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The impact of prenatal environment on postnatal life and performance: Future perspectives for prevention and treatment

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ABSTRACT

The present review aims to offer a non-comprehensive outline of the current state-of-the-art and future perspectives on management and therapeutic tools for intrauterine growth restriction (IUGR) and associated prenatal programming in both human and animal species. Animals are used as models for the study of phenomena related to IUGR, but also for research on prenatal therapies with the main objective of designing and developing preventive and therapeutic strategies. The research is currently paying attention on maternal-focused pharmacological treatments and nutritional strategies but also on fetal-focused treatments. Fetal-focused treatments, administered either directly at the fetus or by using infusion of umbilical cord, amniotic sac or placenta, which avoids the administration of substances at high doses to the mother for allowing their availability at the fetoplacental level. The results obtained in this area of research using large animals (rabbits, pigs and ruminants) have a dual interest, for translational biomedicine and for veterinary medicine and animal production.

1. Introduction: Prenatal environment and postnatal life

The viability and life performance of all living organisms is known to be determined by the interaction between genetics and environment (i.e.: photoperiod, weather conditions and temperature, water and nutrients accessibility and oxygen availability). For many years, it was believed that the capability of the individual to success in life (in terms of reproductive fitness and life-long health) was purely determined by its performance during the postnatal period (from birth to death), relegating the prenatal period (from conception to delivery) to a second place. The interest in pregnancy events raised only by the early 20th century. In the late 1940's, C.A. Smith first reported that poor maternal nutrition could influence fetal development [1]. His studies were followed by W.A. Cochrane observations, who also described a connection between maternal overnutrition and poor prenatal growth [2]. However, it was not until the late 1980′s when Prof. D.J. Barker and colleagues studied different epidemiological birth records and found a link between low birth-weight and the appearance of metabolic and cardiovascular diseases (diabetes and hypertension) at adulthood [3].

These evidences gave way to the concept of prenatal programming [4]. Prenatal programming is produced by the high susceptibility of the embryo and the fetus to changes in their environment (i.e.: in intrauterine conditions; mainly nutritional) and by their ability to modify the expression of their genome through epigenetic changes to adapt to such intrauterine conditions [5]. These changes allow their survival but influence youth growth, the adult phenotype and the appearance of non-communicable diseases.

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2. The relevance of maternal and placental factors in IUGR and prenatal programming

The appearance of IUGR may be related to genetic, infections or, more frequently, to an intrauterine environment inadequate for the development of the fetus. The main factor affecting the intrauterine environment is the availability of nutrients and oxygen required by the fetus for its development.

Traditionally, the low availability of oxygen and nutrients by the fetus has been linked to maternal malnutrition or hypoxia; mainly states of malnutrition in case of socioeconomic disadvantage, food shortages and inadequate diets or hypobaric hypoxia states in case of pregnant women living or visiting high altitudes.

Currently, a low availability of oxygen and nutrients is still the main cause in developing areas but there has been a strong increase in the incidence of IUGR in developed countries. Such increase has been linked to occurrence of IUGR caused by placental factors (abnormal placental development and function and, therefore, shortage of transfer of nutrients and oxygen to the fetus).

In fact, the term *placental insufficiency* is a global term used to define the failure in the supply of nutrients and oxygen by the placenta to the fetus. Possible causes have been related to alterations in maternal or fetal blood supply, reduced transport capacity by the placenta and/or changes in the placental structure which may diminish the transfer of nutrients and oxygen to the fetus. Currently, it is estimated that approximately 60% of IUGR cases are related to placental insufficiency [6,7]. Placental insufficiency is nowadays a rising problem, since it seems to be usually linked to different factors; mainly, delays in childbearing age, inadequate lifestyle, stress, sedentary habits, pollution, alcohol and tobacco consumption, obesity, diabetes or preeclampsia. Most of these factors are highly related to the contemporary lifestyle, so we can anticipate future increases in the prevalence of the disorder.

The complexity of IUGR and fetal programming makes necessary to use preclinical models *in vivo*, since *in vitro* models can only replicate very specific aspects of the global process, such as placental exchange, during very short periods. Other aspects of pregnancy, such as the development of the uteroplacental circulation or the proper embryo and fetal development make absolutely necessary the development of *in vivo* models. Obviously, *in vivo* experimentation cannot be carried out in human beings, so the use of animal models is unavoidable. Animal models more frequently used in experimental studies on IUGR and prenatal programming are based on the use of laboratory rodents (rats, mice and guinea pigs [8–10]). Currently, it is increasing the use of large animals (mainly rabbits, pigs and small ruminants; [10–12]) in which the results obtained have a dual interest, both from the translational point of view in biomedicine and from the point of view of veterinary medicine and animal production.

Animal models can be used and are, in fact, used for the study of phenomena related to restricted intrauterine growth, but also for the research on prenatal therapies. The main objective would be the availability of preventive and therapeutic strategies.

3. Preventive and therapeutic strategies

Current actions to prevent and improve the appearance of delays in prenatal growth are mainly based on changes in lifestyle and diet, since there are no therapeutic strategies with proven validity.

Among the possible treatments under study, it has been observed that improvements in placental development and functionality can be obtained by favoring the processes of placental neoangiogenesis and vasodilation. Among the various mechanisms involved in the appearance of placental insufficiency, vascular disorders that are related to insufficient blood flow and problems in the fetoplacental circulation stand out. The primary causes of these vascular alterations are unknown, although deficiencies have been reported in the numerous angiogenic growth factors that regulate this process; mainly vascular endothelial growth factor (VEGF), placental growth factor (PlGF), platelet-derived growth factor (PDGF), and transforming growth factor (TGF-β) [13–15]. Based on this knowledge, the most appropriate strategy seems to be based on actions on VEGF and the nitric oxide (NO) route. In healthy pregnancies, vascular dilatation and neoangiogenesis at the time of implantation and during the subsequent development of the placenta are determined by proangiogenic factors; mainly by PlGF and VEGF. VEGF is a potent mitogen, specific to endothelial cells, that promotes angiogenesis, vasodilatation and vascular permeability through autocrine mechanisms that involve the production of NO and prostacyclin PGI2 [16].

3.1. Pharmacological therapies

The first studies on the use of this route were carried out during the 1990s and were based on the use of low-dose aspirin [17,18]. Acetylsalicylic acid inhibits the activity of cyclooxygenase in platelets and, therefore, increases the ratio between PGI2 and thromboxane A2 (TXA2). PGI2 acts as a vasodilator and inhibitor of platelet aggregation, while TXA2 acts as a vasoconstrictor and stimulator of platelet aggregation. Hence, the ratio increase would result in the improvement of systemic and, therefore, uteroplacental blood flow. Thus, it has been described that the use of low-dose aspirin from early stages of pregnancy is useful to prevent intrauterine growth retardation in case of early onset preeclampsia [19,20]. However, to the date, the results obtained do not support routine prophylactic or therapeutic use in other cases of IUGR which causes are different from the vascular features of preeclampsia.

Vasodilatation and placental angiogenesis are mainly induced by NO and endothelial NO synthase (eNOS or NOS3). Both factors act from the moment of implantation, favoring vasodilatation and angiogenesis in the maternal endometrium [21–23]. In the post-implantation period, during placental development, NO and NOS3 are involved in tissue remodeling, immunosuppression and vasoregulation processes [24]. On the other hand, it has been described that decreases in the bioavailability of NO are related to occurrence of IUGR [25].

Therefore, the increase in the bioavailability of NO could prevent or alleviate alterations in fetal growth. In this sense, sildenafil citrate (commonly known by its brand name Viagra®) is a selective inhibitor of phosphodiesterase type 5 (PDE-5), which prevents the hydrolysis of cyclic guanosine monophosphate (cGMP), which acts as the biological signal for NO synthesis [25] and, therefore, increases NO bioavailability. Therefore, the use of sildenafil can help to optimize placental development and function and, thus, can help to avoid IUGR [26–29]. Observational studies in the case of the human species have shown promising results [30–34], but an experiment conducted by our group using rabbits as an experimental model has shown that maternal treatment with sildenafil can induce an excess of blood supply to the fetal brain and therefore fetal hypertension [29]. Consequently, complementary studies must be carried out before assessing their clinical application.

A different alternative would be the use of metformin (3-(diaminomethylidene)-1,1-dimethylguanidine), an anti-hyperglycemic drug widely used for the treatment of insulin resistance and glucose intolerance associated with diabetes [35]. The drug is currently considered as a potential agent for preventing large-for-gestational-age (LGA) offspring in pregnant women with diabetes [36,37]. However, as metformin favors the transfer of glucose to tissues, there are also evidences addressing that improves fetal development and metabolism in underfed pregnancies [38].

3.2. Nutritional strategies

The NO and VEGF route can be favored not only by pharmacological treatments but also through nutritional supplementation with NO precursors; mainly, in the form of amino acids. The best known is arginine, the main substrate of NOS, but there are several other amino acids that are precursors to NO (ornithine, leucine, glutamine and proline). These amino acids also regulate the synthesis of polyamines and proteins; therefore, in addition to favoring placental development and the transfer of nutrients through the placenta, they are also positive for fetal tissues development. The results obtained in experimental conditions in animal models (sheep and pigs) suggest that amino acid supplementation may be a promising strategy to reduce the incidence of IUGR and its associated disorders [39–41]. However, previously to practical implementation, it is necessary to develop further studies to determine the real requirements of amino acids and proteins during pregnancy [42], the real metabolic bioavailability of dietary amino acids after digestion and absorption [43] and the real availability for the fetus after placental transport [44]. In this sense, there is evidence addressing that IUGR would be associated with a decrease in the placental ability for transporting amino acids. Obviously, this would limit the effectiveness of therapies based on their administration.

A possible alternative is the use of vitamins favoring protein synthesis, like group-B vitamins (B6, B9 and B12). Vitamin B6 (pyridoxine) is involved in the synthesis of DNA, RNA and proteins, favoring the energy balance of the offspring [45]. On the other hand, the effects of vitamin B9 (folic acid) shortage are well known (placental deficiency, abortion or delays in fetal growth and deficiencies in the formation of the neural tube, leading to spina bifida and anencephaly [46]). In pigs, it has been described that vitamin B9 supplementation improves development and metabolic traits in IUGR fetuses [47,48]. Finally, vitamin B12 (cyanocobalamin) favors the synthesis of phospholipids essential for offspring development [49]. There is also a positive correlation between vitamins in the group B and therefore their combination favors embryo and fetal development and viability, decreasing IUGR incidence [50].

In addition to the effects of B vitamins on protein synthesis, there are vitamins with antioxidant effects; specifically, vitamins A, C and E. Maternal supplementation with antioxidant agents may alleviate occurrence of IUGR, since the condition is characterized by a weakened antioxidant defense system of the fetuses. Vitamin E (tocopherol) is the main known *in vivo* antioxidant agent, which specifically prevents the oxidation of PUFAs [51]. Vitamin C (ascorbic acid) is essential for offspring development and its deficit in pregnant sows has been found to cause hematological and skeletal abnormalities in developing fetuses [52], because the fetus is not able to synthesize it so its availability depends on maternal transport. A paradox is that maternal supplementation with vitamin C does not imply an increase in its plasma concentration in the pregnant sow, but levels rise significantly in the fetus [53]. Sheep studies also indicate a very active transfer of vitamin C and E from the mother to the fetus, with beneficial effects on the antioxidant status and body development of the fetus mainly in twin pregnancies [54] that are characterized by being hypoxemic [55]. Vitamins C and E acts synergistically, so combined supplementation of both implies an increase in the availability of vitamin E, more expensive than vitamin C, without increasing the dose [56–58]. Such combined treatment has a well-known beneficial effect on fetal development in sheep singleton pregnancies developed at high altitudes, which are affected by chronic hypoxia and oxidative stress [59].

Other group of antioxidant agents are polyphenols; in fact, the most abundant dietary antioxidants. Our group has proven the usefulness of maternal supplementation with hydroxytyrosol (a polyphenol present in olive leaves and fruits [60,61] with even higher antioxidant capacity than vitamin E [62]) for improving fetal oxidative status, decreasing the appearance of LBW neonates in a swine model of IUGR and favoring postnatal development [63–65].

However, all these strategies are still in a preclinical stage and further studies on their efficiency, long-term safety and real translational value are needed.

4. The future: Focused fetal therapies

The therapies described are based on actions at the systemic level, by administering the substances at high doses to the mother to allow their availability at the fetoplacental level. The problem derived from the need to administer high doses of any substance to the mother to achieve therapeutic concentrations in the fetus has led to the research and development of other routes, based on focused fetus treatments, either directly at the fetus or by using infusion of umbilical cord, amniotic sac or placenta. These strategies allow to achieve adequate fetal concentrations of therapeutic substances for the treatment of IUGR, without requiring the delivery of high doses to the mother but also avoiding problems derived from inadequate placenta transfer.

The fetal-focused route may be used for administration of any substance but has been used primarily for the administration of gene therapy, specifically for inducing adenovirus-mediated (Ad) overexpression of growth factors, like VEGF (which increases uterine flow and improves fetal growth; [66]) or IGF-1 (inducing reprogramming of fetal growth, increasing pre- and postnatal offspring development and preventing liver, musculoskeletal and cardiovascular dysfunctions; [67,68]). The use of advanced therapies like mesenchymal stem cells (MSC) has also been assessed as an alternative for the prevention and treatment of IUGR. MSCs can be especially useful because of their capacity for favoring immunomodulation and neoangiogenesis [69,70]. In addition, a main therapeutic advantage of MSCs is the possibility of using allogeneic MSCs from healthy donors, without the need for considering histocompatibility between donor and recipient [71]. In fact, the use of allogeneic MSCs as drugs has already been approved in several countries, both for human and veterinary medicine [72–74].

However, these techniques are still on early research, due to the risks of fetal injury in case of direct administration or due to the risk of fluid/blood loss of in case of administration in the umbilical cord, placenta or amniotic sac. Experimental data focused administration has been only obtained using invasive methods for inoculation (laparatomy), which implies that the technique is still hardly extrapolated to practice.

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