'Importance of Congenital Cytomegalovirus: Prevention and Early Detection' Workshop organized by Hospital Clínic de Barcelona on June 18th. This event, designed for both lay audiences and professionals, aimed to educate on preventing and identifying cytomegalovirus infection in pregnancy.
- In 2021, Dr. Teresa Cobo participated in the researcher's night with an online micro-talk titled "OPTIMIZATION of antenatal management of pregnant women with preterm birth threat using prediction models: multicenter randomized clinical trial (OPTIM-PTL)" and Dr. Francesca Crovetto with a presentation in the Barradas Auditorium entitled "The Importance of lifestyle during pregnancy". Dr. Eduard Gratacós, Dr. Fàtima Crispi and Dr. Francesca Crovetto were interviewed in "Tea Break Talk with the Fetal Medicine Research Centre Barcelona, and initiative organized by CEREBRA. They talked about how to improve the health of future generations right from the beginning of life and they explained the results found in the IMPACT study.
- In 2020, some of our researchers were invited to Radio or TV programs, an example was Dr. Lola Gómez Roig, who was invited on January 13th to a gathering in Betev. (local TV) to talk about women's health after giving birth. It was a very interesting gathering not only for women but for society in general. Unfortunately, this topic continues to be a taboo today, and gatherings of this type are necessary to move towards a more sensitized society. Additionally, Dr. Elisenda Eixarch participated in the researcher's night (on-line this year), where presented "Fetal surgery: saving lives

before birth” with more than 120 attendees (non-expert audience).

In 2013, we introduced iNatal, an interactive social platform designed to offer valuable information on health issues during pregnancy. Over the years, iNatal has grown into a leading web-based resource for pregnancy in Spanish. It is highly recommended by professionals in Maternal and Fetal Medicine. Through consistent scientific and editorial efforts, iNatal web has received over 5.6 million visits and 3.2 million new users in 2023. The platform's user base is primarily concentrated in Mexico, Spain, Colombia, Argentina and Peru, as indicated by statistics.

We actively engage with our community on multiple social media platforms, including Twitter, Instagram, Facebook, and LinkedIn. Across these channels, we share our research outcomes, audience-engaging activities, and the latest news in Fetal and Maternal Medicine. We are gaining a significant increase in followers across all our social media channels every year. By the end of 2023:

- Our Facebook page (www.facebook.com/BCNatalResearch) reached to 2,502 followers.
- Our Instagram account (@BCNatalResearch) reached to 2,457 followers.
- Our Twitter account (@BCNatalResearch) reached to 3,112 followers.
- Our LinkedIn page (Fetal Medicine Research Center) reached to 2,033 members.

Since the launch of our website, www.bcnatalresearch.org, in 2021 we've consistently shared our research progress and latest outcomes. Our website is a valuable resource for experts in the field of Fetal and Maternal Medicine, providing access to our materials and offering inspiration from our contributions.

We maintain exceptional standards in article production, consistently publishing in high-impact international and open-access scientific journals. This approach ensures the maximum dissemination of our results within the scientific community.

Our researchers have attended and presented their work in various prestigious congresses, to name a few:

- In 2023, our researchers attended to multiple congresses, to name a few: 20th World Congress in Fetal Medicine (among others: Miriam Illa, Elena Monterde, Daniel Sanin, Nuria Prat), ISUOG World Congress 2023 (among others, Eduard Gratacós, Fàtima Crispi, Elisenda Eixarch, Francesca Crovetto), MFM's 43rd Annual Pregnancy Meeting (among others: Teresa Cobo, Clara Murillo, Julia Ponce); XIII Congreso Internacional de Ultrasonido en Obstetricia y Ginecología. Sociedad Peruana de Ultrasonido en Obstetricia y Ginecología (Fàtima Crispi invited as a Keynote speaker); 2nd Annual Conference of the Ho Chi Minh Society for Maternal-Fetal Medicine (Eduard Gratacós invited as keynote speaker).
- In 2022, our researchers participated in the 19th World Congress in Fetal Medicine 2022 (among others: Elisenda Eixarch, Fàtima Crispi, Francesc Figueres and Francesca Crovetto, Ameth Hawkins, Lina Youseff, Marta Rial and Leticia Benítez); ISUOG World Congress 2022 (among others: Eduard Gratacós, Elisenda Eixarch, Fàtima Crispi, Lina Youssef, Francesca Crovetto, Leticia Benitez, Laura Nogué, Ayako Nakaki) remarkably, two of our students were invited to present their work in oral communications, in addition, all of them participated in the poster session of the congress; 55th Annual Meeting of the Association for European Paediatric and Congenital Cardiology 2022 (Patricia García); and VI International Fetal Medicine Symposium (Josep Maria Martínez); SFM National Fetal Growth Congress (Eduard Gratacós invited as a keynote speaker).

- In 2021, our researchers have participated in several prestigious congresses like the ISUOG (among others: Eduard Gratacós, Miriam Illa, Francesca Crovetto, Lina Youssef, Marta López, Laura Guirado, Laura Nogué, M^a Laura Boutet, Michael Hawkins, Karen Castillo, Johanna Parra, David Coronado, Marta Rial, Juan Otaño) and Fàtima Crispi was invited as a keynote speaker and some students presented their work with 5 oral presentations and 5 posters; Annual Craniosynostosis Conference (Elisenda Eixarch); the SEGO congress (Teresa Cobo); XXVIII European Congress of Perinatal Medicine (Fàtima Crispi was invited as a keynote speaker); 3rd World Congress on Maternal Fetal Neonatal Medicine (Eduard Gratacós invited as a keynote speaker); Women In Data Science (WiDS) (Elisenda Bonet-Carne).
- In 2020, some of our students have attended several prestigious conferences where they presented their work (most of them online), such as ISUOG or OHBM. We have also participated in several webinars to discuss how covid affected pregnancy. Luckily, before the pandemic there was time to attend in person the “in-utero MRI 2020” workshop in Oxford, UK. Dr. Eixarch was invited as a speaker to talk about MRI-planned laser ablation in Twin-to-Twin Transfusion Syndrome. And the students Kilian Vellvé and Ayako Nakaki presented a poster and were selected for an oral presentation; Vellvé talked about our collaborative work with Utah and OHSU on reduction of T2* values in the placentas of growth-restricted fetuses and Dr. Nakaki presented results on IVIM correlation with placental size in growth-restricted fetuses.

7. ADDITIONAL COMMENTS

Please note any additional comments relating to this report or anything that has not been covered in any other section.

We would like to make a special mention to our contract agreements with the following companies and institutions:

In 2023:

- The University Hospital of Düsseldorf (UKD): Recruitment of pregnant patients and sample extraction for the project BMBF-EDI-4-ALL (new).
- Roche International: Identification of biomarkers for preeclampsia in the 3rd trimester - PE37 (renewed).

In 2022:

- Hologic, INC: Clinical validation of a non-invasive vaginal test to assess the risk of intra-amniotic inflammation and/or infection during gestation with threatened preterm labor (renewed).
- Medix Biochemica: Validation of “Actim IAI Intra-amniotic infection” marker (renewed).
- Roche International: Identification of biomarkers for preeclampsia in the 3rd trimester - PE37 (renewed).
- Brudy Technology, S.L: We initiated a collaborative agreement with them as a company specialized in medical research in nutrition. With this collaboration, we have received support to conduct the FETAL BRAIN CARE clinical study (on-going).

In 2021:

- Transmural Biotech S.L.: Agreement to host engineers to collaborate with Artificial Intelligence projects (renewed).
- Institut esMindfulness: Reduction of maternal stress based on mindfulness program (renewed).
- Hologic, INC: Clinical validation of a non-invasive vaginal test to assess the risk of intra-amniotic inflammation and/or infection in pregnant women with threatened preterm labor (renewed).
- Medix Biochemica: Validation of “Actim IAI Intra-amniotic infection” marker (renewed).
- Fundación ASISA: To perform research using new technologies and artificial intelligence (renewed).
- Roche International: Identification of biomarkers for preeclampsia in the 3rd Trimester - PE37 (renewed).

In 2020:


- Transmural Biotech S.L.: Agreement to host 2 engineers to collaborate with Artificial Intelligence projects (renewed).
- SIEMENS: Solution on preeclampsia screening on general population of pregnant women (renewed).
- Perkin-Elmer: Identification of biomarkers for fetal growth restriction in late pregnancy (renewed).
- Institut esMindfulness: Reduction of maternal stress based on mindfulness program (renewed).
- Hologic, INC: Clinical validation of a non-invasive vaginal test to assess the risk of intra-amniotic inflammation and/or infection in pregnant women with threatened preterm labor (renewed).
- Medix Biochemica: Validation of “Actim IAI Intra-amniotic infection” marker (renewed).
- Fundación ASISA: To perform research using new technologies and artificial intelligence (renewed).
- Roche International: Identification of biomarkers for preeclampsia in the 3rd Trimester - PE37 (new).

8. DISCLAIMER

PLEASE NOTE: An electronic signature is required

I certify that the statements and data included in this report are true, complete and accurate to the best of my knowledge.

Date: GRATACOS
SOLSONA
Signature: EDUARDO -
46227155F

 Digitally signed by
GRATACOS SOLSONA
EDUARDO - 46227155F
Date: 2024.03.26 16:03:18
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