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COMMENTARY

Back to the future: our health history begins long before birth

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THE ORIGIN OF LIFE: THE ONLY THING WE KNEW WAS BIRTH

Until now, the gathering of health history from a patient by a doctor began with a personal birth history, birth, type of delivery, prematurity, development and first movements, and proceeded to family history, social history and past medical history. In fact, we gather all medical information from birth to date when we see a patient. However, times are changing. The lesson we learn from studies such as that of Zanardo *et al.*[1] is that prenatal history can also be included in a patient's medical information.

ULTRASOUND AND ACCESS TO PRENATAL LIFE: FROM OBSERVATION TO PRENATAL DIAGNOSIS

Until the advent of ultrasound, the only thing we knew was birth. As a result of the development of ultrasonography and its application to pregnancy, we have gained access to prenatal life. The slow but continuous evolution of such an application from a simple observation led to full and concrete prenatal diagnosis: the fetus became the subject. We now know almost everything about the fetus: its early development from embryo to the fetal stage; the developmental chronology of body and limb movements; when it starts mouthing, suckling, yawning; and how it grows. We can explore brain and body anatomy, see the crystalline movements, recognize sleep and wake states and see how it startles if it hears loud sounds. We can also explore its peculiar circulation and understand if the fetus is well or if it is trying to compensate for low oxygen supply; this is the case of intrauterine growth-restricted (IUGR) fetuses, which initiate a brain-sparing effect to save the noble organs in the event of hypoxemia. We have an access route that is becoming closer to the models we use for born individuals every day.

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WHAT WE ARE IN ADULTHOOD IS SOMETIMES PREDICTABLE AT BIRTH (BARKER'S HYPOTHESIS)

Once it was acknowledged that we could closely evaluate the fetus, the viewpoint that changed the meaning of fetal diagnosis was Barker's hypothesis. This environmental epidemiologist, in a short study,[2] observed that the death rates from cardiovascular mortality were closely related to neonatal mortality rates, and that neonatal mortality was higher in low birthweight babies and in babies born in areas where mothers had poorer health and higher childbirth mortality. He therefore suggested that research on cardiovascular mortality should be redirected to the intrauterine environment, rather than the environment of subsequent infant and adult life. He concluded that the new models for studying adult degenerative disease had to consider fetal programming and the fetal environment. He threw the pebble in the pond, but may not have expected how far the ripples would go. In PubMed (http://www.ncbi.nlm.nih.gov/pubmed), to date, there are over 150 studies quoting or recalling Barker's hypothesis.

The hypothesis has been tested and largely confirmed. Many authors[3] have found that birthweight is related to the development of diseases later in life. The relationship is acknowledged between low birthweight and diabetes, hypertension, stroke and coronary heart disease in adulthood, and is mediated by the patterns of postnatal growth.

WHAT WE ARE IN CHILDHOOD AND IN ADULTHOOD IS SOMETIMES PREDICTABLE BEFORE BIRTH!

Starting from the relationships between birthweight and adult disease, the research has expanded and focused on the mechanisms that may lead to intrauterine growth restriction and/or the intrauterine environment as the primer for neonatal and childhood conditions, with positive results.

The features of metabolic syndrome (central obesity, insulin resistance, glucose intolerance, dyslipidemia, atherosclerosis, hypertension, hyperinsulinemia and even polycystic ovarian syndrome (PCOS)) are sometimes evident during childhood and adolescence in individuals born to obese mothers[4] as a result of impaired fetal nutrition.

Maternal diet, in turn, affects fetal nutrition and growth, and nutritional interventions in pregnant women seem to produce positive fetal–neonatal effects on lipid concentrations, insulin resistance and vascular function.[5]

The above hypothesis of a prenatal environmental effect as the origin of PCOS had already been raised in animal models,[6] but other prenatal hormonal variations may also alter fetal status. Both in monkeys and sheep, excess testosterone exposure *in utero* causes excess luteinizing hormone secretion, due to reduced hypothalamic sensitivity to negative steroid feedback, and relative insulin excess from increased abdominal adiposity. Excess luteinizing hormone and insulin are both features of PCOS: the intrauterine hormonal environment would target tissue differentiation so that excess intrauterine testosterone may lead to PCOS in adolescence, even in humans. The uterine environment has even been postulated to predispose individuals to cancer, which is particularly attributable to maternal diet.[7] Maternal diet

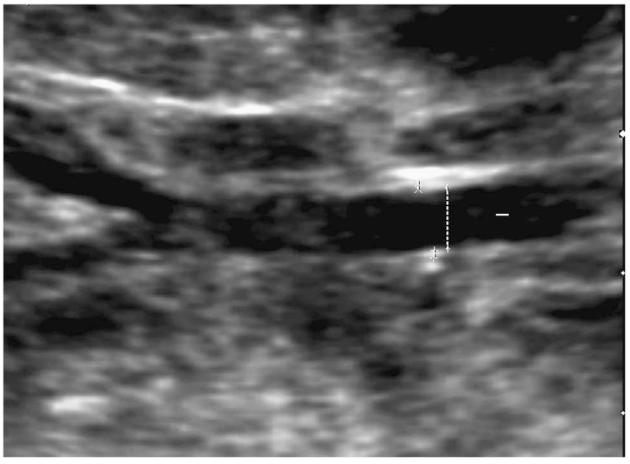

Figure 1 Fetal aortic wall thickness.

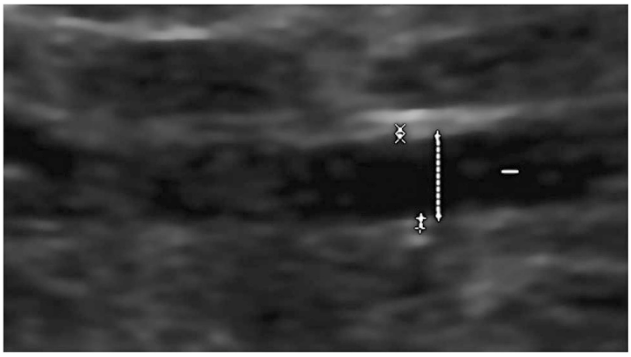

Figure 2 Infant aortic wall thickness.

or maternal exposure to endocrine factors may alter the fetal epigenome, sensitizing the mammary gland to the possible triggering of cancer development by other environmental factors. Animal models have shown that a maternal diet leading to a high birthweight may predispose offspring to breast cancer,[8] and that modifying the maternal diet with fiber reduces this risk.[9]

The article by Zanardo *et al.*[1] addresses the question of the relationships between the intrauterine environment and neonatal and childhood conditions. It is likely that what we see in neonates or infants may be the result of what occurs during prenatal life. What is astonishing, though, is the possibility to measure the same parameters *in utero* and after birth, with a strict correlation not only between the features, but also between the technologies used to assess them. The evaluation of fetal aortic wall thickness is one of the first techniques directly derived from infant diagnostics. Ultrasound exploration of the fetus had previously led to the understanding of the vascular adaptation of IUGR fetuses to hypoxemia, which is characterized by blood flow restriction in the abdomen, so that an adequate supply is received by the heart and brain in a process that may cause subsequent necrotizing enterocolitis in small newborns. With this article, we move a step forward. We compare fetal and infant parameters and predict what will happen in infancy and possibly adulthood with a prenatal test. To be strict, we antedate the infant diagnosis at a prenatal stage.

The test is easy to perform in experienced hands. Unfortunately, fetuses sometimes fail to maintain a stable position, and the 'collaboration' can be difficult. Regardless, the result is a technique that is highly reproducible and comparable between the fetus (Figure 1) and infant (Figure 2).

WHAT'S NEXT? EVOLUTIONAL CARDIOLOGY

At this stage, we have increasing evidence that Barker's hypothesis is more applicable than expected. We also have epidemiological, observational and experimental evidence that corroborates the great opportunity we have to explore the fetus, and move all our observations backward: from the elderly to adults, from adults to youths and from infants to fetuses. The medical branch that seems to have the best chance to evolve in this sense is cardiology. We are at the beginning of the evolution of cardiology, and the collaboration between obstetricians and cardiologists will definitely be the keystone.

Two closing considerations. We have to scientifically admit that life is a continuum that begins long before the date of birth. Such life lays its foundations in the very early days after conception, with trophoblast chorionic gonadotropin modifying the maternal ovaries, continuing with placental lactogen hormone, which modifies maternal insulin resistance, and ending with the contribution of fetal cortisol to maternal labor. Throughout the entirety of prenatal life, the mother and fetus interact daily, affecting the state of the newborn: life is always life after fertilization, and this is food for ethical thought.

Finally, it is dramatic how little a role the father has in this life and how we are destined to admit women's supremacy in the biological basis of future health. However, this may only be a gynecologist's point of view!

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