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Lectures

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FROM WOMB TO ADULTHOOD

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LECT 1

PLASTIC IN PLACENTA: WHAT IS IT? WHAT TO DO?

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In the last century, the global production of plastics has grown exponentially to reach over 350 million tons per year produced in the world, part of which ends up polluting the environment [1]. Microplastics (MPs) are defined as plastic particles smaller than 5 mm [2]. MPs are found everywear.

In experimental contexts cellular absorption, accumulation of MPs and nanoplastics have been demonstrated, in animals and human tissues [3-6]. Within biological tissue, plastic particles can cause a foreign body reaction and trigger local immunoreactions [7].

MPs can act as a carrier for other chemicals, such as environmental pollutants or plastic additives, which can leak and cause exposure to hazardous substances [5-8].

We found MPs in human placenta [9] and in human breastmilk [10]. MPs were found also in meconium of newborns, even in higher concentrations than in adults' stool [11] and blood [12]. All this confirms that the exposure to MPs begins indeed in the earliest stages of human life. MPs interact with humans' placental cells; if they are capable to alter energy pathways, as they do in animal models, there could be numerous concerning consequences.

Our group also demonstrated and photographed, for the first time, the presence of MPs in the intracellular compartment of human placentas; we localized MPs and demonstrated the presence of important morphological and structural alterations of the cellular intracytoplasmic organelles associated with their presence [13].

Using variable pressure scanning electron microscopy (SEM) and transmission electron microscopy (TEM), the study demonstrated that MPs are within lipid membranes and can be easily confused with cell organelles such as lysosomes, peroxisomes, lipid droplets and multivesicular bodies; this amply demonstrates that Johann Wolfgang von Goethe (1749-1832) was right when he claimed that: "We only see what we know".

In all the observed samples, the stress of the endoplasmic reticulum is demonstrated, which is dilated (cribriform aspect of the syncytium trophoblast cells); there are many vesicles communicating with each other discreetly electrondense, with secretory material inside, covered by ribosomes and not (degranulation).

The presence of the alterations of the intracytoplasmic organelles, together with the presence of the MPs, in all the samples examined, is very important, since endoplasmic reticulum stress and mitochondrial dysfunction could play a decisive role in the progression of human non-transmissible diseases (NTDs). This gives rise to the hypothesis that environmental pollution from plastics is partially responsible for the epidemic of NTDs that characterizes the modern world [14].

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LECT 2

THE "PLACENTAL PARADOX": A PERPLEXING PHENOMENON IN THE FIELD OF PERINATAL PATHOLOGY. HOW TO SOLVE IT?

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One of the more perplexing phenomena in the field of perinatal pathology is represented by the so called "placental paradox", mainly due to the enigmatic reputation of this organ [1]. During the years, placenta has been defined as "the black box of gestation" or, alternatively, "the witness of the intrauterine life" [2]. In spite of these definitions, placenta remains one of the most poorly understood human organs, even though many of the inflammatory, immune-mediated and vascular pathologies occurring in the placenta have analogies in other human organs and tissues.

One of the most intriguing fields in the recent literature on placental pathology is represented by the attempts to correlate the most important placental pathology constellations with their clinical correlates, both in the newborns and in pregnant women. In particular, many studies have been focused on the gross and histological placental findings commonly associated with preeclampsia, intrauterine growth restriction, infection and preterm delivery. Lesions such as increased syncytial knots, villous agglutination and distal villous hypoplasia have been defined as signs consistent with maternal vascular malperfusion.

In these studies, the necessity to correlate placental pathology with the health status of the fetus and of the newborn has emerged as a key point for the solution of the "placental paradox".

Which are the main factors at the basis of this "paradox"? Which the solutions to bypass this block in the communications of placental data to perinatologists, in order to help them to better treat newborns?

The most intriguing problem, typical of the placenta, is represented by the frequent occurrence of pathological changes in placentas in physiological conditions, with normal outcome. Pathological changes suggestive for an acute or chronic maternal inflammatory response, including chorioamnionitis, and for an acute or chronic fetal inflammatory response, including chorionic vasculitis, have been described in variable percentages in term pregnancies with normal maternal and fetal outcome. The frequency of all acute placental inflammatory lesions in women with a normal outcome has been reported in 42% of at-term placentas [3]. Moreover, 78% of the placentas show lesions generally considered consistent with an acute or chronic inflammation or with maternal or fetal malperfusion, in the absence of any clinical correlate. On the other hand, in the same years, subtle pathological lesions such as massive perivillous deposition in at-term placentas, previously reported as a simple sign of at-term placenta, have been indicated as a pathological sign of maternal anti-fetal rejection [4].

With these findings taken together, given the discrepancies possibly existing between placental pathological changes and their clinical significance, the dialogue between gynecologists, perinatologists and pathologists appears mandatory in the interpretation of placental changes. Most placentas may show mild-moderate lesions consistent with vascular or inflammatory pathologies, in the absence of maternal or neonatal significant lesions. Given that the vast majority of acute histological chorion-amnionitis at term are nearly always noninfectious, caution should be taken, in the pathological diagnosis, when defining these lesions as "consistent with intra-amniotic infection" [5].

In order to bypass the "placental paradox", with the aim of better utilizing the placenta as a useful witness of gestation, the diagnostic process regarding placental pathology should change. Referring to the definition of the placenta as the black box, we suggest the accurate study of the placenta in cases of a "crash" of gestation: preterm delivery, intrauterine growth restriction, fever and other signs of neonatal infection. We suggest that the clinical questions should come to pathologists, from neonatologists and gynecologists. Then, dedicated pathologists will be able to give to clinicians relevant information, regarding the role of placenta in maternal and neonatal pathology related to placental deficiency. With this approach, the "pathological" diagnoses based only on histopathology, in the absence of any clinical pathology, will be avoided, reinforcing the dialogue between perinatologists and pathologists.

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LECT 3

PREVENTION IN PERINATOLOGY OF ALLERGIC DISEASE LATER IN LIFE

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The prevalence of allergic diseases is constantly increasing in Western countries as well as other non-communicable diseases. In recent decades, physicians have seen a marked increase in the prevalence of asthma, which is currently a public health problem. It has been hypothesized that this increase is also attributable to changes in the nutritional field already during the pregnancy phase. If the diet is characterized by a reduced intake of antioxidants, an increased ratio of omega-6:omega-3 fatty acids, vitamin D deficiency, we have an increased risk of developing allergic diseases in the newborn. Observational studies have reported the association between asthma and dietary deficiency of dietary antioxidants (vitamin E, vitamin C, carotenoids, selenium, polyphenols, fruit), as well as PUFA and vitamin D.

But let's not forget that the composition of the intestinal flora, the so-called microbiota, plays a central role in the post-natal development not only of the immune system but also of other organs and systems. In human milk the presence of elements such as oligosaccharides is an important factor that determines an intestinal flora in which *Bifidobacteria spp.* and *Lactobacilli spp.* are dominant. Breast milk is therefore also functional food, rich in elements that stimulate the immune system. Such early stimulation is critical to the development of the child's immune system. For this the microbiota and its formation in the newborn are essential: several factors contribute to direct the microbiota already in the uterus during pregnancy [1, 2].

Early supplementation with probiotics and vitamin D can influence the immune response by increasing the possible response towards a tolerance to antigens that come from the outside world.

Adequate levels of vitamin D in pregnant women therefore seem to offer prospects in terms of prevention of recurrent infections of the respiratory system and prevention of asthma and wheezing in children. Moreover, it is still very controversial and debated whether prenatal intake of vitamin D and/or antioxidants can exert a protective effect on the development of wheezing and asthma. Most of the data that investigated a possible link between these elements and vitamins and asthma derive from association studies in the population, where low levels of intake or serum levels correspond to a higher incidence of the disease. Supplementation data is more controversial. Many of the studies that have tested various factors subject to supplementation show positive and promising results; however, these are often very heterogeneous studies in terms of population, timing and dosage of intake [3, 4]. This does not allow, even to systematic reviews, to draw unambiguous conclusions [5]. It is clear, therefore, that while further controlled studies are needed to clarify the role of vitamin D and antioxidants in preventing the development of asthma and allergic diseases, from a practical point of view we also have promising indications on the rationale for use

in supplementation. for the prevention and control of these pathologies.

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LECT 4

NUTRITION AND FOOD MODELS FOR GROWTH AND DEVELOPMENT IN INFANCY AND CHILDHOOD

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> *"If you can't be a pine at the top of the hill, be a shrub in the valley. Be the best little shrub on the side of the hill. Be a bush if you can't be a tree. If you can't be a highway, just be a trail. If you can't be a sun, be a star. For it isn't by size that you win or fail. Be the best of whatever you are".*
>
> Martin Luther King

Nutrition is a science studying the relationship between diet and the health or disease of the human being. Hence, the choice of food introduction undoubtedly represents the first phase of a much more complex function of our body.

The existence of a link between food and health from the prenatal stage and the development of some diseases has been known since ancient times. Lately, the feeding of children, particularly in the neonatal period and during infancy, has undergone a radical evolution, both in research and clinical practice [1].

Although most of the studies conducted so far and those currently ongoing aim to clarify many of the clinical and evolutionary aspects of nutrition, many of the adopted nutritional practices still have cultural bases linked to the geographical and environmental contexts.

In both term and preterm infants, all the new findings in this field start from mother's milk, from a perspective of research, evolution and innovation. Milk can be considered "alive" food, and it has driven research providing a model which is the goal to reach for formula milk. Exclusive and prolonged breastfeeding is currently recommended as the best practice for feeding infants until 24 months of age.

Especially in the most preterm infants, the survival rate increase has then raised the question of whether nutrition aspects might have an influence on the short- and long-term clinical outcomes. Like other aspects of the care of these vulnerable babies, nutritional science has undergone several changes over time, showing even deeper attention of caregivers to feeding. Given the importance of human milk in improving neonatal outcomes, donor human milk has been introduced into routine clinical practice in many Neonatal Units. The spread of donor human milk banks is currently promoted in order to reduce the incidence of necrotizing enterocolitis and other complications of extreme prematurity. This new attitude has also favored a new view of nutrition, now considered able to prevent morbidities in the later stage of life and morbidities in later stages of childhood, both regarding growth and neurocognitive development. The velocity growth rate is currently under great debate, given conflicting evidence on how much and how fast extremely premature infants must be fed and grow. In animal models, the evidence regarding the implication of specific early diets on the so-called "programming" is surprising [2]. In humans, these effects seem to be present as well [3]. In fact, nutrition in the early stages of life has shown an impact during adult life, with effects mainly on the risk of cardiovascular disease, bone metabolism and cognitive functions [4].

The nutritional path is therefore a "continuum" from prenatal stage to childhood, adolescence and also adulthood, and is part of a comprehensive approach. In our view, this is currently the frontier of developmental nutrition, and future directions of research should focus not just on meeting the nutritional needs but also on providing the best nutrition to reach the individual potential in long-term health. Hence, the involvement of different professionals is mandatory.

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LECT 5

NUTRITION IN PRETERM INFANTS: CERTAINTIES AND DOUBTS

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Nutrition is one of the critical points in the care of premature infants. Its role is not limited just to promoting growth, but influences many other aspects of the postnatal period.

Quantitatively and qualitatively, adequate nutrition significantly promotes optimal brain maturation, improves respiratory function and immune response, reduces the risk of necrotizing enterocolitis, retinopathy of prematurity and bronchopulmonary dysplasia, and, not least, is associated with a shorter length of hospital stay.

Both parenteral and enteral nutrition accompany premature infants from birth to discharge and, unlike all other supports, represent the most constant and lasting intervention in neonatal intensive care. This should therefore represent one of the most solid and standardized aspects of neonatal care and instead it is one of the most controversial fields of neonatology. As a result, nutritional management, particularly of critically ill infants, varies widely and there are still doubts about which are the most effective and safe strategies.

In the past few years, we have pushed for very early and very rich parenteral nutrition, guided by the needs we thought were suitable for a fetus of the same gestational age. This aggressive choice has certainly improved growth outcomes but raised several doubts about safety because higher plasma amino acid concentrations, elevated BUN, metabolic acidosis, electrolytes abnormalities, etc., have often penalized the clinical course, especially in the most immature infants. It has been suggested that active nutritional support during the first week of life in extreme preterm infants and during the acute phase of critical illness may be even harmful and that permissive underfeeding improves outcomes, possibly by avoiding the induction of "nutri-traumas" such as hyperglycemia, suppressed autophagy, mitochondrial dysfunction, and refeeding syndrome.

The picture is made even more complex by the fact that the products we use for parenteral nutrition are not specific for infants but are the same ones that adults use. Among these, in particular for lipid mixtures, we do not yet know which are the most effective and safe.

The situation should be a little clearer on the enteral side but unfortunately also in this field the choices are difficult and not uniform.

After years of discussion we have become convinced that, even in the critically ill newborn, it is useful to start early enteral trophic feeding. But then we started wondering which milk to use, which feeding technique, when to start increasing, how quickly to increase, which criteria to use to reduce or suspend enteral intakes; all the answers we found were different and unsatisfactory.

Faced with such an uncertain picture, however, we have at least two certainties.

Firstly, mother milk, something more than just food, which in the absence of side effects guarantees countless short- and long-term benefits, from good feeding tolerance to better neurological development.

Secondly, standardization. What largely data suggest is that, irrespective of protocol, morbidity is reduced and growth is improved after the introduction of a standardized feeding protocol in the Neonatal Intensive Care Unit; that is, "when everybody is on the same page outcome improves".

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LECT 6

DONKEY MILK: A REVOLUTION IN HUMAN NUTRITION SINCE NEONATAL AGE

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Donkey has had a special place next to man since about 10,000 years ago, when it became a domesticated animal. Its history is linked to the human one, so much that it is mentioned in literature, religious books, and mythological poems. Donkey milk, in particular, played a leading role in ancient times, and today it is making a great comeback as a functional food for human nutrition of the 3rd millennium. Its first appearance in history was as a cosmetic of excellence: Cleopatra, Poppea, Messalina, and Paolina Bonaparte used it to preserve beauty and nutrition of their skin.

The alimentary role of donkey milk has also been known since ancient times: Herodotus and Hippocrates, in the 5th and 4th centuries BC, described its nutritional and medicinal virtues. Pliny the Elder, who lived during the Roman Empire period, widely described health benefits of donkey milk in his "*Naturalis Historia*".

During the Renaissance, donkey milk was studied for the first time with a scientific eye: the famous French naturalist Georges-Louis Leclerc (18th century) emphasized the healthy role of donkey milk in his "*Histoire Naturelle*".

During the 19th century, in Europe, *asinerias* started to arise to fulfill the request of donkey milk for both the bourgeoises – who consumed it regularly – and the low-income families – who reserved it to sick infants or elders.

Throughout the 20th century and until after the First World War, donkey milk was used as a substitute for breast milk; with the increasing industrialization and the war, however, it became much more difficult to find donkeys that could provide enough milk for the practice to remain in common use.

In the last decades, scientific community has re-experienced the value of donkey milk in human nutrition: in effect, its "competitor" – that is, cow milk – has a macro- and micronutrients composition less similar to human milk. Donkey milk is particularly suitable for people affected by allergy to cow's milk protein because of its clinical tolerance and nutritional adequacy, associated to the low levels of caseins and other proteins with high immunogenic power, and to a good palatability. Moreover, donkey milk has a good influence in regulating intestinal microflora, and it contains good quantitative of lysozyme and lactoferrin, known

for their antimicrobial activity. Also sialylated oligosaccharides – which have an anti-infective role and could stimulate newborn's immune system – are present in donkey milk in higher quantities than in cow milk.

Thanks to the percentage of omega-3 fatty acids contained in donkey milk, it is possible to state that this food could represent an instrument of prevention for cardiovascular diseases. Recent works hypothesize a role of donkey milk even in the therapy of Crohn's disease, and as an anticancer adjuvant.

Bearing in mind the above-mentioned properties of donkey milk, it is possible to consider that it could be suitable to produce a human milk fortifier, to feed preterm infants in the Neonatal Intensive Care Units (NICUs). Our research group has therefore created a novel donkey milk-derived fortifier (DMF), and randomized controlled trials have been made to compare DMF with the classic bovine milk-derived fortifier (BMF): results of the studies demonstrated that DMF could improve feeding tolerance and reduce gastroesophageal reflux episodes in preterm infants compared to BMF, with similar auxological outcomes when infants have been discharged from NICUs [1, 2]. Moreover, other studies demonstrated no differences between DMF and BMF regarding auxological and neurodevelopmental outcomes at 24 months of age [3, 4].

Rising scientific knowledge in donkey milk properties allow us to state, in agreement with a recent *The Telegraph* article, that donkey milk could be "the next big thing" in children nutrition.

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LECT 7

OBESITY FROM THE FETUS TO THE ADULT: STATE OF THE ART

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According to estimates of the World Health Organization for 2016, a respective 40% and 13% of the global population presented overweight and obesity. This steady increase observed in worldwide obesity rates during the past decades has led to the creation and establishment of a global obesity epidemic – globesity [1] – constituting an existent public health emergency. In this context, unveiling the many aspects hidden behind the etiology of obesity, starting with the role of endometrial life and the potential interplay with genetic and environmental factors in later-on obesity onset, is now deemed more vital than ever.

According to the Developmental Origins of Health and Disease (DOHaD) approach, the origins of various types of adult disease can be traced back to endometrial life, with nutrition throughout all stages of endometrial and early life to have been found associated with different birth phenotypes, which are, in turn, related to environmental adaptations during infanthood and childhood, and, even, metabolic abnormalities in adulthood [2]. For example, undernutrition during gestation was shown to significantly and permanently affect the fetus' body function and metabolic regulations in a way that was associated to the manifestation of later-on metabolic disfunction and cardiovascular problems [3].

Obesity, in itself, is a multifactorial disorder, in its core determined by factors of genetic makeup, cardiometabolic profile (i.e. glucose and lipid indices, metabolomic biomarkers and types of gut microbiota strains), lifestyle habits (i.e. smoking, dietary habits, physical activity regime, etc.) and environmental parameters (geographic and contextual determinants). The genetic architecture of increased body weight has been the subject of many genome-wide association studies (GWAS) during the past years, with significant findings putting genetics to the forefront of obesity etiology [4] (i.e. relation between the *FTO* gene and increased weight) and allowing for the development of approaches using individualization to effectively prevent weight gain. However, as obesity for an individual of any age is

determined by a variety of factors, its onset heavily relies on the interplay between genetic liability, circumstances surrounding birth and early-life and the impact of the current obesogenic environment. In that regard, current evidence suggests that the maternal obesogenic environment has been indeed shown to provoke epigenetic modifications related to the fetus' metabolic pathways, namely the expression of fetal umbilical cord miRNAs and the melanocortin 4 receptor (*MC4R*) gene, in turn related to gestational diabetes and later-on predisposition for increased body weight, type 2 diabetes and different phenotypes of eating behavior during childhood and early adulthood.

With current findings on obesity dictating the vitality of early life determinants on both the onset and the severity of childhood and adult increased weight, the reciprocal interaction between genetic predisposition and conditions surrounding the endometrial life are being brought to the center of our attention. Shedding a light on this vice-versa relationship will not only allow for a deeper understanding of obesity origins, but also broaden the horizon for the development of new preventive strategies consisting of individualized obesity treatment at its very beginning.

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LECT 8

NEONATAL ASPHYXIA: HYPOTHERMIA AND MELATONIN

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Hypoxic ischemic encephalopathy (HIE) is a cerebral injury resulting from inadequate blood flow and oxygen to the brain. HIE affects approximately 2/1,000 live births and is associated with a high risk of lifelong morbidity and mortality [1].

The HIE-mediated damage occurs through three different phases. After a few minutes from the hypoxic ischemic insult, a primary energy failure, hypoxic depolarization, acidosis, adenosine triphosphate (ATP) depletion, increased intracellular Ca^{2+} levels, and cell death feature the first phase of HIE. After hours/days (6-15 hours), starts the second phase or latent period of HIE, characterised by apoptotic cascade, secondary inflammation and recovery from oxidative stress. All these events can result in a damaged tissue resolution or the onset of a secondary energy failure. The latter is characterised by increased caspase activity, ATP depletion, inflammation, microglia activation, and cell death. All these events open the way to tertiary brain damage (tertiary phase), leading to impaired neurogenesis and synaptogenesis, arrest of axonal growth and oligodendrocyte maturation, thus, resulting in adverse long-term outcomes.

Therapeutic hypothermia is the established, standard treatment for moderate-to-severe HIE as it suppresses a broad range of potential injurious factors [1]. During the latency and secondary energy failure periods, hypothermia is able to induce a reduction in brain energy utilization, apoptosis, and release of excitatory neurotransmitters, free radicals, and cytokine. Nevertheless, therapeutic hypothermia is not effective in half of the cases, and it protects whether it started as soon as possible after hypoxia-ischemia [1]. Accordingly, several putative neuroprotective agents are currently investigated to improve HIE's short- and long-term outcomes. In this regard, researchers look to melatonin, an endogenously produced indolamine mainly released by the pineal gland, as a potential treatment for HIE, also thanks to its neuroendocrine, neuro-immunological and antioxidant properties. Specifically, melatonin, both in a receptor-dependent and receptor-independent manner, scavenges free radicals, induces antioxidant enzymes and chelation of transition metals resulting in a significant reduction in cellular apoptosis and tissue loss, and preserving the function of the injured tissue. In their systematic review and meta-analysis, Ahmed et al. [2] reported that melatonin administration in newborns with HIE was associated with an improvement in brain injury as assessed by electroencephalogram (EEG) and magnetic resonance imaging.

Recently, there is emerging evidence that therapeutic strategies able to act through complementary mechanisms to hypothermia, such as melatonin supplementation, may improve outcomes. Accordingly, randomized clinical trials evaluated melatonin as an adjuvant to hypothermia in treating HIE [3, 4]. Authors revealed that the group receiving melatonin and hypothermia experienced an improvement in EEG, white matter injury, mortality rate and long-term neurological abnormalities [3-5]. However, these findings were not confirmed by other studies, which were also affected by several biases. Thus, despite the available clinical evidence for melatonin as a potential therapy for HIE, larger and well-designed clinical trials are urgently needed to confirm the neuroprotective role of melatonin in combination with therapeutic hypothermia in optimizing outcomes of HIE as well as data on administration timing, dosage, and treatment duration of melatonin supplementation.

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LECT 9

RESPIRATORY SYNCITIAL VIRUS INFECTION: NOT ONLY PRETERM INFANTS

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Respiratory syncytial virus (RSV) infection is a seasonal disease responsible for a huge burden on healthcare systems worldwide. Manifestations of RSV disease in children range from mild upper respiratory tract infections to severe lover respiratory tract infections (LRTIs), including pneumonia or bronchiolitis, which can lead to hospitalization and serious complications such as respiratory failure [1].

RSV is a seasonal virus, characterized by variable epidemiology, depending on geographic area and climate. In the Northern Hemisphere, virus diffusion generally occurs from October/November to March/April, with peak incidence in January/February. However, in the last two years, non-pharmaceutical intervention (NPI) measures aimed at controlling the spread of SARS-CoV-2 have deeply affected the epidemiology and seasonality of RSV worldwide [2].

Approximately 30-40% of children experiencing RSV-associated bronchiolitis in the first year of life subsequently develop recurrent bronchospasm and/or asthma. It is still not clear whether these children have a genetic predisposition to develop asthma or whether there is a direct damage from RSV that induces changes in the airways. This induction might include chronic epithelial and airway reactivity changes in the still developing infant lung, lung injury, and immunomodulatory changes [3].

Certain high-risk groups, like premature infants, infants with underlying medical conditions such as chronic lung disease of the premature (CLDP) or bronchopulmonary dysplasia (BPD), haemodynamically significant congenital heart disease (hsCHD), immunocompromised conditions, neurologic and neuromuscular disease (NMD), are prone to severe RSV-related illness with higher morbidity and mortality rates [4].

Premature infants are disproportionately affected by RSV, and have a higher risk of worse outcomes due to interrupted lung development and reduced mother-transmitted antibodies.

Although there are no recommended treatments or approved vaccines for RSV, passive immunization with the monoclonal antibody palivizumab has been shown to reduce RSV-related hospitalizations and is currently indicated to prevent severe lower respiratory tract disease caused by RSV in certain categories of high-risk children aged < 2 years [5].

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LECT 10

SEVERE BRONCHIOLITIS AS A CAUSE OF ARDS: PHYSIOPATOLOGY AND MANAGEMENT

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Bronchiolitis is one of the most frequent acute diseases of the lower respiratory tract in infants worldwide, and respiratory syncytial virus remains the most common and aggressive viral disease. The course of the disease is usually benign, but its severity may change by evolving into parenchymal disease. In the more severe cases, its clinical and radiological characteristics may be consistent with acute respiratory distress syndrome (ARDS). Management of these cases includes admission to pediatric intensive care and invasive mechanical ventilation [1]. In this instance, the chest X-ray shows bilateral alveolar consolidation, and lung function tests reveal that the elastic component of the respiratory system rather than airway resistance is the main determinant of the super-imposed work of breathing (WOB).

ARDS is a life-threatening respiratory failure characterized by lung tissue inflammation, increased permeability to proteins across the pulmonary endothelial and epithelial barriers, and is described as a restrictive disease with reduced lung compliance caused by loss of surfactant function, atelectatic lung regions and accumulation of interstitial/alveolar plasma leakage [1].

In 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) developed a specific definition of pediatric ARDS (PARDS) in order to overcome the limitations of various definitions, which were primarily designed and validated for adults [2]. The variables considered for the diagnosis of PARDS are:

- timing: within 1 week of a known clinical insult (direct or indirect);
- lung imaging: diffuse, bilateral, and irregular opacities or infiltrates, or complete opacification of the lungs;
- origin of oedema: excluded hydrostatic oedema (cardiac failure or fluid overload);
- oxygenation deficit: defined by oxygenation index (OI) or by oxygenation saturation index (OSI) if arterial blood gas analysis values are not available.

Over the past decades, pathology and computed tomography scans of ARDS lungs of adult patients have demonstrated uneven distribution of aerated areas and dense consolidated regions, with the remaining alveolar surface for gas exchange largely reduced. Gattinoni defined this condition as “baby lung” because the alveolar surface available for gas-exchange has the lung-dimensions of that of a 5-6-year-old child [3]. The functioning part of this lung is considered to be as small as 25% of the physiological volume. During mechanical ventilation, lung inhomogeneity is therefore characterized by the presence of three different areas:

- the aerated ventral areas (baby lung), which have the highest compliance and may easily become overdistended (volutrauma);
- the intermediate areas of collapse, characterized by reversible lung closure, which are prone to cyclic recruitment-derecruitment (atelectrauma);
- the consolidated and atelectatic areas, which usually affect bilateral dependent zones, and are characterized by irreversible lung closure.

Mechanical ventilation with a lung-protective strategy is the cornerstone of the treatment. The essential concept is the "open lung strategy", characterized by the following rules:

- Vt in the range from 3 to 6 mL/kg per IBW for those with reduced respiratory compliance, and closer to the expected or normal physiological range (5-8 mL/kg per IBW) for those with better preserved respiratory compliance;
- plateau pressure ≤ 28-30 cmH_2O;
- alveolar recruitment with "best PEEP" (5-15 cmH_2O) in order to facilitate the uniform distribution of Vt and maintain FRC above closing volumes. PEEP should be set according to an oxygenation target so that combinations of its level and FiO_2 are increased or decreased in tandem as hypoxemia worsens or improves.

If adequate oxygenation and ventilation cannot be met with the lung protective strategy, the following therapeutic tools should be considered: exogenous surfactant, inhaled nitric oxide (iNO), high frequency oscillatory ventilation (HFOV), prone position and neuromuscular blocking agents (NMBA).

In PARDS, the effects of surfactant used with the same strategy employed in premature infants are often only transient because it is rapidly inactivated, and repeated administrations are frequently needed for the treatment of severe respiratory failure [4]. BAL with saline-diluted surfactant is another mode of supplementation that may have greater efficacy since the endogenous surfactant pool is restored simultaneously with the removal of inhibitors and toxic agents from the alveoli [5].

In conclusion, neonatologists and pediatric intensivists treating these patients must be aware of the remarkable differences in pathophysiology and treatment between neonatal respiratory distress syndrome (RDS) and PARDS caused by severe bronchiolitis.

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LECT 11

THE SOUND OF SILENCE IN THE NEONATAL INTENSIVE CARE UNIT: SPEECH AND MUSIC INSIDE AN INCUBATOR

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While predominantly low frequency noises below 500 Hz are transmitted to the fetus *in utero*, the extrauterine hearing exposure of a preterm infant in the Neonatal Intensive Care Unit (NICU) consists of multiple high frequency noises exceeding recommended values for neonates by far. This has been documented in several studies and has been associated with adverse outcomes such as stress responses, sleep deprivation and hearing difficulties later on.

In order to understand the dynamics of sound within an incubator and give clinicians an idea about "what can be heard inside the box", we performed audio recordings within an incubator in the Pediatric Simulation Center of the Medical University Vienna. We found a protective effect of the incubator from mid- and high-frequency noises, whereas frequencies below 250 Hz were boostered and actually louder inside than outside the box. Most concerningly, we found high interior noise levels from respiratory support, masking against any other source of noise or sound (such as mothers voice or singing) even in low-flow conditions [1].

Interestingly, while ongoing exposure to unphysiologic noise is generally perceived to be harmful, the lack of physiologic acoustic stimuli in the NICU setting seems to be of less concern. However, children born preterm are at higher risk to develop language deficits and it has been shown that the amount of language exposure in the NICU correlates with language outcomes in preterm infants.

This was first published by Pineda et al., investigating the effect of open wards compared

to private rooms on the brain development of premature infants. The authors were able to demonstrate less mature aEEG cerebral maturation scores at term-equivalent age as well as lower Bayley III language scores at 2 years in infants nursed in private rooms and concluded that the differences in outcomes might be related to a relative sensory deprivation associated with private rooms [2].

In order to investigate the effect of prematurity on language development, we performed functional near-infrared spectroscopy (fNIRS) studies and investigated neural speech discrimination in preterm infants at term-equivalent age compared to full-term controls [3]. We showed that preterm infants cannot discriminate speech from non-speech as compared to term infants, pointing to an altered development of the functional network underlying language acquisition already at term age. In another fNIRS study of our group we could show a significant positive correlation between gestational age at birth and neural discrimination between forward and backward speech at term-equivalent age, with a significantly different pattern of response in infants born prior to or after 32 weeks of gestational age, indicating a critical threshold at around that time of gestation [4].

The presentation will focus on the dilemma of high levels of noise in the NICU but at the same time lack of meaningful acoustic input such as human language during a critical time for auditory brain development, rendering strategies to simply decrease noise problematic since they may cause auditory deprivation. Potential solutions of this conundrum with be discussed.

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LECT 12

THE MICROBIOME IN PERINATAL MEDICINE: A PROTAGONIST

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The pillars of the foundation of each individual are represented by strategic steps such as pregnancy, birth, breastfeeding and growth. Recent studies suggest that human bacterial colonization starts during fetal life. Thus, the previous paradigm of the "sterile womb" has not been confirmed. Placenta, amniotic fluid, cord blood and fetal tissues have each their own specific microbiota, influenced by maternal health and habits and having a decisive influence on pregnancy outcome and offspring outcome. In particular it is believed that prenatal microbiota educates the fetal immune system. The first thousand days from conception are of outstanding importance for all future health, which is equivalent to all future life (Perinatal Programming and Developmental Origins of Health and Disease). In this puzzle, the real protagonists are the pioneer bacteria, the ones that arrive first and colonize the body districts first, control the territory and never want to leave. It becomes difficult to replace them, for better or for worse. How to obtain the best microbiota? This is the identity card of the newborn: skinny grandparents, a healthy mother who has an uneventful pregnancy, a spontaneous birth at term, breastfeeding for 6 months. In this case the newborn will receive the microbes of the good beginning of life (*Lactobacilli spp.* and *Bifidobacteria spp.*), the "old friends" of the human beings. For example, in the case of a C-section, breast milk is a lifeline because it supplies the good bacteria, the same ones that the baby should have received from the maternal vagina in case of spontaneous birth. In fact, during the perinatal period, neonatal microbiota seems to be influenced by delivery mode, drug administration and many other conditions. Special attention must be reserved for early neonatal nutrition, because breastfeeding allows the transmission of a specific and unique lactobiome able to modulate and positively affect the neonatal gut microbiota. The physicians of the future will become actual microbiota engineers, manipulating in our favor the communities of bacteria we harbor. Already in the near future, it will be possible to

integrate and modulate our microbiota artificially, obtaining an individualized super-microbiota: we will become not super-humans, but "augmented" humans. Thus, the newborn of the future, the "augmented" newborn, can also be strengthened through a treatment of good bacteria administered to the future mother before conception, or to the pregnant mother or to the newborns themselves after birth, with positive effects for the whole life in terms of health. Pioneer bacteria are real pillars of health, that influence the whole life of each subject. In conclusion the perinatal microbiome is really a protagonist of our life.

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LECT 13

NEW AND OLD STRATEGIES TO PREVENT NEONATAL INFECTIONS

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Neonatal infections are a big challenge for neonatologists also in relation to their high incidence and rate of mortality and sequelae. Severe infections represent the main cause of neonatal mortality, accounting for > 1 million neonatal deaths worldwide every year [1]. Among newborns, very low birth weight and preterm infants show a greater risk, due to the deficiencies of the barriers in terms of skin and mucosal structures and an incomplete immune system. Malnutrition and dysbiosis as well as the invasive procedures and prolonged stay in Neonatal Intensive Care Units (NICUs) may increase the colonization and infections rate and related mortality. Clinical sepsis is the most frequent and dangerous spectrum due to a bacterial or mycotic infection. Localized infections, such as respiratory or urinary tract frequently may subsequently and suddenly assume the clinical spectrum of a generalized sepsis. The early or late onset of a sepsis in a newborn may be important to establish its mode of transmission: mother to infant during labor and delivery in the early onset and horizontal due to nosocomial transmission in the late ones. Both Gram-positive and Gram-negative bacteria may be found as responsible for neonatal infections. NGS analysis and metabolomic evaluations may be useful to the early diagnosis of the infections and to predict their evolution and destiny, although their introduction in the clinical practice activity is still low.

The most relevant approach to neonatal infections is prevention. Preventive strategies include an efficient management of pregnancies at high risk for premature delivery, also to identify those conditions with a prolonged rupture of the membranes. In addition, a strict policy to improve the cleaning the hands of medical and nursing staff in the NICUs is the most important instrument to reduce the rate on neonatal infections and sepsis. Minimization of the invasive procedures on newborns in the NICU, isolation and cohorting of affected newborns, adoption of antiseptic modalities in the management of central catheterization and parenteral nutrition, promotion of breastfeeding, use of the human milk from donors and collected within the bank structures are important tools in the perspective of a prevention of the neonatal infections. A good organization of the NICU to avoid overcrowding and understaffing is necessary to reduce neonatal infections and improve overall neonatal survival. Furthermore, we consider the epidemiological surveillance of the bacterial ecology within the NICUs as an efficient preventive measure of nosocomial infections. These data may be useful in view of a precocious diagnosis of neonatal sepsis due to multi-resistant drug bacteria, such as the MRSA (methicillin-resistant *S. aureus*) and other classes and strands of both Gram-positive and Gram-negative bacteria, such as the extended-spectrum beta-lactamase-producing *Escherichia coli* [2]. We may identify epidemic spread and outbreak of multi-resistant bacteria to adopt the useful methods to a minimization of the risk for high-risk newborns [3]. Neonatal Units are a high-risk area for the selection and transmission of multi-resistant organisms. Very few new antibiotics with activity against Gram-negative bacteria are under development, and no significantly new Gram-negative antibiotics will be available in the next future [4]. In this perspective, an antibiotic

stewardship policy to reduce the generalized use of broad-spectrum antibiotics, may be important also to reduce the circulation within and outside the NICU of these dangerous bacteria.

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LECT 14

NECROTIZING ENTEROCOLITIS: LOOKING TO OLD DATA WITH NEW EYES

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Necrotizing enterocolitis (NEC) remains one of the most devastating acquired diseases of prematurity. Although the incidence rate of NEC varies considerably globally between 1-10%, NEC consistently most commonly affects the very low and extremely low birth weight premature newborn (VLBW and ELBW, respectively) [1]. In progressive cases of NEC complicated by intestinal perforation or gangrene, mortality ranges between 30-40%. Survivors of NEC, face both short- and long-term morbidity including a significant risk of neurodevelopmental impairment [2]. Despite improvements in overall outcomes, NEC remains among the most common causes of acquired gastrointestinal disease and a leading cause of overall morbidity and mortality among preterm newborns.

Clinically, NEC is marked by the sudden onset of generalized signs of distress in a seemingly otherwise stable premature newborn and yet can rapidly progress to a fulminant course. The standard treatment for NEC remains the withdrawal of enteral feedings, the institution of broad-spectrum antibiotics, general physiologic support, and the surgical removal of irreversibly compromised intestine and colon. The hallmarks of clinical course and presentation, taken together outline a narrow diagnostic window and limited therapeutic options in support of full recovery. Thus, a focus on the development of effective prevention strategies based on a shared understanding of NEC is paramount.

Although the precise pathogenesis of NEC remains obscure, patterns of common features and relatively new biologic data on human infants with NEC has provided an opportunity to revisit the questions of NEC causality in the hopes of deriving new preventive strategies. NEC is a complex multifactorial disease involving a combination of 1) developmental immaturity of the intestine barrier, dysmotility and nutrient processing; 2) enteric inflammation and innate immunity activity associated with gut colonization marked by an abundance of potential pathogens of the phyla *Proteobacteria* (containing the *Enterobacteraceae* taxa); 3) clinical practice variables including enteral feeding, perinatal antibiotics, stooling patterns, and transfusions [3, 4].

Given recent findings suggesting an abnormal gut colonization pattern predominated by specific species of *Enterobacteriaceae* in premature newborns with NEC, a deeper understanding of measures linking microbes to the metabolic and inflammatory phenotype accompanying the dysbiotic gut of premature newborns that may precede and contribute to NEC onset are critically needed. Studies of microbiome assemblage in premature neonates have largely established a microbial signature of heightened risk among VLBW newborns [4]. It remains unknown the precise pathophysiologic link between the gut microbiome and the pathogenesis of NEC. Accordingly, we and others have developed a new metabolic hypothesis of NEC. This hypothesis holds that at the intersection of prematurity, enteral feedings, and enteral dysbiosis lies metabolism resulting from the interaction between colonizing microbes and enteral feeding substrate.

We recently published our findings on a functional microbe metabolic taxonomy associated with NEC [5]. We found that by focusing on the metabolic function of the newborn gut microbiome, patterns of enteral fermentation that accompany the potential pathogenic *Enterobacteriaceae* blooms emerge that were notable for producing specific metabolites – short-chain fatty acids (SCFA) – that can be toxic and cause injury to the structurally premature newborn gut. Thus, we have developed a "metabolic model of NEC" hypothesis to unite historical observations regarding NEC occurrence with more recent increased understanding of biologic

patterns that rapidly change in the NICU in the first weeks of life. In developing this model, we have obtained data supporting the connection between the metabolic capability of leading pathogens of the *Enterobacteriaceae* taxa to produce high levels of the SCFA formate that in turn is the candidate toxin for producing a NEC like mucosal injury in a dose and development dependent manner in preclinical models. These observations have led us to a plausible novel understanding of NEC pathophysiology and suggests effective prevention strategies targeting the newborn gut microbiome and abnormal functional fermentation by potential gut pathogens. Thus, an analysis of the premature newborn gut microbiome and metabolome may facilitate and qualify the development of novel NEC prevention strategies, like the use of probiotics to alter the gut colonization pattern and biochemical phenotype.

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LECT 15

VACCINATION IN PRETERM AND LOW BIRTH WEIGHT INFANTS IN INDIA

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Prematurity and low birth weight (LBW) in neonates are a major public health problem, worldwide [1]. LBW could be ascribable to restricted fetal growth or preterm birth, or an association of both conditions. The incidence of infection and death is higher in preterm and LBW infants than in full terms appropriate for gestational age. Prematurity alone is associated to nearly 1 million deaths each year [1]. Five years ago, about 50% of all deaths under 5 years of age were declared from only 5 developing countries, among which about 1 out of 3 of these deaths (33%) were reported in Nigeria and India alone.

India showed a significant improvement in pediatric health after the application of initiatives by the Government of India (GOI). In 2017, the GOI established a goal of 16 deaths per 1,000 live births for neonatal mortality by 2025 [2], and a target of fewer than 10 neonatal deaths per 1,000 live births by 2030, within the India Newborn Action Plan. Hence, prematurity and LBW deserve particular attention, since the high incidence of these conditions in India. Thus, vaccination in preterm and LWB in this country is fundamental to reduce their morbidity and mortality.

In 2017, in India about 1 million out of the 5 of total children under 5 years of age died. Moreover, in India 23.4% of the worldwide total of preterm neonates die. Adequate nutrition, clear water, proper care and immunization of both mother and infants could prevent the majority of morbidity and deaths due to infectious diseases in these patients. The WHO and the Indian Academy of Pediatrics (IAP) advise to immunize all infants, without any restrictions based on gestational age or birth weight, with the only exception of the hepatitis B vaccine (due to a reduced immune response of the birth dose). In India, there is a significant delay or a complete lack of immunization in preterm infants, similarly to developed nations, despite the vaccination recommendations. This topic needs to be investigated.

Neonatal health is mainly dependent on their first line of defence (physical barriers) followed by innate rather than adaptive immune response. At birth, both immune defence mechanisms are undeveloped. This causes an increased susceptibility of infants to infections, including those preventable by

vaccinations (vaccine preventable disease [VPD]). The hospitalization and death from VPDs is higher in preterm and LBW infants and the risk of infection positively correlates with the degree of prematurity and LBW [3]. Delays for each vaccine was defined as administration of the dose after 28 days of the minimum recommended age. Vaccine hesitation is a common barrier in various age groups. For example, Islamic religion and young maternal age (< 20 years of age) are associated with lower odds of full immunization and higher odds of delayed vaccination for DPT-1. Female infant, birth weight < 2,000 g, delivery by unskilled staff, more children and a lack of knowledge of vaccination risks/benefits among mothers were correlated with lower probability of full immunization as well. On the opposite, high level of maternal education was strongly associated with improved infant vaccination status [4, 5]. In this context, it is important to improve the prevention of infections through immunization campaigns. Indirect immunization strategies like maternal immunization (vaccination) and cocooning could strongly decrease the incidence of VPDs in infants (e.g. tetanus, pertussis, influenza, etc.). Vaccination in pregnancy can protect the mother, the developing fetus and the newborn through maternal antibodies transfer via the placenta and subsequently the breast milk, against VPDs. The IAP suggests that immunization of individuals who deal with neonates may reduce their risk of infection. Thus, in preterm and LBW infants, applying the same vaccination schedule of full-term and normal birth weight infants is essential. Indeed, vaccinated preterm and LBW infants show an immune response directly proportional to their gestational age and birth weight. It is important to highlight, that vaccines have a good safety profile and good levels of efficacy even when combined, without altering the immune response, independently of prematurity or birth weight. In conclusion, routine childhood vaccinations reduce or eliminate the risk of VPDs and should be performed in all preterm and LBW infants.

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LECT 16

PRESEPSIN: A NEW DIAGNOSTIC BIOMARKER IN EARLY-ONSET NEONATAL SEPSIS

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Neonatal early-onset sepsis (EOS) represents one of the major causes of mortality in preterm infants accounting for up to 50% [1].

EOS is defined as "a bacterial infection occurring in the first 3 days of life" and it is mainly due to bacteria acquired before and/or during delivery [2].

The possibility of an early EOS diagnosis is still a challenge in the clinical practice due to the non-specific symptoms and the poor performance of standard-of-care diagnostic parameters such as blood culture, C-reactive protein (CRP) and procalcitonin (PCT) in terms of accuracy and diagnostic value.

In this regard, the soluble cluster of differentiation CD14 subtype, namely presepsin (P-SEP), has been shown to be an early reliable diagnostic tool of sepsis in newborns [3, 4]. Based on literature studies the P-SEP strengths are the following: i) rapid activation and kinetics (2 hours after infection); ii) early peak of concentrations (less than 3 hours); iii) the measurability in non-invasive biological fluids; iv) results output in 15 minutes [3]. Moreover, the P-SEP sensitivity and specificity as predictor of EOS have been reported to be from 66% to 97% and from 75% to 100%, respectively [3].

However, several limitations need to be considered: i) lack of consensus on a valuable P-SEP cut-off value; ii) small number of enrolled patients; iii) the heterogeneity of the design of the study (i.e., inclusion and exclusion criteria, monitoring time-points); iv) the different assay used for P-SEP measurement (CLEIA vs. ELISA) [3]. Of note, similarly to CRP and PCT, the P-SEP reliability as early biomarker of EOS might be affected by several bias, as perinatal asphyxia (PA). Recently, P-SEP blood and urine levels of PA newborns have been recently found not to be affected by PA and/or multiorgan failure in the first 24 hours of life [5].

Results open the view for further studies aim at validating P-SEP usefulness as early EOS diagnostic tool in non-invasive biological fluid.

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LECT 17

CONTROVERSIES IN SCREENING AND PRENATAL DIAGNOSIS

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The last 20 years have witnessed an enormous progress in prenatal genetic screening and in invasive prenatal genetic diagnosis for detecting chromosomal diseases.

Without any doubt, the combined screening using the ultrasound evaluation of fetal nuchal translucency in the 11th-14th gestational week along with maternal serum biochemical screening by pregnancy-associated plasma protein-A (PAPP-A) and free beta subunits of human chorionic gonadotropin (free beta-HCG) has revolutionized prenatal and perinatal genetic care [1].

The high 90-93% combined screening sensitivity with 2-3% of false positives has been the most efficient and common first trimester risk assessment in perinatal centers for many years. Adding other ultrasound soft markers such as fetal nasal bone, tricuspid valve regurgitation and ductus venosus velocimetry, we obtain less false positives (1-2%) and more sensitivity (93-96%) for aneuploidies compared to other genetic and congenital abnormalities.

Ultrasonographic skills, experience, certification and accreditation by the Fetal Medicine Foundation of London are requested to achieve optimal results [2].

More recently, the introduction of cell-free fetal DNA (cff-DNA) in maternal blood for trisomies 21, 18 and 13 and for sex chromosome aneuploidies has increased the screening sensitivity of 99.9% (trisomy 21), of 96% (trisomy 18), of 92% (trisomy 13) with very low false positive rates [3].

Several criticisms on this last genetic screening test are reported: no call results in 2-4% of cases, high cost and validation only for trisomy 21-18-13 and sex aneuploidy and no screening available for 20-30% of the other cromosomic aneuploidies.

Even if cff-DNA is at present the best screening test, it is also considered a "super screening" with the potential to change the landscape of prenatal care [4].

For obtaining diagnosis of fetal genetic diseases and to confirm a positive screening test we use first trimester chorionic villous sampling or second trimester amniocentesis. These prenatal invasive techniques are diagnostic and if performed by expert operators both have a similarly low fetal loss rate of 1:800 [2]. A recent systematic review and updated meta-analysis from 2,943 citations revealed a very low fetal loss risk of 1:1,000 cases for both procedures [5].

The widespread use of appropriate genetic screening tests has caused a decline in invasive prenatal procedures, in amniocentesis mostly, while chorionic villous sampling stays constant. The invasive procedures are centralized in specialized centres in order to maintain the operator skills and tutoring of trainees [2].

Genetic screening and prenatal procedures, as well as the utilization of analysis techniques as micro-array and exome tests, raise several social, legal, ethic and economic controversies [6].

Obstetric and genetic counselling for obtaining informed consent is mandatory before all screening tests and invasive procedures in order to illustrate to the couple all benefits and disadvantages, risks and limitations of all procedures and analysis [3].

Undoubtedly, the possibility to highlight ultrasound fetal abnormalities in the first trimester in at least

50% of cases has brought considerable advantages for the couples who aim to plan their pregnancy with less anxiety and greater responsibility and serenity.

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LECT 18

INDUCTION OF LABOUR: WHEN, HOW, WHY

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Labour induction is a medical procedure that consists of using pharmacological and non-pharmacological methods in order to induce labour. Induction of labour should be offered to patients when the risk of continuing pregnancy exceeds the risk of labour induction and delivery.

INDICATIONS [1-3]

In women with uncomplicated pregnancies, induction of labour is recommended between 41^{+0}-42^{+0} weeks in order to avoid the risks of prolonged pregnancy.

In case of premature rupture of membranes at term (PROM > 37 weeks), induction is indicated 24 hours after the rupture of membranes; in a woman carrying GBS (group B *Streptococcus*), induction should be offered immediately after the GBS-positive test.

In case of preterm premature rupture of membranes (p-PROM < 37 weeks), induction should not be offered before 34^{+0} weeks unless there are additional obstetric indications (infection, maternal/foetal complications).

In case of intrauterine foetal death, if there is evidence of ruptured membranes, infection or bleeding, induction of labour should be offered immediately.

In women with gestational hypertension or with mild pre-eclampsia at term, at 37 weeks or after, immediate induction of labour is the preferred management option.

In women with gestational hypertension at 38 weeks, labour induction has a better outcome, so if it is possible, do expectant management.

In uncomplicated pregnancy with pre-gestational diabetes, the perfect timing is 39^{+0}-39^{+6} weeks.

In case of gestational diabetes, according to blood glucose levels and insulin/diet therapy, we can wait for induction until 40 weeks.

There are not enough data about the benefits and risks of labour induction compared to expectant management in suspected foetal macrosomia in women without diabetes, but it could be eventually offered at 39 weeks.

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease. Women with high levels of total bile acid (TBA) have a higher risk of maternal-foetal complications. According to TBA levels, induction is recommended from 35 to 39 weeks.

There are not enough data about induction of labour for small-for-gestational-age (SGA) foetus or intrauterine growth restriction (IUGR). Induction is safe in SGA and later-IUGR in absence of Doppler abnormalities.

TECHNIQUES

Cervical ripening is a mechanical or medical process used prior to induction in case of unfavourable cervical status. Prostaglandins promote several biochemical and biophysical changes that lead to cervical ripening and to an increase in myometrial contractility. Dinoprostone (PGE2) is available in different formulation, intravaginal and intracervical gel and in timed-release formulation. An advantage of the vaginal insert is that it can be removed in cases of uterine tachysystole or abnormalities of the foetal heart rate (FHR) tracing.

The time for delivery and the use of oxytocin are decreased by the use of misoprostol. Induction of labour by a commercially produced low-dose (25 μg) misoprostol tablet for oral induction is feasible in an outpatient as well as an inpatient regimen [4]. The number of caesarean sections is also significantly decreased.

Mechanical methods have been theorized to work both by direct physical pressure and by causing the release of local prostaglandins. A double-balloon catheter, specifically designed, is gradually distended with saline or hygroscopic dilators designed to absorb moisture and gradually expand the cervical canal. Amniotomy is the procedure by which the amniotic sac is ruptured. This procedure is usually performed with the purpose of inducing or expediting labour.

Synthetic oxytocin administration is the most common and proven method of labour induction. When oxytocin is administered, uterine activity and FHR should be continuously monitored. Oxytocin dosing regimens are categorized as either high or low dose, differing in the initial dose, time period between incremental dosing, and maximal dose. The low-dose regimen is associated with a lower rate of adverse reactions (tachysystole, pain, rarely hyponatremia, hypotension, prolonged QT interval).

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LECT 19

PREECLAMPSIA, FETAL INTRAUTERINE GROWTH RESTRICTION AND MATERNAL CARDIOVASCULAR ADAPTATION: A KEY TO FIND A NEW THERAPEUTICAL APPROACH

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Preeclampsia (PE) is a hypertensive disorder often occurring in human pregnancies that is a leading cause of premature delivery and fetal growth restriction (FGR). It is associated with long-term complications for both the mother and the newborn, such as cardiovascular diseases, metabolic and neurological disorders, having a massive social-economic impact. Despite PE has been intensively investigated during the past decade, its etiopathogenesis is still an enigma, remaining a major challenge to both preclinical and clinical scientists. This may account for the absence of therapies for this syndrome and for the fetal intrauterine growth restriction (IUGR).

A cardiovascular maternal maladaptation, together with an inflammatory and dysregulated oxidative status, characterizes PE and FGR, in a vicious circle with a reduction of cardiac output and an increase in total peripheral resistances that leads to impaired pregnancy outcomes and increased morbidity later in life, both for the mother and the offspring. We have tested the hypothesis of the existence of a direct correlation between impaired maternal hemodynamic phenotype and utero-placental characteristics/function and altered utero-placental blood flow. According to this objective we investigated maternal hemodynamics in a group of selected women affected by FGR compared with a control group. IUGR fetuses were then divided in real FGR and small for gestational age.

All hemodynamic measurements have been acquired with the USCOM 1A machine. The USCOM has been validated against invasive gold standards and flow probes and has proof of effectiveness in PE and IUGR. USCOM uses continuous-wave Doppler to determine maternal parameters by a non-imaging transducer placed at the suprasternal notch to measure transaortic or transpulmonary blood. Cardiac output, stroke volume, total peripheral vascular resistances, and the inotropic capacity of the heart are rapidly acquired by experienced personnel. The relations with the Doppler umbilical artery flow, middle cerebral artery flow and umbilical vein flow have been studied and evaluated.

Growth-restricted fetus had significantly lower umbilical vein diameter ($p < 0.0001$), umbilical vein velocity ($p = 0.02$), umbilical vein flow ($p < 0.0001$), and umbilical vein flow corrected for fetal weight ($p < 0.01$) compared with adequate and small for gestational age fetuses. The maternal hemodynamic profile in FGR was characterized by elevated systemic vascular resistance and reduced cardiac output. A significant correlation between increased maternal resistances and umbilical vein absolute flow was found.

Our results will allow to strengthen the relevance of using hemodynamic evaluation before and during the diagnosis of FGR: USCOM may become part

of the routine work. Several pilot experiences have indicated the possibility to improve the fetal umbilical flow acting on the maternal hemodynamics. The use of NO donors linked with the increaser in plasma volume and in the reduction of maternal resistances have brought potential positive effects on fetal intrauterine growth. The demonstration that this mechanism acts directly on the increase of the umbilical vein absolute flow is a further stimulus to connect the function of fetal-placental unit with the appropriate study of maternal maladaptation to pregnancy. Only through the complete evaluation of the system a correct therapeutical approach might be found in the future to increase gestational age and fetal growth and to reduce acute and chronic neonatal morbidity.

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LECT 20

HOW TO FEED AN IUGR NEWBORN: A NEW CHALLENGE FOR THE NEONATOLOGIST

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Intrauterine growth restriction (IUGR) is defined as the inability of the fetus to develop according to its biological potential due to pathological causes, of which the most common is placental dysfunction. Its correct diagnostic classification during pregnancy allows the early recognition of fetuses at risk whose adequate prenatal and postnatal management improves their short- and long-term outcomes. The IUGR infant, whether full-term or preterm, is burdened by high morbidity and mortality. In fact, the insufficient supply of oxygen and nutrients during fetal life determines a remodeling of the fetal circulation, known as "brain sparing", which involves the preservation of vital organs (brain, heart, adrenal glands) but which at the same time causes impaired development of other organs and systems including the gastrointestinal one. The latter presents not only an abnormal morphology of the villi, with a reduction of the absorbent surface, but also an alteration of the protective mucous barrier. It is partly due to histological and ultrastructural alterations of the intestinal wall (reduction of microvilli, goblet cells and tight junctions), but it is also closely related to variations in the intestinal microbiome as emerges from recent experimental studies. It follows that the impairment of the anatomical and functional development of the intestine, associated with abnormal bacterial colonization, is responsible for the feeding difficulties and the predisposition to necrotizing enterocolitis (NEC) that make the nutritional management of these newborns a challenge for the Neonatologist. There are still obscure points on what is the optimal growth to be pursued in this population of heterogeneous infants (born at term, preterm, late preterm and preterm of extremely low gestational age). Today there is still debate about what their nutritional needs are, how to proceed with enteral feeding, how and when to wean them from total parenteral nutrition.

Surely the use from the first days of colostrum, of mother's milk or, in her absence, of donated milk improves food tolerance, promotes the development of the intestine and the growth of these newborns, reducing the risk of NEC. Lactoferrin has a similar effect by modifying the microbiota and regulating intestinal development. The use of well-defined and shared food protocols within the operating Units and the use of appropriate growth charts have to date proved to be valid tools for the nutritional management of IUGR infants. Subsequent studies are needed to define which diagnostic and therapeutic tools can be of help to conduct a correct and as much individualized as possible nutrition for these newborns. The contributions of the omics sciences (proteomics, microbiomics, metabolomics) appear promising, not only to better understand the pathophysiology, but also to develop strategies to optimize the nutrition and development of infants with IUGR.

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LECT 21

VITAMIN D FROM THE ANCIENT WORLD TO THE FUTURE

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Vitamin D originates from Earth's earliest life forms. The seaweed of the Sargasso Sea, Emiliana huxleyi, had the possibility of absorbing UVB rays with the consequent synthesis of vitamin D, which today we know had the purpose to maintain its cytoskeleton, to protect its genetic heritage from oxidation, and to defend it against phytopathogens.
With the transition of life from the sea to the land, there was a need to ensure adequate intestinal absorption of calcium and its accumulation in the skeleton, which guaranteed the upright posture. Hence the vitamin D skin synthesis.
Since vitamin D was identified in the 1920s, many studies contributed to the understanding of the mechanisms by which the two sources of vitamin (cod liver oil and sun) cure/prevent the rickets. Food fortification with vitamin D contributed to the eradication of rickets around the world. In the 1950s, a disease characterized by facial abnormalities, aortic stenosis, mental retardation, and hypercalcemia was reported in England which was attributed to a toxic effect of vitamin D. Food fortification was banned in almost all countries and the consequence was the resurgence of rickets.
When the determination of 25(OH)D was developed in the 60s, a new epidemic spread worldwide: the vitamin D deficiency. The definition of this deficit was based on the plasma concentration useful to prevent the clinical/laboratory manifestations of rickets, and it varies from 20 to 30 ng/ml. Furthermore, studies on the mechanisms of vitamin D action have allowed to highlight other multiple potential clinical effects. In this way, associations were found between almost all the pathologies that affect humans and a reduced plasma concentration of 25(OH)D, while it was not possible to identify a sure causal role.
On the other hand, vitamin D as a nutrient could not have drug-like effects. Its effects would be evident only if deficient subjects reach the state of sufficiency and often in synergy with other nutrients.
Scientific contributions on the mechanisms of vitamin D, genomic and non-genomic, have shown that every system of our organism also has its own metabolism of vitamin D. Hence the revision of the importance of determining the 25(OH)D as the only useful parameter to define the deficit. On the other hand, in many extra-skeletal pathologies, it was possible that the positive effect of vitamin D was associated with levels of 25(OH)D higher than that generally considered.
Vitamin D deficiency, even if defined with lowest levels, is highly prevalent worldwide, even in countries with abundant sun exposure. Hence the need to re-evaluate our knowledge on skin synthesis (difficult to predict) and on real nutritional intake (very low).
What we know today about vitamin D is not conclusive, but it is the starting point for the future that will have to set specific goals:
- to define with certainty the plasma concentration of the deficit;
- to define the dose to be administered as well as the best administration way to avoid the deficit;
- to define the monitoring to be implemented to avoid toxicity;
- to reach a sufficient state for our population.

Only the achievement of a state of sufficiency can allow to study its extra-skeletal effects to have statistically significant results. In this way it will be possible to also evaluate the therapeutic role of vitamin D in many other pathologies: autoimmune, allergic, infectious, cardiological, metabolic, neurological, and even cancer.
Today the determination of 25(OH)D simplified the evaluation of the complex metabolism of vitamin D (skin synthesis, dietary intake, supplementation) defining the state of sufficiency or deficiency. In the future we must find a way to evaluate the complex effects, genomic and non-genomic, of vitamin D in our organism by overcoming variants such as the individual response or the conditioning of pre-existing pathologies. Perhaps only the omics sciences, metabolomics above all, can contribute to give the best answers. The future of vitamin D has only just begun.

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LECT 22

HIGHLIGHTS FROM THE NATIONAL CONGRESS OF THE ITALIAN SOCIETY OF CHILDHOOD AND ADOLESCENT GYNECOLOGY

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The National Congress of the Italian Society of Childhood and Adolescent Gynecology was held in Cagliari on 19-20 May, 2022.

The first day, in a debate between gynecologists and others specialists, we discussed the management of young patients suffering from chronic diseases. A fruitful exchange between Profs. Palumbo, Porcu and Farris highlighted the problems related to the reproductive life of young oncological patients. The need for differentiation of contraceptive therapy based on the underlying pathology was discussed with particular attention to the increased thromboembolic risk of combined oral contraceptives (COCs), their effects on liver function and the stimulation of hormone-sensitive tumors. There was also an intense debate on fertility preservation with oocyte cryopreservation.

The attention was then placed on patients suffering from spinal cord injury. Dr. Dei and Dr. Campus focused on the need to investigate, treat post-spinal injury amenorrhea and inform on sexual development and rehabilitation of young adolescents. The contraceptive possibility of these patients who have an increased thromboembolic risk was discussed.

Another theme discussed by Prof. Fulghesu and Dr. Songini was the influence of DMT1, DMT2 and insulin resistance on the contraceptive prescription and reproductive pathology management.

Drs. Lucchetti and Motta with regard to ano-uro-genital pathology adviced to research genital tract malformations in female patients with known renal abnormalities, given the possible association between Müllerian and Wolffian anomalies.

The second part of the Congress dealt with the influence of endocrine pollutants on growth and development in childhood and adolescence. Particular attention was paid to the effect that these substances have on pubertal development and on the epigenetic mutations they cause during fetal development.

Prof. Fanos pointed out how maternal habits and maternal microbiome in the first 1,000 days (from the pre-conceptional period to the first 6 months) of a child's life may influence the child's growth and susceptibility to diseases' development.

Prof. Genazzani talked about therapeutic possibilities of insulin resistance patients. Physical exercise, COCs and antiandrogens can be associated with insulin sensitizers, such as metformin and inositol; α-lipoic acid may be a successful additional option.

Genetic diseases have been widely discussed, considering the geneticist's approach to the rarest syndromes till the pharmacological treatment of diseases with greater prevalence such as congenital adrenal hyperplasia. Prof. Bruni and Dr. Mazzanti, dealing with the delicate subject of Turner syndrome, stressed the importance of a differentiated target therapy according to the pre- or post-pubertal phase. Moreover, a very recent study by Kanatsu-Shinohara et al. [1] was presented, revealing the possible restoration of fertility in female mice with viral vector-mediated gene therapy.

Drs. Giolito and Tridenti reiterated the importance of the risky implications of adolescent pregnancies: the greater probability of undergoing a preterm birth, lower therapeutic compliance and development of postpartum depression require a close follow-up with a multidisciplinary approach. Half of the pregnancies in this age group are interrupted as unwanted: the voluntary interruption of pregnancy (VIP) therefore remains a care need that must be guaranteed by the National Health Service (NHS).

The final discussion was very effective: from Prof. Fulghesu's previous intervention regarding the different contraceptive options for polycystic ovary syndrome (PCOS) patients, to the use of the new estrogen (estetrol) in association with the well-known drospirenone as new frontier in EP therapy.

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LECT 23

LONG-TERM OUTCOME OF INFANTS WITH INTRAUTERINE GROWTH RESTRICTION

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Infants with intrauterine growth restriction (IUGR), defined as the failure of the fetus to reach its growth potential and concomitant changes in placental blood flow, are at increased risk for stillbirth and for significant postnatal morbidity and mortality (reported to be 5- to 10-fold higher than in infants with appropriate growth profile). However, IUGR infants represent a heterogeneous population and short- and long-term outcomes depend on the identified cause of IUGR, timing of onset and physical presentation. More importantly, IUGR infants should be distinguished from small for gestational age (SGA) infants, diagnosed postnatally according to their birth weight at or below the 10th or the 3rd centile, and including both infants that are constitutionally normally small due to maternal height, weight, ethnicity, and parity (with no additional risk for morbidity), and infants who are small because of growth-restriction.

Therefore, a new clinical definition of growth restriction in the newborn has been proposed, including birth weight less than the 3rd percentile or the presence of at least 3 factors including birth weight < 10th percentile, head circumference < 10th percentile, prenatal diagnosis of fetal growth restriction, maternal pregnancy information (hypertension or pre-eclampsia).

Based on physical presentation, IUGR infants can be divided into symmetric and asymmetric and this categorization is based on the idea of brain sparing. Symmetric IUGR is usually related to genetic disorders or TORCH group infections, accounts for 20-30% of cases of IUGR and is associated with a higher infant mortality. Asymmetric infants are more common (70-80%) and chronic fetal hypoxia and malnutrition (utero-placental insufficiency) are the most common causes that alter intrauterine growth. IUGR can be further categorized according to the timing of onset into early and late. Early IUGR arises before 32 weeks of gestational age; it represents a severe condition and the main challenge in the obstetrical management is the timing of delivery based on the balance between the risks of stillbirth and those related to a preterm birth. Late IUGR is a more common and less severe condition generally linked with a milder placental deficit and less fetal hemodynamic adaptation that occurs after 32 weeks of gestation; abnormal umbilical artery Doppler is less common but the natural history of late IUGR is less predictable and there is a risk of sudden decompensation and stillbirth.

Based on the abovementioned characteristics of IUGR/SGA infants, prediction of infant's long-term outcomes is challenging.

When chronic fetal hypoxia and placental compromise occur, the growth and maturation of fetal organs are altered with consequences mainly on cardiovascular, lung and brain development, making IUGR infants at higher risk of relevant long-term morbidities.

Fetal growth restriction induces increased peripheral vascular tone resulting in structural heart changes and vessel wall rigidity that cause significantly higher blood pressure in later life and increased risk of ischemic heart and cerebrovascular disease in adulthood. IUGR also affects normal pulmonary development with decreased surfactant production, especially in early-onset IUGR, and consequently increased susceptibility to long-term respiratory morbidities such as bronchopulmonary dysplasia, resulting in long-term respiratory complications and impaired lung function in childhood that can persist into adulthood. IUGR is also strongly linked to suboptimal brain development represented by altered white matter myelination and brain connectivity and a decreased cortical gray matter volume; impaired brain development is in turn associated with long-term neurological dysfunction such as a higher risk of cerebral palsy, hyperactivity disorders and poor cognition at school. The combination of early-onset IUGR, fetal brain sparing, impaired cerebrovascular regulation, and preterm birth represents the greatest risk factor for developing neurological deficits.

In conclusion, infants with IUGR require close clinical monitoring to early identify the complications that may arise, so that both preventive and active intervention can be taken.

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LECT 24

PRECISION MEDICINE IN PEDIATRIC IMMUNO-ALLERGOLOGY: THE ASTHMA MODEL

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Asthma is a major health issue in the pediatric population worldwide. In recent years our knowledge of childhood asthma has greatly improved, with the characterization of different clinical phenotypes and airway inflammatory pathways (endotypes) [1]. The understanding of the immunological bases of pediatric asthma has paved the way for the development of targeted therapies [1]. In this context, pediatric asthma can be considered a model for the application of the "precision medicine" approach [1, 2].

Asthma management aims to maintain the control of the disease, consequently decreasing the risk of asthma exacerbations. For most children, low doses of inhaled corticosteroids (ICS) and/or one or more controllers allow for the achievement of good disease control. These treatments suppress bronchial inflammation; however, they are not disease-modifying, with possible inflammatory reactivation on their discontinuation. Moreover, they are ineffective in patients with severe uncontrolled asthma. For all these reasons, the identification of targeted and individualized therapies represents a fundamental and ever-evolving research field [2].

Asthma phenotypes are closely related to endotypes, which in turn are determined by different cellular and molecular pathways. Two major distinct inflammatory endotypes have been recognized so far: type 2 (T2) and non-T2 endotype [1, 2].

T2 asthma has a predominant eosinophilic inflammation and is driven by allergy in more than half of patients. Interleukin (IL-)4, IL-5, and IL-13 (Th2 cytokines) are among the main cytokines involved in its pathogenesis [3]. Immunoglobulin E (IgE) contribute to the initiation and amplification of this inflammatory cascade. Moreover, IgE seems to play an important role in airway remodeling, since receptors for IgE have been found on airway smooth muscle cells.

Non-T2 asthma is characterized by either a neutrophilic infiltrate or a limited cellular infiltrate (pauci-granulocytic) [2]. The neutrophilic inflammation involves Th1 and Th17 cytokines (IL-8, IL-17A, IL-22) and is mainly triggered by infections and/or inhaled pollutants, while the pauci-granulocytic inflammatory profile is still largely unknown. Systemic and metabolic inflammation may also contribute to non-T2 endotype, considering its high prevalence in obese and older patients.

Although both endotypes may coexist in a few patients, the T2 endotype is observed in most asthmatic patients, in particular in children. Thus, the development of novel biologic treatments has been focused mainly on T2 asthma [1-3].

Omalizumab (binding to the high-affinity IgE receptor), mepolizumab (binding to IL-5) and dupilumab (binding to IL-4 receptor α subunit, thus blocking IL-4 and IL-13) are the biologicals approved for pediatric asthma [1-4]. These drugs have revolutionized the therapeutic approach to T2 asthma, particularly in patients with severe disease and resistant to standard treatment. However, current unmet needs include the identification of the optimal treatment duration along with the approach to discontinuation, and the definition of long-lasting effects.

Moreover, the wide interpersonal variability in response to biological treatment confirms the complex mechanisms underlying asthma. It is essential to further improve our knowledge regarding the biomarkers for assessing therapeutic efficacy. Interestingly, recent studies have shown that metabolomics, through the study of baseline urinary metabolomic profile, can differentiate children with severe asthma responding to omalizumab from non-responders [5].

In a near future, not a single biological but two or more targeted therapies could be co-administered, providing the possibility to block or influence two or more key pathways, thus, representing a novel and promising strategy to immunomodulate asthma. Moreover, for non-T2 asthma, the clinical development of the biological drugs is still in the primeval stage and further understanding of the pathological mechanisms underlying this condition

is essential to improve the care of patients with this specific endotype.

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LECT 25

A MODERN CONCEPT OF THERMALISM APPLIED TO HEALTH AND WELL-BEING. A SYSTEMS MEDICINE MODEL OF INTEGRATION IN CLINICAL PRACTICE AND NEW THERAPEUTIC SOLUTIONS

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Thermal Medicine is one of the oldest forms of medical therapy and should be included in the field of traditional Medicine (in agreement with the World Health Organization [WHO] criteria).

Thermae represent an integrated set of natural resources, facilities and services where different form of medical culture can harmonize each other, aimed to offer therapy, rehabilitation, and health preservation. The use of water for therapeutic purposes has followed the cultural, economic, and scientific evolution of the populations and, depending on these factors, thermalism has cyclically known periods of intense exploitation and others of lesser use.

In this historical moment, characterized from a medical point of view by the fast development of "-omics" (metabolomic, lipidomic, etc.) and very sophisticated therapeutic, diagnostic, and surgical techniques, the role of the Thermal Medicine could appear marginal. However, the progressive awareness of the fact that a modern and efficient health system cannot be limited to providing only assistance and treatment of specific pathologies but must promote the overall (psycho-physical) well-being of the citizen can make possible to re-evaluate thermalism.

Thermalism would cease to be considered only in terms of therapeutic efficiency and could regain its centrality in the dynamics linked to the improvement of lifestyle and prevention, favoring the protection of health (with the connected socio-economic advantages) [1, 2]. Based on these assumptions, it is possible to hypothesize a paradigm shift by abandoning the static idea of a thermal center as a hydrotherapy plant in favour of a more dynamic one that identifies it as a place aimed at the overall well-being of the individual.

This vision also brings thermalism closer to Systems Medicine. The unifying and characterizing element of Systems Medicine is the centrality of the patient as a "person" (Personalized Medicine), an expression of the complexity of his being – together – body and mind. From it derives the personalized diagnostic approach to the patient, which considers all the different aspects of the ethiopathogenetic path of the disease: physical, emotional, mental, social, and environmental. From it also derives the main goal of the medical-integrated and personalized approach to the patient: the achievement and maintenance of his psycho-physical and social balance and well-being, through all the tools offered by XXI century Medicine and in compliance with the Hippocratic principle *primum non nocere*.

INTEGRATED THERMAL MEDICINE: WITHIN SYSTEMS MEDICINE

The merging of Thermal Medicine within Systems Medicine is the most natural and spontaneous consequence, and it shows how integrated Medicine is not only possible but highly recommended as a mean of prevention and active contrast to medicalized lifestyle, in favor of health and wellbeing (with subsequent drug-economy benefits).

In "*The Milan Declaration 2022 – New goals for Medicine*" [3] inalienable needs of a new vision of Medicine are defined:

- need for a new model of human being that interprets the person as a complex system;
- need for new therapies that allow a complex approach to the patient, in which pharmacological interventions (of synthetic or biological or natural

origin) and non-pharmacological interventions and Complementary Medicines can intersect and intervene harmoniously on the individual;
- need for real and effective transdisciplinary integration.

Systems Medicine appears capable of meeting these needs, through:
- the translation from a reductionist approach to a systemic one;
- the transition from a strictly biomedical and specialized view of human Physiology and disease to an interdisciplinary vision;
- a multidisciplinary approach to medical science;
- an expanded and systemic vision of health and disease, consistent with and akin to the emerging concept of One Health, proclaimed by the WHO, which includes in the vision of human wellbeing also the whole ecosphere: man, animals, plants, climate and environment.

These are crucial issues both for the development of the modern Thermal Medicine and for the appropriate execution of the proposed therapeutic treatments. Only following these walkways, the Thermal Medicine will be definitively included and integrated in Systems Medicine in order to ensure safe and effective preventive and therapeutic treatments.

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LECT 26

RARE DISEASES: FROM GENOMICS TO ESONOMICS

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In the 60s-80s, and after the diffuse activation of laboratories of cytogenetics throughout the world, syndromic conditions due to altered chromosomal numbers (such as trisomies, Turner syndrome, Klinefelter syndrome) as well as due to altered chromosome structure (such as Wolf's syndrome, Cri du chat syndrome, 18q- syndrome, etc.) were identified. Shortly after, together with the evolution of cellular and molecular biology (FISH, CGH array etc.) it became possible to identify the causative mutations, the genetic duplications responsible for several conditions, and it also became feasible to define the mode of transmission for numerous diseases allowing for the introduction of genetic counselling in clinical settings.

More recently, the application of esonomics has allowed the identification of novel genes responsible for diverse clinical conditions, the definition of precise genotype-phenotype correlations, as well the characterization of specific metabolic/signaling cascades that may become the targets for personalized treatment in the near future for affected individuals.

LECT 27

"THE HOUSE WITH THE WINGS"

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The contribution presents the research-intervention that the Italian Society of Pediatric Psychology has defined to create a functional support centre to the consulting activities, in a dimension of continuity with the Hospital and in particular with the Obstetrics and Gynecology Units, Clinics for high-risk pregnancies, Neonatology Units, starting from the Territory of Palermo, through an integrated work perspective. This centre can have some fundamental implications for health: to ensure continuity between Territorial Services and Hospital, to retain users in using Services in Maternal and Child Area, in a logic of continuity, to contract health care costs in terms of reducing improper access, to reduce the number of requests for the use of services, to reduce the use of drugs.

The research-intervention path develops in an experimental prevention logic, starting from the consideration of the risk of an erroneous circle, as indicated by the most recent studies of metabolomics, microbiomics and epigenetics, between the metabolism of the pregnant woman, her dysfunctional psychological functioning, and disorders or in any case of impairments in the

developmental trajectory of the child, starting from the prenatal phase [1, 2].

The study underlines how the path of the research-intervention gives to the Counseling Services an additional safety function for pregnancies on a biopsychosocial level, with the aim to reach a social and organizational pact of the Community, which defines better health conditions for the development of the fetus first and of the newborn after, as well as of the child. The strengthening action of connection between the Territory and the Hospital, through some specific directions (research, intervention and prevention), finds its methodology in the integrated work, which aims to promote and support a food style functional to the mental health, both in pregnant women and among adolescents involved in prevention paths at school with a specific workshop, starting from the Counseling Services. In this sense, the research-intervention aims to define a good practice of prevention/cure of dysfunctional lifestyles and dietary trends in pregnancy in order to counteract maladaptive parental competence and potential repercussions on the development of the unborn child. The research-intervention can be identified as a proximity action, in the sense of a path that responds to the needs of access to cure and the possibility of taking charge women in the individual conditions. The goal of this specific path can be identified in the support and accompaniment of pregnant women, in this particular weakness condition, to prevent stress, depression and related impairments in the development of the fetus, newborn [3]. The contribution reports how the research presents the assumption of a metabolomic perspective [4], as the most innovative aspect, considering the literature of the field and assuming some important reference perspectives: epigenetic and psychological.

A further interesting and innovative aspect of the research must also be identified in focusing on connection between possible interventions in pregnancy, which support healthy food styles and reduce stress, orienting well-being outcomes on women and children, such as underlines a recent review [5].

The contribution presents the process of the research-intervention path. Precisely the process and some reference data make possible different flights that "The House with the Wings" allows in terms of the effectiveness of the all professionals involved, in terms of the quality of care and on the organizational level.

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LECT 28

THE BURDEN OF COVID-19 IN CHILDREN AND ADOLESCENTS

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For over 2 years and a half, all of mankind has been facing the COVID-19 pandemic. The knowledge that has gathered so far regarding SARS-CoV-2 infection is insufficient and there are many questions awaiting answers, but what is apparently obvious thus far is that there is a lower incidence and decreased disease severity of COVID-19 infection in children.

MORBIDITY AND MORTALITY IN SARS-CoV-2 INFECTION IN CHILDREN AND ADOLESCENTS

Most children with SARS-CoV-2 infection are asymptomatic or have mild symptoms and usually recover with no sequelae. COVID-19 morbidity and mortality are very low in children when compared to adults [1]. Even so, one must not fail to recognize the possibility of severe disease in children. An underlying medical condition in children aged 5 to 11 years carries a 12-fold increase in hospitalization rates and a 19-fold increase in the risk of admission to a Pediatric Intensive Care Unit (PICU). However, the vast majority in this age group that were hospitalized (78%) were previously healthy children [1].

A review of 1,475 children from various countries who were hospitalized with acute COVID-19 reported a moderate to severe degree of illness in 615 (42%). In a recent prospective study in Israel [2], including 579 children with SARS-CoV-2 infection that were either hospitalized or developed multisystem inflammatory syndrome in children (MIS-C), 103 had moderate to severe illness. Moreover, 20% of those with COVID-19 and 56% of those with MIS-C were hospitalized in PICUs, and 7% and 20% of these respective groups required mechanical ventilation.

An element of great interest is the persistence of symptoms after COVID-19. Starting from 2021, prolonged COVID-19 symptoms have also been described in the pediatric setting. However, the exact prevalence of persistent symptoms after SARS-CoV-2 infection in children (long COVID-19) is not currently known.

Children play an important role in the transmission of SARS-CoV-2. New virus variants are expected to emerge, and the disease breaks out particularly in populations with low immune coverage, like pediatric patients. Children and adolescents have similar or higher viral loads of SARS-CoV-2 compared to adults [3, 4]. Several studies showed lower infectivity rates among children. Infectivity correlates with age. Adolescents and adults exhibit similar infectivity rates.

LONG-TERM COMPLICATIONS OF SARS-CoV-2 INFECTION

The most frequent long-term complications of SARS-CoV-2 infection in children are: myocarditis, multisystem inflammatory syndrome in children (MIS-C/PIMS) and long COVID-19.

SARS-CoV-2 infection is associated with an increased risk of myocarditis of 30-fold higher in children under age 16 years and 16-fold higher in the general population, according to data from the Centers for Disease Control and Prevention (CDC). Moreover, scientific data suggest that myocarditis in the setting of SARS-CoV-2 infection, both in severe COVID-19 and in multisystem inflammatory syndrome, exhibits a much higher risk than derives from vaccination with a mRNA COVID-19 vaccine [1]. Clinical symptoms of myocarditis have been identified in 0.5% (1:200 cases) [1].

MIS-C/PIMS associated with SARS-CoV-2 infection [5, 6] was first described in April 2020 in the UK. Clinical manifestations occur approximately 2-4 weeks after SARS-CoV-2 infection and include: persistent fever, gastrointestinal signs and symptoms, mucocutaneous and cardiac symptoms, and elevated inflammatory markers. Some signs and symptoms are similar to those seen in Kawasaki disease, toxic shock syndrome and/or acute COVID-19 disease [6]. Most cases are found in children aged 1-14 years with a median of 9 years. More than half (56%) of MIS-C cases are males. Most children that developed this long-term complication of SARS-CoV-2 infection were free from comorbidities [1]. 53-80% children diagnosed with MIS-C had cardiac involvement and 20% needed mechanical ventilation [1, 2].

Depending on the population assessed, methods of data collection and the time elapsed from the acute illness, the incidence of long COVID varies, reaching nearly 30% (physical and mental symptoms in children recovering from SARS-CoV-2 infection) [1]. In the UK there was an online survey among 297,743 individuals over the age of 2 years based on self-reported or parental reports of symptoms; 4 weeks after infection, 0.2% of children aged 2-11 years and 0.9% of children aged 12-16 years had symptoms of long COVID. The most frequent symptoms were: fatigue, shortness of breath, headache, cough, dizziness, muscle and joint pain, hair loss, tremor and sleeping difficulty.

SIGNIFICANT INDIRECT EFFECTS OF COVID-19 IN CHILDREN AND ADOLESCENTS

Although children are not in the frontline of this pandemic, they risk becoming its greatest victims, as their lives changed significantly. All children, regardless of age, have been deeply affected, especially from a socio-economic standpoint and, in some cases, by the measures aimed at limiting SARS-CoV-2 infection [1].

Moreover, the negative effects of the COVID-19 pandemic on child welfare were not equally distributed. Children from low-income areas, already at a disadvantage, have experienced and continue to bear a disproportionately large burden stemming from the COVID-19 pandemic.

For long periods, schools have been closed, influencing not only the educational process, but also child nutrition, growth and development, and social wellbeing. Moreover, an increase in domestic violence involving children, with significant psycho-emotional consequences in the medium and long term was also observed [7].

The burden of the COVID-19 pandemic manifested in various ways: there was an increase in poverty, a major crisis arose in education, and new threats concerning children's health and even survival emerged.

Around 42-66 million children wound up living in extreme poverty as a direct consequence of the

ongoing health crisis. This is an addition to the over 386 million children already suffering from extreme poverty in 2019.

In 2020, 188 countries resorted to long-term school closure, affecting over 1.5 billion children and young adults. Over 2/3 of countries introduced social distancing and distance learning (using e-platforms); in low-income countries, however, only 30% of children could access this type of learning system. This aspect meant that at least 463 million children from poor families could not attend classes due to lack of funding for digital learning (no internet access, no electronic devices, no financing, etc.).

Opening/closing schools, social distancing, and medical care disruptions could have negative medium and long-term effects on children's and adolescent's health and welfare.

The negative impact of closing schools manifested as: decreased reading abilities and poor outcomes in tests, poor critical thinking skills, reduced creativity and information processing, behavioral changes (depression, anxiety, eating disorders, etc.), low financial resources for children with disabilities (including access to specialized educators and structured learning environments).

An increase in numbers of children with malnutrition is to be expected, as around 368.5 million children from 143 countries have stopped receiving a warm meal at school, which, in normal circumstances, would have been provided daily. Another 6 to 7 million children under 5 years of age have suffered from acute malnutrition in the year 2020.

Healthcare services utilization has decreased substantially during the pandemic, which resulted in a drop in immunization rates (by 34%), children's health status screening (by 49%), dental procedures (by 69%), and mental health services (by 58%).

There was also a significant impact on national immunization programs, threatening objectives such as the eradication of vaccine-preventable diseases (VPDs) like poliomyelitis and measles [8]. In 129 countries where statistical data were available, more than half reported moderate to significant disruption, or even complete cessation of routine immunization services in March-April 2020, owing to personnel relocation to areas where patients with COVID-19 were being treated [8].

The spread of the SARS-CoV-2/COVID-19 and the various measures employed during the pandemic have had significant impact on children's health and welfare [9]. Health services and social assistance disruption (changes in the usage of the emergency pediatric medical service during the COVID-19 pandemic) manifested in various ways in Emergency Departments (EDs), such as increasing numbers of presentations for medical conditions in children and adolescents with psychosocial issues [9].

The COVID-19 pandemic has had significant impact on children's and adolescents' mental health. There is an alarming increase in depression and anxiety rates for this category. The number of calls to social assistance hotlines has risen, including those for suicide crises. Eating disorders, worsening symptoms of preexisting eating disorders (including hospitalizations) have dramatically increased [10].

The impact of COVID-19 pandemic on children and adolescents is multifaceted:

- the aspects of morbidity and mortality rates secondary to SARS-CoV-2 infection;
- community stress generated by the novel coronavirus infection;
- child, adolescent and family trauma;
- additional consequences (delayed medical care, delayed immunization, obesity, etc.).

In this difficult time for us all, we need to focus more on children and adolescents in order to improve their physical and mental health and, in the end, their overall wellbeing.

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LECT 29

THE NATURAL HISTORY OF POMPE DISEASE

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Pompe disease is an inherited metabolic myopathy due to lysosomal acid-alpha-glucosidase (GAA) deficiency, discovered by Belgian biochemist, Henri-Géry Hers in 1963. This enzyme normally breaks down glycogen in the milieu of lysosomes. GAA deficiency result in lysosomal glycogen accumulation, particularly in cardiac, smooth and skeletal muscles with clinical manifestation of progressive myopathy, respiratory weakness and premature death. Residual GAA enzyme activity affects disease onset and severity, although other factors, including dysregulation of cytoplasmic glycogen metabolism, are suspected to modulate the disease course. This disorder is multiethnic but has been reported to be less frequent in some population as in Australians (1/146,000) and more frequent in African Americans (1/40,000). The *GAA* gene is located on chromosome 17 and more than 300 causing mutations have been so far identified, with most patients being compound heterozygotes. The disease can present at any age. Although the clinical spectrum is on a continuum of the disease severity, Pompe disease is typically divided into subtypes based on age of symptom onset and extent of organ involvement. The management guidelines divide Pompe disease into infantile and late-onset forms. The infantile form is the most severe, with rapid progression to cardiorespiratory failure within the first year. Clinical features of diffuse hypotonia and weakness are present within the first days to months of life. Involvement of cardiac muscle leads to a hypertrophic cardiomyopathy. Dysfunction of respiratory musculature, including the diaphragm, leads to a weakened cough, which predisposes these children to recurrent pulmonary infections. Furthermore, respiratory muscle weakness leads to the development of hypoventilation and subsequent respiratory failure with death within the first year of life. A subset of the infantile form has a milder phenotype, with onset of symptoms in the first year of life but with less severe to no cardiomyopathy. Late-onset Pompe disease (LOPD) includes childhood, juvenile and adult-onset disease. It generally presents with limb-girdle type weakness, respiratory symptoms, particularly shortness of breath, and occasionally respiratory failure. Low level of GAA (30-40% of normal) are usually found. LOPD is often a challenging diagnosis clinically and may result in delays in diagnosis for up to 6-7 years. Missed diagnosis or not diagnostic histopathology are not unusual in LOPD and frequently labelled as inflammatory myopathy or not specific findings. With genetically proven Pompe disease, muscle biopsy may frequently be normal and some authors have recommended this invasive test be avoided. For diagnosis, blood-based enzyme activity assays as well as enzyme assays in cultured skin fibroblasts and muscle are considered accurate and sensitive. Dried blood spot (DBS) screening testing started in 2004, has been recommended and demonstrated to be the most used test for diagnosis of Pompe disease, resulting appropriate to newborn screening. Genetic testing is recommended for confirmation of diagnosis. In the past the treatment was mostly palliative. With the advent, in 2006, of specific enzyme-replacement therapy (ERT) with alpha-glucosidase approved for Pompe disease, careful management of these patients is necessary so as to allow for the full benefit of ERT in both infant and adult patients. Trials in LOPD demonstrated sustained improvement with ambulation and stable pulmonary function and ERT was subsequently extended for use. In conclusion and in this scenario, a selective screening aimed to identify affected patients among high-risk population may be functional to optimize their diagnosis and treatment. ERT effectiveness is optimized by early diagnosis, before extensive damage has been engendered in these patients.

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LECT 30

THE NETWORK OF THE ITALIAN ASSOCIATION OF PEDIATRIC HEMATOLOGY AND ONCOLOGY (AIEOP) CENTERS AS A MODEL OF NATIONAL AND INTERNATIONAL COOPERATION

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The Italian Association of Pediatric Hematology and Oncology (AIEOP) is a network of 49 Centers, structures of the National Health System dedicated to the care of children and adolescents suffering from oncological and/or hematological and/or immunological pathologies. The Centers are identified according to requirements that align with qualitative, structural, technological and quantitative standards relating to hospital care and work in synergy with the aim of minimizing territorial inhomogeneity in access to care, guaranteeing cutting-edge care nationwide and safeguarding the patient's and family's quality of life as much as possible (e.g. by facilitating care close to home). AIEOP is a scientific society operating throughout the national territory and it is included in the list of scientific societies accredited by the Ministry of Health in accordance with Gelli law (GU l. 24/2017).

The five main strengths and strategic points of the AIEOP network are presented hereafter.

1. The AIEOP database is called Mod.1.01, a system that allows the automatic archiving of data, through the official AIEOP website, where Centers can register new cases by filling in the electronic form of Mod.1.01 and access the information contained therein in a controlled, structured and GDPR-compliant form. Prot.Mod.1.01 was approved as a "Protocol of retrospective and prospective observational study on subjects enrolled in the AIEOP and IPINET centers" (EC Policlinico di Sant'Orsola, 18/12/2013). Currently registered patients are more than 60,000 since 1989.
2. The centralized revision of the diagnosis represents an added value in support of therapeutic choices as tumors in pediatric and adolescent age fall within the definition of rare pathology and require diagnostic expertise. AIEOP supported a process of reorganizing the centralization process by stipulating agreements with all the reference services and ensuring the economic coverage of the shipping costs of biological samples throughout the national territory. The purpose of this intervention is to guarantee each patient the treatment at the nearest AIEOP center while making the services provided by the reference laboratories usable.
3. The design of common diagnosis and treatment protocols has been widely promoted by AIEOP. The adoption of cooperative treatment protocols and the constant participation in national and international clinical trials has in fact represented the fundamental tool that has made it possible to significantly improve the overall survival rate, which today exceed 80-85%.
4. The survivor's passport is a document that contains personalized recommendations on the long-term follow-up that each patient should receive based on the specific type of cancer and therapy administrated.
5. The development and refinement of collaborative networks in the pediatric field is a fundamental tool for improving the quality of care and promoting the translation of scientific evidence into clinical practice.

At the national level, the most important collaboration is that with the National Rare Cancer Network (RNTR), established with the agreement

of 21 September 2017 between the Government, the Regions and the autonomous Provinces of Trento and Bolzano. Collaborations are also active with the main adult oncological and hematological scientific societies (AIOM, SIE, etc.) and the scientific societies of the main pediatric specialties (SIP, FIARPED, SINEPE, etc.). In Europe, AIEOP is one of the 29 affiliated companies of SIOPE, it is an active part of the ITCC and it is included in the ERN PaedCan network. Furthermore, AIEOP collaborates with the Parents' Associations both nationally and internationally.

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LECT 31

BREASTFEEDING AND NUTRITION IN POST COVID-19: EXPERIENCE AND WISDOM

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Breastfeeding represents the gold standard for infant feeding, primarily because it is an indispensable source of essential nutrients for proper growth and healthy development but also because it is a vehicle for important immunological components that are essential in the formation of the infant's nascent immune system. Breast milk also provides a unique microbiome, composed of beneficial, commensal and potentially probiotic bacteria, which can make a valuable contribution in colonizing the developing infant microbiota and in promoting proper maturation and integrity of the intestinal barrier [1, 2]. It also proves to be of great support in creating a deep bond between mother and baby [2]. Nonetheless, during the COVID-19 pandemic, although national and international guidelines recommended breastfeeding by SARS-CoV-2 positive mothers, considerable insecurity remained in clinical practice regarding the safety of infants. However, the most recent scientific evidence from the systematic literature review continues to support the importance of encouraging breastfeeding despite the high transmissibility of SARS-CoV-2, while adhering to all safety and hygiene measures for the mother and close contacts [2]. In addition, the safety, immunogenicity and efficacy of COVID-19 vaccination in lactating mothers are reported [3, 4]. Metabolomic study of breast milk metabolites (molecules weighing < 1,500 daltons) could help in understanding the consequences of the virus on this biofluid. In fact, particular metabolites could reflect some infection-induced metabolic changes in the host and thus represent specific biomarkers for COVID-19. Although there is very little data on this issue to date and when compared with metabolomics studies conducted on the serum of COVID-19-infected adults, given that the composition of breast milk generally mirrors that of the mother's blood, an alteration in metabolites derived from the intestinal flora emerges in particular. This underscores a potential correlation between COVID-19 and intestinal dysbiosis and supports the importance of breastfeeding also in reducing the severity of COVID-19 due to the beneficial effect on the integrity of the intestinal barrier and the microbiota, thus performing an immune-modulating action [4].

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LECT 32

COMPLEMENTARY FEEDING: METABOLOMICS DATA

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Metabolomics enables the instantaneous identification of changes in the composition of endogenous and exogenous metabolites that originate from the interaction between specific pathophysiological states, gene expression, and the environment, bringing out discriminating biomarkers in the early diagnosis of various diseases, anticipating their outcome, and evaluating and monitoring the therapeutic effect. Particularly in pediatrics and neonatology, such technology may offer encouraging new perspectives for improving outcomes of critically ill patients by enabling early recognition of metabolic profiles associated with disease development, with a view to personalized medicine [1]. In this context, nutrimetabolomics, one of the branches of such diagnostic technology, which allows the recognition of specific clusters of metabolites associated with nutrition, appears particularly important in the early ages of development, during which nutrition plays a critical role [2]. The impact of human and artificial milk on the metabolome of the large intestine, both before and after weaning, in the animal model has recently revealed significant metabolic differences in the luminal content of the cecum, proximal and distal colon, and rectum but especially an important change, with the introduction of solid food, in sugar metabolism influenced by the neonatal diet [3]. In this context, studies on the nutrimetabolomics of weaning in humans are still very limited [2]; however, it was found that daily administration of probiotics during complementary feeding decreased levels of palmitoleic acid, an important monounsaturated fatty acid strongly linked to visceral obesity, and those of putrescine, a key polyamine in intestinal barrier integrity [2]. There was also evidence that a relatively small amount of animal foods is sufficient to change the metabolism of children, as a different metabolic profile emerged in children who followed a vegan diet from birth compared to lacto-ovo-vegetarians and omnivores, although nutrient intake matched current national recommendations. Metabolomics would therefore appear to assess nutritional adequacy in greater depth, raising the need for more detailed, longitudinal, and cross-sectional studies on child nutrition [2, 4].

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LECT 33

AUTISM SPECTRUM DISORDER (ASD): COMBINING CLINICAL AND RESEARCH APPROACHES

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Autism spectrum disorder (ASD) is a lifelong condition clinically characterized by social skills impairment in addition to restricted and stereotyped patterns of behaviors [1]. The diagnosis of ASD usually identifies common inherited genetic variants that interface with a complex biological system based on the detection of the individual molecular phenotype. Metabolites are the building blocks of the molecular phenotype, and for this reason metabolomics in recent years has emerged as a possible approach to identify complex phenotypes. For instance, in a recent study we found a correlation between the clinical phenotype of autistic children and their urine metabolome [2]. Furthermore, the severity of ASD core symptoms and problematic behaviors were associated with specific metabolic perturbations. These aspects can also have an impact on the treatment which currently does not recognize any effective pharmacological intervention on the core symptoms. For these reasons it is essential that diagnostic and therapeutic approaches to ASD must be combined on a double level: clinical and research.

In such context, research on gut microbiota could play a pivotal role [3]. In fact, gut dysbiosis may be not only related to the high incidence of gastrointestinal (GI) symptoms within autistic pediatric population (3.5 times more in comparison

to typical development peers). But the gut microbiota dysregulation of ASD individuals could be connected to the onset of internalizing and externalizing symptoms through neural and endocrine pathways, the so known gut-brain-axis [2].

Noteworthy, probiotic supplementation and, in particular, precision microbial intervention, represent a promising area of research in ASD, with considerable clinical implications.

A recent preclinical study found that supplementation with *L. reuteri* selectively rescues social deficits in idiopathic ASD models via the vagus-nerve, suggesting that the effect is not dependent on other gut microbes [4].

Based on this knowledge, and to test the hypothesis of prosocial effect of *L. reuteri*, a randomized double-blind placebo-controlled trial was performed at the Child Neurology and Psychiatry Unit, Tor Vergata University Hospital.

Specific aim of the study was to assess the effect of 6-month *L. reuteri* supplementation on behavioral profile, with a specific focus on social deficits and on GI symptomatology, in a sample of 43 young ASD individuals (age range 3-8 years).

At baseline, participants were blindly randomized to *L. reuteri* or placebo supplementation. A standardized clinical assessment of cognitive skills, socio-communicative behaviors and GI symptoms was performed for each patient at baseline (T0), after 3 months (T1) and after 6 months (T2) of supplementation.

Preliminary findings suggest that probiotic supplementation with *L. reuteri* improves social deficits and GI symptoms in children with ASD.

As a whole, findings revealed that, from both a clinical and preclinical point of view, *L. reuteri* supplementation represents a promising therapeutic area for ASD.

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LECT 34

HOW GUT MICROBIOTA IMPACTS AUTISM SPECTRUM DISORDER

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Over the past two decades, the rapid evolution of the molecular techniques allowed the DNA sequencing from the entire microbial communities colonizing the human body, that is the human microbiome. As a consequence, human microbiome research has exploded capturing the interest of the whole scientific community and the imagination of the general public. By using the search term "human microbiome", in 2003 the number of PubMed citations were approximately 100; at the date of September 3, 2022, they are 109,186. Today the terms microbiome, microbiota, and human microbial colonization are commonly used not only by researchers and scientists but even by the mass media and ordinary people. Although the terms microbiome and microbiota are often used interchangeably, they differ to each other; the former refers to the collection of genomes of all the microorganisms found in a given environment, the latter encompasses all the living members forming the microbiome [1]. The largest microbiota of the human body houses the gastrointestinal (GI) tract with about 10^{13}-10^{14} prokaryotic organisms. Recent evidences demonstrated the early microbial colonization of the fetus by the transfer of microbial strains from the mother to the fetus via placenta. At birth, the baby is further colonized by the direct transfer of microorganisms from the birth canal and perianal area or, when born by caesarian section, from the skin; even breastfeeding provides microbial colonization during the neonatal and weaning age [2].

Undoubtedly, the microbiome strongly influences the human life, intended as wellness, the preservation of health (both physical and mental), and the onset and progression of disease, by maintaining the homeostasis. The close relationship between the microbiome and the host is driven by a complex interplay with various systems of the human body including nervous, endocrine, and immune systems; notably, the microbiome affects the human metabolism by synthesizing metabolites that may be essentials (e.g., short chain fatty acids) or toxic (e.g., phenols, indoles) for

human metabolic pathways in various organs (e.g., brain). Alterations of the homeostatic balance of the microbial ecosystem, namely dysbiosis, consists of the loss of the microbial diversity in conjunction with the overgrowth of such microbial strains, mostly pathogens (e.g., *Clostridium difficile*, *Escherichia coli*), and the depletion of various so-called beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus* genera and *B. subtilis* species. Dysbiosis activates changes in the microbial metabolome and in the interactions with the immune, endocrine and nervous systems; these changes are associated with systemic diseases including autoimmune diseases, cancer, psychiatric and neurological syndromes, and neurodevelopmental disorders, especially autism [3].
Gut microbiota plays a major role in autism spectrum disorder (ASD); in fact, the gut bacterial homeostasis impacts in brain development, behavioral functions, and blood-brain-barrier integrity. Interestingly, microbial dysbiosis alters the mRNA splicing, including that of genes associated with autism, as recently demonstrated in a mouse model of autism [4].
Overall, in autistic subjects, gut dysbiosis is common and is associated with inflammation and leaky gut. Changes in the microbial metabolome due to dysbiosis lead to the excess of metabolites acting as neurotoxins, for example p-cresol, hippuric acid, quinolinic acid, indole-3-acetic acid, propionic acid. Several factors contribute to promoting gut inflammation and dysbiosis; lifestyle, food selectivity, drugs are the most frequent. Nevertheless, GI diseases are the most common medical condition associated with ASD [5]. A large body of literature investigated the gut microbiome in children and adults with ASD; however, much remains to be clarified. For example, the notion that *Bacteroidetes* are significantly reduced, leading to a higher *Firmicutes*/*Bacteroidetes* ratio is not yet fully established; at least 5 studies found an increased *Firmicutes*/*Bacteroidetes* ratio as many found it decreased. Unfortunately, further results emerging from the literature on gut dysbiosis in ASD are controversial. Some studies found the overgrowth of *Akkermansia spp.* in autism, whereas others reported the depletion of this genus. Various factors affect differences between studies including disease severity and phenotype, type of biological sample (stool, endoscopic biopsies), site of the biopsy sampling, diet and medications, techniques utilized for metagenomics. Most studies found that *Fecalibacterium prausnitzii*, *Coprococcus spp.*, and *Bifidobacteria spp.* are significantly reduced in autism. An early study found that *Veillonaceae*, *Prevotellaceae*, and *Lachnospiraceae* were significantly reduced in autistic children compared with neurotypical children; conversely, *Lactobacillaceae* were increased.
The research on microbiome in autism is challenging; new perspectives for effective individualized therapeutic treatments may originate from our understanding of gut dysbiosis in individuals with ASD. The supplementation with probiotics and the reduction of inflammation and oxidative stress may contribute to ameliorate autistic core symptoms and to help autistic children and their families in the management of this destructive disease.

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LECT 35

THE MYSTERIES OF SLEEP IN PEDIATRIC AGE

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Sleep is a fascinating and still mysterious dimension, despite more than 100 years of study.
Sleep is a primordial homeostatic function, regardless of age.
Sleeping is not just resting the body, but it has an articulated and complex role for the immune, hormonal and metabolic functions.

In the complexity of neurodevelopmental disorders, it is undeniable that altered sleep contributes significantly to the worsening of cognitive and behavioral aspects. Regardless of the underlying pathology, it is extremely important to preserve the integrity of sleep in its correct modulation and regulation.

When the regulatory genes of circadian rhythms are altered, a domino effect occurs on the neurochemical pathways that govern sleep, creating new balances that pharmacological treatments or alterations of the microbiome can accentuate. It is evident that in the developmental age the duration of sleep is particularly far from the optimal standards, especially due to the concomitance of inadequate parental attitudes that tend to entrust the role of babysitter to technological devices, in fact creating habits such as to disturb sleep in its phases in very young children.

The modern vision of the developmental age medicine cannot ignore a deep and serious knowledge of the regulatory mechanisms of sleep and of the important sequelae that such alterations have in the long term. The effects on the cognitive sphere are even irreversible and also explain the worsening of motor and behavioral symptoms even in complex pathologies such as autism, cerebral palsy, epilepsies. Furthermore, the hypnic macrostructural patterns in neurodevelopmental disorders, including genetic ones, are similar with fragmentation of the stability of the NREM stages and reduction of REMs. These similarities suggest that sleep represents an essential key to understanding the pathogenesis and evolution of pathological pictures in neuroscience.

LECT 36

PERIODIC FEVER, APHTHOUS STOMATITIS, PHARYNGITIS, ADENITIS (PFAPA): A MISTERY TO RESOLVE

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PFAPA (periodic fever, aphthous stomatitis, pharyngitis, adenitis) is a syndrome featured by recurrent episodes of fever, aphthous, sore throat, and lymphadenitis and affecting the pediatric population aged between 2 and 5 years of age without a prevalence of gender (M = F). Recent studies support the role of inflammasome-related genes in the onset of PFAPA. An aberrant innate immune response to exogenous triggers as well as a familial recurrence are factors that cannot be excluded in the PFAPA pathogenesis [1]. Globally, PFAPA shows a good prognosis and frequently it disappears during childhood; however, this syndrome impacts negatively on the health and quality of life of little patients and their families especially due to the lack of a specific treatment. Glucocorticoids are the first-line treatment in PFAPA thanks to their ability to suppress the attacks readily and completely in most patients; however, their use does not prevent further attacks, and sometimes their administration has been associated with an increase in the frequency of the attacks [2]. Recently, the discovery of the immune mechanisms involved in PFAPA pathogenesis has pawed the way to novel therapeutic approaches promising new advances in managing and treating patients with PFAPA. In this regard, pidotimod, a synthetic dipeptide molecule, showed biological activities both in the adaptive and the innate immune mechanisms, resulting in a significant improvement of PFAPA's clinical outcomes [3]. Authors demonstrated that patients receiving pidotimod plus betamethasone showed a significant decrease in the frequency of fevers, episodes of pharyngitis, aphthous stomatitis, and betamethasone use on need when compared to patients receiving only betamethasone on need. Interestingly, the treated group did not report any adverse event (AE) during the treatment period. However, it remains to be elucidated the mechanisms by which pidotimod can modulate the immune response in patients affected by PFAPA. With the aim to fill this gap, we are currently looking to the metabolomics profile of patients with PFAPA also under treatment with pidotimod. We strongly believe that the analysis of low-molecular-weight metabolites in biological samples could provide the opportunity to identify new pathogenic mechanisms underlying PFAPA, discover how pidotimod acts in patients with PFAPA, identify the best candidate for treatment with pidotimod as well as biomarkers of disease able to reflect strictly the course of disease.

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LECT 37

OUR CHILDREN ON OUR PLANET: INTRODUCTION TO THE TOPIC

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The impact of pollution on the lives of our children on our planet represents largely virgin territory for investigation. There are many unanswered questions: how much does the pollution of the planet affect the journey of the fetus inside the uterus? what is plastic doing in the placenta? is it true that, by deforming intracellular organelles, plastic is a leading player in the development of metabolic syndrome? since we know that breast milk is an extraordinary living biological fluid, would it not be worthwhile to know the presence and impact of endocrine disruptors in milk? We are rightly concerned about all macroscopic environmental changes, but we are not sufficiently attentive to the fetus. In light of all these questions, one question sums them all up: are the fetus and the newborn the fathers of man, and not vice versa? This is a provocative question, deriving directly from the concepts that David Barker illustrated in the hypothesis named after him and developing the idea of perinatal programming. According to his theory (now no longer a theory but a certainty), not only does the infant not represent a small adult, but the infant (or even the fetus) would be "the father" of the adult person, because the response of a developing organism to a specific change, occurring during a critical time window of the perinatal period, alters the trajectory of development itself qualitatively and quantitatively, causing permanent effects on the phenotype. Until not so long ago, we thought that the newborn was an essentially healthy being and that the human progressively deteriorated inevitably with time. Today, on the other hand, it is believed that the infant harbors within itself, from the prenatal period, the vocation to become ill. A great deal is decided prenatally and perinatally, beyond genetic inheritance: this is what is called epigenetics. From a general point of view, nutrition is the most important epigenetic element from even the pre-conceptional period.

Pollution has been called "the gift our mother never wanted to give us". Think, for example, of endocrine disruptors, heavy metals, and ultrafine particulate matter. Here we want to mention 6 good reasons to protect nascent life from exposure to chemicals (American Academy of Pediatrics, 2018):

1. a child's organs are rapidly developing, which is precisely why they are more vulnerable to harm from chemical exposure;
2. the impact of chemicals per kg of weight is much higher in the fetus and infant;
3. infants have lower levels of chemical-binding proteins, and this provides more opportunities for toxicants to reach target organs;
4. similarly, detoxifying systems are less developed in children than in adults;
5. the longer life expectancy makes the development of adverse events more likely, even in the long term;
6. finally, the immaturity of the child makes the blood-brain barrier more permeable, which we now know is not a barrier at all.

We are conducting a European project together with Colleagues from Parma and Reggio Emilia (LIFE18 ENV/IT/000460 – Life MILCH – Mother and Infant dyads: Lowering the impact of endocrine disrupting Chemicals in milk for a Healthy Life) that evaluates the impact of endocrine disruptors on breast milk and formulated milks.

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LECT 38

THERAPEUTIC CHOICES AND RESPECT FOR THE ENVIRONMENT

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Among the areas in which the "One Health" proposal of the World Health Organization is articulated, there are some that are considered particularly relevant and these include environmental health and antimicrobial resistance. In this context, the researches studied, above all in recent years, the environmental diffusion of pharmaceutical products (PP) and transformation products (TP, metabolites of drugs and products of biotic or abiotic transformations that are produced in their disposal processes and in the environment itself are placed). The environmental diffusion of PP occurs mainly through: a) the discharge of effluents from urban wastewater treatment plants containing both drugs excreted after use and unused drugs thrown into the sink or toilet; b) the spreading of animal breeding effluents; c) the discharge of effluents from production plants; d) the use of sludge or purification water for agricultural use; e) the improper landfill of unused drugs and contaminated waste. In world-wide studies, PP and TP have been found in water (surface or depth, marine [in particular near river estuaries] and ocean), soil (especially cultivated) and the atmosphere. It should also be emphasized that many of these substances tend to persist for a long time in the environment because even if their chemical-physical characteristics would make them not very persistent, their continuous environmental introduction determines a real long persistence. They are therefore defined as "pseudopersistent".

Damage to various ecosystems can result as demonstrated in algae, invertebrates and fish. Harmful effects for humans can come from the food chain (various PP and TP act as endocrine disruptors) and indirectly from the spread of resistance to anti-bacterial drugs. Microorganisms exposed to antibiotics at low, sub-lethal or sub-inhibitory doses can in fact develop resistance that can persist and spread into the environment even through specific genes (antibiotic resistance genes [ARGs]) with a horizontal genetic transfer. In conclusion, it is necessary to better understand the phenomena of bioaccumulation and the changes that drugs can induce in the various ecosystems and make purification systems more effective. It is also useful for a patient education work to be drawn up aimed at a more rational pharmacological use, at a more used separate collection and at avoiding the dispersion of unused drugs.

Finally, it is recommended research on the presence of any pharmacological residues in the developmental age and on the possible risks that this presence can entail in growing organisms whose greater sensitivity is known compared to adulthood towards various chemical contaminants. In this sense, it is interesting to recall recent experiences that demonstrate the presence in the urine of a child population of residues of antibiotics often used in animal farms. These researches in fact highlight a possible negative effect on normal growth, with a higher incidence of obesity in the most exposed subjects.

LECT 39

ENVIRONMENTAL ENDOCRINE DISRUPTORS AND THE MOTHER-INFANT DYAD: THE LIFE MILCH PROJECT

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The research topic of the "developmental origins of adult diseases" demonstrated that fetal and early postnatal life are highly critical periods for the long-term modulation of immune, reproductive, brain and metabolic function. These developmental stages are characterized by high plasticity and sensitivity to environmental inputs that can modulate a tissue/organ function. Among the environmental factors involved in the worldwide deterioration of health, endocrine disrupting chemicals (EDCs) have raised high concern particularly for their effects on reproductive, metabolic and neuro-behavioral health [1-3]. EDCs are environmental chemicals with hormone-like activity that can disrupt the programming of endocrine signaling pathways during development, resulting in adverse health effects much later in life. EDCs are found in many everyday products and consequently, even at low environmental concentrations, human exposure to EDCs is ubiquitous and chronic, spanning the whole lifespan from conception to adulthood. In particular, maternal exposure to EDCs during pregnancy and lactation results in fetal and neonatal exposure via *utero* and breastmilk. Breast milk is the best

source of nutrition for infants and women must be encouraged to breastfeed. However, potential risks associated with maternal exposure to EDCs need to be factored into overall public health interventions. EDCs can also be present in infant formula and/or its containers.

The Life MILCH Project is a longitudinal pilot study that aims to determine the association between mothers' life and nutritional habits, levels of EDCs in maternal (and formula) milk and infants' growth, health and neurobehavioral development in the first year of life, in order to identify specific measures to reduce exposure of the mother-infant dyad to environmental EDCs. Pregnant women in the third trimester of gestation are enrolled at Parma and Cagliari University Hospitals and Reggio Emilia Hospital. At recruitment, women's lifestyle and nutritional habits are recorded through two questionnaires, maternal urine and plasma samples are collected for assessing EDCs levels. At delivery, cord blood sample, placenta, newborns' growth parameters (e.g., body weight, anogenital distance, subcutaneous fat) and urine are collected. Mother-infant dyads are recalled 1, 3, 6 and 12 months after delivery for biological sampling (breastmilk, maternal and infant urine), questionnaires and evaluation of infants' growth and neuro-behavioral development. Perceptive, socioemotional, cognitive, behavioral and global developmental areas are assessed by different neurobehavioral tests at any time-point and by the Bayley III Scale at 6 and 12 months of age. Analysis of biological samples for different EDCs is carried out at PeptLab in Florence University.

Based on the collected data, a risk assessment model for EDCs exposure will be developed to unravel how maternal lifestyle and nutritional habits affected levels of EDCs in breast milk and their impact on infants' development. Based on this evidence-driven analysis, the project will develop a prevention/awareness campaign and interventions for reducing maternal exposure to EDCs; it is hypothesized that a change in food habits and lifestyle would reduce the levels of some EDCs in the mother, the breastmilk and consequently in the baby. These prevention activities will be carried out in the three project locations and with three specific targets: pregnant women and/or breastfeeding mothers, women of childbearing age, health professionals. The efficacy of the prevention campaign and intervention will be assessed by a subsequent biomonitoring of the levels of EDCs in the breast milk of the women who have participated in the campaign during pregnancy/nursing, including an assessment of their infants' development and EDC exposure levels.

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LECT 40

QUANTITATIVE ANALYSIS OF PHTHALATES, BISPHENOLS, PARABENS, PYRETHROIDS, PAHs, POLAR PESTICIDES AND METALS IN BABY BOTTLES AND INFANT FORMULA, TO DEFINE THEIR ROLE AS EDCs IN THE LIFE MILCH PROJECT

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The EFSA and ECHA guidance document described, in 2018, the substances with endocrine disrupting properties in pesticides and biocides [1]. According to this latest document, an endocrine disrupting chemical (EDC) is a substance showing an adverse effect also at very low concentration in an intact organism, having an endocrine mode of action, i.e., altering the function(s) of the endocrine system. EDCs are highly heterogeneous, ubiquitous, and present in everyday life. In fact, they are used in different industrial processes: bisphenol A (BPA) and phthalates are used as plasticizers in plastics and/or food storage materials; parabens in cosmetic and pharmaceutical preservatives; polycyclic aromatic hydrocarbon (PAHs) in industrial solvents and their byproducts; metals (i.e. Pb, Cd) in children's products; pesticides (chlorpyrifos, glyphosate) and insecticides (pyrethroids) are extensively used by farmers. Thus, monitoring the

levels of these different EDCs in pregnant women and/or in children can be essential to understand the EDCs impact on the health of infants (general health status, cognitive development, metabolic regulation, development of intolerances and allergies, etc.). The amount of EDCs in breast milk/infant formula was widely documented in the literature, but often such studies focus on a single group or at most two groups of EDCs.

Considering that multiple exposures result in cumulative effects and synergistic effects can also be observed, the aim of our study performed in the context of Life MILCH project [2] is to increase knowledge concerning correlation between exposure to EDCs and damage to health, in particular to reduce the impacts of these chemicals on infants' health, helping also the EU to improve the know-how on multiple exposures and cumulative effects. Currently, EU chemical regulations do not generally consider these cumulative effects, notably for EDCs exposures.

With this idea in mind and considering our previous experience [3-5], we proposed a series of sensitive and rapid methods for measuring EDCs levels.

Appropriate methods for simultaneous identification of different EDCs group were set up. In particular, 6 UPLC-MS/MS and 1 ICP-AES were set up for a total of 56 chemicals: 14 phthalates, 4 bisphenols, 11 PAHs, 7 parabens, glyphosate and its major metabolites, 3 pyrethroid insecticides, 15 metals. These methods were applied to the quantification of EDCs in infant food, including breast milk, infant formula, and baby bottles.

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LECT 41

ENDOCRINE DISRUPTORS: EFFECTS AND CONSEQUENCES

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Endocrine disrupting chemicals (EDCs) are a number of chemical substances, present in the environment, that affect the endocrine system. Effects are different based on amount, mode of exposition (ingestion, contact, inhalation, transplacental, transdermal) duration, and particularly time of exposure during lifetime (critical time windows).

Most of their effects are mediated by changes in epigenetics that are transmitted through generations and control gene expression since life *in utero*, contributing to programming metabolism, endocrine function and future disease throughout life. The main mechanisms are DNA methylation, which is conditioned by breastfeeding also, which in turn conditions early-life BMI trajectories and adipogenesis [1], histone modifications and non-coding RNAs. Among these latter the most studied are miRNAs. These show changes in placenta in relationship with pregnancy outcome, are involved in growth and metabolism (insulin signaling for instance, thus insulin sensitivity). Lifestyle, eating habits, exposure to EDCs contribute to gestational diabetes that leads to changes in fetal programming of adipocytes, liver, islet cells, heart, muscle, brain and liver.

Currently, the concept of "exposome" has developed as the result of the interaction of external environment (radiation, stress, lifestyle, infections, drugs, diet and pollution), with the individual's metabolism and chemical environment giving as a result specific biomarkers detectable in blood and biological fluids. Among these, metals and endocrine disruptors. The exposome has subsequent effects depending on its interactions with the individual genetic and acquired susceptibility: this is defined resposome. When there is an imbalance among these factors, this leads to unhealthy conditions and disease [2].

Critical time windows of exposure amplify the effects of exposure to EDCs. Evidence both in animals and humans suggest the importance of this in the onset of obesity and type 2 diabetes. Furthermore, adipose tissue can represent a deposit for EDCs amplifying their effects. Some EDCs are currently identified as obesogens such as bisphenols, phthalates, parabens, non-steroid estrogens, brominated flame retardants, organotins and polychlorinated biphenyls that are commonly contained in cans, thermal paper, vinyl flooring, personal care products, food preservatives, drugs, clothing, furniture, solvents, pesticides and paints. From a molecular point of view, it has been shown that EDCs can interact with PPAR gamma and retinoic acid receptors, and with the aryl hydrocarbon receptor (AhR) [3].

Exposure to EDCs has been shown to have effects on the timing of pubertal development and on testicular and ovarian function. Induced epigenetic changes would cause polycystic ovary syndrome (PCOS) phenotypes in females and would pass on to at least 3 generations. An anti-androgenic effect has been shown for EDCs such as phthalates, tributyltin, parabens and bisphenols. Finally, an increase in aromatase activity in adipose tissue has been observed which determines an increase in estradiol. In addition, interferences with thyroid function and modulation of adipocytokine action have been described [4].

In recent years the role of microbiota has been highlighted, showing how it can change in relationship with diet and obesity, and also its role in metabolism and cardiovascular disease. Persistent organic pollutants have been shown to modify gut microbiota and some of the mechanisms of action include AhR activation and increased stress oxidation [5].

Finally, it is currently known that EDCs can favor the onset of diabetes by modifying insulin secretion and beta-cell function, reducing beta-cell mass, reducing peripheral glucose uptake, modifying liver glucokinase activity and by inducing epigenetic changes having an effect on glucokinase [4].

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LECT 42

OXYSTEROLS, OXIDATION AND MILK QUALITY: A NEW PARAMETER

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Cholesterol belongs to a class of organic molecules called lipids, Specifically, it is a sterol with that can easily undergo oxidation, both enzymatic and not enzymatic. This oxidation leads to a wide variety of cholesterol oxidation products (COPs), most commonly named oxysterols. The major and most studied oxysterols species found in animal products (e.g., meat, fish, egg and milk) of non-enzymatic origin are 7α-hydroxycholesterol (7αOHC), 7β-hydroxycholesterol (7βOHC), 7-ketocholesterol (7KC), 5,6α-epoxycholesterol (α-epoxy), 5,6β-epoxycholesterol (β-epoxy), cholestan-3β,5α,6β-triol (TRIOL), 25-hydroxycholesterol (25OHC). Concerning 7αOHC and 25OHC, they are partly generated enzymatically as well [1].

While some of the enzymatic ones possess broad antiviral activities, the non-enzymatic mostly originate from the deterioration of the nutritional value of foodstuff after exposure to heat, light, radiation and oxygen. This raises questions about their potential health risks, considering that their action is related to several pathologies [2]. Nowadays, gas chromatography combined to mass spectrometry (GC-MS) allows to measure all these

oxysterols accurately and precisely in raw as well as in industrially processed food and food ingredients.
In order to verify their significance as biomarkers of cholesterol autoxidation and animal origin raw material freshness, we evaluated the presence of selected oxysterols in whole milk powder (WMP) and in chocolates containing WMP of increasing shelf-lives [3], and monitored their evolution throughout industrially employed storage procedures, even considering two different primary packaging. Our work highlights that non-enzymatic total COPs increase proportionally to the shelf-life of the WMPs, thus reflecting their importance as nutritional quality indicators for ingredients' freshness. The same trend was also observed on chocolate prototypes. Another noteworthy finding, based on the expected theoretical COPs, the effect of processing was quantitatively less significant in the generation of oxysterols than the contribution of the autoxidation of the WMPs over time. In this case, shelf-life was found to be the primary determinant of COPs generation. Lastly, the choice of primary packaging plays a fundamental role to dampen their formation and accumulation in processed foodstuff, thus preserving their characteristics over time.
Even though more quantitative data on COPs in composite products and a systematic estimation of daily intake are still needed, a reduced consumption has been suggested considering the hypothesized undesirable health effects of such compounds at relatively high concentrations. The measurement of enzymatic and non-enzymatic oxysterols could represent a useful and innovative tool to monitor and increase the commercial and nutritional value of both milk ingredients and finished products, highlighting their quality and freshness in relation to the processing and storage procedures applied. These findings support the general concept of the urgency of redefining food quality parameters.

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LECT 43

EVOLUTION OF THE INTESTINAL MICROBIOTA: EACH AGE HAS ITS OWN SPECIFICITIES

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The gut microbiota can be considered a functional human organ, and consists of microorganisms, especially bacteria, whose activity is influenced by diet, lifestyle and the use of drugs. Throughout life, from birth to old age, several factors affect its stability, complexity and qualitative-quantitative composition. The first period of life after birth represents a key moment for the microbiota-host interaction: colonization by microorganisms, which begins already in the prenatal period, increases at delivery, which represents the first crucial moment. As complex is the microbiota of an adult, the gastrointestinal tract of a newborn born at term is relatively simpler, being dominated mainly by *Bifidobacteria* and *Lactobacilli*. The loss of these bacteria during the first stage of life can lead to negative consequences for the health, including increased susceptibility to autoimmune/metabolic diseases. Breastfed infants maintain the dominance of *Bifidobacteria* and *Lactobacilli*, while those fed with formula have a different microbial composition. It is important to know that the gut microbiota of an infant, until the moment of complementary feeding, is particularly rich of these two families, which reach up to 70% of the microbial population. A valid support in case of intestinal dysbiosis can be represented by the integration of probiotics based on *Bifidobacteria* and *Lactobacilli*. In particular, *Bifidobacteria* are deficient in obese subjects and their integration may be useful to reduce the negative metabolic effects of overweight. In a cross-over, randomized double-blind placebo-controlled trial we showed an improvement of metabolic parameters, particularly insulin sensitivity, in obese children and adolescent, after supplementation with *Bifidobacterium breve* strains. In addition, when choosing a probiotic, some important features should be considered, such as the use of state-of-the-art technologies that make the strains alive and viable up to the target organ, the gut. In particular, some technologies such as microencapsulation considerably increase the survival rate of bacterial strains in intestinal transit and their ability to colonize the gut. So, bacterial strains can be attacked by the acidic environment of the digestive system and their properties can be altered even before they reach the intestine. The strains are individually coated with a thin protective lipid layer to make them resistant to gastric juices during passage

through the digestive tract. This ensures adequate action at the target organ level, with a 90% survival rate of microencapsulated strains, compared to 10-25% of non-microencapsulated. Finally, age-specific formulations respect the diversity and needs of each organism: strictly selected and documented probiotic strains, probiotic strain amounts studied for each age target, specific and practical galenic forms depending on the age, which guarantee a tailored supplementation.

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LECT 44

REGRESSION ALGORITHMS & PATTERN RECOGNITION FOR AUGMENTED EPIDEMIOLOGY

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"While an unprecedented global effort is underway to combat the COVID-19 pandemic, persistent threats to the health of our planet also require urgent remedies. Climate change, environmental pollution, biodiversity loss and unsustainable use of natural resources pose multiple risks to human, animal and ecosystem health. They include infectious and noncommunicable diseases, antimicrobial resistance and water scarcity".

Of increasing interest, therefore, is the design, piloting and implementation of a multinational epidemiological surveillance system using clinical, environmental, social and other data collected systematically in Italy and other major EU countries.

The compelling nature of this need is due to the paradigm shift aimed to enable a shift from an ex-post monitoring model to a "predictive" paradigm based on Pattern Recognition and AI Agent techniques that enable automated alerts critical for more timely and effective health and environmental policy taking.

Indeed, health systems can benefit from AI to help drive sustainability, efficiency and patient outcomes, starting with a new surveillance approach.

Since the European Commission adopted new recommendations on the European electronic health record exchange to unlock the flow of patient summaries across borders, creating a digital health infrastructure that supports evidence-based decision making has become a priority for EU countries.

The pandemic has further reaffirmed the need for decision makers to have new tools not only to track disease evolution and epidemiological conditions in the population in a timely manner, but also to more rapidly inform intelligence, based on predictive techniques and scenario analysis, around the evolution of infectious diseases and their correlation with social and environmental factors.

A "One Health" approach, in this regard, will go a long way toward ensuring close coordination between human, environmental and social dimensions, determinants and policy levers.

In fact, current epidemiological detection practices, based on a long-term ex-post monitoring model, have limitations, such as lack of standardization, fragmentation; quality data acquisition exists to varying degrees in Member States, not just in the clinical space. This variability, combined with disease-specific surveillance goals and priorities, necessitates a disease-by-disease, country-by-country, and even territory-by-territory approach.

Investment is therefore needed with the goal of overcoming these limitations.

One of the possible models to support this evolution is Pattern Recognition.

"The field of Pattern Recognition is about the automatic discovery of regularities in data through the use of computer algorithms, and the use of regularities is to take actions such as classifying data into different categories".

Pattern Recognition algorithms (classification, regression, clustering...) allow us, having assigned

a target variable, to automatically discover which features occur in conjunction (repeated regularities) with the investigated phenomenon.

This approach also shows us another interesting effect, i.e., the possibility of highlighting, discovering, target features and relationships that are not known or apparently not obvious.

Therefore, it is necessary to use a large amount of available data: environmental, veterinary and climatic data, electronic health record data and clinical pathology data referring to regional areas, anonymized; by doing so, the intent is to represent over time from a dataset defined by the boundaries of the territory for which the set of all data is incident. This enriched dataset will allow, through the adoption of algorithms implementing predictive objectives, to introduce risk stratification models with prediction components. At the same time, to introduce "sentinel" techniques of observation of the territory in the continuous and immediate search for clinically relevant phenomena for the population. Thus, the meta-objective is to identify and predict the evolution of a health phenomenon by analyzing through big data repositories those factors found to be precursors or occurring concomitantly and serving as descriptors of the phenomenon itself.

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