www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2021;10(1):e100146
doi: 10.7363/100146
Published online: 2020 Nov 08

Lectures

Selected Lectures of the 16th International Congress on Neonatology and Pediatrics • On Demand

CAGLIARI (ITALY) • NOVEMBER 20TH-DECEMBER 31ST, 2020

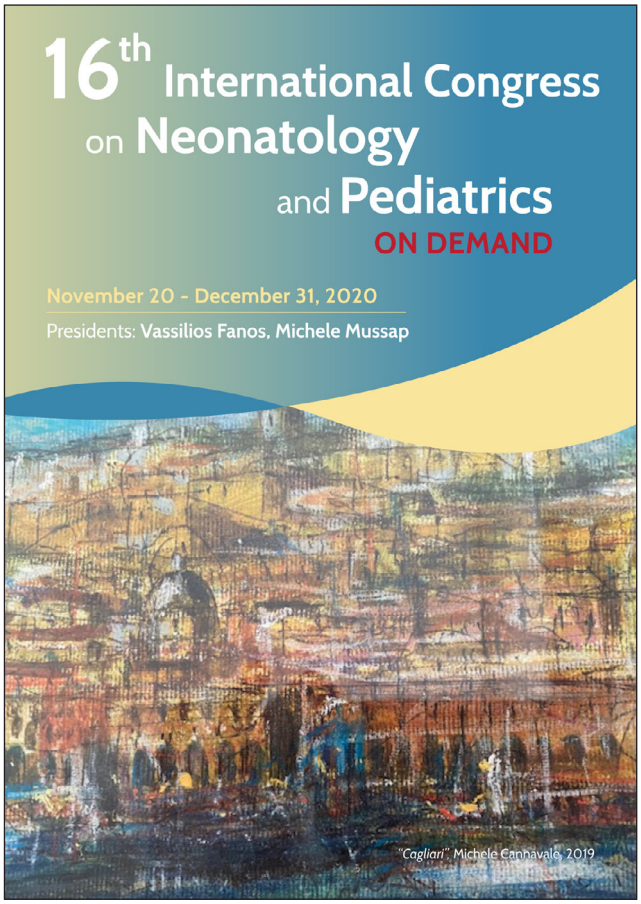
The Workshop has been organized with the patronage of SIN (Italian Society of Neonatology), UENPS (Union of European Neonatal and Perinatal Societies) and UMEMPS (Union of Middle-Eastern and Mediterranean Pediatric Societies).

PRESIDENTS

Vassilios Fanos (Cagliari, Italy), Michele Mussap (Cagliari, Italy)

INTERNATIONAL FACULTY

Eugenio Baraldi (Padua, Italy), Pier Paolo Bassareo (Dublin, Ireland), Enrico Bertino (Turin, Italy), Despina D. Briana (Athens, Greece), Giuseppe Buonocore (Siena, Italy), Angelica Dessì (Cagliari, Italy), Gavino Faa (Cagliari, Italy), Ruggiero Francavilla (Bari, Italy), Johan Garssen (Utrecht, The Netherlands), Salvatore Leonardi (Catania, Italy), Melania Puddu (Cagliari, Italy)



How to cite

[Lecture's authors]. [Lecture's title]. In: Selected Lectures of the 16th International Congress on Neonatology and Pediatrics, On Demand; Cagliari (Italy); November 20-December 31, 2020. J Pediatr Neonat Individual Med. 2021;10(1):e100146. doi: 10.7363/100146.

LECT 1

THE IMPACT OF ASSISTED REPRODUCTION, INTRAUTERINE GROWTH RESTRICTION AND PREMATURITY ON THE NEURODEVELOPMENT OF TWINS

D.D. Briana

Neonatal Intensive Care Unit, 3rd Department of Pediatrics, National and Kapodistrian University of Athens Medical School, Athens, Greece

Genetic and perinatal environmental factors contribute to long-term neurodevelopmental outcomes. Although current evidence is poor, these associations are probably mediated by epigenetic influences. Twinning is currently considered a complex multicausal trait and has become a topic of great scientific interest due to the raise in multiple birth rates, secondary to the increasing use of assisted reproduction procedures. A few reports have investigated how the unique genetic and environmental influences which are implicated in the origination of a mono- or dizygotic twin pregnancy affect phenotypes and outcomes. However, population-based studies document a consistently higher incidence of neurodevelopmental disability in twins than singletons. Lower birth weight and lower gestational age in twin pregnancies are considered the main implicated factors. Other common pregnancy complications specific to twins, such as twin-to-twin transfusion syndrome, intrauterine death of a co-twin and birth weight discordance may also adversely affect neurodevelopment, and lead to long-term cognitive and neuromotor disabilities. Despite heterogeneity in the estimates across studies, current knowledge implicates fetal growth restriction, prematurity and zygosity as predisposing factors to adverse neurodevelopment outcomes of twins. Assisted reproduction techniques per se do not seem to alter the risk of twins for less optimal development and health. Differences in selection/exclusion criteria, inadequate sample sizes, suboptimal measurement of all relevant covariates, variation in defining adverse outcomes and the retrospective nature of the analysis are probably responsible for the conflicting reports in the available literature. Future studies should compare the long-term outcome of naturally conceived twins with those conceived following assisted reproduction techniques and define individual, longitudinal trajectories of growth and development. Worldwide population-based twin registries will provide more precise and clear evaluation of the long-term outcomes of twinning. This presentation analyzes the current available evidence concerning the impact of assisted reproduction, fetal growth restriction and prematurity on the neurodevelopment of twins. The neurodevelopmental aspects discussed include cerebral palsy, motor disability, cognitive impairment, autism spectrum disorders, as well as other common behavioral and psychiatric diseases.

REFERENCES

- Lorenz JM. Neurodevelopmental outcomes of twins. Semin Perinatol. 2012;36(3):201-12.
- Babatunde OA, Adebamowo SN, Ajayi IO, Adebamowo CA. Neurodevelopmental Outcomes of Twins Compared With Singleton Children: A Systematic Review. Twin Res Hum Genet. 2018;21(2):136-45.
- Briana DD, Malamitsi-Puchner A. Twins and neurodevelopmental outcomes: the effect of IVF, fetal growth restriction, and preterm birth. J Matern Fetal Neonatal Med. 2019;32(13):2256-61.

LECT 2

PFAPA (PERIODIC FEVER – APHTHOUS STOMATITIS – PHARYNGITIS – ADENOPATHY) SYNDROME: LIGHTS IN THE DARK?

S. Manti, G.F. Parisi, M. Papale, P. Barone, S. Leonardi

Pediatric Respiratory Unit, San Marco Hospital, AOU Policlinico Vittorio Emanuele, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

Periodic fever, aphthous stomatitis, pharyngitis, adenopathy (PFAPA) syndrome is a self-limited and benign autoinflammatory disease belonging to the heterogeneous group of the "periodic diseases" [1]. The incidence of PFAPA is 2.3 per 10,000 children, with a prevalence in younger than 5 years of age and male gender. PFAPA syndrome is defined clinically as it is featured by febrile episodes lasting for 3-6 days with recurrence every 3-8 weeks, pharyngitis, cervical adenitis, and aphthous stomatitis [1]. Although glucocorticoids, tonsillectomy or

adenotonsillectomy, colchicine, and biological drugs are currently approved as therapeutic options for treating PFAPA, they are non-specific and seem not to change the outcome [1]. Recently, taking into advantage the evidence of abnormal host immune response in patients with PFAPA, it has proved that the administration of immunostimulant, such as Pidotimod (PDT, 3-L-pyroglutamyl-L-thiaziolidine-4-carboxylic acid), a synthetic dipeptide molecule, alone or in combination with bacterial lysates drugs can be able to attenuate the PFAPA course [1, 2]. In this regard, by conducting a preliminary, prospective, controlled, open, cross-over study trial enrolling 22 children, we successfully tested the efficacy of PDT in treating PFAPA syndrome [3]. All enrolled children were randomly allocated to treatment with PDT and betamethasone 0.5-1 mg on need or betamethasone 0.5-1 mg on need. Each treatment period was for 3 months (Phase 1), after that patients were switched to the other arm (Phase 2). Patients receiving PDT and betamethasone showed a significant decrease in clinical symptoms including the frequency of fevers, the number of episodes of pharyngitis and aphthous stomatitis as well as the patients using betamethasone on need. Although a decrease in the frequency of the number of episodes of fever, pharyngitis, and aphthous stomatitis was also reported at the end of phase 2, it did not appear statistically significant. Moreover, any serious adverse event was reported throughout the duration of the study [3]. In conclusion, PDT was acting as an immunomodulatory agent with a good clinical efficacy as assessed by a significant decrease in the disease severity, thus, resulting in a new potential pharmacological strategy in the control of PFAPA syndrome [3]. Moreover, decreasing the routine corticosteroid use, PDT could be also able to prevent indirectly the side effects associated with frequent corticosteroid use [3]. Further researchers are required to confirm our preliminary findings as well as to assess the efficacy and safety of PDT in the long-term. Probably, help can come from metabolomics in detecting metabolites produced during metabolic processes as well as identifying the metabolite patterns of the patient also facilitating physicians to make better clinical and therapeutic decisions [4].

REFERENCES

[1] Vanoni F, Theodoropoulou K, Hofer M. PFAPA syndrome: a review on treatment and outcome. Pediatr Rheumatol. 2016;14:38.

[2] Manti S, Parisi GF, Papale M, Licari A, Salpietro C, Miraglia Del Giudice M, Marseglia GL, Leonardi S. Bacteriotherapy with Streptococcus salivarius 24SMB and Streptococcus oralis 89a nasal spray for treatment of upper respiratory tract infections in children: a pilot study on short-term efficacy. Ital J Pediatr. 2020;46(1):42.

[3] Manti S, Filosco F, Parisi GF, Finocchiaro GG, Papale M, Giugno A, Barone P, Leonardi S. Proposal for a new therapeutic high dosage of Pidotimod in children with periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome: a randomized controlled study. Ital J Pediatr. 2020;46(1):106.

[4] Fanos V, Pintus R, Dessì A. Clinical Metabolomics in Neonatology: From Metabolites to Diseases. Neonatology. 2018;113(4):406-13.

LECT 3

EARLY LIFE INTERVENTIONS AND IMMUNE HEALTH RELEVANCE FOR SPECIALIZED NUTRITION

J. Garssen

Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
Global Centre of Excellence Immunology, Danone Nutricia Research, Utrecht, The Netherlands

Immune health receives lots of attention especially during the recent COVID-19 episodes all over our globe. Health and immune health mean reacting in a proper and resilient way. Ability to adapt and reset. It is very clear that a balanced and resilient immune system plays a pivotal role in the protection and recovery against all kinds of danger triggers such as pathogens including Coronaviruses, toxins, allergens, etc. A resilient immune system helps to recognize, signal, protect, fight and to recover but also to reset (back to normal, balancing pro- and anti-inflammation). In a way the immune system can be seen as our sixth sense organ, by nature aimed at proper reactions to signals from the outside and inside, all together our "exposome".

It is very well known and validated that early life plays an essential role in training and developing a healthy immune system. If during this period something went wrong or was not optimal, this might lead to higher susceptibility and severity of immune related disorders early but also later in life. Infections, allergies, auto-immunities, metabolic disorders, diabetes, etc. are examples that can be linked easily to immune dysregulation early in life. It is a bit like programming a computer. Early life events imprint/program our

immune system for a significant and essential part. That means an enormous responsibility for the parents, neonatologists/paediatricians, etc.
We as scientist, medical doctors active in paediatrics/neonatology/immunology, need to explain that early life interventions including nutrition is of utmost importance and why! We all know that the upper-best nutrition during early life is human milk. It is fascinating how all the individual molecules/structures, lipid vesicles, microbes, oligosaccharides and many more present in human milk seem to interact and help to develop optimal immune health in the baby. As an example, the unique human milk oligosaccharides, unique antigenic epitopes and even microbes present in human milk seem to interact in a unique manner with immune cells in the offspring. All together creating a healthy resilient immune system via optimal programming. Some of the structures from human milk seem to be highly relevant for managing some immune related disorders in later life as well, suggesting the highly relevance and potency of the unique molecules present in human milk. Early life immune programming can make the difference without any doubt.

LECT 4

COVID-19 AND KAWASAKI SYNDROME: WHAT WE KNOW

P.P. Bassareo

Mater Misericordiae University Hospital and Our Lady's Children's Hospital Crumlin, University College of Dublin, Dublin, Ireland

The Coronavirus disease 2019 (COVID-19), responsible for the current pandemic of a severe acute respiratory distress syndrome, is the third spillover of an animal Coronavirus (SARS-CoV-2) to humans resulting in a major epidemic, and the second pandemic event over last 20 years. COVID-19 is dramatically putting under pressure healthcare systems worldwide [1]. At the beginning of the disease, children seemed to be less affected and with milder symptoms than adults [2]. Afterward, however, a warning was released in Bergamo (Italy) – one of the worst epicentres of the disease in the world – regarding the possible association between COVID-19 and Kawasaki disease (KD) or Kawasaki-like disease, with an incidence up to 30-fold than usual [3]. Then, similar notifications came mainly from the UK, France, and the USA. Following that, the definitions of Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in Europe and Multisystem Inflammatory Syndrome in Children (MIS-C) in the USA were coined to refer to this new disease. The last two definitions seem to be somewhat interchangeable. The reality is that PIMS-TS/MIS-C is more similar to certain KD complications such as toxic shock syndrome and macrophage activation syndrome than to classic KD. PIMS-TS/MIS-C and KD share the viral origin (however just supposed for KD) and consequent dysregulated innate immune system inflammatory reaction. PIMS-TS/MIS-C symptoms occur about 2-4 weeks after the onset of COVID-19 or having been in touch with somebody positive for COVID-19, rather than in the acute phase of the infection. The clinical features are slightly different, since PIMS-TS/MIS-C affects older children than KD and presents more often with abdominal pain and other gastrointestinal symptoms (50-60%), shock, and multi-organ dysfunction. Regarding the cardiovascular system involvement, in PIMS-TS/MIS-C myocarditis is more common than coronary artery aneurysms formation. Differences between KD and PIMS-TS/MIS-C are present also concerning laboratory tests and immunology.
On balance, PIMS-TS/MIS-C seems to be a new and multifaceted entity, distinct from KD, notwithstanding having some features in common. The dysregulated innate immune system reaction is responsible for PIMS-TS/MIS-C onset and outcome. A multidisciplinary approach, involving paediatric intensivists, paediatric cardiologists, infectious disease specialists, immunologists, and rheumatologists, is needed [4].

REFERENCES

[1] Bassareo PP, Melis MR, Marras S, Calcaterra G. Learning from the past in the COVID-19 era: rediscovery of quarantine, previous pandemics, origin of hospitals and national healthcare hospitals, and ethics in medicine. Postgrad Med J. 2020 Sep 9. [Epub ahead of print].

[2] Sanna G, Serrau G, Bassareo PP, Neroni P, Fanos V, Marcialis MA. Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review. Eur J Pediatr. 2020;179(7):1079-87.

[3] Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395(10239):1771-8.

[4] Bassareo PP, Fanos V, Calcaterra G. Coronavirus disease 2019, Kawasaki disease, and multisystem inflammatory syndrome in children. J Pediatr. 2020;224:184.

LECT 5

HUMAN MILK AS A MAGIC FLUID

A. Dessì

Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy
Department of Surgery, University of Cagliari, Cagliari, Italy

Breast milk has been known as the most complete food in nature since ancient times. In Egyptian culture, woman's milk was considered miraculous: a liquid able to heal diseases.

Even today, breast milk is undoubtedly the best food for the newborns, since it is able to modulate itself according to their needs from the very early stages of life, in order to ensure their proper development.

The peculiar characteristic of breast milk is precisely the inter- and intra-variability of its composition: in fact, not only is it different from mother to mother (also reflecting her nutritional status), but it is personalized according to the daily routine, the phase of breastfeeding and the gestational age of the newborn. For this reason, it is also considered the food of choice for the nutrition of preterm infants, also through appropriate fortification, to be preferred to the formula milk specific for them [1].

Probably, what contributes to the uniqueness of breast milk are its components as well. It is a complex mixture of nutrients and biologically active compounds (such as hormones, cytokines, growth factors) which, together with its microbiota and stem cells, contribute to its many beneficial effects on both mother and child.

Furthermore, according to very recent studies published in literature, it would seem to have a protective effect even in case of maternal disease from COVID-19.

In fact, in case of COVID-19 positivity, not only the milk should not be considered a priori a transmission vehicle (indeed, there are no studies that confirm this hypothesis) but breastfeeding should be encouraged in the light of literature-proven benefits such as the passage of antibodies and the presence of lactoferrin [2].

Nevertheless, despite numerous scientific evidences, according to UNICEF data, only 41% of children born in 2018 were fed exclusively with breast milk for the first 6 months of life, as recommended by the World Health Organization.

Science is, unfortunately, useless without concrete help to mothers and in the absence of proper communication and humanization in this context. There is a tendency to give static "rules" without considering the immense variability from woman to woman and from newborn to newborn. Trying to follow these "dogmas", the mother is often affected and feels inadequate, not being able to enjoy the wonderful experience of being a mother and breastfeeding her neonate [3].

Breastfeeding is not always "automatic" and what would be useful to mothers is, first of all, knowing how to listen to them, as they are very reliable in the description of their problem, and then it is also necessary to dedicate time to them, encouraging the opening of surgeries in support of mothers in order to offer adequate and personalized help to each one of them.

REFERENCES

[1] Ballard O, Morrow AL. Human Milk Composition: Nutrients and Bioactive Factors. Pediatr Clin North Am. 2013;60(1):49-74.

[2] Davanzo R, Moro G, Sandri F, Agosti M, Moretti C, Mosca F. Breastfeeding and coronavirus disease-2019: Ad interim indications of the Italian Society of Neonatology endorsed by the Union of European Neonatal & Perinatal Societies. Matern Child Nutr. 2020;16(3):e13010.

[3] Wagner EA, Chantry CJ, Dewey KG, Nommsen-Rivers LA. Breastfeeding concerns at 3 and 7 days postpartum and feeding status at 2 months. Pediatrics. 2013;132(4):e865-75.

LECT 6

NEUROPROTECTION OF NEONATAL BRAIN TODAY

G. Buonocore

Department of Pediatrics, Obstetrics and Reproductive Medicine, University of Siena, Siena, Italy

Newborns, particularly preterm infants, are susceptible to oxidative stress (OS), due to the immaturity of the antioxidant systems and the presence of conditions that lead to excessive free radicals (FR) production, including infections, blood transfusions, hyperoxia, hypoxia, ischemia [1]. The excess of free iron and the reduced ability to bind and metabolize it, are additional characteristics leading to OS in the neonatal period. The negative effects of FR on cells, organs and systems led to recognize OS as a common denominator disease typical of prematurity, currently referred to as "oxygen radical disease of the newborn". The brain is extremely sensitive to the action of FR, due to its high concentration of oxygen, low antioxidant concentration, free iron content, presence of polyunsaturated fatty acids

(adrenic and docosahexaenoic acid), target of free radicals, on neuronal membrane. Poor myelination and deficiency of antioxidant enzymes (superoxide dismutase, glutathione peroxidase and catalase) contribute to the vulnerability to oxidative damage, through mechanisms of excitotoxicity, and mitochondrial damage. Furthermore, the OS can initiate an inflammatory response, and vice versa the inflammatory response generates FR inducing OS [2]. The pathogenetic mechanisms of hypoxic-ischemic brain damage occur in three phases: reduced energy due to the hypoxic insult; re-oxygenation and reperfusion; impaired development of synaptic and axonal growth. All three phases recognize the involvement of OS. Therefore, there is today a growing interest in the development of new protective antioxidants measures, both in the prevention and in the treatment of neonatal asphyxia. Selective nitric oxide synthetase inhibitors, allopurinol, melatonin and erythropoietin are among the first drugs ready for clinical trials of efficacy and safety in combination with hypothermia, for the treatment of hypoxic-ischemic encephalopathy. Some of the limiting factors that still represent a barrier in the experimentation are the presence of a therapeutic window and the poor bioavailability of these molecules to reach the effective concentration in the brain parenchyma. The use of nanomaterials, such as dendrimers, used as drugs carriers could facilitate their passage through the blood brain barrier. It is also appropriate to use specific biomarkers of neuronal damage within the first hours of the hypoxic-ischemic insult to allow early identification of infants who may benefit from neuroprotection and to monitor the effectiveness of dosages and administration times [3].

REFERENCES

[1] Perrone S, Tataranno ML, Stazzoni G, Ramenghi L, Buonocore G. Brain susceptibility to oxidative stress in the perinatal period. J Matern Fetal Neonatal Med. 2015;28(Suppl 1);2291-5.

[2] Buonocore G, Perrone S, Longini M, Paffetti P, Vezzosi P, Gatti MG, Bracci R. Non protein bound iron as early predictive marker of neonatal brain damage. Brain. 2003;126(Pt 5):1224-30.

[3] Perrone S, Laschi E, Buonocore G. Oxidative stress biomarkers in the perinatal period: Diagnostic and prognostic value. Semin Fetal Neonatal Med. 2020;25(2):101087.

LECT 7

PROBIOTICS: ARE ALL THE SAME?

R. Francavilla, V.N. Dargenio, F. Cristofori

Pediatric Section, Interdisciplinary Department of Medicine, University "Aldo Moro", Bari, Italy

For a range of indications, probiotics have been suggested, ranging from hypothetical long-term immunomodulatory effects to proven benefits in the treatment of various health conditions. Probiotics are considered healthy, but the safety of probiotics is correlated with some concerns. In terms of the safety of probiotics, there are primarily three theoretical concerns [1]: the development of diseases including bacteremia or endocarditis; toxic or metabolic consequences on the digestive tract; and the transmission of antibiotic resistance to gastrointestinal flora. Accessible epidemiological evidence, clinical trials and acute toxicity studies have recommended that lactic acid bacteria (LAB) typically contained in fermented foods and used in existing probiotics should be considered secure. Lactobacilli, Lactococci, Bifidobacteria, and yeast are species commonly considered healthy.

There is a growing number of commercial products available which contain probiotics. In order to fulfill the definition given by the International Scientific Association for Probiotics and Prebiotics of "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [2], they need to be alive by the end of shelf-life and must be present in a sufficient number within the product to survive through the acid and alkaline gastrointestinal tract sites. The quality of the final product therefore relies heavily on the manufacturing processes by which such processes are carried out such as: fermentation, matrix composition, cell harvesting, spray-drying, freeze-drying; storage conditions like temperature, humidity, and pH are just several of a wider array of manufacturing determinants that can affect microbial survival, growth, viability, and ultimately the study results and/or clinical outcomes.

Quality assessment studies are carried out worldwide with the aim to evaluate the quality of the commercial probiotic products and the findings are: a) misidentification at the strain level; b) mislabeling regarding incorporated probiotic strains; c) inconsistent number of viable cells per dose; d) contamination; e) reduced functional properties; f) transferable antibiotic resistance.

A recent paper by ESPGHAN Working Group for Probiotics and Prebiotics [3] addressed this problem and agreed on the following statements:

1. Probiotics may differ in their effects on health and therefore a correct identification of microorganisms at strain level is needed to induce the desired health effect.
2. In the healthy population, probiotic products meant to boost otherwise normal diets are different from drug-like probiotic products prescribed for particular clinical situations/ indications. Subsequently, it is important to undergo comprehensive clinical trials needed for the respective application envisaged.
3. To confirm the viability and strain-level recognition of the active ingredient (strain or strains), probiotic products should be subjected to rigorous quality testing by the respective authorities. The results of these tests should be released.
4. In view of the rapid advancement of technology, quality management should be conducted using validated and standardized methods in accredited laboratories. Under that same auspices of the respective regulatory agencies, the reference laboratories shall carry out standardization and validation control.

REFERENCES

[1] Sharma P, Tomar SK, Goswami P, Sangwan V, Singh R. Antibiotic resistance among commercially available probiotics. Food Res Int. 2014;57:176-95.

[2] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Berni Canani R, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014;11(8):506-14.

[3] Kolaček S, Hojsak I, Berni Canani R, Guarino A, Indrio F, Orel R, Pot B, Shamir R, Szajewska H, Vandenplas Y, van Goudoever J, Weizman Z; ESPGHAN Working Group for Probiotics and Prebiotics. Commercial Probiotic Products: A Call for Improved Quality Control. A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2017;65(1):117-24.

LECT 8

VITAMIN D: FROM ROOTS TO METABOLOMICS

M. Puddu

Department of Surgical Sciences, University of Cagliari, Cagliari, Italy

The role of vitamin D in calcium homeostasis is well known and most people associate it only with bone health. Actually, over the years, several studies highlighted its versatility in performing actions that are independent of those carried out in the skeletal system and concern almost the totality of other tissues. Cardiovascular, infectious, autoimmune and cancer pathologies are associated with its deficiency.

Its origins lie mainly in the skin where UV rays produce vitamin D3 or cholecalciferol from 7-dehydrocholesterol. In small quantities (20%) it is also taken with food as vitamin D2 (ergocalciferol). To become metabolically active both must be hydroxylated first in the liver (25-OH) and then in the kidney (1,25-OH).

The importance of vitamin D is already evident in the early stages of life. Its presence affects the successful outcome of pregnancy and promotes fertility, conception, implantation and development of the embryo, also in case of in vitro fertilization.

In the first two trimesters the transplacental passage is poor but the placenta is able to hydroxylate the 25-OH to 1,25-OH vitamin D to satisfy the needs of the fetus and to perform an immunomodulatory and anti-inflammatory function useful for the good course of pregnancy. Its deficiency at these stages appears to be associated with several pregnancy pathologies, primarily with preeclampsia, as well as with alterations in fetus bone and lung development. From 24 weeks of gestational age the fetus begins to produce 1,25-OH vitamin D, essential for calcium homeostasis. A lack of vitamin in the third trimester appears to be related to a higher incidence of preterm delivery and caesarean section, with a more unfavorable course of neonatal infections and necrotizing enterocolitis (NEC), and with more severe respiratory distress. In addition, given the role of the vitamin in the processes of cell differentiation and proliferation, especially in the heart and brain, inadequate levels could lead to defects in the development of these organs.

As reported above, preterm babies, particularly those < 28 weeks, have a low concentration of vitamin D at birth due to the abrupt interruption of maternal intake. They therefore require a supplementation even if fed with formula milks, taking some time to reach the volumes that ensure an adequate supply.

For the last few years some pharmaceutical companies have proposed that vitamin D supplementation is combined with fatty acids ω3, in particular docosahexaenoic acid (DHA), which shows similar effects to vitamin D both in pregnancy (reduction of preterm deliveries)

and in neonatal and adult age (CNS maturation, cardiovascular health).
Recently our group investigated, through nuclear magnetic resonance (NMR), urinary metabolomic profile of two cohorts of preterm infants, supplemented one with vitamin D only and the other with vitamin D and DHA. Study results are interesting and seem to show that infants taking both supplements are better protected from oxidative stress than those receiving only vitamin D.

REFERENCES

• Larqué E, Morales E, Leis R, Blanco-Carnero JE. Maternal and Foetal Health Implications of Vitamin D Status during Pregnancy. Ann Nutr Metab. 2018;72(3):179-92.

• Wagner CL, Hollis BW. The implications of vitamin D status during pregnancy on mother and her developing child. Front Endocrinol (Lausanne). 2018;9:500.

• Fanos V, Corbu S, Laconi A, Pintus R, Dessì A, Ledda G, Puddu M, Cesare Marincola F. Exploring the effect of vitamin D and DHA supplementation on the urine metabolome of preterm infants by 1H NMR-based metabolomics. J Pediatr Neonat Individual Med. 2019;8(2):e080225.

LECT 9

RESPIRATORY SYNCYTIAL VIRUS: PRESENT AND FUTURE

L. Bonadies, A. Galderisi, E. Priante, V. Mardegan, E. Baraldi

Neonatal Intensive Care Unit, Department of Women's and Children's Health, University of Padua, Padua, Italy

Respiratory Syncytial Virus (RSV) is an RNA virus that causes respiratory tract infections (most frequently bronchiolitis) with typical seasonality. These infections are often self-resolving, but in some cases and in special populations like preterm and infants with BPD, congenital heart diseases or immunodeficiencies, RSV infections can be severe and need intensive care unit admission. Worldwide RSV is one of the major causes of morbidity and mortality for children of less than 5 years, causing around 3.4 million hospitalizations every year and a high mortality in low resources countries. The majority of children hospitalized with RSV infection were previously healthy.
RSV Low Respiratory Tract Infections (LRTIs) begins with an upper airway infection, usually transmitted by contact or respiratory droplets, that reach the lower tract causing epithelial necrosis and inflammatory cells infiltration at both respiratory (bronchi and alveoli) and vascular (arteriole and capillary) side, that combined with enhanced mucus secretion cause airway obstruction and airtrapping. The highest rate of hospitalizations is observed during the first 2-3 months of life [1].
We lack effective treatment for RSV-associated bronchiolitis, that currently rely on supportive care, including nasal suction, hydration and nutrition, as well as respiratory support such as Humidified Heated High Flow Nasal Cannulae, CPAP and, ultimately, mechanical ventilation. Several anti-viral drugs are being investigated to treat the acute phase of the disease.
In the absence of a treatment, prophylaxis is a culprit for management of RSV infection in at risk groups. Palivizumab (a chimeric monoclonal antibody directed against the antigenic site A on the fusion F protein of RSV) reduces RSV infection incidence and severity when injected intramuscularly once a month during epidemic season. Other promising antibodies have been tested during the last decade with alternate fortune. A recent study showed encouraging results with Nirsevimab (a monoclonal antibody binding the site 0 epitope with an extended half-life), reducing RSV-confirmed medically attended LRTI and hospitalizations for RSV by 70% and 78%, respectively, with a single intramuscular injection [2]. Viral sequence analysis will be precious in the development of new RSV monoclonal antibodies for the detection of new circulating RSV strains.
RSV vaccines are the forefront promise to prevent early infection and its consequences, with more than 15 vaccines under evaluation. Recently the analysis of data from 7 clinical trials demonstrated that live-attenuated RSV vaccines can protect against RSV disease. Mothers' vaccination has been shown to be protective during the first months of life due to transplacental prenatal antibody transfer.
Children with early RSV LRTI are likely to develop recurrent wheezing and asthma in later ages, suggesting a long-term benefit derived from prevention of RSV disease [3].
RSV is a major cause of morbidity in Western countries, and is associated with an high mortality rate in low- to middle-income countries [1]. This makes a compelling necessity to achieve effective population-based prevention strategies. Vaccines, monoclonal antibodies and antivirals are in the late-stage clinical development and represent a promising resource for the near-future.

REFERENCES

[1] Mazur NI, Martinón-Torres F, Baraldi E, Fauroux B, Greenough A, Heikkinen T, Manzoni P, Mejias A, Nair H, Papadopoulos NG, Polack FP,

Ramilo O, Sharland M, Stein R, Madhi SA, Bont L; Respiratory Syncytial Virus Network (ReSViNET). Lower respiratory tract infection caused by respiratory syncytial virus: Current management and new therapeutics. Lancet Respir Med. 2015;3(11):888-900.

[2] Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, Simões EAF, Esser MT, Khan AA, Dubovsky F, Villafana T, DeVincenzo JP; Nirsevimab Study Group. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. N Engl J Med. 2020;383(5):415-25.

[3] Baraldi E, Bonadies L, Manzoni P. Evidence on the Link between Respiratory Syncytial Virus Infection in Early Life and Chronic Obstructive Lung Diseases. Am J Perinatol. 2020;37(Suppl 2):S26-30.

LECT 10

GROWTH: NATURE OR NURTURE? WHERE DOES INEQUALITY BEGIN?

E. Bertino, G. Maiocco, S. Sottemano

Department of Neonatology, University of Turin, City of Health and Science of Turin, Turin, Italy

The 1,000 days between a woman's pregnancy and her child's second birthday offer a brief but critical window of opportunity to shape a child's development. It is a time of both tremendous potential and enormous vulnerability. How well or how poorly a child fares during his first 1,000 days can mean the difference between a thriving future and one characterized by struggle. There are three crucial stages in the first 1,000 days: pregnancy, infancy and toddlerhood.

But to what extent could we sway growth and neurodevelopment? That is, are they influenced mostly by genes and hereditary factors (nature), or by environmental variables (nurture)? This is an "old age" debate still opened today.

Ethnic background could be regarded as primary factor in determining biological differences, yet recent studies show that most of genetic variation occurs within populations: differences between ethnic groups are minor compared to differences among people overall, because the course of human migration is too recent to establish subspecies features [1, 2].

The International Consortium of INTERGROWTH-21st researchers recently evaluated 1,307 healthy 2-year-old children of urban, well-nourished, educated mothers enrolled in early pregnancy in Brazil, India, Italy, Kenya and the UK, and demonstrated that attainment of neurodevelopmental milestones (relating to cognition, language ability and motor skills) is similar among children across diverse geographical and cultural settings: 10% of the variability is based on the child's genes (nature), while the rest is environment (nurture) [3].

Implications on global health and social policies are evident, and INTERGROWTH-21st Project has created new international growth standards for fetuses, newborns and children, which perfectly match, after 6 months of age, the existing WHO Child Growth Standards: INTERGROWTH-21st Charts could be considered as instruments to guide and monitor interventions aimed to improve the well-being of mothers and infants at a global level, to narrow the gap between high- and low-income countries [4, 5].

REFERENCES

[1] Stepanov VA. Genomes, Populations and Diseases: Ethnic Genomics and Personalized Medicine. Acta Naturae. 2010;2:15-30.

[2] Rosenberg NA, Kang JT. Genetic Diversity and Societally Important Disparities. Genetics. 2015;201:1-12.

[3] Villar J, Fernandes M, Purwar M, Staines-Urias E, Di Nicola P, Cheikh Ismail L, Ochieng R, Barros F, Albernaz E, Victora C, Kunnawar N, Temple S, Giuliani F, Sandelis T, Carvalho M, Ohuma E, Jaffer Y, Noble A, Gravett M, Pang R, Lambert A, Bertino E, Papageorghiou A, Garza C, Stein A, Bhutta Z, Kennedy S. Neurodevelopmental milestones and associated behaviours are similar among healthy children across diverse geographical locations. Nat Commun. 2019;10(1):511.

[4] Villar J, Cheikh Ismal L, Victora C, Ohuma, EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble A, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384:857-68.

[5] Villar J, Giuliani F, Bhutta ZA, Bertino E, Ohuma EO, Cheikh Ismail L, Barros FC, Altman DG, Victora C, Noble A, Gravett MG, Purwar M, Pang R, Lambert A, Papageorghiou AT, Ochieng R, Jaffer YA, Kennedy SH. Postnatal growth standards for preterm infants: the Preterm Postnatal Follow-up Study of the INTERGROWTH-21st Project. Lancet Glob Health. 2015;3:e681-91.

LECT 11

OMICS IN AUTISM

M. Mussap

Department of Surgery, University of Cagliari, Cagliari, Italy

Autism is a major psychiatric disorder characterized by a number of abnormalities, including repetitive behaviors, failure in speech and in non-oral communication, deficit in social responsiveness with restricted interests. Additional traits include sensory modulatory dysfunction, varying levels of cognition and

motor disturbances, and poor eye contact. Recently, the term autism has been replaced by an umbrella term, autism spectrum disorder (ASD), embracing a wide range of behavioral, communication, and social disorders, Asperger's syndrome, and other related conditions. Moreover, children with ASD have an excess of minor physical anomalies, which are defined as morphological deviations present in less than 5% of the population. Unfortunately, no one knows for sure and definitively what causes autism. The prevalence of ASD has shown an extraordinary increase over time worldwide, documented both by data from the World Health Organization (WHO) and data obtained from systematic reviews and public surveys. WHO estimated 0.76% of the world's children with ASD in 2010; similar data (0.70%) were reported in 2017 by Lyall et al., even though epidemiological estimates can considerably vary by demographic factors, namely ethnicity and socioeconomic status, as well as diagnostic criteria. In the United States, a very recent survey performed in 11 states on children aged 8 years assessed an overall prevalence of 16.8 autistic children every 1,000 non-ASD children (equal to 1 child every 59), with a higher prevalence in boys (26.6 per 1,000) than in girls (6.6 per 1,000). Worldwide, autism affects 2 to 3 times more males than females. ASD develops from the interplay between a multitude of factors: genetics, epigenetics, environment, socioeconomic status, maternal and neonatal infections, prenatal nutrients (i.e. folic acid), immune system, gut microbiota composition, maternal exposure to potentially toxic drugs (e.g. thalidomide), environmental toxicants, and infant feeding (breastfeeding or formula feeding). Genetic etiology ranges from identifiable monogenic syndromes to large chromosome imbalances. Chromosomal microarray analysis (CMA) is recommended as the first-tier genetic test for individuals with ASD with a yield ranging from 7.0% to 9.0%. Whole-exome sequencing (WES) on research cohorts of individuals with ASD have highlighted sequence-level *de novo* mutations in the etiology of ASD. Therefore, the role of genetics cannot be dissociated from the context of epigenetic mechanisms and specific interactions. Despite a worldwide agreement on the urgent need for a timely identification of ASD as early in life as possible, most children with ASD are diagnosed far too late. The delay in diagnosis hampers initiating effective measures for managing cognitive impairment and adopting educational training both for parents and preschool staff. Despite this wholly unsatisfactory scenario, encouraging perspectives are emerging from new insights into non-genetic factors involved in the origin of ASD and from advanced diagnostic tools, namely metabolomics. Metabolomics is the study of the small molecules, namely metabolites, contained in body fluids as well as in human cells, tissues or organs. Metabolites are involved in primary and intermediary metabolism. The Metabolomics Society defined metabolomics as "the study of metabolic changes". The term "metabolomics" is equivalent to metabolite target analysis, metabolite profiling, metabolic fingerprinting, metabolic profiling. Metabolomics provides a functional readout of changes determined by genetic blueprint regulation, protein abundance and modification, and environmental influence. Analysis of published data from the literature shows that the main metabolic perturbations recognized in autistic subjects consist of: high concentrations of mammalian-microbial co-metabolites; nicotinic-acid metabolism; production of cellular energy due to mitochondrial dysfunction; antioxidant status; amino acid metabolism. Some of the most relevant factors modulating gene expression by epigenetic mechanisms are fetal/neonatal gut colonization and dysbiosis. There is a large worldwide consensus on the role of an intact gut microbiota in shaping brain neurochemistry and emotional behavior. Gastrointestinal flora can be considerably altered by several environmental factors, such as: maternal bacterial flora and diet; perinatal antimicrobial use; mode of birth (spontaneous delivery or caesarian section); type of feeding; dietary intake. Notably, psychological stress during pregnancy and at birth can induce changes in the composition of gastrointestinal microbial flora. Gut dysbiosis raises abnormal metabolites and their escape into the bloodstream; most of them are neurotropic. This means that they rapidly pass the blood brain barrier and then could act as neurotransmitters or could modify biochemical pathways within the central nervous system, altering neurotransmitters synthesis and release. In conclusion, alterations in the composition and metabolic products of the gut microbiome have been implicated in the complex pathophysiology of ASD and these alterations can be easily revealed by changes in urine metabolome of newborns. The early identification of risk

factors for ASD can improve children outcome with early therapeutic interventions such as gut microbiota transplantation. This implies a drastic reduction in the severity of ASD symptoms and, in turn, a better socio-relational outcome and a considerable saving of money.

REFERENCES

- American Psychiatric Association, American Psychiatric Association DSM-5 Task Force. Diagnostic and Statistical Manual of Mental Disorders: DSM-5, 5th ed. Washington, DC: American Psychiatric Publishing, 2013.
- Harris J. Leo Kanner and autism: a 75-year perspective. Int Rev Psychiatry. 2018;30:3-17.
- Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med. 2015;45:601-13.
- Lyall K, Croen L, Daniels J, Fallin DM, Ladd-Acosta C, Lee BK, Park BY, Snyder NW, Schendel D, Volk H, Windham GC, Newschaffer C. The Changing Epidemiology of Autism Spectrum Disorders. Annu Rev Public Health. 2017;38:81-102.
- Mussap M, Noto A, Fanos V. Metabolomics of autism spectrum disorders: early insights regarding mammalian-microbial cometabolites. Expert Rev Mol Diagn. 2016;16:869-81.
- Mussap M, Moretti C, Noto A, Fanos V. Metabolomics and Autism. In: Selected lectures 12th International Workshop on Neonatology. J Pediatr Neonat Individual Med. 2016;5(2):e050246.
- Fanos V, Noto A, Mussap M. The juniper bush of autism spectrum disorder (ASD): Metabolomics, microbiomics, acetaminophen. What else? J Pediatr Neonat Individ Med. 2018;7(2):e070205.
- Noto A, Fanos V, Barberini L, Grapov D, Fattuoni C, Zaffanello M, Casanova A, Fenu G, De Giacomo A, De Angelis M, Moretti C, Papoff P, Ditonno R, Francavilla R. The urinary metabolomics profile of an Italian autistic children population and their unaffected siblings. J Matern Fetal Neonatal Med. 2014;27(Suppl 2):46-52.
- Lussu M, Noto A, Masili A, Rinaldi AC, Dessì A, De Angelis M, De Giacomo A, Fanos V, Atzori L, Francavilla R. The urinary ^{1}H-NMR metabolomics profile of an Italian autistic children population and their unaffected siblings. Autism Res. 2017;10:1058-66.

LECT 12

PLACENTA AND NEONATAL INFECTION: INTRIGUING CONNECTIONS

G. Faa[1], S. Angioni[2], V. Vallascas[1], M. Moi[1], F. Ledda[1], P. Van Eyken[3], D. Fanni[1], C. Gerosa[1]

[1]Division of Pathology, Department of Medical Sciences and Public Health, AOU Cagliari, University of Cagliari, Cagliari, Italy

[2]Division of Obstetrics and Gynecology, Department of Surgical Sciences, AOU Cagliari, University of Cagliari, Cagliari, Italy

[3]Department of Pathology, Ziekenhuis Oost Limburg, Genk, Belgium

Chorioamnionitis is a common morbidity affecting 2-5% of all pregnancies. Conflicting results have been reported regarding the impact of chorioamnionitis on the clinical outcome of newborns and, in particular, of preterm infants. The report of histological chorioamnionitis in preterms was indicated as a risk factor for cerebral palsy and for an increased incidence of preterm labor, low birth weight and mortality rate. Moreover, chorioamnionitis has been suggested to have consequences later in life, with poorer mental and motor development in infancy [1]. Histological chorioamnionitis was not found to be associated with intraventricular hemorrhage, nor with white matter injury. With the aim to shed light on these conflicting data, some authors underlined the necessity to better specify the type of chorioamnionitis: i) subclinical, i.e. histological in the absence of clinical evidences; ii) clinical, without significant histological changes; iii) clinical with histological evidence of chorioamnionitis. The last subtype has been subdivided into two variants: a) with fetal vasculitis and b) without involvement of fetal vessels. Thanks to this better pathologic characterization, histologic chorioamnionitis with fetal vasculitis was associated with increased risk of premature rupture of membranes and preterm birth [2]. In another study, histological chorioamnionitis was reported to be associated with prematurity (< 34 weeks of gestation), fetal distress and early onset sepsis. In very preterm infants, both clinical and histological chorioamnionitis were associated with the insurgence of bronchopulmonary dysplasia. Cardiotocography features of chorioamnionitis were found to be a risk factor for a higher rate of Neonatal Intensive Care Unit admission and adverse perinatal outcome. Histologic chorioamnionitis has been hypothesized to have relevant consequences on postnatal immune responses, with higher susceptibility to infections not restricted to the perinatal period, but even in infancy and adulthood [3].

All these data taken together, the histological analysis of placenta appears mandatory in all pregnancies and, in particular, in all preterm deliveries. The histological analysis of the placenta might give neonatologists important prognostic data on the clinical outcome of preterm infants, eventually solving the placenta enigma: why are so many relevant pieces of information only rarely utilized in clinical practice?

REFERENCES

[1] Xiao D, Zhu T, Qu Y, Huang Q, Li X, Mu D. Maternal chorioamnionitis and neurodevelopmental outcomes in preterm and bery preterm neonates: a meta-analysis. PlosOne. 2018;13(12):e0208302.

[2] Palmsten K, Nelson KK, Laurent LC, Park S, Chambers CD, Parast MM. Subclinical and clinical chorioamnionitis, fetal vasculitis and risk for preterm birth: a cohort study. Placenta. 2018;67:54-60.
[3] Sabic D, Koenig JM. A perfect storm: fetal inflammation and the developing immune system. Pediatr Res. 2020;87:319-26.

LECT 13

METABOLOMICS AND HUMAN MILK

V. Fanos[1,2], F. Bardanzellu[1], M. Puddu[2]

[1]*Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy*
[2]*Department of Surgery, University of Cagliari, Cagliari, Italy*

Human breast milk (HBM) is considered a magic biofluid from ancient times and is the gold standard food for preterm infants. In addition to the classical nutrients (proteins, carbohydrates, lipids, vitamins, and minerals), milk contains several bioactive components, including growth factors, anti-microbial components, and stem cells, which can integrate *in vivo* in the tissues (brain, liver, thymus, kidneys) of the neonate and differentiate in mature cells (for example in the brain, they transform in neurons, astrocytes, and oligodendrocytes). The application of metabolomics to HBM is a relatively new and exciting field, offering a potent approach to investigate the complex relationships between nutrition and infant's health (nutrimetabolomics). Different investigations evidenced the power of metabolomics as a key technology to improve breast milk's biochemical heterogeneity. We published the first paper on HBM, the first review on metabolomics in HBM, the first paper on fortifiers and organic milk. We report our results of HBM metabolome regarding the so-called "secretory phenotype" [1] and our previous studies on the metabolomics of milk of mothers with great obstetrical syndromes (preeclampsia, intrauterine growth restriction, gestational diabetes) and obese mothers.

These conditions are associated with altered HBM composition, albeit via unclear mechanisms. For example, in women with gestational diabetes mellitus, the reduction of several metabolites involved in glucose and lipid metabolism could have potentially significant implications for brain function and cardiometabolic homeostasis postnatally in the developing child.

Thus, a deficiency of metabolites in the HBM of mothers with gestational diabetes mellitus, preeclampsia, and IUGR may also shape after birth unfavorable metabolic imprinting in a developing child, according to the perinatal period [2].

The positive or negative influence of maternal overweight and obesity on the offspring, potentially exerted by breastfeeding, should be analyzed in close correlation with maternal age, genetic and epigenetic factors, including diet, and taking into account the interactions occurring between HBM metabolites and lactobiome [3]. Our results can lead to the comprehensive description of such biofluid and the related effects on breastfed subjects, potentially highlighting the personalized needs of HBM supplementation and/or short- and long-term prevention strategies to optimize offspring health.

REFERENCES

[1] Dessì A, Briana D, Corbu S, Gavrili S, Cesare Marincola F, Georgantzi S, Pintus R, Fanos V, Malamitsi-Puchner A. Metabolomics of Breast Milk: The Importance of Phenotypes. Metabolites. 2018;8(4):E79.
[2] Bardanzellu F, Puddu M, Peroni DG, Fanos V. The Human Breast Milk Metabolome in Overweight and Obese Mothers. Front Immunol. 2020;11:1533.
[3] Bardanzellu F, Puddu M, Fanos V. The Human Breast Milk Metabolome in Preeclampsia, Gestational Diabetes, and Intrauterine Growth Restriction: Implications for Child Growth and Development. J Pediatr. 2020;221:S20-8.