

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



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1. Summary of the progress achieved during the 2020

Regardless of the pandemic situation we have been able to continue our work during this 2020.

- IMPACT 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 (submitted, under review). These results are very relevant because they will facilitate the implementation of new non-pharmacological strategies for improving fetal development.
- We have created two new systems for segmenting and plotting fetal brain ultrasound and resonance imaging.
- During the pandemic period we completed a study of COVID-19 in pregnant women and also identified low weight at birth as a risk factor to develop severe COVID-19.
- In the future, we will continue monitoring IMACT trial children, 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.
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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:**

- Improved the characterisation of the phenotypic variability of fetal smallness and published our 10-year experience of protocol-based management of fetal growth restriction (*Meler et al. Ultrasound Obstet Gynecol 2020*).
- We have described the potential diagnostic and prognostic value of hemopexin and α 1-microglobulin heme scavengers in placental-disease related disorders including fetal growth restriction and preeclampsia (*Youssef et al. PlosONE 2020*)
- We demonstrated that ultrasound (fetal neurosonography) is a useful tool to detect differences in fetal brain cortical development and corpus callosum in fetal growth restriction (*Paules et al. Ultrasound Obstet Gynecol 2021*).

- 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 have set up a system for collecting images of low-risk pregnancies and we currently have a database with more than 50,000 images. These images are available as a public image repository to be used for other researchers (Fetal Planes DB at Zenodo: 10.5281/zenodo.3904280) and are essential for the developing of new imaging biomarkers based on artificial intelligence.
- We have provided new data about changes in cortical development in fetal ventriculomegaly demonstrating that differences observed with controls are correlated with regional changes ventricular volumes (Benkarim 2020).

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 IMPACT trial and advance in the other trials:

- We were able to complete the IMPACT that has randomized 2,225 pregnancies into usual care, nutritional intervention based in Mediterranean Diet or stress reduction based on Mindfulness. The results indicate a significant and important improvement in maternal and fetal health with both interventions. In brief, both Mediterranean Diet and mindfulness during pregnancy significantly improves fetal growth and reduces pregnancy complications. These are very relevant results as for the first time a non-pharmacological intervention during pregnancy

demonstrates to improve fetal growth. We are now preparing the results to be published and disseminated.

- 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. We have now restarted the recruitment and we expect to complete the trial on 2021 (now 80% of recruitment already completed).
- Regarding EMOTIVE project, an interventional programme for reducing alcohol consumption during pregnancy aiming to improve perinatal outcomes and children neurodevelopment, we temporarily stopped the inclusion due to CPVOD-19 and currently we have recruited the 25% of the total sample size ($n = 532 / 2,184$). We also have created a sub-cohort of 400 fetuses to evaluate the longitudinal prenatal brain development along pregnancy.
- Finally, due to pandemic we were not able to start the FETAL BRAIN CARE project, a randomized double-blinded trial with maternal supplementation with lactoferrin and docosahexaenoic acid (DHA) in severe IUGR. During this year we have been working in the set-up all the resources needed to start recruitment during the first trimester of the year.

3. Other research objectives reached (not defined in the proposal)

During the COVID19 pandemic, we conducted a population-based study to assess the impact of SARS-CoV-2 infection on pregnancy. We prospectively assessed more than 2000 pregnancies (including more than 300 SARS-CoV-2 positive pregnant women) and demonstrated that COVID-19 infection is mainly asymptomatic or mild in most pregnant women (*Crovetto et al. Lancet 2020*). In addition, we could also demonstrate that in the vast majority of pregnancies SARS-CoV-2 infection has small or negligible consequences on pregnancy and delivery results (*Crovetto et al. Clin Infect Dis 2020*). These results are very relevant and reassuring for pregnant women helping in the healthcare resource planning and clinical management.

In addition, we assessed the prognostic factors for severe COVID19 and admission to Intensive Care Unit in non-elder adults. We could demonstrate that being born low birth weight is a significant and independent risk factor for COVID-19 (*Crispi et al. Sci Reports 2020*). This new information further supports the importance of early life in adult diseases and might help in the prognostic risk classification of adults infected by SARS-CoV-2.

4. 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, four of our students (Maria Laura Boutet, Ana Moreno, Paz Ahumada and, Lucas Trigo) have visited other research universities (University of Lund in Sweden and KU Leuven in Belgium). However, due to the pandemic the stays and international exchange program have been interrupted since March 2020.

The 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, mostly about how covid affected pregnancy. Luckily, before the pandemic there was time to attend in person the “in-utero MRI 2020” workshop in Oxford, UK (from the 7th to the 10th of January). Dr. Eixarch was invited as a speaker to talk about MRI-planned laser ablation in Twin-to-Twin Transfusion Syndrome. And the students K.Vellvé and A. Nakaki presented a poster and were selected for an oral presentation; Vellvé talked about our collaborative work with UUtah and OHSU on reduction of T2* values in the placentas of growth-restricted fetuses and Nakaki presented results on IVIM correlation with placental size in growth-restricted fetuses.

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

- Lina Youssef, 30th of January, Thesis entitled “Omics approach to characterize different phenotypes of preeclampsia and fetal growth restriction”, directors: Dr. Fatima Crispi, Dr. Gratacós.
- Laura Guirado, 9th of October, Thesis entitled “Cardiopatías con obstrucción del tracto de salida del ventrículo derecho: estudio del remodelado cardiovascular fetal mediante ecocardiografía”, directors: Dr. Olga Gómez, Dr. Fátima Crispi.

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.

5. 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 2020, we have written and published 16 clinical guides, 3 of them about covid-19 and pregnancy and performed webinars for healthcare professionals with more than 20,000 attendees.
- 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 have had more than 50,000 visits (from April 2020) and the platform have generated more than 600 media (TV, press, radio) appearances and three different press releases.
- Different researchers have been invited to Radio or TV programs, an exemple was Dr. Lola Gómez Roig, who was invited on January 13th to a gathering in Betevé (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.
- We have also participated in the researcher's night (on-line this year), where Dr. Eixarch presented "Fetal surgery: saving lifes befor birth" with moret han 120 attendees (non-expert audience).
- iNatal, wich is our interactive social platform inatal, launched in 2013, is one of the largest Spanish-speaking web-based platform for pregnancy. iNatal provides objective, useful information about health issues during pregnancy, while encouraging the active participation of its users. Our research fellows directly contribute by updating the high quality contents of inatal. The hard work of the scientific and editorial team has contributed to the success of this social platform. During 2020, iNatal receiven more than 4.3M visits and reached to more than

15,000 registered users. 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 2020, we have increased the followers in all of our social media channels:
 - Our new facebook page (www.facebook.com/BCNatalResearch) has 1,440 followers. Additionally, iNatal Facebook page (www.facebook.com/inatal_org) has had 11,048 visitors during the 2020.
 - Our new instagram account (@BCNatalResearch) reached to 836 followers.
 - By the end of 2020, 1,830 people are following us in our Twitter account (@BCNatalResearch).
 - Our Linkedin page (Fetal Medicine Research Center) currently has more than 1,000 followers.
- We are currently working on our new website, that will be launched at the beginning of 2021.
- We will continue to publish our results in high-impact international open access scientific journals in order 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 ...).

6. Scientific Impact

- During 2020, BCNatal Fetal Medicine Research group has published 72 papers in international scientific journals accumulating a total of 386.6 points of Impact Factor. Even though some projects were affected by the Covid-19 pandemic situation, within this programme we have published 8 papers and 1 public image database (see *Annex 1. Publications*).

- The main scientific impact of the programme has been finishing 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 several scientific implications; we now know that diet and mindfulness have a measurable impact on the health and well-being of future pregnancies.
- 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 program 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.

7. Social Impact achieved or foreseen

- 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 (*submitted, under review*). 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.

8. Other comments (if needed)

- We have established and / or renewed collaboration agreements with the following companies:
 - 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).

Annex 1. Publications

1. E Meler, E Mazarico, E Eixarch, A Gonzalez, A Peguero, J Martinez, D Boada, K Vellvé, M D Gomez, E Gratacos and F Figueras. (2020). A 10-year experience of protocol-based management of fetal growth restriction: perinatal outcomes in late pregnancy cases diagnosed after 32 weeks. *Ultrasound Obstet. Gynecol.* DOI: 10.1002/uog.23537.
2. Lina Youssef, Lena Erlandsson, Bo Åkerström, Jezid Miranda, Cristina Paules, Francesca Crovetto, Fatima Crispi, Eduard Gratacos, Stefan R Hansson. (2020). Hemopexin and α 1-microglobulin heme scavengers with differential involvement in preeclampsia and fetal growth restriction. *PLoS One.* DOI: 10.1371/journal.pone.0239030.
3. 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
4. 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
5. Oualid Benkarim, Gemma Piella, Islem Rekik, Nadine Hahner, Elisenda Eixarch, Dinggang Shen, Gang Li, Miguel Angel González Ballester, Gerard Sanroma. (2020). A novel approach to multiple anatomical shape analysis: Application to fetal ventriculomegaly. *Med. Image Anal.* DOI: 10.1016/j.media.2020.101750.
6. Francesca Crovetto, Fàtima Crispi, Elisa Llurba, Francesc Figueras, María Dolores Gómez-Roig, Eduard Gratacós. (2020). Seroprevalence and presentation of SARS-CoV-2 in pregnancy. *Lancet.* DOI: 10.1016/S0140-6736(20)31714-1.
7. 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, on behalf of the KidsCorona Pregnancy COVID-19 group. (2021) Impact of Sars-Cov-2 Infection On Pregnancy Outcomes: A Population-Based Study. *Clin Infect Dis.* Accepted
8. Cobo T, Aldecoa V, Figueras F, Herranz A, Ferrero S, Izquierdo M, Murillo C, Amoedo R, Rueda C, Bosch J, Martínez-Portilla RJ, Gratacós E, Palacio M. (2020). Development and validation of a multivariable prediction model of spontaneous preterm delivery and microbial invasion of the amniotic cavity in women with preterm labor. *Am. J. Obstet. Gynecol.* DOI: 10.1016/j.ajog.2020.02.049.
9. Ibrahim H Polat, Silvia Marin, José Ríos, Marta Larroya, Ana B Sánchez-García, Clara Murillo, Claudia Rueda, Marta Cascante, Eduard Gratacós, Teresa Cobo. (2020) 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.2020.02.049.