

ANNUAL REPORT FOR:



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 - Clinical and Research Center of Maternal/Fetal and Neonatal Medicine of Barcelona

Hospital Sant Joan de Déu, Hospital Clínic and University of Barcelona



TABLE OF CONTENT

1. Summary of the progress achieved during the 2020	3
2. Specific research objectives reached per Work Package (WP)	3
2.1. WP 1: A better and more refined <u>risk identification</u> of complications.....	3
2.2. WP 2: Developing new imaging brain biomarkers.....	4
2.3. WP 3: Preventing neurological damages by prenatal therapy.....	4
3. Training and educational (WP 4).....	5
4. Dissemination and actions for the society (WP 5)	6
5. Scientific Impact	8
6. Social Impact achieved or foreseen	8
7. Other comments	9
Annex: 1. Publications	10

1. Summary of the progress achieved during the 2021

Regardless of the pandemic situation we have been able to continue our work during this 2021.

- We have successfully published the results of the IMPACT trial, including demonstrating that Mediterranean diet and stress reduction during pregnancy improves fetal growth and pregnancy results.
- We identified new therapeutic targets for preventing fetal growth restriction and preeclampsia by using proteomics and metabolomics.
- We confirmed that neurosonography is a sensitive tool to detect differences in cortical development in late-onset small fetuses.
- In the future, we will continue with the follow-up of the children born within the IMPACT trial, we will continue with the EMOTIVE trial to see the effects of reduced alcohol consumption in pregnancy and RATIO37 to optimize the time of delivery.

2. Specific research objectives reached per Work Package

1. **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. During this year, we have:
 - 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 JAMA Cardiology*)
 - We are assessing maternal lifestyle including nutrition, physical activity and sleep quality before and during pregnancy and its effect on fetal growth and development in a large cohort of pregnancies.

2.2. 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.

According to our aims, during this year:

- 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).
- We showed that fetuses with congenital heart disease have a smaller corpus callosum, specifically those with poorer brain oxygenation (Perez-Cruz et al. UGO 2021).

2.3 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.

During this year the COVID-19 pandemic situation altered the work-plan of some of our clinical studies. However, we managed to complete the RATIO 37 trial and advance in the other trials:

- Results from the IMPACT trial were published (Crovetto Trials 2021, Crovetto JAMA 2021) and disseminated demonstrating the beneficial effect of Mediterranean diet and stress reduction on fetal growth and pregnancy results.
- The COVID-19 pandemic stopped the recruitment of the RATIO 37 ratio that evaluates the potential utility of fetal brain Doppler ultrasound in reducing stillbirth. During 2021, we have restarted the recruitment and we have completed the trial with 11.582 patients recruited.

- During this year we have restarted the recruitment for the EMOTIVE project, a randomized trial testing motivational interview to reduce alcohol consumption during pregnancy to improve perinatal results. We currently have recruited the 38% of the total sample size (n = 823/ 2,184). In a sub-cohort of 215 fetuses we are evaluating the impact of this intervention in brain development before birth.
- In 2020, due to the pandemic we were not able to start the FETAL BRAIN CARE project, a randomized double-blinded trial that will provide maternal supplementation with lactoferrin and docosahexaenoic acid (DHA) for severe IUGR pregnancies. In 2021, there has been a shortage of reactants and lab components that have caused a delay in the production of the maternal supplementation, which has impeded us to start the study. We plan to be able to start the recruitment in the first trimester of 2022.

3. Training and educational (Work Package 4)

We aim to have 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 dedicates a great amount of effort to training and teaching in the subspecialty of Maternal and Fetal Medicine.

This year, even with Covid-19 restrictions, two of our students (Kilian Vellvé and Leticia Benitez) have visited other research centers (Oregon Health & Science University – Advance Imaging Research Center (AIRC), Portland, OR, USA and the Universitäts Klinikum of Düsseldorf, Düsseldorf, Germany).

The students (M^a Laura Boutet, Michael Hawkins, Karen Castillo, Johanna Parra, David Coronado, Marta Rial, Juan Otaño) have attended the ISUOG conferences where they presented their work with 5 oral presentations and 5 posters.

Two students of our research group have defended their PhD Thesis during this year:

- Iris Soveral Rodrigues da Silva Dias, 8th of January, Thesis entitled “Evaluation of left-sided congenital heart defects by advanced fetal echocardiography and cold blood biomarkers”, directors: Dr. Olga Gómez, Dr. Fatima Crispi.
- Talita Micheletti, 13th of September, Thesis entitled “Development of a sealing system for iatrogenic preterm prelabor rupture of membranes after endoscopic fetal surgery”, directors: Dr. Elisenda Eixarch and Professor Jan Deprest.

Regardless of Covid-19, we have continued our weekly Journal Club via an on-line platform to share our progress in the different research projects and have also invited different 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 both Spanish and English.

4. Dissemination and actions for the society (Work Package 5)

We aim to perform 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. With this in mind, our research activity has been covered by the media, helping us to promote the importance of research during the early stages of life. The group has been in the headlines of many national and international media, and has participated in important social events.

- During 2021, we have written and published 2 clinical guides.
- Different 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 (regional Radio) to talk about premature babies or Dr. Fàtima Crispi and 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.
- We have also participated in the researcher’s night 2021, Dr. Tere Cobo 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”.

- iNatal, which is our interactive social platform inatal, launched in 2013, is one of the largest Spanish-speaking web-based platforms for pregnancy. iNatal provides objective, useful information about health issues during pregnancy, while encouraging the active participation of its users. The hard work of the scientific and editorial team has contributed to the success of this social platform. During 2021, iNatal got more than 8M visits from more than 5M users, reaching the similar levels than those seen pre-pandemic. We know that many Spanish-speaking maternity professionals recommend our content to patients.
- We also actively participate in social media (Twitter, Instagram, Facebook and LinkedIn) where we share with the community not only our research but also our activities and news. Although our participation in social media has been affected by the pandemic, during 2021, we have increased the followers in all of our social media channels:
 - Our new Facebook page (www.facebook.com/BCNatalResearch) has 1,955 followers.
 - Our new Instagram account (@BCNatalResearch) reached to 1,414 followers.
 - By the end of 2021, 2,275 people are following us in our Twitter account (@BCNatalResearch).
 - Our LinkedIn page (Fetal Medicine Research Center) currently has more than 1,200 followers.
- We launched our new website the beginning of 2021: www.bcnatalresearch.org.
- We will continue to publish our results in high-impact international open access scientific journals to have the maximum dissemination in the scientific community. We will also continue to pay special attention to dissemination to society and the general public using different media (radio, television, press, social networks, web, Facebook, Twitter ...).
- Our researchers have participated in several prestigious congresses like the ISUOG (Miriam Illa, Francesca Crovetto, Lina Youssef, Marta López, Laura Guirado and Laura Nogué), the Annual Craniosynostosis Conference (Elisenda Eixarch), the SEGO congress (Tere Cobo) or in other dissemination activities like Women In Data Science (WiDS – Elisenda Bonet-Carne).

5. Scientific Impact

- During 2021, BCNatal Fetal Medicine Research group has published 84 papers in international scientific journals accumulating a total of 561.724 points of Impact Factor. Even though some projects were affected by the Covid-19 pandemic situation, within this programme we have published 15 papers and 1 public image database (*see Annex 1. Publications*).
- The main scientific impact of the programme has been publishing the IMPACT study, which shows for the first time that a non-pharmacological intervention (based on Mediterranean diet and mindfulness) during 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.

6. Social Impact achieved or foreseen

- 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. Specific papers about detail brain changes will be published within 2022. These results are very relevant because they will allow the implementation of new non-pharmacological strategies for improving fetal development.
- We managed to continue the ongoing trial studies, which might have a high impact when finished.
- 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.

7. Other comments

- We have established and / or renewed collaboration agreements with the following companies:
 - Transmural Biotech S.L.: Agreement to host engineers to collaborate with Artificial Intelligence projects (on-going).
 - 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).

Annex 1. Publications

1. 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. (2021). Complement and coagulation cascades activation is the main pathophysiological pathway in early-onset severe preeclampsia revealed by maternal proteomics. *Sci Rep*. DOI: 10.1038/s41598-021-82733-z.
2. Lina Youssef, Rui V. Simões, Jezid Miranda, María Luisa García-Martín, Cristina Paules, Francesca Crovetto, Nuria Amigó, Nicolau Cañellas, Eduard Gratacos & Fatima Crispi. (2021). Paired maternal and fetal metabolomics reveal a differential fingerprint in preeclampsia versus fetal growth restriction. *Sci Rep*. DOI: 10.1038/s41598-021-93936-9.
3. Crispi F, Rodríguez-López M, Bernardino G, Sepúlveda-Martínez Á, Prat-González S, Pajuelo C, Perea RJ, Caralt MT, Casu G, Vellvé K, Crovetto F, Burgos F, De Craene M, Butakoff C, González Ballester MÁ, Blanco I, Sitges M, Bijmens B, Gratacós E. (2021). Exercise Capacity in Young Adults Born Small for Gestational Age. *JAMA Cardiol*. DOI: 10.1001/jamacardio.2021.2537.
4. C Paules, J Miranda, C Policiano, F Crovetto, L Youssef, N Hanner, A Nakaki, F Crispi, E Gratacos, E Eixarch. (2021). Fetal neurosonography detects differences in cortical development and corpus callosum in late-onset small fetuses. *Ultrasound Obstet Gynecol*. DOI: 10.1002/uog.23592
5. Burgos-Artizzu XP, Coronado-Gutiérrez D, Valenzuela-Alcaraz B, Vellvé K, Eixarch E, Crispi F, Bonet-Carne E, Bennasar M, Gratacos E. (2021). Analysis of maturation features in fetal brain ultrasound via artificial intelligence for the estimation of gestational age. *Am J Obstet Gynecol MFM*. DOI: 10.1016/j.ajogmf.2021.100462.
6. Pérez-Cruz M, Gómez O, Gibert M, Masoller N, Marimon E, Lip-Sosa D, Bennassar M, Bonet-Carne E, Gómez-Roig MD, Martínez-Crespo JM, Gratacos E, Eixarch E. (2021). Corpus callosum size by neurosonography in fetuses with congenital heart defect and relationship with expected brain oxygen supply patterns. *Ultrasound Obstet Gynecol*. DOI: 10.1002/uog.23684.
7. Crovetto F, Crispi F, Casas R, Martín-Asuero A, Borràs R, Vieta E, Estruch R, Gratacós E; IMPACT BCN Trial Investigators. (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*. DOI: 10.1001/jama.2021.20178.
8. Xavier P Burgos-Artizzu, Nuria Baños, David Coronado-Gutiérrez, Julia Ponce, Brenda Valenzuela-Alcaraz, Ana L Moreno-Espinosa, Laia Grau, Álvaro Perez-Moreno, Eduard Gratacós, Montse Palacio. (2021). Mid-trimester prediction of spontaneous preterm birth with automated cervical quantitative ultrasound texture analysis and cervical length: a prospective study. *Sci Rep*. DOI: 10.1038/s41598-021-86906-8.
9. Meler E, Mazarico E, Eixarch E, Gonzalez A, Peguero A, Martinez J, Boada D, Vellvé K, Gomez-Roig MD, Gratacós E, Figueras F. (2021). Ten-year experience of protocol-based management of small-for-gestational-age fetuses: perinatal outcome in late-pregnancy cases diagnosed after 32 weeks. *Ultrasound Obstet Gynecol*. DOI: 10.1002/uog.23537.
10. Polat IH, Marin S, Ríos J, Larroya M, Sánchez-García AB, Murillo C, Rueda C, Cascante M, Gratacós E, Cobo T. (2021). Exploratory and confirmatory analysis to

- investigate the presence of vaginal metabolome expression of microbial invasion of the amniotic cavity in women with preterm labor using high-performance liquid chromatography. *Am J Obstet Gynecol*. DOI: 10.1016/j.ajog.2020.07.040.
11. Bennasar M, Ponce J, Torres X, Gómez O, Sabrià J, Gratacós E, Borrell A, Martínez JM. (2021). Perinatal outcome after selective termination in dichorionic twins discordant for congenital anomaly. *Acta Obstet Gynecol Scand*. DOI: 10.1111/aogs.14249.
 12. Torres X, Martínez JM, Gómez O, Martínez-Portilla RJ, García-Otero L, Crispi F, Masoller N, Sepúlveda-Martínez Á, Marimón E, Gratacós E, Figueras F, Bennasar M. (2021). Prescriptive standards of echocardiographic morphometric and functional parameters in uncomplicated monochorionic diamniotic fetuses. *Prenat Diagn*. DOI: 10.1002/pd.5999.
 13. Micheletti T, Eixarch E, Bennasar M, Torres X, Martínez-Crespo JM, Deprest J, Gratacós E. (2021). Risk Factors Associated with Preterm Prelabor Rupture of Membranes after Cord Occlusion in Monochorionic Diamniotic Twins. *Fetal Diagn Ther*. DOI: 10.1159/000516513.
 14. Ortiz JU, Torres X, Bennasar M, Eixarch E, Gómez O, Crovetto F, Lobmaier SM, Martínez JM, Gratacós E, Crispi F. (2021). Left myocardial performance index in monochorionic diamniotic twin pairs complicated by selective fetal growth restriction with abnormal umbilical artery Doppler. DOI: 10.1002/pd.6037
 15. Boutet ML, Casals G, Valenzuela-Alcaraz B, García-Otero L, Crovetto F, Cívico MS, Borrás A, Manau D, Gratacós E, Crispi F. Cardiac remodeling in fetuses conceived by ARTs: fresh versus frozen embryo transfer. (2021). *Hum Reprod*. DOI: 10.1093/humrep/deab159.