ANNUAL REPORT FOR:

CEREBRA
Working wonders for children with brain conditions

FETAL RESEARCH PROGRAMME 2020-2023:

PREVENTING PRENATAL BRAIN DAMAGE WITH NEW TOOLS FOR IMPROVED RISK IDENTIFICATION AND THERAPY

A multidisciplinary research programme spanning from personalized medicine and patient empowerment to new biomarkers and prenatal therapies

BCNatal FETAL MEDICINE RESEARCH CENTER

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1. Summary of the progress achieved in 2022

After the previous difficulties due to the COVID-19 pandemic, we are delighted to tell that 2022 has been a year of fully normal activity. Among the main highlights:

- Our investigation on assisted reproductive technologies shows that infants conceived with these technologies are more prone to have impaired neurodevelopment (Boutet et al., 2022).
- We have completed all the preparatory steps for the FETAL BRAIN CARE study. We aim to start recruiting patients soon in 2023.
- Our study on fetal cortical development in pre-eclampsia has shown that this adverse condition during pregnancy predisposes the fetal brain to a poor development (Basso et al., 2022).

2. Specific research objectives reached per Work Package (WP)

2.1 WP 1: Progressing towards an improved and more refined <u>risk assessment</u> of complications during pregnancy which aims to better comprehend fetal brain conditions that have the potential to cause neurological damage during the lifetime. Our research outcomes in 2022 have been as follows:

2.1.1 We identified assisted reproductive technologies as a risk factor for suboptimal neurodevelopment (Boutet et al., 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.

2.1.2 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., 2022). 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.

2.2. WP 2: Developing novel imaging biomarkers for the brain to detect neurodevelopmental disorders of prenatal origin which aims to generate new tools to improve the detection of pregnancies with fetuses at high risk to be affected with neurological impairment. Our research outcomes in 2022 have been as follows:

2.2.1 We have demonstrated that pre-eclampsia (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., 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.

2.2.2 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., 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.

2.3 WP 3: **Exploring the benefits of prenatal therapy preventing neurological damages** with the aim to examine and evaluate multiple therapeutical strategies during pregnancy or shortly after birth to minimize and prevent long-term neurological complications.

2.3.1 Results from the IMPACT 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, Crispi, Borras, et al., 2021; Crovetto, Crispi, Casas, et al., 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., 2022). Therefore, promoting an anti-inflammatory diet such as Mediterranean diet could improve both maternal and fetal health.

2.3.2 During 2022, we have analysed the results of the RATIO 37 study that evaluates in a cohort of 11,582 patients the potential utility of fetal brain Doppler ultrasound to reduce stillbirth and neonatal complications including hypoxic brain events. We expect to publish the results of this study in 2023.

2.3.3 In 2022, 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 46% of the total sample size (n = 1005/ 2,184).

2.3.4 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. The initial preparation of the project has faced various setbacks. After sorting them out in 2022, we have finally completed all preparatory steps to start patient recruitment. We plan to start the recruitment and include 50-80 patients during 2023.

2.3.5 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 3706 pregnant patients from 11 centers in Spain, Poland, Belgium and Czech Republic.

3. WP 4: Training and educational programmes

We aim to teach and train the next generation of researchers specialized in Maternal and Fetal medicine through exceptional educational programs and encourage researchers to pursue outstanding doctoral studies with us and our European partners.

This year, 5 students of the last cohort of our international and multicentre FetalMed-PhD program have successfully graduated:

- Maria Laura Boutet, October 26th, with her thesis entitled “Fetal programming in assisted reproductive technologies”, directed by Dr. Gemma Casals and Dr. Stefan Hansson.
- Ameth Hawkins Villarreal, November 4th, with his thesis entitled “Assessment of prenatal imaging, fetal blood parameters, and new pharmacological interventions, in congenital cytomegalovirus infection”, directed by Dr. Anna Goncé.
- Ana Lisbeth Moreno, November 16th, 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.
- Marta Rial, June 16th, 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, January 11th, 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.

We encourage and support our researchers to participate in international conferences to disseminate their work and to be aware of the latest breakthrough in the field. A group of students (among others: Leticia Benitez, Laura Nogue, Ayako Nakaki and Lina Youssef), have attended the ISUOG World Congress 2022 on Ultrasound in Obstetrics and Gynecology. 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. Another cohort of our students (among others: Ameth Hawkins, Lina Youssef and Marta Rial) attended to the FMF 19th World Congress in Fetal Medicine. There, they had the opportunity to exchange ideas and discuss with the leading international experts in Fetal Medicine.

In contrast to the previous two years, in 2022, our weekly Journal Club meetings have been scheduled regularly. All researchers have had the opportunity to share the progress of their projects with the rest of the group. In addition to that, international external speakers have been invited to present their work.

Finally, we continue fostering our tight relationship with Fetal i+D Education where our students enrol multiple online courses both in Spanish and English.

4. WP 5: Knowledge dissemination and actions to reach out society

We dedicate enormous efforts to disseminate our knowledge in Maternal and Fetal Medicine to a broad audience. We increase our impact by promoting the participation of patients and engage the public opinion. As a result, our activity has often been echoed in the media and the group has been in the headlines of many national and international channels. In addition, we have participated in social events with high impact.

- During 2022, we have produced 2 new clinical guidelines for good practice and we have updated 14 more; all of them are related to gestational complications.
- 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, Fàtima Crispi, for her contribution in Maternal-Fetal Medicine at *Premios a la Investigación Fundación Jesús Serra.* The official website of Hospital Clínic reported our blood test to distinguish sever COVID-19 symptoms from preeclampsia during pregnancy. In addition, they advertised our workshop on the importance of preventing and detecting congenital CMV.
- In 2013, we launched an interactive social platform called iNatal. The platform demands interactions from users and it was created with the aim to provide useful information about health issues during pregnancy. Since then, iNatal has become a web-based platform of reference for pregnancy in Spanish, indeed, professionals in Maternal and Fetal Medicine recommend iNatal to patients. Thanks to the continuous scientific and editorial effort iNatal increased 81% the total number of users and has received more than 4.9 M visits in 2022. Statistics show that most of our users are located in Mexico, Spain, Argentina, Colombia and Peru.
- We actively participate in various social media platforms - Twitter, Instagram, Facebook and LinkedIn - where we share with our community our research outcomes, activities to engage the audience and the latest news related to Fetal and Maternal Medicine. We are delighted to communicate the increase of followers in all of our social media channels:

Social Media platform	Followers
Facebook page - www.facebook.com/BCNatalResearch	2,473
Instagram account - @BCNatalResearch	1,977
Twitter account - @BCNatalResearch	2,702
LinkedIn page - Fetal Medicine Research Center	1,657

- Since we launched our website - www.bcnatalresearch.org - in 2021, we have been posting all our research progress and latest outcomes. Experts in the field of Fetal and Maternal Medicine can access the material and get inspired by our contribution.
- We maintain our exceptional standards on article production with a publish record in high-impact international and open access scientific journals to have the maximum dissemination of our results in the scientific community.
- We are committed to disseminate our knowledge with the general public by being present in multiple media channels such as radio, television, press, social networks, website, Facebook, Twitter.
- Our researchers have attended and presented their work in various prestigious congresses, to name a few: 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), 55th Annual Meeting of the Association for European Paediatric and Congenital Cardiology 2022 (Patricia García), and VI International Fetal Medicine Symposium (Josep Maria Martínez).

5. Scientific Impact

- BCNatal Fetal Medicine Research group 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 7 papers (*see Annex 1. Publications*).
- The main scientific impact of the programme 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 recently 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 chid neurodevelopment. We are currently preparing these manuscripts for publication in high quality journals.

6. Other comments

We would like to make a special mention to our collaboration agreements with the following companies:

- We continue an agreement with Hologic, INC for a project involving a 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.
- We maintain an ongoing agreement with Medix Biochemica for the validation of “Actim IAI Intra-amniotic infection” marker.
- We have renewed our agreement with Roche International for the Identification of biomarkers for preeclampsia in the 3rd trimester - PE37.
- We have initiated a collaborative agreement with Brudy Technology, S.L. which is a company specialized in medical research in nutrition. With this collaboration, we will receive support to conduct the FETAL BRAIN CARE clinical study.

Annex 1. Publications

Basso, A., Youssef, L., Nakaki, A., Paules, C., Miranda, J., Casu, G., Salazar, L., Gratacos, E., Eixarch, E., Crispi, F., & Crovetto, F. (2022). Fetal neurosonography at 31-35 weeks reveals altered cortical development in pre-eclampsia with and without small-for-gestational-age fetus. *Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *59*(6), 737–746. https://doi.org/10.1002/UOG.24853

Boutet, M. L., Eixarch, E., Ahumada-Droguett, P., Nakaki, A., Crovetto, F., Cívico, M. S., Borrás, A., Manau, D., Gratacós, E., Crispi, F., & Casals, G. (2022). Fetal neurosonography and infant neurobehavior following conception by assisted reproductive technology with fresh or frozen embryo transfer. *Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *60*(5), 646–656. https://doi.org/10.1002/UOG.24920

Casas, R., Castro-Barquero, S., Crovetto, F., Larroya, M., Ruiz-León, A. M., Segalés, L., Nakaki, A., Youssef, L., Benitez, L., Casanovas-Garriga, F., Vieta, E., Crispi, F., Gratacós, E., & Estruch, R. (2022). Maternal Dietary Inflammatory Index during Pregnancy Is Associated with Perinatal Outcomes: Results from the IMPACT BCN Trial. *Nutrients*, *14*(11). https://doi.org/10.3390/NU14112284

Crovetto, F., Crispi, F., Borras, R., Paules, C., Casas, R., Martín-Asuero, A., Arranz, A., Vieta, E., Estruch, R., & Gratacós, E. (2021). Mediterranean diet, Mindfulness-Based Stress Reduction and usual care during pregnancy for reducing fetal growth restriction and adverse perinatal outcomes: IMPACT BCN (Improving Mothers for a better PrenAtal Care Trial BarCeloNa): a study protocol for a randomized controlled trial. *Trials*, *22*(1). https://doi.org/10.1186/S13063-021-05309-2

Crovetto, F., Crispi, F., Casas, R., Martín-Asuero, A., Borràs, R., Vieta, E., Estruch, R., & Gratacós, E. (2021). Effects of Mediterranean Diet or Mindfulness-Based Stress Reduction on Prevention of Small-for-Gestational Age Birth Weights in Newborns Born to At-Risk Pregnant Individuals: The IMPACT BCN Randomized Clinical Trial. *JAMA*, *326*(21), 2150–2160. https://doi.org/10.1001/JAMA.2021.20178

Hawkins-Villarreal, A., Moreno-Espinosa, A. L., Castillo, K., Hahner, N., Picone, O., Mandelbrot, L., Simon, I., Gratacós, E., Goncé, A., & Eixarch, E. (2022). Cortical maturation assessed by magnetic resonance imaging in unaffected/mildly affected fetuses with cytomegalovirus infection. *Ultrasound in Obstetrics & Gynecology : The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*. https://doi.org/10.1002/UOG.26110

Meler, E., Mazarico, E., Peguero, A., Gonzalez, A., Martinez, J., Boada, D., Vellvé, K., Arca, G., Gómez-Roig, M. D., Gratacós, E., & Figueras, F. (2022). Death and severe morbidity in isolated periviable small-for-gestational-age fetuses. *BJOG : An International Journal of Obstetrics and Gynaecology*. https://doi.org/10.1111/1471-0528.17181