www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2019;8(1):e080127
doi: 10.7363/080127
Received: 2018 Oct 30; accepted: 2018 Dec 03; published online: 2019 Apr 18

Invited review

Off to a good start: environmental imprinting in the childbirth period

Antonio Ragusa[1], Simone Rugolotto[2], Sara D'Avino[1], Chiara Incarnato[3], Alessandra Meloni[4], Alessandro Svelato[1]

[1]Department of Obstetrics and Gynecology, Massa Carrara General Hospital, Massa, Italy

[2]Division of Pediatrics, Rovigo Hospital, Rovigo, Italy

[3]Certified professional midwife, Italy

[4]Department of Surgical Sciences, Division of Gynaecology and Obstetrics, Azienda Ospedaliero Universitaria of Cagliari, Cagliari, Italy

Abstract

Our organism and the expression of our genetic inheritance are conditioned by the environment. This is demonstrated by experimental models on animals, but more and more evidence shows similarities also in humans. Evidence now supports that neonatal and maternal health also depends on the interactions between the environment and the DNA itself. Even though the DNA sequence remains the same over the years, some genetic traits of human beings can be affected by the silencing or activation of some nucleotide sequences, for example by DNA methylation. Today, epigenetics is much more important than we used to think in 1942 when Waddington used the word "epigenetics" for the first time. The environment can modify DNA sequence methylation, affecting protein production and the phenotype. Examples of how epigenetics affects childbirth phenomenon are given and mechanisms are discussed. Four biological mechanisms of epigenetics are presented: genomic imprinting and silencing of the paternal set of chromosomes, the unpredictable "on/off" expression patterns of wild type genes, paramutations, and alternative states of protein folding. Some genes are triggered by stress, maternal nutrition, drugs (namely oxytocin, fentanyl), childbirth modalities, labor, environmental behavior, microorganism colonization. Imprinting theory is a good scientific basis, to explain the permanence of some biological effects at a considerable time after birth. Imprinting is an important mechanism of DNA expression, and different types of imprinting are described. The consequences of antibiotic use in the childbirth period are discussed, along with the importance of awareness in the use of antibiotics for maternal prophylaxis. Prenatal antibiotics and cesarean sections do affect neonatal microbiome considerably and, therefore, may be the causes of inflammatory intestinal disorders,

asthma, obesity, diabetes. Mode of delivery, labor, breastfeeding, and skin-to-skin practice are strictly related to future neonatal health, and the effects are shown here. One of the most important factors to explain the diseases mentioned above is probably the lack of "bacterial contamination" through the birth canal. However, this mechanism cannot be the only one to act, and, in fact, here we also discuss other mechanisms that contribute to the development of future pathologies. Last but not least, the culture and education of the operators, as well as maternal and providers' attendance behavior during childbirth, can change the relative outcomes of children's long-term health.

Keywords

Epigenetics, childbirth period, imprinting, intra-partum assistance, labor, environment.

Corresponding author

Alessandro Svelato, Department of Obstetrics and Gynecology, Massa Carrara General Hospital, Via Enrico Mattei, 54100, Massa, Italy; telephone: +39 349 1272580; e-mail: alessandrosvelato@virgilio.it.

How to cite

Ragusa A, Rugolotto S, D'Avino S, Incarnato C, Meloni A, Svelato A. Off to a good start: environmental imprinting in the childbirth period. J Pediatr Neonat Individual Med. 2019;8(1):e080127. doi: 10.7363/080127.

Definitions

Environment: "The circumstances, objects, or conditions by which one is surrounded" [1]; "the air, water, and land in or on which people, animals, and plants live" [2]; "the surroundings or conditions in which a person, animal, or plant lives or operates" [3]. By analogy, in this paper, we could define the place of childbirth as the surroundings or conditions in which women give birth.

Childbirth period: About the period immediately before and after birth. The perinatal period is defined in diverse ways. Depending on the definition, it starts at the 20th to 28th week of gestation and ends 1 to 4 weeks after birth. According to the WHO, it commences at 22 completed weeks (154 days) of gestation and ends 7 completed days after birth [4]. However, for our review, we have coined a new definition: "Childbirth period". We will only deal with the period closest to the childbirth, which begins at the beginning of the woman's labor (latent phase) and ends the 1st day after childbirth (24 hours after childbirth). In this period, the staff who assist childbirth, represents, together with the place where the childbirth occurs and those who accompany the woman, the environment of childbirth. We define this period as the childbirth period.

Imprinting: "Rapid learning that occurs during a brief receptive period, typically soon after birth or hatching, and establishes a long-lasting behavioral response to a specific individual or object, such as attachment to parents, offspring, or site" [5]. In this paper we will go beyond the ethological definition of imprinting, also considering this phenomenon at the cellular level, both for unicellular with receptors located on the cell walls, and for multicellular, with intra- and extra-cellular receptors [6]. In this paper, we will analyze the phenomena of environmental, biological imprinting during the childbirth period.

Epigenetics: Epigenetics deals with the study of inheritable modifications that lead to variations in gene expression, without altering the DNA sequence, and without causing changes in the sequence of the nucleotides that compose the DNA. Epigenetics studies the mechanisms that can vary the phenotype, without modifying the genotype. Epigenetic instructions, when they involve germ cells, can be transmitted to offspring.

Biological mechanisms underlying imprinting and cellular memory

We know that neonatal and maternal health depends on the interaction between the environment and DNA itself. Even though the DNA sequence does not change over the years, some genetic characteristics of human beings can be affected by silencing or activation of some nucleotide sequences. In another word, today epigenetics does matter much more than we used to think in 1942 when Waddington (1905-1975) used the word epigenetics for the first time [7].

The term epigenetics is used to explain the molecular processes through which genetic traits persist during cell division, without changing the nucleotide sequence of DNA. These are processes that result from the silencing or activation of genes, through modifications of the function of DNA, RNA and proteins. In practice, it is understood that the environment can change the expression of DNA. It is easy to understand what epigenetics means, thinking that all the body cells have the same nucleotide sequence, yet every cell becomes

something different: the liver cells (hepatocytes), the cerebral cells (neurons), the skin cells and so on. It is clear that the differences in expression at the phenotypic level depend on the context in which the genes express themselves and not only on the nucleotide sequence. The environment can modify the activation of the DNA sequence, with changes in protein production and the phenotype. Epigenetic modifications can also be transmitted to future generations. In the case of maternal stress or dietary problems, under- or over-eating will lead to epigenetic modifications of somatic tissue (including that of the brain), and the modifications will be limited to this. If stress or modifications act on primordial embryonic cells, these epigenetic modifications are transmitted to successive generations.

Epidemiological evidence of "programming" as a cause of metabolic diseases in adulthood has been suggested by the work of Barker and colleagues [8]. Although the concept of programming had been discovered previously, it was Barker's epidemiological studies in the late 1980s that led to the clear formulation that events in fetal life can influence the long-term risk of developing metabolic disease [9-11]. Using a cohort of 64-year-old men, all born in Hertfordshire (UK), Barker identified an inverse relationship between systolic blood pressure, increased cardiovascular mortality, and birth weight. Using the same cohort of men, he also demonstrated an inverse link between birth weight, glucose tolerance, and insulin resistance. Individuals with the lowest birth weights were 6 times more likely to develop type 2 diabetes or reduced glucose tolerance. These results were replicated in a large variety of populations of different ethnic groups. In reality, both excessively high birth weight and too low birth weight have been associated with cardiovascular risk factors in adulthood. Therefore, it is the body composition at birth, rather than the weight itself, which represents an indicator for predicting future diseases. Maternal weight before gestation and during pregnancy is significant in this regard, as both are associated with intrauterine fetal growth. The fetus monitors the external environment through the mother's organism. Fetal weight is modulated by the fetus itself, according to maternal nutrition: the fetus can modulate fetal weight gain adapting itself to maternal nutrition, without changing his genetic heritage, modulating and changing the expression of its DNA. Diseases that arise in adult life are determined not only by genetic factors but also by numerous epigenetic factors that come into play already during fetal life, during childbirth period and after birth [12].

There are numerous epigenetic mechanisms, the main epigenetic phenomena being (**Fig. 1**):

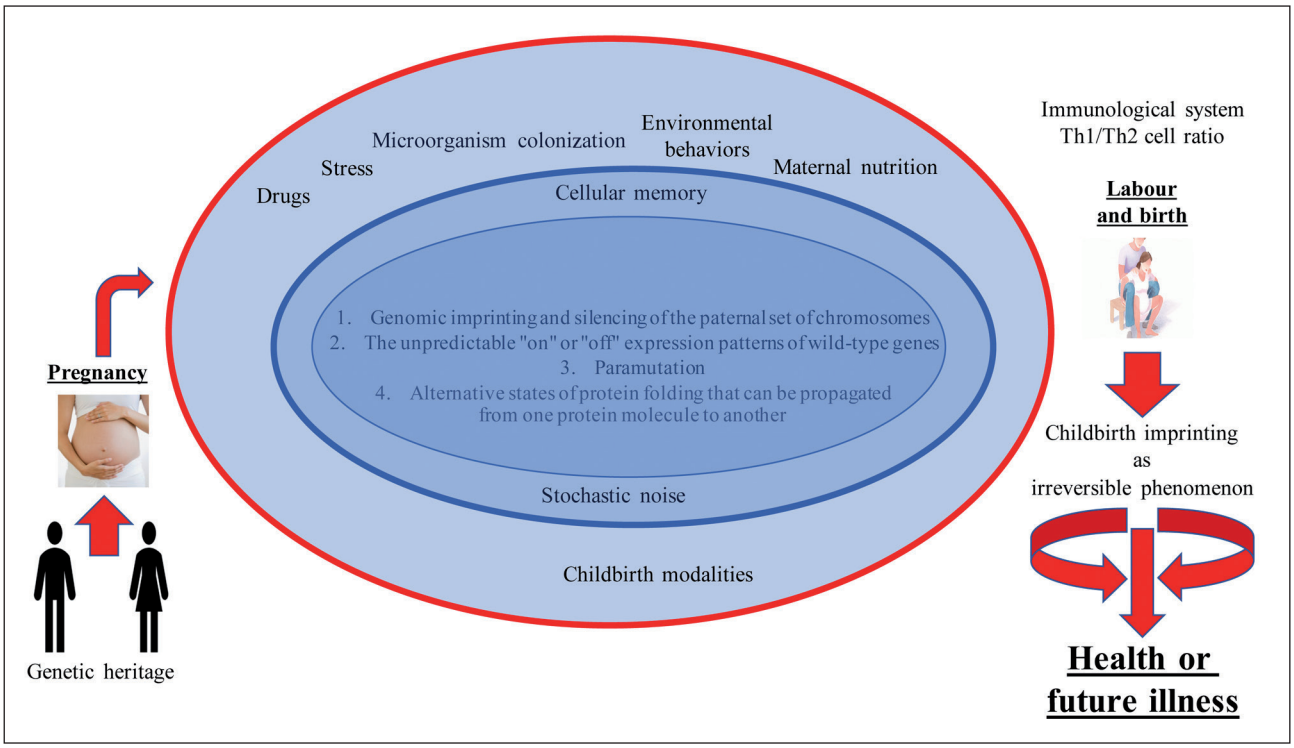

Figure 1. Pregnancy, labor and birth as complex systems. They are characterized by a huge amount of interdependencies.

1. genomic imprinting and silencing of the paternal set of chromosomes [13];
2. the unpredictable "on" or "off" expression patterns of wild-type geneses, position-effect variegation, transgenes, etc.;
3. paramutation [14];
4. alternative states of protein folding that can be propagated from one protein molecule to another.

All these phenomena have cellular memory in common [15, 16]: once a gene is triggered by stress, maternal nutrition, drugs, childbirth modalities, presence or absence of labor, environmental behaviors, microorganism colonization, it can completely change its expression. For example early or delayed clamping of the umbilical cord or, once again, type of breastfeeding, etc., determine a change in gene expression. Hormone imprinting theory is an excellent scientific basis to explain the permanence of some biological effects at a considerable time after birth. As Csaba writes: "Birth is a milestone in a person's life. Before birth, the mother's body protects the fetus, and the mother's hormones, which pass through the placenta, influence the fetal endocrine system. After birth, the infant starts its life, and the brain-controlled endocrine system chemically directs the actions of the organism. This requires the setting of the relation between the receptor and the hormone system" [17]. The fetal to neonatal transition is one of the most complex processes in biological existence. Very little is known about this transition at molecular and biochemical levels. The transition of the fetus from a hypoxic *in utero* environment to an oxygen environment is not without consequences. We do, however, know something more about this delicate transition phase in non-human primates [18].

In this animal model, during the first 3 days of life, Beckstrom and others observed an increase in substances related to the reduction-oxidation pathways of the electron transport chain. In particular, myoinositol and glutamic acid undergo necessary changes in this transition phase. Both of these substances are essential for intracellular homeostasis [19], gene expression [20, 21], and fat metabolism [22]. Once again, the changes determined at the time of birth remain in adulthood, thanks to the epigenetic mechanism and cellular memory. This mechanism is mediated above all, but not only, by the modeling of the newborn's immune system. The immune system of the newborn undergoes an enormous change that begins from the moment of the breaking of the membrane in labor (PROM), which is of both metabolic [23] and immunological nature.

Currently, we do not know if the fetus lies in a sterile environment during gestation, as some authors believe [24] or in an environment colonized by prokaryotes of various kinds, as others claim [25]. In any case, before PROM, the fetus may be subject to contact with a small number of prokaryotes, if any, or even no microorganisms at all. As soon as the mother's waters break, this is the moment in which the primordial relationship with the prokaryotes is established, at least from the quantitative point of view: it is the moment of the PROM. At this moment: "This continues a chain of maternal heritage that stretches through female ancestry for thousands of generations, if all have been vaginally born and breastfed. This means a child's microbiome, that is the trillions of microorganisms that live on and in him or her, will resemble the microbiome of his/her mother, the grandmother, the great-grandmother and so on, if all have been vaginally born and breastfed" [26].

In intrauterine life, low Th1/Th2 cell ratio defend the fetus against rejection by the maternal immune system, the endocrine factors contribute to Th2 dominance in the fetus [27] during labor, after PROM, and in extrauterine life because of exposure to microorganisms, increased Th1 cytokine production, along with high Th1/Th2 ratio, are required to maintain an efficient immune response [28]. Also, after birth, maternal hormone supplies of estrogen, progesterone, testosterone, and anti-inflammatory prostaglandins cease rapidly to be present in the neonatal circulation.

The switch from Th2 dominance to Th1 is determined by a complex cellular and humoral network, if we alter this delicate passage artificially; it takes place right at the moment when the fetus passes from fetal to neonatal circulation and must be prepared for complex, unpredictable and long-term consequences.

The term imprinting was conceived by the Austrian ethologist Konrad Lorenz (1903-1989), in the 1940s, following the experience that he had with a goose named Martina. When Martina came out of the egg, the first living being she saw was Lorenz, so she identified him as her mother and began to follow Lorenz everywhere. All attempts to reunite Martina with her birth mother failed, and Lorenz realized that imprinting is an irreversible phenomenon. In ethology, imprinting is a particular form of early learning, found primarily in the infants of birds and mammals in a short growth phase called "sensitive

period", during which they recognize and follow the mother or her surrogate, e.g., another animal or any moving object.

Similarly, the term "hormonal imprinting" was coined by Csaba in the 1980s [29]. In the original first experiments by Csaba, newborn rats were treated with thyrotropic hormone or gonadotropic hormone, then, in the adult age group, the blood thyroxin level after treatment was measured. The neonatal gonadotropin treatment decreased the adults' thyroxin level by 70% and TSH treatment by 40% [30]. The scientist analyzed this phenomenon in numerous subsequent works [6, 31-33]. Other authors have subsequently confirmed the work of Csaba; however, to our knowledge, no published results have questioned the work on perinatal imprinting [34, 35]. When a hormone comes into contact with its receptor for the first time, it establishes a relationship that will last for the whole life of the individual, but the system is redundant, and the type of relationship that the receptor establishes with its reference hormone can change flexibly, to favor progressive adaptation to the environment of the new living being. Functional systems of the organism develop from open loop systems without feedback control into closed systems controlled by a feedback mechanism. This delicate mechanism is very flexible and can be continuously modified throughout life (**Fig. 2**), but it is particularly sensitive in the perinatal period. Receptors are programmable for only a brief developmental period, after which time the tissue/organ becomes permanently unresponsive to imprinting [36].

When this change is pathological (for example, due to the administration of hormone analogs, related hormones, drugs, and environmental contaminants, such as endocrine disruptors or pollutants [12], also by quantitative alterations, e.g. when the physiological hormone is present in too high or too small amounts) imprinting will be pathological.

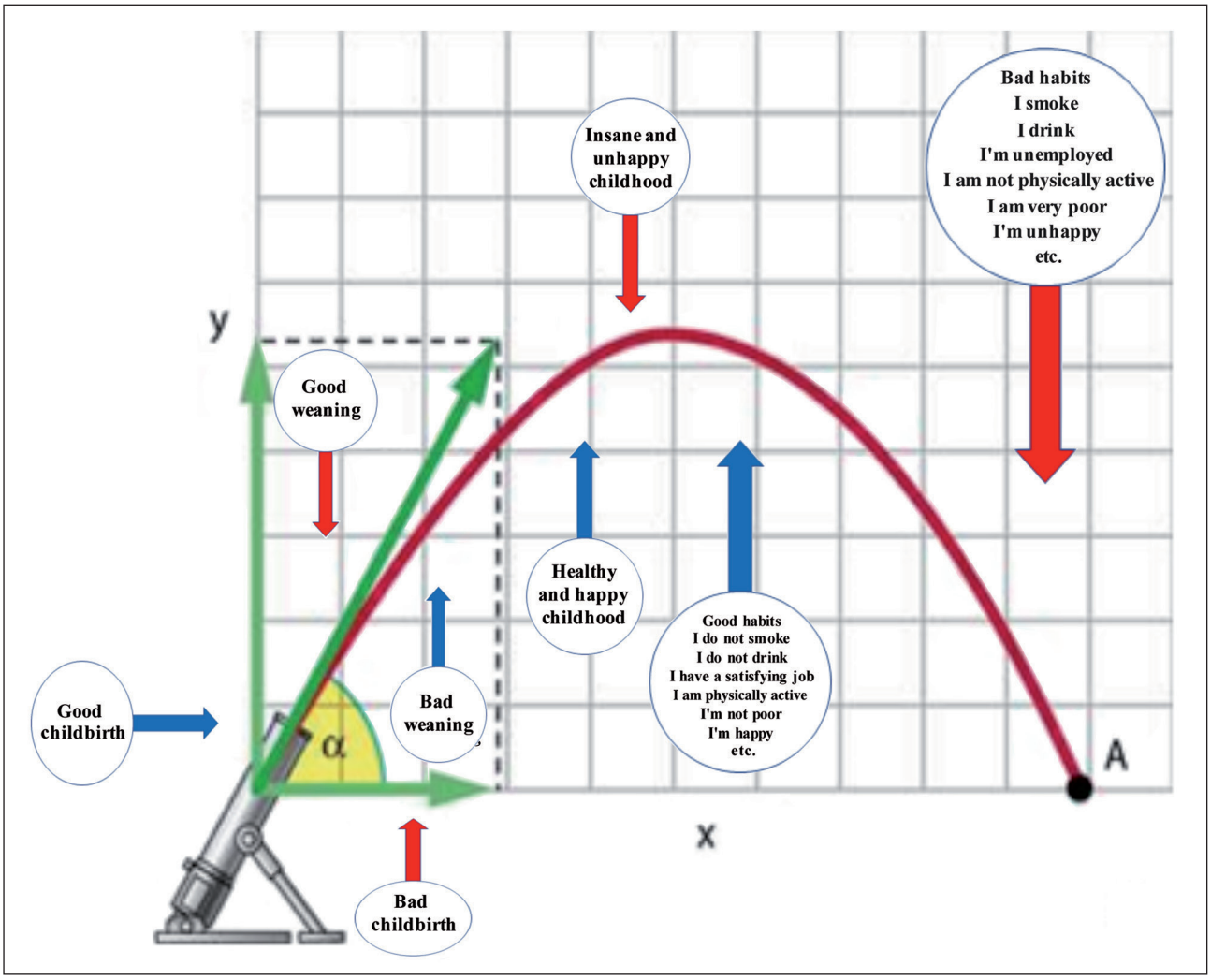

Figure 2. The diagram shows, in a simplified way, how complex interaction with the environment can modulate genetic expressivity throughout the entire course of life.

These different mechanisms can assume the overall name of faulty hormonal imprinting [37]. Cells of multicellular organisms have plasma membrane receptors and intracellular receptors. Both types of receptors require imprinting in the perinatal period and are subject to faulty imprinting. We can, however, provide some terminological clarity. The original term, reported by Csaba as "hormonal imprinting", has been successively called "metabolic imprinting" or "epigenetic imprinting". In our case, all these definitions must be replaced by the term "childbirth imprinting", describing hormonal imprinting-like phenomena caused by hormonal or/and non-hormonal factors. All of these phenomena are, of course, different from "genome imprinting" [38], which is a differential expression of a gene or genes as a function of whether they were inherited from the male or the female parent, e.g., a deletion on chromosome 15 that causes Prader-Willi syndrome if inherited from the father, causing Angelman's syndrome instead if inherited from the mother.

The childbirth period commences at the beginning of labor and ends 1 completed day after birth. Childbirth imprinting is a fundamental biological phenomenon that underlies the relations among drugs, hormones, nutrition, endocrine disruptors, pollutants environmental contaminants, experiences of early life and the future development of later diseases. Imprinting, in this context, is an integral part of cellular memory and learning. Ultimately, these early imprints can form *in-utero*, during birth and immediately after birth. Naturally, the outcome of the perturbations of the perinatal environment is also highly dependent upon the genetic background of the individual [39].

Moreover, randomness also plays a fundamental role; epigenome can modulate the effects of stochastic noise to facilitate phase transitions in development and disease, but these random effects could change direction depending on events during childbirth (use of synthetic oxytocin, antibiotics, cesarean section, etc.) [40]. Stochasticity, referring to the nondeterministic nature of specific dynamic systems, ultimately stems from the fact that biological processes are fundamentally driven by random collisions between small numbers of macromolecules with multiple potential conformational states [41, 42]. A few proposed mechanisms for the underlying stochasticity of cellular phenotypes include: "bursting" due to stochastic remodeling (opening and closing) of promoters; variable amplification at translational level; and influences from upstream components (e.g., morphogens, signaling molecules, and the extracellular matrix), which are often variable across cellular microenvironments and are subject to noise themselves [43, 44]. The picture emerging from these recent studies is that noise systems offer the significant advantage of generating nongenetic cell-to-cell variability – that is, cells that behave uniquely despite being genetically identical to each other [45, 46].

An excellent example of the close relationship between environment, genotype, and phenotype are the so-called Small for Gestational Age (SGA) newborns or IUGR (IntraUterine Growth Restriction) fetuses. Due to this interaction that can lead to pathologies, these infants have a low birth weight because the uterine environment was very poor, and did not provide enough energy for different reasons. Only those fetuses who can adjust to this hostile environment will survive. After birth, if these newborns grow up in an environment rich in energy, a higher percentage of them develop cardiovascular disease compared to newborns with appropriate birth weight [47]. Maternal weight before gestation also affects the newborn, who adapts to this environment [48].

Complex systems are characterized by the enormous amount of interdependencies, and by non-linear reactions, often difficult to detect at first [49]. Non-linear reactions are distinguished from linear reactions; if we double the dose of a drug or a radiation dose, we do not merely get double the effect, but a more significant effect of the double or minor; sometimes, if we exceed the lethal dose or the subject is particularly sensitive, we even determine his death. In practice, if we trace these reactions on a graph, they form a curved line and not a straight line (linear) [50]. We should not think only of simple causal associations: administer the antibiotic and account for the adverse reactions and success with the disease. We should think, administer the antibiotic, count adverse reactions and success against the disease, but also long-term actions and those on the other components of the organism, not only on the disease. We must enter into the concept of complexity.

The question that this paper asks is the following: is all that we have seen regarding the perinatal period also valid for the childbirth period? There is indeed a clear association between what happens in the perinatal period and diseases such as obesity, diabetes, autism, asthma, allergy, schizophrenia, autoimmune diseases, inflammatory bowel diseases [51]. Is this influence also true for events occurring

in the childbirth period? Can drugs, attitudes, nutrition, mode of delivery, characteristic of the childbirth period, affect the future health of the newborn? In the embryo, the primordial germ cells (i.e., the precursors of spermatozoa or egg cells) undergo a process regarding the reprogramming of epigenetic information from the 2nd week of life of the embryo and until the 9th week. In practice, all the processes that make methylation (which is the main epigenetic mechanism) effective are inhibited; however, this process does not erase the entire epigenome: about 5% of our DNA is resistant to reprogramming [52]. The regions that resist contain particularly active genes in neurons, where they can perform essential functions during development. Analysis of human disease data indicates that these genes are associated with disorders such as schizophrenia, metabolic disorders, and obesity. These genes could be very susceptible to change in the childbirth period.

Epidemiological data

Many women experience, at the first meeting with their baby, a feeling of joy, which they can not define; it is a state of intense bliss, accompanied by a feeling of creative omnipotence often followed by a moment of disbelief: "Did I do this?" In the exact moment they see the newborn for the first time, many women can experience Kairos (καιρός), a word that in ancient Greece meant "right or opportune moment" or "supreme moment" or even "a time in the middle", a moment of an indeterminate period of time, in which something special happens. As a deity, Kairos was semi-unknown in Greece, and even today the fleeting joy, represented by Kairos, is neglected. In international scientific literature, very few articles are describing this joy [53] while there is a multitude that speaks of the pain and fatigue of childbirth. Women, if requested, have a great capacity for describing pain, fatigue, and suffering. They can use a myriad of synonyms and metaphors, the complexity of which depends only on their cultural level, but they have only a few terms to describe joy. The time of Kairos at birth is precious and powerful, but vulnerable. It needs to be safeguarded to ensure that its presence continues to emerge. This means that gynecologists, midwives, and other birth attendants have the task of protecting Kairos' time from the sometimes harsh and potentially gruesome births. The overwhelming majority of women believe that birth and the transition to motherhood are difficult. The exasperation for "safety" and the organizational needs of institutional places where labor/delivery takes place [54] mean that operators do not limit interventions (limited supply of water and food, use of synthetic oxytocin, antibiotic prophylaxis, amniotomy, episiotomy, excessive use of cesarean section, etc.), all of which involve iatrogenic effects on reasonable conditions, to cases where there is a real medical indication. This has also been recognized in Italy; the Italian Health Ministry has released a detailed and exhaustive document in this regard [55]. This document concludes with the recommendation to reduce unnecessary interventions during labor and delivery.

Nutrition in the childbirth period

The nutrition of the mother and secondarily of the fetus during gestation is an important modality which affects adult health. In pregnancy, compared with extra-gravidic condition, blood sugar levels remain high after meals, and lower on fasting, despite the 30% increase in neoglucogenesis. The increase in peripheral insulin resistance (maximum peak at 32 weeks) remains constant until the end of pregnancy. As a consequence, there is a decrease in the use of glucose, the induction of glycogenolysis and neoglucogenesis and the active use of fats. Ketosis develops extremely rapidly, especially during labor [56]. Evidence shows no benefits or harm connected to the restriction of fluids and food in labor; there is no justification for women at low risk of complications to the restriction of fluids and food in labor. Unfortunately, to our knowledge, there are no studies specifically regarding women with increased risks of complications, but since there is no evidence to support restrictions in this group of women, it seems reasonable not to restrict the intake of fluids or food even in this category [57]. Of course, all this must be balanced with the risk of pneumonia *ab ingestis*, and ultimately with the risk of urgent cesarean section. Although some persist in conducting studies on the subject, neither increased intravenous hydration nor oral hydration or administration of dextrose in intravenous fluids during labor improves labor performance [58-60]. Rather than being dehydrated, which is what happens if we do not allow women to drink during labor, it is better to be attached to a drip. However, the best solution is to allow women to drink during labor. Women may prefer to increase their oral intake rather than being attached to a drip, and we

have to consider whether it is justifiable to persist with a policy of "nil by mouth". Furthermore, at least one trial raised concerns about the safety of dextrose [61].

A new approach to the treatment of dystocia that originates from prolonged and exhausting labor seems, on the other hand, more promising. It is well-known that in sports medicine, lactic acid can affect strong performance and can be decreased by bicarbonate given orally before physical activity. Similarly, the authors evaluated whether the oral intake of bicarbonate changes the amniotic fluid levels and enhances delivery outcome in dystocic deliveries [62]. This approach did not require an intravenous drip, and the first results seem promising. Unfortunately, we know nothing of the effect that the intake of certain foods/nutrients given in labor, or immediately after birth, could have on the health of the newborn, but we believe this is an exciting topic for future studies.

Drugs in the childbirth period

Synthetic oxytocin administration during labor decreases neonatal suction during the 1st hour of breastfeeding and the probability of a successful skin-to-skin phase [63]. Moreover, when synthetic oxytocin was given to mice perinatally in a single dose, a "hormone imprinting" phenomenon was observed, changing their social and sexual behavior. These experiments show how a single dose of synthetic oxytocin, administered at birth, will affect the whole future adult life of the mouse [64]. This happens because synthetic oxytocin, administered at birth, influences the metabolism of dopamine and serotonin in the hypothalamus. There is a decrease in the turnover in the hypothalamus of these two neurotransmitters that can act on the development of future diseases such as autism and schizophrenia. Naturally, the development of complex diseases such as autism or schizophrenia is multifactorial and requires the complex interweaving of numerous factors that act synergistically. Indeed it cannot be argued that the administration of oxytocin in labor determines, for itself, the onset of diseases.

A multifactorial genesis disease, not yet fully understood, is Prader-Willi syndrome; this neurogenetic disorder also is caused by the alteration of several imprinted contiguous genes including *Magel2*. Infants affected by Prader-Willi syndrome present various clinical manifestations, including poor suckling behavior and feeding problems. Using *Magel2*-deficient mice with 50% neonatal mortality and the altered onset of suckling activity and subsequent impaired feeding, the researchers were able to demonstrate that a single oxytocin injection, 3-5 hours after birth, can save the mutant pups with the *Magel2* phenotype, allowing all them to survive. Furthermore, the injection of a specific OT receptor antagonist in wild-type pups recapitulated the feeding deficiency seen in *Magel2* mutants, and a single injection of OT, 3-5 hours after birth saved the phenotype of *Magel2* mutant pups, allowing all of them to survive. The administration of a drug (in this case synthetic oxytocin) in a period rich in changes and adjustments for the mammals' body, such as the childbirth period, can have unexpected effects in the short- and long term.

We must also take into account the fact that synthetic oxytocin administered in labor could have negative consequences on the mother, for example by increasing the incidence of hemorrhage [65, 66]. This happens because oxytocin used to induce or augment labor may desensitize the oxytocin receptors, thereby impairing oxytocin's post-delivery effects on uterine contractility [67].

The administration of synthetic oxytocin during labor may increase postpartum depression [68] and reduce the woman's ability to breastfeed [69], problems that, in turn, can affect the health of the newborn. The adverse effects of this drug are still evident two months after giving birth; non-exclusively breastfeeding, greater depressive, anxious, and somatization symptoms were associated with higher synthetic oxytocin dose administration in labor [70].

A recent study shows that maternal oxytocin changes the parent-partner relationship during the perinatal transition period. The authors have analyzed data from a longitudinal study of 269 child-bearing women in which endogenous oxytocin was measured in blood plasma during the 1st and 3rd trimesters and at 7-9 weeks postpartum; relationship status was assessed at the outset and 2.5 years postpartum. Lower maternal oxytocin was associated with a higher risk for relationship dissolution by the time the child was a toddler [71]. For every standard unit increase in the mothers' mean level of endogenous oxytocin, the odds were 5.9 times greater than the relationship would survive the transition to parenthood. Moreover, analyses of 1st, 3rd trimesters and at 7-9 weeks postpartum time points revealed a similar pattern of results. In practice, the authors have shown that the blood concentration of endogenous oxytocin predicts relationship survival in dating couples

a long time after birth. The equation is therefore simple: the more synthetic oxytocin is administered in labor, the less the new mother can produce during postpartum [72]; the less oxytocin produced during postpartum, the more likely the couple will have emotional problems in the future. Of course, this parallelism cannot be confirmed at present, because oxytocin is a hormone placed at the center of a very archaic, complex and evolutionarily network [73]. Consequentially its effect on the relational and effective system of mammals also depends on many other factors (genetic, environmental, relational) and not exclusively on the administration of synthetic oxytocin. However, these preliminary results are exciting and require further caution in the administration of synthetic oxytocin. In a recent study, salivary levels of oxytocin were measured in 40 low-income mothers at 34- to 48-months postpartum. Mother-child dyads were observed in an interaction task in their home, and videos were later coded for parenting behavior [74]. Mothers' early stress was assessed using the Adverse Childhood Experiences Scale. The results showed that in mothers with low Adverse Childhood Experiences Scale results, higher oxytocin secretion was associated with more positive parenting. On the contrary, mothers with high Adverse Childhood Experiences Scale results higher oxytocin secretion was associated with lower levels of positive parenting. This is an extraordinary result since it demonstrates that oxytocin acts with different effects in different contexts and therefore questions many results of longitudinal studies, even with numerous samples, where the different substrate of the population is not taken into account.

A strong inverse correlation was found between the amount and duration of exposure to fentanyl, used for epidurals, and the sucking capacity of newborns during the 1st hour after vaginal delivery. The more the newborns are exposed to fentanyl, the higher difficulties they have. These results also suggest that intrapartum exposure to fentanyl significantly decreases the infant's chance of performing skin on skin with the mother during the 1st hour after delivery [63].

From 19-44% pregnant women are prescribed antibiotics during pregnancy [75]. We know that the use of some antibiotics during pregnancy increases the risk of spontaneous abortion [76, 77]. Macrolide prescribed in pregnancy can even increase the risk of cerebral palsy or epilepsy [75, 78].

These data suggest caution before prescribing an antibiotic during gestation; we must be sure that the cost-benefit ratio, in the specific case, is in favor of the benefits; but what do we know about the consequences of antibiotic use in the childbirth period? Cesarean section and exposure to antibiotics in the 2nd or 3rd trimester of pregnancy were independently associated with higher offspring risk of childhood obesity [79]. The results of this study are exciting, although it can not be ruled out that they are due to another possibility, i.e. that childhood obesity could be related not to the use of antibiotics, but rather to underlying maternal infections that required antibiotic use. Unfortunately, most studies in the obstetrics field have focused on the benefits of antibiotics for short-term maternal and neonatal complications, but with very little interest in long-term consequences. However, there is a clear dose-effect relationship with regards to exposure to antibiotics in pregnancy and obesity in childhood [80]. In particular, in the latter study, the magnitude of association was most active for repeated exposure during the 2nd trimester. However, some studies prove the opposite, namely that the relationship with the development of obesity and the administration of antibiotics is more significant the earlier the administration, being the maximum if it occurred during the 1st trimester [81]. The use of antibiotics is in the childbirth period is associated with increased antibiotic resistance in infantile late-onset bacterial severe infections [82]. Antibiotic resistance has become a severe problem; in Italy, the percentage of *E. coli* with resistance to third-generation cephalosporins has exceeded 50% [83]. The analyses of specific antibiotic resistance genes showed a higher occurrence of some β-lactamase coding genes in infants whose mothers received intrapartum antibiotic prophylaxis [84].

The problem does not lie in the use of antibiotics for therapy; generally, if there is a disease, physicians make careful choices, accurately balancing the cost/benefit ratio. The problem is the rampant and excessive use of antibiotics for prophylaxis, a condition in which the disease does not exist, but physicians want to prevent a disease that could appear. Let us take the example of group B streptococcus (GBS) prophylaxis. The first problem is screening. How accurate is testing for GBS? 91% of pregnant women who screened negative for GBS at 35-36 weeks were still GBS-negative when the standard gold test was performed during labor. The remaining 9% became GBS positive. These 9% were "missed" GBS cases, and did not receive antibiotics. 84% of pregnant women who screened positive for GBS at 35-36 weeks were still GBS

positive when the standard gold test was performed during labor. However, 16% of the GBS-positive women became GBS-negative by the time they went into labor. These 16% received unnecessary antibiotics [85].

Furthermore, identification of group B-agglutinating isolates as *S. agalactiae*, based on latex assays only, is responsible for false reports of GBS carriage, then for useless intrapartum antibiotic prophylaxis [86]. Today it would be possible, at low cost, to improve the appropriateness of screening, using already available technologies [87]. The Xpert GBS test is a rapid polymerase chain reaction (PCR) test for detecting GBS colonization in women who are about to give birth. The Xpert GBS test could be used to identify GBS colonization at the onset of labor and could potentially reduce the unnecessary use of intrapartum antibiotic prophylaxis. The assay detects GBS from combined vaginal and rectal swab specimens, and results are given in 50 minutes or less, compared with 24-48 hours for conventional bacterial culture techniques. The individual test cartridges cost £38.80 [88].

The problem is the bias of the present, also called hyperbolic discounting, during which decisions are made to obtain immediate gratification, ignoring the possibility of gain deferred over time [89]. This attitude influences our behavior, above all, in three critical areas of our life: nutrition, professional life, and savings. In the case of intrapartum antibiotic prophylaxis, the professional and scientific community evaluated only the short-term costs and benefits of antibiotic prophylaxis, while, unfortunately, studies on long-term beneficial costs are lacking [90].

However, essential data are beginning to emerge, in a longitudinal, prospective study of a cohort of Canadian infants born in 2010-2012, which evaluated infant gut microbiota, the authors found that at 3 months of life neonatal microbiota differed significantly depending on intrapartum antibiotic prophylaxis exposures, and differences persisted up to 12 months for infants delivered by emergency cesarean section. The taxon-specific composition also differed, with *Bacteroides* and *Parabacteroides* under-represented, and *Enterococcus* and *Clostridium* over-represented at 3 months, following maternal intrapartum antibiotic prophylaxis. Microbiota differences were especially evident following intrapartum antibiotic prophylaxis with emergency cesarean section, with some changes, increased *Clostridiales* and decreased *Bacteroidaceae*, persisting up to 12 months, particularly among non-breastfed infants [91]. The study demonstrates the complexity of relationships between intrapartum antibiotic prophylaxis, mode of delivery and subsequent breastfeeding; to this complexity, we must also take into consideration maternal diet throughout pregnancy [92]. The development of the human infant intestinal microbiota is a sequential process that begins *in utero* and continues during the first 3 years of life. We certainly know that microbiota is altered in children who are delivered by cesarean section, fed formula, or treated with antibiotics, compared to babies born vaginally, breastfed, or unexposed to antibiotics. We are not yet sure if these disturbances can influence the future health of these babies. The ecosystem of the human gut consists of trillions of bacteria forming a bioreactor that is fuelled by dietary macronutrients to produce bioactive compounds, and evidence is now emerging that, through interactions with the gut-brain axis, the bidirectional communication system between the central nervous system and the gastrointestinal tract, the gut microbiome can also influence neural development, cognition and behavior [93].

Furthermore, intrapartum use of antibiotic is associated with pediatric eosinophilic esophagitis [94]. Use of antibiotics is considered a potential risk factor for the development of inflammatory bowel disease [95]. This evidence is consistent with the concept of perinatal programming of intestinal inflammatory disorders. Animal models have shown that the early-life environment affects the development of the gastrointestinal tract [96].

Ultimately, there is no convincing evidence of benefit for mothers or newborns from the routine use of antibiotics for PROM at or near term, and "Given the unmeasured potential adverse effects of antibiotic use, the potential for the development of resistant organisms, and the low risk of maternal infection in the control group, the routine use of antibiotics for PROM at or near term in the absence of confirmed maternal infection should be avoided" [97]. Prophylactic antibiotics are associated with significantly lower rates of chorioamnionitis by 51% and endometritis by 88% only in women with latency longer than 12 hours [98].

The evidence does not allow definitive conclusions to be drawn regarding antibiotic prophylaxis for GBS: "Despite a wide range of adverse events reported in 17 observational studies and 13 randomized controlled trials, the evidence was inconsistent and at high risk of bias" [99]. However, the numerous side effects seen in the short term and, above all, the association with altered

neonatal microbiome, and the consequences, some probable, others certain, regarding the development of diseases in the future, should suggest adopting the precautionary principle [100, 101] and therefore adopting the prophylaxis only in the case of positivity for GBS, of course having used an effective method for its detection, or in the case of PROM greater than 12 hours.

Breastfeeding

Breastfeeding is associated with health benefits not only in childhood but also in adulthood. In children who are breastfed, there is a reduction in the incidence of infections of the gastrointestinal tract, respiratory tract and otitis media, along with protective effects against chronic diseases such as celiac disease, diabetes, obesity, and chronic inflammatory diseases of the intestine. In adulthood, breastfeeding is associated with a lower risk of developing type 2 diabetes, hypertension, hypercholesterolemia, some types of cancer, osteoporosis [101-106]. There are positive effects on neurodevelopment and cognitive abilities. Nutrients in breast milk do not have an exclusively nutritive function; molecular biology studies have shown that nutrients can modify, directly or indirectly, via hormones, the expression of many genes [107]. We will not elaborate much on the long-term effects of breastfeeding since this paper deals only with the childbirth period. However, it is in these early hours after birth that attendants have the opportunity to influence the future of maternal breastfeeding positively.

In 1989, WHO and UNICEF published a joint declaration entitled: "*Protecting, promoting and supporting breastfeeding. The special role of maternity services*" [108]. This document describes how the staff working in labor wards may encourage breastfeeding. The 10 steps are a summary of the main recommendations of the joint declaration. All of these steps are, of course, important, but some are to be implemented immediately after birth in the childbirth period:

- help mothers initiate breastfeeding within a half-hour of birth;
- show mothers how to breastfeed, and how to maintain lactation even if they should be separated from their infants;
- give newborn infants no food or drink other than breast milk, unless medically indicated;
- practice rooming-in, allow mothers and infants to remain together 24 hours a day;
- encourage breastfeeding on demand;
- give no artificial teats or pacifiers to breast-feeding infants.

Ultimately, breast milk is one of the most important epigenetic factors after birth; it can influence gene expression and therefore also the phenotype. Perhaps breast milk can modulate different physiological functions and protection of the newborn against various diseases. For example, about obesity, a study evaluated how breastfeeding can counteract the harmful effects of *PPARG2* gene polymorphism in adolescents [109]. Furthermore, in children predisposed to otitis media, breastfeeding is a protective factor [110]. Last but not least, breastfeeding is a protective factor for the development of many diseases even in the mother [111].

Mode of delivery

Cesarean sections can effectively reduce maternal and perinatal mortality and morbidity if they are performed due to precise medical indications [112], but no scientific evidence proves the benefits of cesarean sections for mothers and newborns when there is no clinical justification [112]. On the contrary, the cesarean section has been proved to increase maternal death, maternal morbidity, peripartum hysterectomy, hospital admissions during puerperium, amniotic fluid embolism, placental malposition during successive pregnancies [113]. Therefore, a cesarean section always has to be cautiously considered [114]. If we consider neonatal health, a cesarean section increases perinatal iatrogenic lacerations, respiratory disorders, difficult cardiovascular adaptation, lower breastfeeding prevalence, anemia, asthma, laryngitis, gastroenteritis, ulcerative colitis, celiac disease, lower respiratory tract infections, idiopathic juvenile arthritis, death, obesity, type 1 diabetes, metabolic syndrome, cancer, leukemia [115-121]. The latter risk, leukemia, is likely to be explained by the fact that birth stress predisposes newborns through a complex biochemical mechanism to improve preneoplastic cell clearance capabilities [122]. One of the most important factors to explain the diseases mentioned above is probably the lack of "bacterial contamination" along the birth canal [123].

An increased body of evidence has shown that early microbiota colonization exerts a strong influence on the later health status of the individual [124]. However, this mechanism cannot be the

only one to act, as, for example, in newborns from cesarean section, who have been exposed to labor, many of the previously described adverse effects, which occur in adult life, are much less pronounced [125]. One study divided three main groups of bacteria into newborns from vaginal birth: in the first group, there was a high prevalence of *Bifidobacterium spp.*, in the second of *Streptococcus spp.* and in the third of *Bacteroides spp.*, while in the cesarean section the first group was mainly composed of *Bifidobacterium*, the second was characterized by high levels of *Clostridium spp.* Moreover, low levels of *Streptococcus spp.*, in the third, mainly *Enterobacteriaceae*, *Ruminococcus spp.* and *Lachnospiraceae* [126]. It is interesting to note that the same authors did not show differences in the microbiota, related to the delivery mode, at the age of 6 and 12 months; the multiple mechanisms that determine the differences of future health probably act at birth (first relationship with the receptor, modulation of the immune system, recognition of antigens, etc). Subsequently, the plasticity typical of young organisms can remodulate colonization, which also depends on other factors (maternal nutrition, breastfeeding, weaning, etc.). The fact of having been in labor or not before performing a cesarean section can change the attitude and the response to external agents of the newborn's immune system. Labor, above all after PROM, can result in different exposure to specific microbes and this leads to an increase in the number of neutrophils and natural killer cells, an increase in IL-13 and INF-gamma and IL-20 levels. The decrease of these factors, as in the elective cesarean section, can alter the relationship between Th1 and Th2 with the higher risk of developing immunological diseases [127].

Rat pups born by cesarean section demonstrate long-term reciprocal changes in dopamine levels and metabolism in the nucleus accumbens and prefrontal cortex [128]. Adrenaline administration to rats at birth following cesarean section prevents these long-term neurological changes as well as an increase in tyrosine hydroxylase activity, in response to a stress challenge in adulthood [129]. The interactions are very complex.

Moreover, cesarean sections reduce breast-feeding attitudes, which can contribute to the difficulties that can exist in the first months of life [130].

Labor and delivery are not mere mechanical events, on the contrary, they represent a highly refined mechanism, evolving over millions of years of selective competition and mutations to ensure the future health of those who manage to move down the birth canal, at the highest risk of their entire existence (**Fig. 3**). The primary mechanisms by which all this happens are hormonal surges or stress response associated with labor and vaginal delivery; transfer of the maternal microbiome to the infant during parturition; transgenerational transmission of disease traits through epigenetics [45].

All interventions must be evaluated from a "first, do not harm" perspective. Just because a cesarean section is a relatively safe procedure, potential long-term consequences cannot be ignored [131]. The interactions occurring at the time of birth are very complex; only recently researchers have begun to try to clarify them. For example, nutrition interacts in a structured way with the mode of delivery; elevated levels of *Streptococcus* were present in the feces of children whose mothers consumed high amounts of fish and seafood, born by spontaneous delivery, and low levels of neonatal *Clostridium spp.*, if born by cesarean section [132]. High fruit consumption was associated, however, with low levels of *Bifidobacterium* in vaginal births; high levels of the latter are observed if the mother consumed large quantities of red meat in cesarean sections [132].

Of course, among offspring of women with first births, planned cesarean delivery, compared with vaginal delivery, was associated with a small absolute increased risk of asthma requiring hospital admission, salbutamol inhaler prescription at 5 years of age, and all-cause of death by age 21 years [133]; this was not found in unscheduled cesarean delivery.

Recently, the mode of delivery has been related to the academic skills of adolescents [134]. These authors, analyzing a cohort of 1,489,925 births, extracted from the Swedish Medical Birth Register and National School Register, were able to demonstrate, using logistic regression analysis, with quantile regression, a slight association between birth by cesarean section and school performance. Elective cesarean sections were associated with a 1-3 point decrease in scores, while an emergency cesarean section was associated with a 2-5 point decrease in scores. Despite the high number of individuals involved, these results are to be considered very preliminary and need further confirmation. The authors themselves are aware that: "the effect was quite small and given the complex nature of the relationship, should be interpreted with caution".

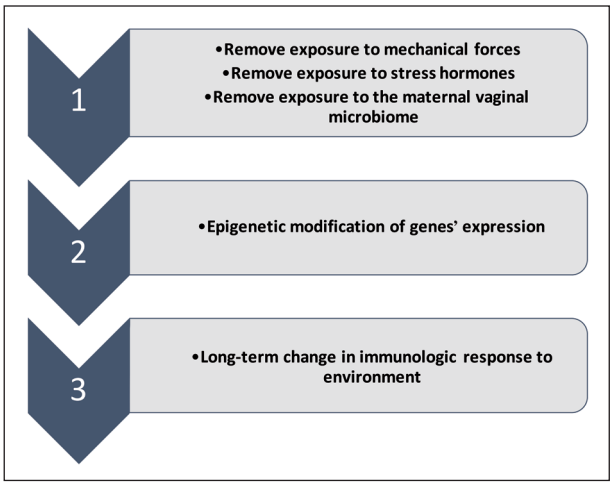

Figure 3. The three biological mechanisms explain why mode of childbirth can change the profile of future health of newborns.

Movement in the childbirth period

Unrestricted movement during labor allows the mother to find a position that is more comfortable for her [135]. Women who walked were so satisfied that 99% of them stated that they would like to walk during future labors [136]. However, can walking or moving during childbirth affect the infant's future health? Unfortunately, to our knowledge, there are no studies that evaluate this issue. However, there are theoretical assumptions that movement during the childbirth period can change future neonatal health. Parturition imposes an increased energy demand on the laboring woman. Labor is characterized by increased concentrations of nutrients including glucose [137, 138], ketone bodies [139] and lactic acid [140].

Much of the control of energy homeostasis is mediated by central neural systems, which are genetically determined. However, these systems are also highly flexible and readily modified by environmental inputs. Energy homeostasis is the balance between energy intake, expenditure, and storage [35]. The childbirth period could be a crucial time during which extrinsic factors can permanently alter the set-point around which body weight is regulated.

Maternal movements during childbirth can change the magnitude of the imbalance between energy inputs and outputs. Reduced physical activity in labor might be a cause of this imbalance. Neuronal plasticity occurs within the central nervous systems with the formation of new neural connections as much as during the formation of long-term memories [141, 142]. Some neurons of the central nervous system are susceptible to metabolic and hormonal changes. These neurons are located mainly, but not exclusively, in the nucleus tractus solitarius, in the postrema area, in the raphe pallidus and obscurus [143, 144]. Some of these neurons receive and send information from the periphery to hypothalamic areas, in this way they can mediate feeding metabolic and behavior processes involved in the control of energy homeostasis and affect the forebrain and limbic structures involved in the affective and rewarding properties of food [145-148]

The setting and subsequent change in cellular memory that occurs at high degree at the time of birth could determine a different ability for these hormones to produce and respond to the action of their central mediators (adrenaline, noradrenaline, and 5HT). A single injection of norepinephrine in the paraventricular nucleus increases food intake, while chronic administration causes hyperphagia and obesity in rats [149, 150]. Movement, in turn, can change the production and consumption of leptin and insulin in mother and fetus. Given their strong neurotrophic properties, both excess or lack of insulin and leptin during the childbirth period are likely to be effectors of developmental changes in metabolism homeostasis that could ultimately lead to enhanced metabolic efficiency, which predisposes the individual to become obese.

Recent studies have evaluated the first urine of newborns from vaginal birth or elective cesarean section, in which the authors were able to confirm that fetuses whose mothers did not undergo labor have a different metabolic pattern, showing lower fatty acid omega oxidation, as evidenced by lower urinary excretion of dicarboxylic acids [151]. It would be interesting to know if these differences can be partially due to the mother's movement.

Movement during labor could initiate important physiological trajectories, and the absence of this stimulus could have effects on adult health. Nevertheless, these conclusions are only inferential, since we lack definitive studies that establish the critical periods and underlying factors in the childbirth environment, which promote this resetting. However, the short-term benefits of movement during labor are known [152], and we know that in pregnancy, intrapersonal issues were the most frequently reported barriers and enablers regarding physical activity during pregnancy [153]. Even during childbirth, the most crucial element to allow free movement to women in labor is probably the attitude of those who attend the birth. In practice, we should give women permission to move and use

the positions they find most comfortable. Innate behaviors should not be limited unless there is a medical need and the woman giving birth has chosen to comply with the recommended restrictions. The area where the birth takes place must be big enough to accommodate the person in labor and the medical support team. There should be bathtubs and showers for water therapy, birth balls and other objects that encourage movement, and the delivery bed should not be placed in the middle of the room. Practices that limit mobility, such as the adoption of continuous electronic monitoring of fetuses or the administration of intravenous fluids, should not be used, unless necessary. If these practices become necessary, doctors and midwives should try to reduce their impact on the woman's mobility. For example, portable electronic monitors, equipped with telemetry, could be used so that the woman can move around, rather than ask her to stay in bed.

Maternal and providers' attendance behavior

The epigenetic mechanisms can cause the characteristic phenotypic traits of the parents to be transmitted either directly, through the microRNA, or indirectly to the progeny. For example, mothers of rats who give more parental care (good parenting skills) give birth to offspring capable of greater parental care, vice versa mothers who give little care (bad parenting skills) will give birth to offspring with low parental care attitude. This transmission of behavior can be completely overturned if the pup born from a caring mother is entrusted to an uncaring mother; the behavior of the pup will be that of the mother to whom it has been entrusted, demonstrating that the acquisition of this behavioral trait is acquired and not genetic [154]. The rat pups, in fact, if exposed to "high care" will reduce the processes of DNA methylation in a particular position of their genetic code. This modification is activated immediately after birth and persists throughout life [155]. Mice that are cared for by their mother react well to stress: they are capable of activating the hypothalamic-hypophysis-adrenal axis (HPA) and the subsequent production of corticosteroids. The balance of the HPA axis causes the corticosteroids to inhibit the hypothalamic hormones, while preventing an excess of it, on the other hand, influences the immune system. What determines this balance is the number of glucocorticoid receptors in the hypothalamus, determined by genetic and epigenetic factors, and on which the future health of the mouse will depend [156]. By analogy, it is good practice that, whenever possible, mothers and babies should be in direct contact for at least the first 1-2 hours after birth. In skin-to-skin care, the baby is naked and is placed on the mother's bare chest, between her breasts. Benefits of skin-to-skin care during infancy may persist for years [157]. It has been demonstrated that childhood stress and adversity can lead to hypomethylation of retrotransposons in humans [158, 159]. Moreover, early life experience, in mice, can drive structural variations of the genome via long interspersed nuclear element-1 (LINE-1 or L1) retrotransposons, since maternal care alters methylation of the YY1 binding site in the L1 promoter. All this is mediated by the mobilization of L1 retrotransposons in the hippocampus of the mouse brain [160].

These few examples show the responsibility that obstetricians have when they witness the birth, going well beyond a single moment. In fact, during the first moments of life, many nucleotide sequences are activated and de-activated, the modalities with which this process takes place will determine long-term consequences. A fascinating example is the one that occurs by varying the time of clamping the umbilical cord at birth. Randomizing uncomplicated newborns into two groups – delayed clamping (≥ 180 seconds postpartum) or early clamping (≤ 10 seconds postpartum) – Swedish researchers found that, at 4 years of age, the infants who had undergone delayed clamping, especially if they were male, had better motor and social skills, indicating that the optimization of the timing of umbilical cord clamping can affect long-term neurodevelopment in a low-risk population of children born in a high-income nation [161].

Style of the ward where childbirth occurs

What do women want? A positive experience that fulfills or exceeds their prior personal and socio-cultural beliefs and expectations. This includes giving birth to a healthy baby in a clinically and psychologically safe environment with practical and emotional support from birth companions, and competent, reassuring, kind clinical staff [162]. However, we should not think that what is seen above is "only" the desire of pregnant women and their companions; vice versa, giving birth in a place where operators try to comply with these wishes has significant effects on the outcome of childbirth and ultimately on the future of neonatal health. The attitude towards

cesarean sections [163] and episiotomies [164] leads to highly significant differences in terms of rates of episiotomies and cesareans, and these differences are not due to different populations treated, but to the different cultures of the operators [165, 166]. The attitude towards vaginal operative birth lends itself well to exemplify the importance of the operators' cultural factors in determining different approaches to childbirth. The percentages of assisted vaginal delivery show a wide inter- and intra-national geographic variation. The average rates currently reported stand at 10-15% in the USA [167]. Fluctuations, however, are very marked. In the United Kingdom, percentages have fluctuated between 10% and 13% in recent years [168]. In the USA an inverse linear relationship is observed between the use of operative birth and cesarean section [167]; over the years the skills necessary to access a vaginal operative birth in this nation have been reduced, and the percentage of cesarean sections has been raised. In Italy, the use of vaginal operating techniques is historically much less frequent, even if with reported percentages that vary from place to place [169]. In Italy childbirth assistance is radically different from that existing in the USA: the system is generally public and, in most cases, it is the midwives and not the doctors who assist the birth. The culture of care is profoundly different, and in Italy there is not an inverse relationship between the percentage of cesarean sections and operative vaginal births [169].

On the contrary, places of childbirth that favor fewer interventionist approaches generally have lower percentages of cesarean sections and lower rates of recourse to operative vaginal birth [169]. There is a widespread culture in some hospital departments that presupposes the ability of women to give birth spontaneously in most cases if assisted correctly and with empathy from the staff. From individual circumstances, it is possible to assist the woman and the newborn better. As we have seen in this brief review, the convictions, the culture and the education of the operators can change the relative outcomes of childbirth, with subsequent and vital effects on the long-term health of the newborn. What has been said leads to excellent educational opportunities that can be put in place by the teams that assist labor and delivery [170, 171]. Unfortunately, to our knowledge, no randomized controlled trials or cluster-randomized trials have been carried out to evaluate long-term perinatal outcomes about the style of care of the operators during childbirth. There is insufficient evidence to determine the effectiveness of maternity facilities and operators' attitude to improve maternal and neonatal outcomes. However, this could be an active field of study.

Conclusion

There is an accumulation of epidemiological studies detecting risk factors in the childbirth period for health conditions such as type 1 diabetes, obesity, atopy, cancer, and obesity.

We have known for a long time that: "estrogen and progesterone prepare the uterus for embryo implantation and placental development. Prolactin stimulates milk production, whereas oxytocin initiates labor and triggers milk ejection during nursing. These same molecules, interacting with dopamine, also activate specific neural pathways to motivate parents to nurture, bond with, and protect their offspring. Parenting in turn shapes the neural development of the infant social brain" [172]. However, recent evidence suggests that not only parenting can shape the health of newborns, but the teams that attend the birth in the childbirth period can also play a significant role in determining the future health of the fetal-maternal dyad, for example, by disrupting the childbirth environment and by administering non-essential drugs.

We know that more than 90% of the cells of the human body are made of non-human cells. These microorganisms constitute the so-called "microbiome". Microorganisms are essential for the development of the human immune system. Lacking a healthy microbiome, intrapartum antibiotic prophylaxis, cesarean section, or bottle-feeding may affect the healthy development of the human immune system.

The mechanism through which changes in care during the childbirth period determine long-term changes in the health of the unborn child, could be mediated by the response to stochastic perturbations that can be changed, incentivized or reduced by interventions during childbirth. Recently an interesting study found that in the first 2 and a half years of a newborn's life the composition of its intestinal bacteria is determined, while the changes that will take place after this point are quite limited [173]. Pujadas and Feinberg described an exciting model, starting from the original and primal Waddington model [40]. However, Waddington viewed the epigenetic landscape in a deterministic

model, more precisely, in his model genes always determined the changes: "with changes arising only through genetic mutation and with new paths carved by the forces of evolution". The model proposed by Pujadas and Feinberg is interesting because the authors claim that: "the stochastic part of the function is regulated by the developmental state of the cell, and it also depends on the cell's microenvironment when it is in that particular developmental state. This means that the epigenome can developmentally regulate the degree to which external (environmental) noise can influence its landscape and can explain in a theoretical way the high frequency of transitions arising normally during development and disease". In this way, nongenetic phenotypic heterogeneity may arise by chance, or it could evolve by artificial induced selection to a distribution of phenotypes that confers less fitness. If confirmed, this model would lend itself perfectly to explain why the modifications induced by assistance during childbirth (use of synthetic oxytocin, antibiotics, cesarean section, etc.) can lead to long-term health changes. Maladaptation carried out during birth may establish physiological set points for a developmental trajectory for future cardiovascular dysfunction and disease. For this reason, the teams assisting during childbirth should take into account not only short-term health but also how the necessary actions performed during childbirth assistance will influence the infant's future life.

It is intuitive that an organism is strongly influenced by the messages it receives in intrauterine life. These environmental messages are the tools that the new organism needs to face the external environment. In the moment of "revolution" that is birth, in which we stop living in the aquatic environment to move on to external life, where oxygen is obtained by breathing, everything changes: blood circulation, light, gravity, nutrition, etc. The mode of birth is strongly conditioned by the culture and practice of the place in which we are born. The awareness of this power and the possible implications in the future life of an organism should guide our choices. We must do better, also because better health for individual adult organisms means better health of the system, reduction of costs for medical assistance and the possibility of extending useful care to an increasing portion of the world population (**Fig. 4**). Knowledge, sharing of evidence, respect and empathy are the tools that can guide us to do the best we can.

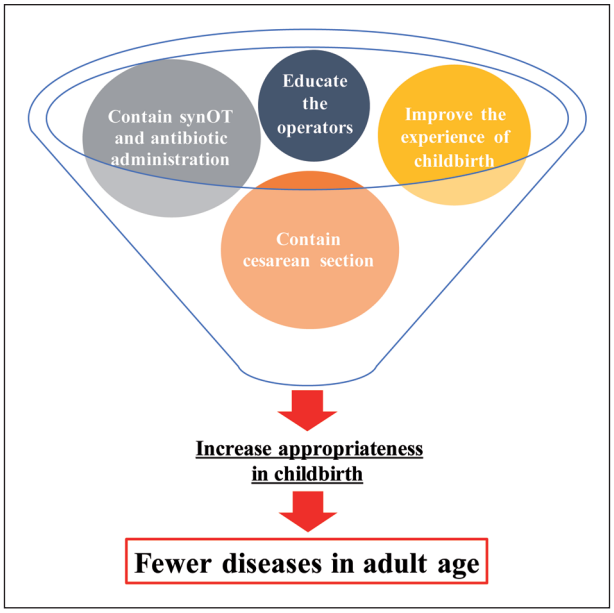

Figure 4. The improvement of appropriateness is obtained by giving each clinical gesture a profound meaning, which does not only include immediate, but also long-term effects. The figure illustrates how, by paying more attention to four of the main items in the labor room, and improving educational aspects, a general improvement of the future conditions of individuals could be achieved.

Declaration of interest

All Authors declare no conflicts of interest. All Authors declare they have not received funding.

References

1. https://www.merriam-webster.com/dictionary/environment, last access: October 29, 2018.
2. https://dictionary.cambridge.org/dictionary/english/environment, last access: October 29, 2018.
3. https://en.oxforddictionaries.com/definition/environment, last access: October 29, 2018.
4. http://www.who.int/maternal_child_adolescent/topics/maternal/maternal_perinatal/en, last access: October 29, 2018.
5. https://www.dictionary.com/browse/imprinting, last access: October 29, 2018.
6. Csaba G. The Faulty Perinatal Hormonal Imprinting as Functional Teratogen. Curr Pediatr Rev. 2016;12(3):222-9.
7. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell. 2007;128(4):635-8.
8. Barker DJ, Gluckman PD, Robinson JS. Conference report: fetal origins of adult disease – report of the First International Study Group, Sydney, 29-30 October 1994. Placenta. 1995;16(3):317-20.
9. Godfrey KM, Barker DJ. Maternal nutrition in relation to fetal and placental growth. Eur J Obstet Gynecol Reprod Biol. 1995;61(1):15-22.

10. Martyn CN, Barker DJ, Jespersen S, Greenwald S, Osmond C, Berry C. Growth in utero, adult blood pressure, and arterial compliance. Br Heart J. 1995;73(2):116-21.
11. Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y, Meade TW. Fetal and infant growth and cardiovascular risk factors in women. BMJ. 1995;310(6977):428-32.
12. Rice JM. Perinatal period and pregnancy: intervals of high risk for chemical carcinogens. Environ Health Perspect. 1979;29:23-7.
13. Barlow DP, Bartolomei MS. Genomic imprinting in mammals. Cold Spring Harb Perspect Biol. 2014;6(2):a018382.
14. Springer NM, McGinnis KM. Paramutation in evolution, population genetics and breeding. Semin Cell Dev Biol. 2015;44:33-8.
15. Steffen PA, Ringrose L. What are memories made of? How Polycomb and Trithorax proteins mediate epigenetic memory. Nat Rev Mol Cell Biol. 2014;15(5):340-56.
16. Turner BM. Cellular memory and the histone code. Cell. 2002;111(3):285-91.
17. Csaba G. The Present and Future of Human Sexuality: Impact of Faulty Perinatal Hormonal Imprinting. Sex Med Rev. 2017;5(2): 163-9.
18. Beckstrom AC, Tanya P, Humston EM, Snyder LR, Synovec RE, Juul SE. The perinatal transition of the circulating metabolome in a nonhuman primate. Pediatr Res. 2012;71(4 Pt 1):338-44.
19. Mohler RE, Tu BP, Dombek KM, Hoggard JC, Young ET, Synovec RE. Identification and evaluation of cycling yeast metabolites in two-dimensional comprehensive gas chromatography-time-of-flight-mass spectrometry data. J Chromatogr A. 2008;1186(1-2):401-11.
20. Humston EM, Dombek KM, Hoggard JC, Young ET, Synovec RE. Time-dependent profiling of metabolites from Snf1 mutant and wild type yeast cells. Anal Chem. 2008;80(21):8002-11.
21. Saugstad OD. Update on oxygen radical disease in neonatology. Curr Opin Obstet Gynecol. 2001;13(2):147-53.
22. Downes CP, Carter AN. Inositol lipids and phosphates. Curr Opin Cell Biol. 1990;2(2):185-91.
23. Meloni A, Palmas F, Barberini L, Mereu R, Deiana SF, Fais MF, Noto A, Fattuoni C, Mussap M, Ragusa A, Dessì A, Pintus R, Fanos V, Melis GB. PROM and Labour Effects on Urinary Metabolome: A Pilot Study. Dis Markers. 2018;2018:1042479.
24. Rehbinder EM, Lødrup Carlsen KC, Staff AC, Angell IL, Landrø L, Hilde K, Gaustad P, Rudi K. Is amniotic fluid of women with uncomplicated term pregnancies free of bacteria? Am J Obstet Gynecol. 2018;219(3):289.e1-289.e12.
25. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Sci Transl Med. 2014;6(237):237ra65.
26. Harman T. Shortchanging a Baby's Microbiome. C-sections and formula feeding could be interfering with a critical biological process. Available at: https://blogs.scientificamerican.com/guest-blog/shortchanging-a-babys-microbiome, date of publication: February 14, 2017, last access: October 29, 2018.
27. Schumacher A, Costa SD, Zenclussen AC. Endocrine factors modulating immune responses in pregnancy. Front Immunol. 2014;5:196.
28. Vásárhelyi B, Tulassay T. Endocrine Factors Determining Immune Polarization during Perinatal Transition. Klin Padiatr. 2017;229(5):261-6.
29. Csaba G. Phylogeny and ontogeny of hormone receptors: the selection theory of receptor formation and hormonal imprinting. Biol Rev Camb Philos Soc. 1980;55(1):47-63.
30. Csaba G, Nagy SU. Influence of the neonatal suppression of TSH production (neonatal hyperthyroidism) on response to TSH in adulthood. J Endocrinol Invest. 1985;8(6):557-9.
31. Csaba G, Kovács P, Pállinger E. Transgenerational effect of neonatal vitamin A or D treatment (hormonal imprinting) on the hormone content of rat immune cells. Horm Metab Res. 2007;39(3):197-201.
32. Csaba G, Inczefi-Gonda A. Direct and transgenerational effect of benzpyrene treatment at adolescent age on the uterine estrogen receptor and thymic glucocorticoid receptor of the adult rat. Acta Physiol Hung. 1999;86(1):29-36.
33. Csaba G, Inczefi-Gonda A. Transgenerational effect of a single neonatal benzpyrene treatment on the glucocorticoid receptor of the rat thymus. Hum Exp Toxicol. 1998;17(2):88-92.
34. Das RK, Banerjee S, Shapiro BH. Irreversible perinatal imprinting of adult expression of the principal sex-dependent drug-metabolizing enzyme CYP2C11. FASEB J. 2014;28(9):4111-22.
35. Levin BE. Metabolic imprinting: critical impact of the perinatal environment on the regulation of energy homeostasis. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471):1107-21.
36. Goldman AS. Animal Models of Inborn Errors of Steroidgenesis and Steroid Action. In: Gibian H, Plotz EJ (Eds.). Mammalian Reproduction. Colloquium der Gesellschaft für Biologische Chemie in 9.–11. April 1970 in Mosbach/Baden, vol 21. Berlin and Heidelberg: Springer, 1970.
37. Csaba G. Hormonal imprinting: its role during the evolution and development of hormones and receptors. Cell Biol Int. 2000;24(7):407-14.
38. Surani MA, Barton SC, Norris ML. Development of reconstituted mouse eggs suggests imprinting of the genome during gametogenesis. Nature. 1984;308(5959):548-50.
39. Curley JP, Champagne FA. Influence of maternal care on the developing brain: Mechanisms, temporal dynamics and sensitive periods. Front Neuroendocrinol. 2016;40:52-66.
40. Pujadas E, Feinberg AP. Regulated noise in the epigenetic landscape of development and disease. Cell. 2012;148(6):1123-31.
41. Pauling L, Delbrück M. The nature of the intermolecular forces operative in biological processes. Science. 1940;92(2378):77-9.
42. Fedoroff N, Fontana W. Genetic networks. Small numbers of big molecules. Science. 2002;297(5584):1129-31.
43. Eldar A, Elowitz MB. Functional roles for noise in genetic circuits. Nature. 2010;467(7312):167-73.
44. Kaern M, Elston TC, Blake WJ, Collins JJ. Stochasticity in gene expression: from theories to phenotypes. Nat Rev Genet. 2005;6(6):451-64.
45. Tribe RM, Taylor PD, Kelly NM, Rees D, Sandall J, Kennedy HP. Parturition and the perinatal period: can mode of delivery impact on the future health of the neonate? J Physiol. 2018;596(23):5709-22.

46. Gilbert SF, Bosch TC, Ledón-Rettig C. Eco-Evo-Devo: developmental symbiosis and developmental plasticity as evolutionary agents. Nat Rev Genet. 2015;16(10):611-22.
47. Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311(6998):171-4.
48. Zhang S, Rattanatray L, Morrison JL, Nicholas LM, Lie S, McMillen IC. Maternal obesity and the early origins of childhood obesity: weighing up the benefits and costs of maternal weight loss in the periconceptional period for the offspring. Exp Diabetes Res. 2011;2011:585749.
49. Cilliers P. Complexity and Postmodernism: Understanding Complex Systems. London and New York: Routledge, 1998.
50. Rickles D, Hawe P, Shiell A. A simple guide to chaos and complexity. J Epidemiol Community Health. 2007;61(11):933-7.
51. Rook GA, Lowry CA, Raison CL. Hygiene and other early childhood influences on the subsequent function of the immune system. Brain Res. 2015;1617:47-62.
52. Tang WW, Dietmann S, Irie N, Leitch HG, Floros VI, Bradshaw CR, Hackett JA, Chinnery PF, Surani MA. A Unique Gene Regulatory Network Resets the Human Germline Epigenome for Development. Cell. 2015;161(6):1453-67.
53. Crowther S, Smythe E, Spence D. Kairos time at the moment of birth. Midwifery. 2015;31(4):451-7.
54. WHO. WHO recommendations: intrapartum care for a positive childbirth experience. Geneva: World Health Organization, 2018.
55. Ministero della Salute, Direzione Generale della Programmazione Sanitaria Direzione Generale della Prevenzione Sanitaria, Comitato Percorso Nascita nazionale. Linee di indirizzo per la definizione e l'organizzazione dell'assistenza in autonomia da parte delle ostetriche alle gravidanze a basso rischio ostetrico (BRO). Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2836_allegato.pdf, date of publication: October 23, 2017, last access: October 29, 2018.
56. Lain KY, Catalano PM. Metabolic changes in pregnancy. Clin Obstet Gynecol. 2007;50(4):938-48.
57. Singata M, Tranmer J, Gyte GM. Restricting oral fluid and food intake during labour. Cochrane Database Syst Rev. 2013;(8):CD003930.
58. Edwards RK, Reed CA, Villano KS, Holmes JL, Tong S, Davies JK. Effect of hydration on spontaneous labor outcomes in nulliparous pregnant women: a multicenter randomized controlled trial comparing three methods. Am J Perinatol. 2014;31(6):455-62.
59. Garmi G, Zuarez-Easton S, Zafran N, Ohel I, Berkovich I, Salim R. The effect of type and volume of fluid hydration on labor duration of nulliparous women: a randomized controlled trial. Arch Gynecol Obstet. 2017;295(6):1407-12.
60. Fong A, Serra AE, Caballero D, Garite TJ, Shrivastava VK. A randomized, double-blinded, controlled trial of the effects of fluid rate and/or presence of dextrose in intravenous fluids on the labor course of nulliparas. Am J Obstet Gynecol. 2017;217(2):208.e1-208.e7.
61. Dawood F, Dowswell T, Quenby S. Intravenous fluids for reducing the duration of labour in low risk nulliparous women. Cochrane Database Syst Rev. 2013;(6):CD007715.
62. Wiberg-Itzel E, Wray S, Åkerud H. A randomized controlled trial of a new treatment for labor dystocia. J Matern Fetal Neonatal Med. 2018;31(17):2237-44.
63. Brimdyr K, Cadwell K, Widström AM, Svensson K, Neumann M, Hart EA, Harrington S, Phillips R. The Association Between Common Labor Drugs and Suckling When Skin-to-Skin During the First Hour After Birth. Birth. 2015;42(4):319-28.
64. Hashemi F, Tekes K, Laufer R, Szegi P, Tóthfalusi L, Csaba G. Effect of a single neonatal oxytocin treatment (hormonal imprinting) on the biogenic amine level of the adult rat brain: could oxytocin-induced labor cause pervasive developmental diseases? Reprod Sci. 2013;20(10):1255-63.
65. Belghiti J, Kayem G, Dupont C, Rudigoz RC, Bouvier-Colle MH, Deneux-Tharaux C. Oxytocin during labour and risk of severe postpartum haemorrhage: a population-based, cohort-nested case-control study. BMJ Open. 2011;1(2):e000514.
66. Belghiti J, Coulm B, Kayem G, Blondel B, Deneux-Tharaux C. [Oxytocin administration during labor. Results from the 2010 French National Perinatal Survey]. [Article in French]. J Gynecol Obstet Biol Reprod (Paris). 2013;42(7):662-70.
67. Phaneuf S, Rodríguez Liñares B, TambyRaja RL, MacKenzie IZ, López Bernal A. Loss of myometrial oxytocin receptors during oxytocin-induced and oxytocin-augmented labour. J Reprod Fertil. 2000;120(1):91-7.
68. Cardaillac C, Rua C, Simon EG, El-Hage W. [Oxytocin and postpartum depression]. [Article in French]. J Gynecol Obstet Biol Reprod (Paris). 2016;45(8):786-95.
69. Ragusa A, Svelato A, Silberstein R, Rinaldo D. Does the use of Oxytocin in the Third Stage of Labour have an Impact on Breastfed Babies Health? Looking for a Viable Alternative. J Pharmacol Clin Toxicol. 2017;5(6):1090.
70. Gu V, Feeley N, Gold I, Hayton B, Robins S, Mackinnon A, Samuel S, Carter CS, Zelkowitz P. Intrapartum Synthetic Oxytocin and Its Effects on Maternal Well-Being at 2 Months Postpartum. Birth. 2016;43(1):28-35.
71. Sunahara CS, Zelkowitz P, Bolger N, Sadikaj G, Samuel S, Gold I, Hayton B, Feeley N, Carter CS, Bartz JA. Maternal oxytocin predicts relationship survival during the perinatal transition period: Preliminary evidence. Int J Psychophysiol. 2018 Apr 26. [Epub ahead of print].
72. Jonas K, Johansson LM, Nissen E, Ejdebäck M, Ransjö-Arvidson AB, Uvnäs-Moberg K. Effects of intrapartum oxytocin administration and epidural analgesia on the concentration of plasma oxytocin and prolactin, in response to suckling during the second day postpartum. Breastfeed Med. 2009;4(2):71-82.
73. Shen H. Neuroscience: The hard science of oxytocin. Nature. 2015;522(7557):410-2.
74. Julian MM, Rosenblum KL, Doom JR, Leung CYY, Lumeng JC, Cruz MG, Vazquez DM, Miller AL. Oxytocin and parenting behavior among impoverished mothers with low vs. high early life stress. Arch Womens Ment Health. 2018;21(3):375-82.
75. Meeraus WH, Petersen I, Gilbert R. Association between antibiotic prescribing in pregnancy and cerebral palsy or

epilepsy in children born at term: a cohort study using the health improvement network. PLoS One. 2015;10(3):e0122034.

76. Muanda FT, Sheehy O, Bérard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. CMAJ. 2017;189(17): E625-33.
77. Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. JAMA. 2016;315(1):58-67.
78. Loewen K, Monchka B, Mahmud SM, 't Jong G, Azad MB. Prenatal antibiotic exposure and childhood asthma: a population-based study. Eur Respir J. 2018;52(1):1702070.
79. Mueller NT, Whyatt R, Hoepner L, Oberfield S, Dominguez-Bello MG, Widen EM, Hassoun A, Perera F, Rundle A. Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. Int J Obes (Lond). 2015;39(4):665-70.
80. Wang B, Liu J, Zhang Y, Yan C, Wang H, Jiang F, Li F, Zhang J. Prenatal Exposure to Antibiotics and Risk of Childhood Obesity in a Multi-Center Cohort Study. Am J Epidemiol. 2018;187(10):2159-67.
81. Cassidy-Bushrow AE, Burmeister C, Havstad S, Levin AM, Lynch SV, Ownby DR, Rundle AG, Woodcroft KJ, Zoratti EM, Johnson CC, Wegienka G. Prenatal antimicrobial use and early-childhood body mass index. Int J Obes (Lond). 2018;42(1):1-7.
82. Ashkenazi-Hoffnung L, Melamed N, Ben-Haroush A, Livni G, Amir J, Bilavsky E. The association of intrapartum antibiotic exposure with the incidence and antibiotic resistance of infantile late-onset serious bacterial infections. Clin Pediatr (Phila). 2011;50(9):827-33.
83. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC, 2017.
84. Nogacka A, Salazar N, Suárez M, Milani C, Arboleya S, Solís G, Fernández N, Alaez L, Hernández-Barranco AM, de Los Reyes-Gavilán CG, Ventura M, Gueimonde M. Impact of intrapartum antimicrobial prophylaxis upon the intestinal microbiota and the prevalence of antibiotic resistance genes in vaginally delivered full-term neonates. Microbiome. 2017;5(1):93.
85. Dekker R. The Evidence on: Group B Strep. Available at: https://evidencebasedbirth.com/groupbstrep/, last update: July 17, 2017, last access: October 29, 2018.
86. Savini V, Gherardi G, Marrollo R, Franco A, Pimentel De Araujo F, Dottarelli S, Fazii P, Battisti A, Carretto E. Could β-hemolytic, group B Enterococcus faecalis be mistaken for Streptococcus agalactiae? Diagn Microbiol Infect Dis. 2015;82(1):32-3.
87. http://www.cepheid.com/us/cepheid-solutions/clinical-ivd-tests/sexual-health/xpert-gbs, last access: October 29, 2018.
88. https://www.nice.org.uk/advice/mib28/resources/xpert-gbs-test-for-the-intrapartum-detection-of-group-b-streptococcus-pdf-63499051847365, last access: October 29, 2018.
89. Jackson MO, Yariv L. Present Bias and Collective Dynamic Choice in the Lab. American Economic Review. 2014;104(12):4184-204.
90. Ragusa A, Svelato A. Adjunctive Azithromycin Prophylaxis for Cesarean Delivery. N Engl J Med. 2017;376(2):181-2.
91. Azad MB, Konya T, Persaud RR, Guttman DS, Chari RS, Field CJ, Sears MR, Mandhane PJ, Turvey SE, Subbarao P, Becker AB, Scott JA, Kozyrskyj AL; CHILD Study Investigators. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. BJOG. 2016;123(6): 983-93.
92. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, D Lieber A, Wu F, Perez-Perez GI, Chen Y, Schweizer W, Zheng X, Contreras M, Dominguez-Bello MG, Blaser MJ. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med. 2016;8(343):343ra82.
93. Rogers GB, Keating DJ, Young RL, Wong ML, Licinio J, Wesselingh S. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol Psychiatry. 2016;21(6):738-48.
94. Jensen ET, Kuhl JT, Martin LJ, Rothenberg ME, Dellon ES. Prenatal, intrapartum, and postnatal factors are associated with pediatric eosinophilic esophagitis. J Allergy Clin Immunol. 2018;141(1):214-22.
95. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, Vavricka SR, Fiocchi C. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol. 2018;15(1):39-49.
96. Ley D, Desseyn JL, Mischke M, Knol J, Turck D, Gottrand F. Early-life origin of intestinal inflammatory disorders. Nutr Rev. 2017;75(3):175-87.
97. Wojcieszek AM, Stock OM, Flenady V. Antibiotics for prelabour rupture of membranes at or near term. Cochrane Database Syst Rev. 2014;(10):CD001807.
98. https://www.2minutemedicine.com/no-benefit-antibiotics-term-rupture-membranes, last access: October 29, 2018.
99. Seedat F, Stinton C, Patterson J, Geppert J, Tan B, Robinson ER, McCarthy ND, Uthman OA, Freeman K, Johnson SA, Fraser H, Brown CS, Clarke A, Taylor-Phillips S. Adverse events in women and children who have received intrapartum antibiotic prophylaxis treatment: a systematic review. BMC Pregnancy Childbirth. 2017;17(1):247.
100. http://www.europarl.europa.eu/thinktank/en/document.html?reference=EPRS_IDA(2015)573876, last access: October 29, 2018.
101. http://www.precautionaryprinciple.eu/, last access: October 29, 2018.
102. Horta BL, Loret de Mola C, Victora CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):30-7.
103. Marangoni F, Cetin I, Verduci E, Canzone G, Giovannini M, Scollo P, Corsello G, Poli A. Maternal Diet and Nutrient Requirements in Pregnancy and Breastfeeding. An Italian Consensus Document. Nutrients. 2016;8(10):E629.

104. WHO. WHO Global Strategy for Infant and Young Child Feeding. Geneva: World Health Organization, 2003.
105. Williams JE, Carrothers JM, Lackey KA, Beatty NF, York MA, Brooker SL, Shafii B, Price WJ, Settles ML, McGuire MA, McGuire MK. Human Milk Microbial Community Structure Is Relatively Stable and Related to Variations in Macronutrient and Micronutrient Intakes in Healthy Lactating Women. J Nutr. 2017;147(9):1739-48.
106. Hall Moran V, Lowe N, Crossland N, Berti C, Cetin I, Hermoso M, Koletzko B, Dykes F. Nutritional requirements during lactation. Towards European alignment of reference values: the EURRECA network. Matern Child Nutr. 2010;6(Suppl 2):39-54.
107. Verduci E, Banderali G, Barberi S, Radaelli G, Lops A, Betti F, Riva E, Giovannini M. Epigenetic effects of human breast milk. Nutrients. 2014;6(4):1711-24.
108. World Health Organization, UNICEF. Protecting, promoting and supporting breast-feeding. The special role of maternity services. 1989.
109. Verier C, Meirhaeghe A, Bokor S, Breidenassel C, Manios Y, Molnár D, Artero EG, Nova E, De Henauw S, Moreno LA, Amouyel P, Labayen I, Bevilacqua N, Turck D, Béghin L, Dallongeville J, Gottrand F; Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) Study Group. Breast-feeding modulates the influence of the peroxisome proliferator-activated receptor-gamma (PPARG2) Pro12Ala polymorphism on adiposity in adolescents: The Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional study. Diabetes Care. 2010;33(1):190-6.
110. Miljanović O, Cikota-Aleksić B, Likić D, Vojvodić D, Jovićević O, Magić Z. Association of cytokine gene polymorphisms and risk factors with otitis media proneness in children. Eur J Pediatr. 2016;175(6):809-15.
111. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, Trikalinos T, Lau J. Breastfeeding and maternal and infant health outcomes in developed countries. Evid Rep Technol Assess (Full Rep). 2007;(153):1-186.
112. Betran AP, Torloni MR, Zhang JJ, Gülmezoglu AM; WHO Working Group on Caesarean Section. WHO Statement on Caesarean Section Rates. BJOG. 2016;123(5):667-70.
113. Lavender T, Hofmeyr GJ, Neilson JP, Kingdon C, Gyte GM. Caesarean section for non-medical reasons at term. Cochrane Database Syst Rev. 2012;(3):CD004660.
114. Mylonas I, Friese K. Indications for and Risks of Elective Cesarean Section. Dtsch Arztebl Int. 2015;112(29-30):489-95.
115. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy. 2008;38(4):634-42.
116. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy. 2008;38(4): 629-33.
117. Decker E, Engelmann G, Findeisen A, Gerner P, Laass M, Ney D, Posovszky C, Hoy L, Hornef MW. Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. Pediatrics. 2010;125(6):e1433-40.
118. Pei Z, Heinrich J, Fuertes E, Flexeder C, Hoffmann B, Lehmann I, Schaaf B, von Berg A, Koletzko S; Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics (LISAplus) Study Group. Cesarean delivery and risk of childhood obesity. J Pediatr. 2014;164(5):1068-73.e2.
119. Mueller NT, Mao G, Bennet WL, Hourigan SK, Dominguez-Bello MG, Appel LJ, Wang X. Does vaginal delivery mitigate or strengthen the intergenerational association of overweight and obesity? Findings from the Boston Birth Cohort. Int J Obes (Lond). 2017;41(4):497-501.
120. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, Parslow RC, Pozzilli P, Brigis G, Stoyanov D, Urbonaite B, Sipetić S, Schober E, Ionescu-Tirgoviste C, Devoti G, de Beaufort CE, Buschard K, Patterson CC. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia. 2008;51(5):726-35.
121. Horta BL, Gigante DP, Lima RC, Barros FC, Victora CG. Birth by caesarean section and prevalence of risk factors for non-communicable diseases in young adults: a birth cohort study. PLoS One. 2013;8(9):e74301.
122. Ragusa A, Svelato A. Childbirth and New Omics Sciences: an Ecological Perspective. Gynecol Women's Health. 2018;8(2):555732.
123. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107(26):11971-5.
124. Kaplan JL, Shi HN, Walker WA. The role of microbes in developmental immunologic programming. Pediatr Res. 2011;69(6):465-72.
125. Thysen AH, Larsen JM, Rasmussen MA, Stokholm J, Bønnelykke K, Bisgaard H, Brix S. Prelabor cesarean section bypasses natural immune cell maturation. J Allergy Clin Immunol. 2015;136(4):1123-5.e6.
126. Shi YC, Guo H, Chen J, Sun G, Ren RR, Guo MZ, Peng LH, Yang YS. Initial meconium microbiome in Chinese neonates delivered naturally or by cesarean section. Sci Rep. 2018;8(1):3255.
127. Thilaganathan B, Meher-Homji N, Nicolaides KH. Labor: an immunologically beneficial process for the neonate. Am J Obstet Gynecol. 1994;171(5):1271-2.
128. El-Khodor BF, Boksa P. Long-term reciprocal changes in dopamine levels in prefrontal cortex versus nucleus accumbens in rats born by Caesarean section compared to vaginal birth. Exp Neurol. 1997;145(1):118-29.
129. Boksa P, Zhang Y. Epinephrine administration at birth prevents long-term changes in dopaminergic parameters caused by Cesarean section birth in the rat. Psychopharmacology (Berl). 2008;200(3):381-91.

130. Hobbs AJ, Mannion CA, McDonald SW, Brockway M, Tough SC. The impact of caesarean section on breastfeeding initiation, duration and difficulties in the first four months postpartum. BMC Pregnancy Childbirth. 2016;16:90.
131. Kennedy HP, Doig E, Tillman S, Strauss A, Williams B, Pettker C, Illuzzi J. Perspectives on Promoting Hospital Primary Vaginal Birth: A Qualitative Study. Birth. 2016;43(4):336-45.
132. Lundgren SN, Madan JC, Emond JA, Morrison HG, Christensen BC, Karagas MR, Hoen AG. Maternal diet during pregnancy is related with the infant stool microbiome in a delivery mode-dependent manner. Microbiome. 2018;6(1):109.
133. Black M, Bhattacharya S, Philip S, Norman JE, McLernon DJ. Planned Cesarean Delivery at Term and Adverse Outcomes in Childhood Health. JAMA. 2015;314(21):2271-9.
134. Curran EA, Kenny LC, Dalman C, Kearney PM, Cryan JF, Dinan TG, Khashan AS. Birth by caesarean section and school performance in Swedish adolescents – a population-based study. BMC Pregnancy Childbirth. 2017;17(1):121.
135. Romano AM, Lothian JA. Promoting, protecting, and supporting normal birth: a look at the evidence. J Obstet Gynecol Neonatal Nurs. 2008;37(1):94-104.
136. Bloom SL, McIntire DD, Kelly MA, Beimer HL, Burpo RH, Garcia MA, Leveno KJ. Lack of effect of walking on labor and delivery. N Engl J Med. 1998;339(2):76-9.
137. Paterson P, Phillips L, Wood C. Relationship between maternal and fetal blood glucose during labor. Am J Obstet Gynecol. 1967;98(7):938-45.
138. Whaley WH, Zuspan FP, Nelson GH, Ahlquist RP. Alterations of plasma free fatty acids and glucose during labor. Am J Obstet Gynecol. 1967;97(7):875-80.
139. Felig P, Lynch V. Starvation in human pregnancy: hypoglycemia, hypoinsulinemia, and hyperketonemia. Science. 1970;170(3961):990-2.
140. Low JA, Pancham SR, Worthington D, Boston RW. Acid-base, lactate, and pyruvate characteristics of the normal obstetric patient and fetus during the intrapartum period. Am J Obstet Gynecol. 1974;120(7):862-7.
141. Levin BE, Keesey RE. Defense of differing body weight set points in diet-induced obese and resistant rats. Am J Physiol. 1998;274(2 Pt 2):R412-9.
142. Levin BE, Sullivan AC. Glucose, insulin and sympathoadrenal activation. J Auton Nerv Syst. 1987;20(3):233-42.
143. Levin BE, Dunn-Meynell AA, Banks WA. Obesity-prone rats have normal blood-brain barrier transport but defective central leptin signaling prior to obesity onset. Am J Physiol Regul Integr Comp Physiol. 2004;286(1):R143-50.
144. Levin BE, Kang L, Sanders NM, Dunn-Meynell AA. Role of Neuronal Glucosensing in the Regulation of Energy Homeostasis. Diabetes. 2006;55(Suppl 2):S122-30.
145. Tang-Christensen M, Larsen PJ, Thulesen J, Rømer J, Vrang N. The proglucagon-derived peptide, glucagon-like peptide-2, is a neurotransmitter involved in the regulation of food intake. Nat Med. 2000;6(7):802-7.
146. Fraley GS, Ritter S. Immunolesion of norepinephrine and epinephrine afferents to medial hypothalamus alters basal and 2-deoxy-D-glucose-induced neuropeptide Y and agouti gene-related protein messenger ribonucleic acid expression in the arcuate nucleus. Endocrinology. 2003;144(1):75-83.
147. Bugarith K, Dinh TT, Li AJ, Speth RC, Ritter S. Basomedial hypothalamic injections of neuropeptide Y conjugated to saporin selectively disrupt hypothalamic controls of food intake. Endocrinology. 2005;146(3):1179-91.
148. Ricardo JA, Koh ET. Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. Brain Res. 1978;153(1):1-26.
149. Leibowitz SF. Paraventricular nucleus: a primary site mediating adrenergic stimulation of feeding and drinking. Pharmacol Biochem Behav. 1978;8(2):163-75.
150. Leibowitz SF, Roossin P, Rosenn M. Chronic norepinephrine injection into the hypothalamic paraventricular nucleus produces hyperphagia and increased body weight in the rat. Pharmacol Biochem Behav. 1984;21(5):801-8.
151. Martin FP, Rezzi S, Lussu M, Pintus R, Pattumelli MG, Noto A, Dessì A, Da Silva L, Collino S, Ciccarelli S, Agostino R, Orfeo L, Atzori L, Fanos V. Urinary metabolomics in term newborns delivered spontaneously or with cesarean section: preliminary data. J Pediatr Neonat Individual Med. 2018;7(2): e070219.
152. Zwelling E. Overcoming the challenges: maternal movement and positioning to facilitate labor progress. MCN Am J Matern Child Nurs. 2010;35(2):72-8.
153. Harrison AL, Taylor NF, Shields N, Frawley HC. Attitudes, barriers and enablers to physical activity in pregnant women: a systematic review. J Physiother. 2018;64(1):24-32.
154. Champagne FA. Maternal imprints and the origins of variation. Horm Behav. 2011;60(1):4-11.
155. Chen J, Evans AN, Liu Y, Honda M, Saavedra JM, Aguilera G. Maternal deprivation in rats is associated with corticotrophin-releasing hormone (CRH) promoter hypomethylation and enhances CRH transcriptional responses to stress in adulthood. J Neuroendocrinol. 2012;24(7):1055-64.
156. Radtke KM, Schauer M, Gunter HM, Ruf-Leuschner M, Sill J, Meyer A, Elbert T. Epigenetic modifications of the glucocorticoid receptor gene are associated with the vulnerability to psychopathology in childhood maltreatment. Transl Psychiatry. 2015;5:e571.
157. Moore ER, Bergman N, Anderson GC, Medley N. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev. 2016;11:CD003519.
158. Nätt D, Johansson I, Faresjö T, Ludvigsson J, Thorsell A. High cortisol in 5-year-old children causes loss of DNA methylation in SINE retrotransposons: a possible role for ZNF263 in stress-related diseases. Clin Epigenetics. 2015;7:91.
159. Misiak B, Szmida E, Karpiński P, Loska O, Sąsiadek MM, Frydecka D. Lower LINE-1 methylation in first-episode

schizophrenia patients with the history of childhood trauma. Epigenomics. 2015;7(8):1275-85.

160. Bedrosian TA, Quayle C, Novaresi N, Gage FH. Early life experience drives structural variation of neural genomes in mice. Science. 2018;359(6382):1395-9.
161. Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L. Effect of Delayed Cord Clamping on Neurodevelopment at 4 Years of Age: A Randomized Clinical Trial. JAMA Pediatr. 2015;169(7):631-8.
162. Downe S, Finlayson K, Oladapo O, Bonet M, Gülmezoglu AM. What matters to women during childbirth: A systematic qualitative review. PLoS One. 2018;13(4):e0194906.
163. Monari F, Di Mario S, Facchinetti F, Basevi V. Obstetricians' and midwives' attitudes toward cesarean section. Birth. 2008;35(2):129-35.
164. Trinh AT, Roberts CL, Ampt AJ. Knowledge, attitude and experience of episiotomy use among obstetricians and midwives in Viet Nam. BMC Pregnancy Childbirth. 2015;15:101.
165. Macleod M, Murphy DJ. Operative vaginal delivery and the use of episiotomy – a survey of practice in the United Kingdom and Ireland. Eur J Obstet Gynecol Reprod Biol. 2008;136(2):178-83.
166. Sagi-Dain L, Sagi S. Episiotomy knowledge, attitudes and practice: a cross-sectional survey of four public Israeli hospitals and review of the literature. Evidence Based Midwifery. 2015;13(4):138-42.
167. Gei AF. Prevention of the first cesarean delivery: the role of operative vaginal delivery. Semin Perinatol. 2012;36(5):365-73.
168. Royal College of Obstetricians and Gynaecologists. Operative vaginal delivery. Green-top Guideline No. 26. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_26.pdf, date of publication: January 2011, last access: October 29, 2018.
169. Ragusa A, D'Avino S. Il parto operativo con ventosa omnicup. In: Danti L (Ed.). Il periodo espulsivo e... dintorni. Milan: Piccin, 2017.
170. Svelato A, Di Tommaso M, Spinoso R, Ragusa A. The reduction of first cesarean sections: a cultural issue. Acta Obstet Gynecol Scand. 2016;95(11):1319.
171. Ragusa A, Gizzo S, Noventa M, Ferrazzi E, Deiana S, Svelato A. Prevention of primary caesarean delivery: comprehensive management of dystocia in nulliparous patients at term. Arch Gynecol Obstet. 2016;294(4):753-61.
172. Rilling JK, Young LJ. The biology of mammalian parenting and its effect on offspring social development. Science. 2014;345(6198):771-6.
173. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, Ross MC, Lloyd RE, Doddapaneni H, Metcalf GA, Muzny D, Gibbs RA, Vatanen T, Huttenhower C, Xavier RJ, Rewers M, Hagopian W, Toppari J, Ziegler AG, She JX, Akolkar B, Lernmark A, Hyoty H, Vehik K, Krischer JP, Petrosino JF. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature. 2018;562(7728):583-8.