

Review

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Maternal protein malnutrition: effects on prostate development and adult disease

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Abstract

Well-controlled intrauterine development is an essential condition for many aspects of normal adult physiology and health. This process is disrupted by poor maternal nutrition status during pregnancy. Indeed, physiological adaptations occur in the fetus to ensure nutrient supply to the most vital organs at the expense of the others, leading to irreversible consequences in tissue formation and differentiation. Evidence indicates that maternal undernutrition in early life promotes changes in key hormones, such as glucocorticoids, growth hormones, insulin-like growth factors, estrogens and androgens, during fetal development. These alterations can directly or indirectly affect hormone release, hormone receptor expression/distribution, cellular function or tissue organization, and impair tissue growth, differentiation and maturation to exert profound long-term effects on the offspring. Within the male reproductive system, maternal protein malnutrition alters development, structure, and function of the gonads, testes and prostate gland. Consequently, these changes impair the reproductive capacity of the male offspring. Further, permanent alterations in the prostate gland occur at the molecular and cellular level and thereby affect the onset of late life diseases such as prostatitis, hyperplasia and even prostate cancer. This review assembles current thoughts on the concepts and mechanisms behind the developmental origins of health and disease as they relate to protein malnutrition, and highlights the effects of maternal protein malnutrition on rat prostate development and homeostasis. Such insights on developmental trajectories of adult-onset prostate disease may help provide a foundation for future studies in this field.

Introduction

Malnutrition comes in many forms, including undernutrition (not enough protein or carbohydrate or food to eat), micronutrient deficiencies (not enough vitamins and minerals) and overweight (linked to an unbalanced or unhealthy diet). Approximately 462 million adults worldwide are underweight, and around 45% of deaths among children under 5 years of age are linked to undernutrition.^{1,2} Indeed, adverse exposures in early life, particularly relating to nutrition, are linked to susceptibility to chronic non-communicable diseases in adulthood.^{3,4} Insight from animal models indicates that maternal malnutrition negatively impacts the intrauterine environment, altering fetal programming and development.

The notion that the intrauterine environment influences the development of the fetus is not new. Past studies of intrauterine undernutrition identified changes in the structure of key fetal organs such as the heart, kidney and brain.^{5–9} What is new, however, is the concept that early life exposure to undernutrition affects adult disease susceptibility. Anthropometry (i.e. weight) at birth was identified two decades ago as predictive of adult coronary heart disease, type 2 diabetes and metabolic syndrome; this finding prompted the ‘Barker hypothesis’ that a suboptimal intrauterine environment induces compensatory responses in the fetus that may permanently affect the adult phenotype.^{5,8,10} For example, a cross-sectional study has shown that low birth weight is associated with decreased overall adult health status as well as reduced reproductive capability.¹¹ Although birth weight is a poor proxy for nutritional events during gestation, the Barker hypothesis has been confirmed in many independent cohorts across the developed and developing world.^{12–14}

Similarly, the ‘thrifty phenotype’ hypothesis proposes that poor fetal nutrition imposes mechanisms of nutritional economy upon the growing individual. Follow-up studies of babies born during the 1944 Dutch famine implicate a role for nutrition in programming disease risk.¹⁵ In conditions of severe intrauterine deprivation, the developing fetus may lose structural units that program physiological function and determine risk of disease in adult life;¹⁶ this phenomenon is termed *nutritional programming*. Programming occurs because developmental plasticity allows the fetus to adapt its tissue structure in response to environmental changes. In this sense, the same genotype can produce different phenotypic outcomes depending upon inputs during development.¹⁷ The conditions of early life, when added to adult

lifestyle – for example, diet, physical activity, smoking habits and alcohol consumption – are the main determinants of our long-term health and well-being.

Together, these hypotheses have become known as the *fetal origins* or the *developmental origins of health and disease* (DOHaD), and produced a new branch of scientific pursuit (Fig. 1). DOHaD establishes that events occurring in critical periods of development are memorized, leading to the formation of an organism with an ‘adapted phenotype.’ Environmental factors in early life, such as nutrition, stress, endocrine disruption and pollution are some of the insults that trigger developmental programming.¹⁸

Nutrient requirements for an organism depend on developmental state, reproductive activity and age.¹⁹ In general, during early life, malnutrition could be a result of intrauterine undernutrition, inadequate breastfeeding, the late introduction of complementary foods or the introduction of inadequate complementary foods.²⁰ Nutritional programming resulting from poor nutrition status during pregnancy can lead to irreversible consequences in tissue formation and differentiation. These consequences stem from the physiological adaptations that occur to ensure nutrient supply to the most vital organs at the expense of others. This programming in response to variations in the quality or quantity of nutrients consumed during pregnancy is geared toward increasing the fetal survival rate.²¹ However, the processes that underlie the disordered organ development are poorly defined.

Animal models are used to provide some mechanistic insight for the link between maternal diet and adult disease. In animal studies, the major challenge is to capture life course exposures and identify ‘windows of susceptibility,’ or those time points during which nutritional exposures have the greatest impact on development and disease. Approaches to studying nutritional programming in animal models range from limiting the total food intake to more specific manipulations such as overfeeding or restriction of macro- and micronutrients.¹⁹ Most animal studies investigating early nutritional programming have centered on the use of rodent models; however, other animal models are also important, including porcine, ovine and primate models.²²

Such animal studies have indicated that the mechanisms underlying the effects of malnutrition on development are related to alterations in placental function, including control of maternal-fetal endocrine exchanges, modified transcription factor expression and the epigenetic regulation of gene expression, via non-coding RNAs, DNA methylation or histone methylation.²³ Such modifications triggered during developmentally sensitive stages of early life play a central role in regulating long-term health and disease outcomes. One of the most extensively studied models, the maternal low-protein rat model, established by Snoeck *et al.* in the early 1990s,^{24–27} has demonstrated that protein content and sources in maternal diets are capable of producing shifts in the fetal environment, driving the tissue remodeling response and altering future disease risk.^{27,28} Evidence also exists that adverse outcomes extend beyond first generation to induce transgenerational effects.²⁹ In this sense, finding strategies to improve maternal nutritional status will benefit the present as well as the future generation.

Given the high prevalence of nutritional deficiencies globally and the growing epidemic of chronic disease, it is increasingly important to understand the impacts of fetal malnutrition on the life course. As our group has been studying prostate development and aging under the umbrella of different models of fetal programming, the main purpose of our study is to discuss the role of maternal low intake of protein in influencing organ development and aging. This review will use prostate reprogramming as a function of maternal nutrition as a specific example. Such insights into the complex molecular context on developmental trajectories of adult-onset disease, specifically focusing on prostate biology, may help future studies on this field.

Proposed mechanisms of fetal programming by low-protein diet

Studies of nutritional programming using animal models have been ongoing since the early 1990s. The most used and best characterized model employs maternal protein restriction during rat pregnancy

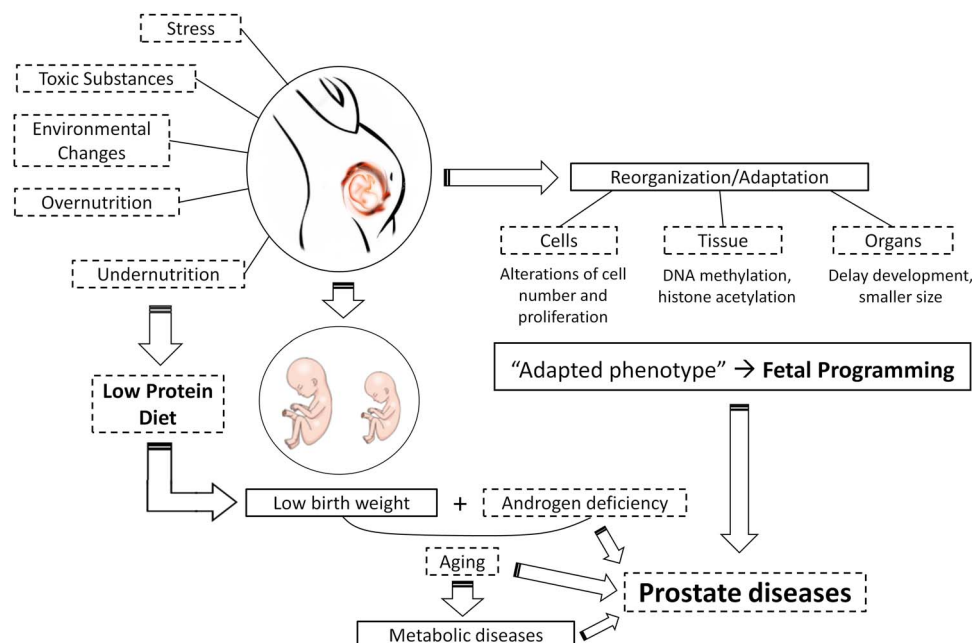


Fig. 1. A schematic example of developmental origins of health and disease hypothesis illustrating prostate reprogramming as a function of maternal protein malnutrition.

and/or lactation periods.¹² The protein requirement for gestation and lactation as a percentage of the diet is similar to that for growth of weanling rats – about 12% – when highly digestible protein of a balanced amino acid pattern is used.³⁰ It is important to understand the difference in metabolic and physiologic responses to isocaloric protein malnutrition and protein energy malnutrition. Although protein malnutrition is more related to cultural constraints, protein energy malnutrition is related to poverty and economic adversity. The latter results in responses that are similar to those of starvation. In contrast, isocaloric protein malnutrition leads to suppression of proteolysis and maintenance of lean body mass and may lead to gain in fat mass.³¹

Studies using rodent models have shown that maternal malnutrition by isocaloric low-protein diet during pregnancy or during early postnatal life can lead to metabolic and physiological changes in adult life even when the animals have free access to a normal diet after weaning.^{32,33} Studies investigating the impact of fetal protein restriction upon longevity have also demonstrated that rats undernourished *in utero* have a shorter lifespan.³⁴

Nutrient deprivation can act as a strong programming stimulus and promotes several structural changes in fetal tissue. Among them are altered cell number, an imbalanced distribution of cell types or hormone receptor numbers in an organ, and altered blood supply.^{27,35–38} Dietary protein provides an important source of amino acids that are essential precursors in the synthesis of hormones, neurotransmitters and nitric oxide. In addition, they act as important regulators in the metabolic pathways related to development and reproduction.³⁹

Physiological responses to dietary proteins are also determined by the proteins' characteristics arising from their amino acid composition, bioactive peptides (BAPs) and digestion kinetics. Thus, nutritional adequacy of amino acids may not be the only characteristic of the maternal diet to impact the offspring.⁴⁰ The timing of fetal programming is also important. For example, the source of protein (casein- *v.* soy protein-based diets) in the maternal diet exerts an effect on body weight and glucose metabolism that is magnified when maternal diet is extended from gestation alone to gestation and lactation in male offspring of rats. This finding highlights an important consideration: study results should be compared cautiously because of wide variation in study design (e.g. protein restriction *v.* protein-free diets, duration of dietary protocol).

A lack of protein in the maternal diet causes characteristic changes in one-carbon metabolism. Certain amino acids, such as methionine, serine and glycine, not only contribute to protein mass, but also play a unique role in the regulation of cellular metabolism and proliferation and may impact fetal growth. Methionine, an essential or indispensable amino acid and a component of all proteins, is the immediate source of the methyl (one carbon) groups required for the methylation of nucleic acids, proteins, biogenic amines and phospholipids.⁴¹ Even low-protein diets with similar protein content may affect programming differently because lower protein intake in humans and other animals has been shown to cause hyper-homocysteinemia and perturbations in one-carbon metabolism. For example, the *low-protein Southampton diet* results in higher systolic blood pressure in offspring,⁴² whereas the *Hope Farm diet* has no effect on blood pressure.⁴³ Adding glycine, which reduces plasma homocysteine, to the Southampton diet normalizes blood pressure.⁴⁴ This suggests that the methionine load is a contributor to the phenotype of the Southampton diet.⁴⁵ Hyper-homocysteinemia can be related to hypomethylation of DNA

that consequently alters organogenesis and embryonic vasculogenesis by influencing its major events, increasing metabolic syndrome risk.^{25,46} Further, supplementation of a low-protein gestational diet with taurine (2.5%) restores normal insulin secretion. Taurine participates in homocysteine metabolism and reduces the demand for cysteine.⁴⁷ In addition, the essential nutrient choline is required for the maintenance of structural integrity and signaling function of cell membranes, for neurotransmission, for transport of lipids, and as a source of methyl groups for methylation and epigenetic programming.⁴⁸

BAPs, or protein fragments that can influence health, have been detected in the plasma of pregnant and lactating women. For example, casokinins originating from all major subunits of casein are much higher than those from soy protein.⁴⁹ BAPs abundant in casein, called β -casomorphins, can affect food intake regulation, gastrointestinal motility and plasma insulin concentration.⁵⁰ These peptides directly influence numerous biological processes evoking behavioral, gastrointestinal, hormonal, immunological, neurological and nutritional responses. However, it remains unknown if BAPs cross the placenta or have a role in the development of regulatory systems.^{51,52} Moreover, the rate of protein digestion and the resulting hormonal responses in dams and peak amino acid concentrations in fetuses may also influence the development of regulatory systems. In this sense, proteins can be classified as either 'fast' or 'slow.'⁵³ Casein is considered a slow protein; whey and soy are fast proteins. Plasma concentrations of serine, tyrosine, valine, isoleucine, branched-chain amino acids, lysine and total amino acids are higher, and arginine and tryptophan are lower after a casein meal compared with after a soy protein meal in humans. Hormonal responses to these proteins are also markedly different.⁵⁴ For example, a higher concentration of plasma insulin is noted after whey protein consumption as compared with casein at 60 min after ingestion. However, to our knowledge, there are no studies examining the role of protein digestion kinetics on fetal programming.

Another potential mediator of the effects of maternal undernutrition on fetal programming is the placenta. The relationship between placental function and fetal nutrition is complex because amino acids can be synthesized *de novo* within the placenta.⁵⁵ Moreover, the ability of the placenta to provide the fetus with substrates depends upon the quality of placentation. Placentation differs between species, with rodents and humans having a discoid, hemochorial placenta, whereas in sheep the placentas are cotyledonary synepitheliochorial, which may represent an evolutionary development and can limit the transport of some molecules from the mother to fetus.^{56,57} In addition, the placenta is a major source of endocrine signals that play a role in maintaining the pregnancy, is involved in modulating fetal growth rate and organ maturation.^{19,58} Despite these putative effects, the role of the placenta in programming has not been investigated in depth.

Fetal programming and developmental plasticity

In mammals, intrauterine development is a critical period of plasticity for most organs and systems. Fetal development occurs through sequential events including morulation, gastrulation and organogenesis. Each step is dependent upon meticulous orchestration of cell differentiation, migration, proliferation and apoptosis. These processes can be perturbed by inadequate environmental stimuli during sensitive periods, producing effects that persist across the life course and lead to pathological conditions in adulthood.⁵⁹

Maternal nutritional and metabolic statuses are critical in determining not only reproduction, but also long-term health and viability of offspring. During the periconceptual and pre-implantation periods, nutrient, oxygen and hormone levels affect development of the oocyte and blastocyst, with consequences for the distribution of cells between the trophoblast and inner cell mass. If developmental plasticity leads to a change or adaptation that is permanent, it is considered a 'programming' change and is associated with persistent effects in structure and/or function. The problem starts when individuals developmentally adapted to one environment are exposed to another.⁶⁰ Accordingly, mice exposed to a low- (6%), medium- (18%) or high- (36%) protein diet *in utero* or through lactation have lower survival rates at 2 years if weaned onto a diet that differed from that of their mother.⁶⁰

Poor intrauterine nutrition results in the growth of vital organs, specifically the brain, at the expense of other organs.⁶¹ Such adaptations may increase the chance of fetal survival by means of 'brain sparing,' but result in difficulty coping with nutritional abundance as an adult.¹⁵ Further, some children return to their genetic trajectory through compensatory growth, recovering size after a period of growth delay or arrest through catch-up growth. This phenomenon often results in over-compensation, whereby the offspring exceeds normal weight and often has excessive fat deposition.⁶² This rapid and excessive growth has been associated with the development of adult obesity, insulin resistance, metabolic syndrome and type 2 diabetes.⁶³ It happens especially with people living in countries that are undergoing swift economic and nutritional transitions, exposing individuals to conditions that promote weight gain.⁶⁴

Maternal protein malnutrition (MPM) during developmental programming can also alter the balance of reactive oxygen species. Proteins such as glutathione and albumin provide amino acids needed for antioxidant synthesis to combat reactive oxygen species.⁶⁵ MPM can lead directly to a pro-oxidative state by creating protein deficiencies. Increasing oxidative stress leads to macromolecular damage, including to DNA, specifically telomeres, that can contribute to permanent effects on the regulation of cellular aging.⁶⁶ In addition, pancreatic β cells are sensitive to reactive oxygen species, and oxidative stress can blunt insulin secretion.⁶⁷ In this sense, early and ongoing exposures to oxidative insults could result in eventual manifestations of metabolic syndrome and related disorders.⁶⁸

MPM can promote changes in both the pregnant rat and the offspring. During organogenesis, environmental insults may cause discrete structural defects that permanently reduce the functional capacity of an organ. The effects of MPM on offspring organ structure alterations include: less kidney microvascular development,⁶⁹ fewer nephrons in the kidney,⁷⁰ fewer pancreatic β cells,⁷¹ fewer brain capillaries,⁷² fewer neurons that control appetite in the hypothalamus,⁷³ delay in lung development⁷⁴ and altered cellular ratio of liver cell types.⁷⁵ Further, MPM affects offspring organ function, including by inducing impaired glucose tolerance,⁷⁶ peripheral insulin resistance,⁷⁷ coronary disease⁷⁸ and hypertension.⁷⁹

In addition, there is evidence that fetal growth and development depend primarily on nutrient and oxygen supply. As nutrient and oxygen availability invariably affect the endocrine environment, the role of hormones as programming signals has also been examined in humans and experimental animals.²¹ Hormones regulate normal growth and development *in utero*, and their concentrations and bioactivity change in response to many of the environmental challenges known to cause intrauterine

programming.²¹ MPM can modify hormone production as well as the capacity of cells to respond to hormone signals.^{18,80,81} As some of these hormones cross the placenta, the fetal endocrine response to adverse conditions reflects the activity of both maternal and fetal endocrine glands, and depends on the type, duration, severity and gestational age at onset of the insult. Subsequently, fetal programming caused by MPM can impair the development of several organs, including the reproductive system. For example, MPM increases maternal estradiol, corticosterone and testosterone levels at gestational day 19 in albino *Wistar* rats, which is a critical period of plasticity for male reproductive system development, particularly the prostate.³² Taken together, these nutritional programming effects may be either direct or mediated by endocrine changes in the mother to alter organ development and function.

Fetal programming and the male reproductive system

Development was historically believed to be gene-led, a matter of activating and switching off the expression of genes. However, the observation that the developing mammal has the ability to respond to environmental insults changes the way in which we think about the developmental process. Adaptive responses triggered by any kind of insult may promote profound and irreversible effects upon the physiology of the fetus. As fetal organs grow at different rates, the timing of the insult is important in determining the tissue specificity of the programmed effects. In altricial species that are immature at birth (e.g. rodents and rabbits), the period of developmental plasticity extends after birth; in contrast, precocial species (e.g. human, sheep, pig) are more physiologically mature at birth.^{22,82} If the insult occurs at the time of organogenesis, the changes may be severe and lead to a permanent developmental deficit. In some systems, a specific trigger or a second challenge may be required postnatally to unmask the intrauterine programming. In several physiological systems, sex-linked differences in intrauterine programming do not appear until puberty, when the onset of gonadal steroidogenesis uncovers physiological abnormalities in peripheral tissues or in the hypothalamic–pituitary–gonadal axis itself. In the majority of physiological systems studied, the adverse consequences of intrauterine compromise become more evident with increasing age, as compensatory adaptations in other tissues and organ systems fail.¹⁶ Yet, while the literature on protein restriction and disease risk is extensive, it is largely based on rodent models; few studies have assessed the specific role of protein restriction in human risk of disease. The effect of this programming in adulthood and during aging is unclear, in part because of the possibility of reversion or the compensation of these adverse effects observed earlier in life.¹⁸

In the last few decades, approximately one in six couples suffer from involuntary subfertility; generally defined as being unable to conceive after 1 year of unprotected intercourse⁸³ and male factors contribute to ~33–50% of these cases.⁸⁴ Given the difficulties in retrospectively assessing *in utero* nutrition in humans, birth weight is commonly used as a proxy for nutritional conditions during fetal life. In this sense, emerging data from clinical studies have associated low birth weight with male subfertility.⁸⁵ Other endocrine pathways, such as the hypothalamic–pituitary–gonadal axis, have also been implicated. For example, men born small for gestational age have higher gonadotropin with lower testosterone and inhibin B levels, suggesting poor testicular responsiveness potentially influencing fertility.⁸⁶ Recently, a cross-sectional study observed reduced sperm motility and higher rates of abnormal

sperm morphology, including asthenozoospermia and teratozoospermia in adult infertile individuals born with low birth weight.¹¹ Other findings were higher follicle stimulating hormone (FSH) values, lower mean testicular volume, as well as lower testosterone levels in adulthood.⁸⁷ Although there are controversies regarding the relationship between the developmental environment and postnatal reproductive function in men, this evidence suggests that early life events may contribute to male infertility.

MPM can directly or indirectly affect hormone release, hormone receptor expression/distribution, cellular function and tissue organization, growth, differentiation and maturation.^{32,38,81,88–91} Further, hormone level alterations *in utero* appear to have long-term consequences for reproductive function.^{92,93} These changes may be isolated or widespread events, depending on the nature and timing of the programming stimulus.^{16,93}

Most of what we know regarding fetal programming and reproductive outcomes comes from experimental studies. A few reports in sheep and rats indicate that male sexual development and the normal ontogeny of gonadal development and function can be disrupted by maternal malnutrition.^{94–96} MPM also delays the time of puberty in rats^{97,98} and can lead to reduced sperm count (at postnatal day or PND-270) and reduced capacity to impregnate female rats.³² The authors attribute those results to lower number of Sertoli cells in the testicles, which leads to a disorganization of the seminiferous tubules. Alteration in germ cell proliferation and maturation is also related to increased oxidative stress and loss of antioxidant defense in the testis.^{99,100} These findings highlight the negative impact of nutritional programming on the male reproductive system.

Another parameter evaluated is the ano-genital distance (AGD). AGD is a biomarker for proper prenatal androgen exposure, especially testosterone synthesized by fetal testes.^{101,102} Androgens, acting through the androgen receptor (AR), regulate male sexual differentiation during development, sperm production beginning from puberty and maintenance of prostate

homeostasis.^{32,103,104} MPM alters AGD in male offspring³² suggesting an impairment of hypothalamic–hypophyseal–gonadal axis and the development and homeostasis of organs that are under androgenic control.¹⁰³ A study from our group found that MPM decreases AGD in male offspring at birth and reduces serum testosterone levels at PND-30.¹⁰⁵ Other studies showed MPM-associated reductions in the serum concentration of luteinizing hormone (LH) and FSH; primary hormones involved in the functioning of the male reproductive system. Those alterations are accompanied by the reduction of testis, epididymis and prostate weights.^{32,33,89,91,106–108} MPM also induces an alteration in serum estradiol^{109,110} reduction of AR expression in the testis,¹¹¹ reduction of leptin receptor expression in the testis and prostate,¹¹² reduction of aquaporin-9 expression in the epididymis,¹¹³ and smaller acini in the dorsolateral prostate (DLP)^{91,110} and ventral prostate (VP).¹⁰⁵ These results suggest an impaired intrauterine androgenic signaling.¹¹⁴ However, the mechanisms involved in this process are still under investigation.

Fetal programming and prostate development

The seminal plasma contains a biochemically complex mixture of glandular secretions that is transferred to the female sexual tract as part of the ejaculate.¹¹⁵ Ejaculation, liquefaction and clotting of seminal fluid create a synchronized cascade that enables sperm to perform all the biological processes necessary to reach and fertilize the egg. The seminal fluid also contains nutrients as well as Zn²⁺, citrate and kallikreins, which are essential for sperm motility and nutrition; these factors are mainly secreted by the prostate gland.¹⁰⁴ In this sense, the prostate morphophysiology has received increasing scientific interest, once seminal plasma composition is determinant of male fertility/infertility and reproductive success. Some studies investigated the effects of MPM on prostate development and aging (Table 1). Independently of the diet protocol, the common findings were alterations of serum androgen levels and

Table 1. Effects of maternal protein malnutrition on rat prostate lobe development

Diet type	Prostate lobe	Principal alterations observed	References
Protein-restricted diet containing 6% protein	Ventral prostate	Delay in prostate morphogenesis Reduction in microvascular angiogenesis Downregulation of aquaporin-1 (AQP-1), insulin/IGF-1 axis, and VEGF signaling pathway	Colombelli <i>et al.</i> ³⁸
	Prostatic bud (pelvic urethra)	Lower number of prostatic buds and proliferation index reduced Downregulation of α -actin and EGF-R signaling pathway	Pinho <i>et al.</i> ¹⁵³
Protein-restricted diet containing 8% protein	Ventral, dorsal and lateral prostate	Delay in prostate morphogenesis Reduced glandular weight, androgen plasma levels, epithelial cell height and alveolar diameter Collagen deposition increased Increased metaplasia, hyperplasia and prostatitis incidence	Rinaldi <i>et al.</i> ¹⁰⁵
	Dorsal prostate	Reduction in glandular weight, epithelial cell height and acinar diameter Collagen deposition increased Androgen receptor expression and levels of estradiol and testosterone significantly decreased	Ibrahim <i>et al.</i> ¹¹⁰
		Reduction in prostate weight Morphological changes in prostate Reduction in estradiol serum concentration Testosterone concentration significantly increased	Ramos <i>et al.</i> ⁹¹
	Ventral prostate	No changes in ventral prostate weight Increased gene expression of prostate leptin receptor isoforms	Gombar and Ramos ¹¹²

IGF, insulin-like growth factor; VEGF, vascular epithelial growth factor; EGF-R, epidermal growth factor receptor.

glandular weight. Thus, early insults during prostate development may permanently alter morphology and/or function. Moreover, these early life exposures appear to influence the onset of late life diseases, such as prostatitis, benign prostatic hyperplasia (BPH) and prostate cancer.^{105,116–118} These diseases are also potentially linked with impaired fertility status at different ages.¹⁰⁴ As the mechanisms underlying these changes are not completely understood, we attempt to clarify some of these changes from the perspective of prostate development.

The prostate gland develops embryologically from the endodermal urogenital sinus (UGS) under the influence of androgens produced by fetal Leydig cells.¹¹⁹ The developmental process is continuous, and can be categorized into five distinct stages involving determination, initiation or budding, branching morphogenesis, differentiation and pubertal maturation.¹²⁰ Briefly, the process starts when epithelial stem/progenitor cells form outgrowths or buds that penetrate into the surrounding UGS mesenchyme in the ventral, dorsal and lateral directions caudal to the bladder.¹⁰³ At birth, the rodent prostate lobes primarily consist of unbranched, solid, elongating buds or ducts that sprout lengthening and morphogenesis start with the formation of ducts.¹¹⁹ Branching morphogenesis begins when the elongating UGS epithelial buds contact the mesenchymal pads that are peripheral to the periurethral smooth muscle.¹²¹ The branching pattern is complex and lobe-specific, and starts in the VP at PND3–5 in the rat and in the DLP 2 days later. The epithelial stem/progenitor cells differentiate in basal and luminal cells. They have differential expression of cytokeratins and AR, accompanied by the onset of lumen formation that reaches the distal ends of the ducts at PND-12.¹²² Epithelial and mesenchymal cell differentiation is temporally coordinated with branching morphogenesis. At the same time, prostatic mesenchymal cells condense around the elongating buds or branching ducts, a periductal layer of smooth muscle cells forms while the interduct cells differentiate into fibroblasts.¹²³ Lumenization of the solid epithelial cords begins in the proximal ducts and spreads to the distal tips,¹²⁴ occurring concomitantly with functional differentiation of luminal epithelial cells.¹²² Prostatic secretory proteins are detectable from PND-20 in rodents, and become more abundant as testosterone serum levels increase.^{125,126} Morphogenesis of the rodent prostate is complete by PND-20, and the final maturation process is reached shortly thereafter with the onset of puberty.¹²⁴

The events of branching morphogenesis are common to all branching organs including kidney, lung and salivary glands. The branching process is regulated by a genetic code specific for particular cell types and organs, but environmental conditions also determine the dynamics of the development, growth, symmetry and function of the branched organ. The pattern of morphogenesis in developing organs, including the prostate, is laid down during the fetal/neonatal period and is a major determinant of the size, function and disease of the gland in adulthood.^{116,124,127}

During development, organogenesis and tissue differentiation occur through a continuous series of tightly regulated and precisely timed molecular, biochemical and cellular events. The temporal programming of rat prostate development is between fetal days 18.5 and 19.5, but can extend after birth.^{128,129} This period coincides with the onset of testosterone production by the fetal testes. Thus, if the synthesis or action of testosterone is insufficient, the masculinization process is impaired, resulting in hypospadias, cryptorchidism, underdeveloped prostate and reduction of AGD.¹²⁹ Studies also described mutations of the AR and alteration in the expression and activity of the 5- α -reductase

enzyme.¹³⁰ However, if androgen action continues to occur after the masculinization process, when both LH and its receptors are expressed, it may also affect the size and/or structure of the testes,¹²⁹ leading to a permanent reduction in testosterone synthesis.

Prostate organogenesis is a complex process that is primarily mediated by the presence of androgens and subsequent mesenchyme–epithelial interactions. The precise mechanism of how androgens mediate prostate epithelial induction and budding is unknown. At present, there are two major hypotheses: the andromedin model and the smooth muscle model.¹³¹ Fibroblast growth factor (FGF) 7 and FGF10 were among the first molecules to be suggested as candidate andromedins.^{132,133} Although FGF7 can stimulate epithelial budding and ductal branching in the absence of dihydrotestosterone (DHT) in neonatal prostate organ culture,¹²⁷ FGF10 is unable to perform this function. The smooth muscle hypothesis proposes that androgen signaling has indirect effects on epithelial growth by regulating the differentiation of smooth muscle. During organogenesis, the two processes are coordinated by reciprocal epithelial–stromal signaling.¹³⁴ Mechanisms of epithelial specification involves the winged-helix transcription factor FOXA1, the homeodomain transcription factor NKX3.1, the homeobox gene HOXB13 and the sex determining transcription factor SOX9.^{135–138} Following the formation of prostatic buds, the epithelium undergoes extensive proximal-distal outgrowth and branching morphogenesis. The activities of Sonic hedgehog (SHH) and bone morphogenic protein (BMP) 4/7 pathways appear to coordinate epithelial–mesenchymal interactions during prostate branching morphogenesis.^{120,139,140} Notch, Activin signaling pathways, glial cell-derived neurotrophic factor and Ephrin signaling are involved as well.¹³¹ However, the precise mechanisms involved and their interactions with other relevant signaling pathways are still largely unresolved.

The interplay between genes and the early environment shapes development and leads to both normal or abnormal structure and function of prostate. For example, SHH play crucial roles in cell survival, proliferation, cell-fate determination and differentiation.¹⁴¹ SHH is expressed differently across prostate lobes or over time and is responsive to a diverse set of intrauterine perturbations. SHH-signaling disruption at later stages of VP development (*in vitro*) resulted in reduced organ size and proliferation of ductal tip epithelia,¹⁴² decreased FGF10 transcript and increased BMP4 expression in the adjacent mesenchyme.¹⁴⁰ In this sense, SHH and FGF are strong candidates for mediating the effects of MPM, as well as WNTs and BMPs. Elucidating how these signaling pathways and transcriptional regulators are integrated to mediate prostate specification/differentiation and whether MPM influences them will be relevant for understanding their roles in prostate development, prostatic hypertrophy and prostate cancer.

Androgens have been described as essential for prostate gland development and maintenance throughout life. In addition to androgens, other hormones regulate prostate growth/function and influence growth/progression of prostate cancer, including estrogens,¹⁴³ retinoids,¹⁴⁴ prolactin,¹⁴⁵ growth hormone (GH), and insulin-like growth factor (IGF)-1.¹⁴⁶ Undernutrition can alter maternal as well as fetal concentrations of many hormones, including estrogen, GH, IGFs, insulin, glucocorticoids, catecholamines, leptin, thyroid hormones and placental hormones such as the eicosanoids, sex steroids and placental lactogen.^{21,32,58,147} These endocrine changes can affect fetal growth and development either directly or indirectly by altering the delivery, uptake and metabolic fate of nutrients in the fetoplacental tissues.¹⁴⁸

However, these hormones and the mechanisms underlying their roles in developmental plasticity, particularly in the prostate gland, remain to be identified.

There is also some evidence that MPM interferes in cell proliferation/differentiation processes³⁵ and triggers the inappropriate activation of certain genes by epigenetic mechanisms.^{78,149} These changes may compromise the physiology, function and longevity of different organs.^{18,150} A few studies demonstrated that MPM during gestation or gestation/lactation delayed VP,^{38,105} dorsal prostate^{91,105} and lateral prostate development and maturation¹⁰⁵ based on the epithelial proliferation rate and glandular morphology.

The transition of undifferentiated epithelial cords of the embryonic prostate into fully differentiated basal and luminal cells in the adult prostate has been an active area of investigation. More recently, lineage-tracing studies using specific Cre drivers have suggested that basal progenitors give rise to the mature prostate epithelium during organogenesis.¹⁵¹ For example, lineage-tracing studies of basal cells using $\Delta Np63cre$ mice have shown that p63-expressing basal cells in the UGS can give rise to all three prostate epithelial cell types¹⁵². However, there is significant co-expression of basal and luminal markers during early organogenesis,¹²² and basally located cells continue to express luminal markers. Therefore, it is unclear whether the progenitors of luminal cells are exclusively basal at this stage.

Considering the cellular complexity of the prostate epithelium, our group initiated investigations on the impact of MPM on binomial cell proliferation/differentiation, as well as the maintenance of cellular phenotypes. We found an imbalance between epithelial basal and luminal phenotypes in VP at PND-10 and 21.³⁸ This phenomenon may be linked to the lower levels of testosterone and DHT in male offspring from protein-restricted dams.^{105,153} MPM also compromised angiogenesis during prostate development, leading to fewer blood vessels.³⁸ Future studies are aimed at elucidating in more detail the mechanisms involved in this developmental programming of prostate.

Another study from our group described that MPM increased the incidence and aggressiveness of prostatitis.¹⁰⁵ Among all prostatic diseases, prostatitis has the greatest potential to affect fertility.¹⁰⁴ Prostatic inflammation is linked with fertility alteration, a pertinent finding for men in their prime reproductive years.¹⁵⁴ Furthermore, recent data support the role of prostatic inflammation as a predisposing factor for development of BPH and prostate cancer.^{104,155} Taken together, these data reinforce the importance of a better understanding of prostate fetal programming and the characterization of the mechanisms involved in this process. Such knowledge could provide much-needed direction for strategies to avoid or treat these diseases.

Fetal programming and prostate aging

In the last decade, a number of animal models have been established to study developmental programming. Most of the long-term health outcomes in offspring exposed to severe nutritional deprivation in early life included cardiovascular disease and metabolic syndromes such as type 2 diabetics, obesity, insulin resistance, dyslipidemia and hypertension in the adult life, especially in aging.^{156–160} However, few studies have evaluated the effects of MPM on the prostate during aging. Aging alone is directly linked to a decrease in sex hormone levels, including testosterone production, reduced testis weight and impaired testis function, thus leading to loss of reproductive potential.¹⁶¹ In humans above the age of 50, with each

successive decade (until age 79) the prevalence of hypogonadism increases; indeed, 55% of individuals in the 70–79 age group have hypogonadism, as compared with 24% in the 50–59 age group.¹⁶² Interestingly, low testosterone levels are linked with insulin resistance implicated in hyperglycemia, hypertension, dyslipidemia and increased risk of vascular disease.^{163–165} Low testosterone also mediates an increase of serum markers of inflammation.^{166,167} This is an important consideration as MPM leads to increased inflammation in a systemic way, starting in the post-breastfeeding period until adulthood.^{149,168,169}

An imbalance between the sex hormones testosterone and estradiol leads to increased incidence in important age-related diseases like Alzheimer's disease,¹⁷⁰ cardiovascular diseases,¹⁷¹ sarcopenia¹⁷² and prostate cancer.¹⁷³ MPM promotes alterations in serum androgen⁹⁸ and estradiol levels.³² Androgens can cause an increase in oxidative stress and alterations in intracellular glutathione levels and the activity of other detoxification enzymes required for the maintenance of the cellular prooxidant–antioxidant balance such as gamma-glutamyl transpeptidase.¹⁷⁴ Chronic increases in oxidative stress over time are known to induce somatic mutations and neoplastic transformation that contributes to prostate cancer initiation, promotion and progression.¹⁷⁵ Even though testosterone is the predominant hormone, estradiol can be synthesized from testosterone in the prostate stromal cells which in turn can trigger expression of pro-inflammatory cytokines within the prostate. This highlights the fact that estrogens play important roles in normal, healthy adult males.¹⁷⁶

Systemic inflammation is related to both MPM and aging. A low-protein diet during pregnancy has been identified as a risk factor for prostate diseases as it induces prostate gland inflammation in adulthood.¹⁰⁵ Chronic inflammation can occur in part through oxidative stress, and in turn can mediate most chronic diseases including cancer. The development of prostate cancer may be triggered by signaling of reactive oxygen species. Increased reactive oxygen species occur either through an increase in reactive oxygen species production or from a loss of antioxidant defense mechanisms. The imbalance results in significant damage to cell structures.¹⁷⁵ More studies are needed to explore and understand better the mechanisms involved in such cases.

The pathogenesis of prostate cancer is unclear, although the hypothesis that male infertility may be a harbinger of certain types of malignancy is gaining clinical acceptance.^{177–179} This connection is likely multifactorial, with a combination of hormonal, genetic, *in utero* and environmental factors.¹⁸⁰ Possible mechanistic links between male infertility and testicular/prostate cancer includes fetal reprogramming by high estrogen levels *in utero* and hormonal disruptions during embryologic development, leading to later problems related to steroidogenesis and spermatogenesis. With abnormal gonadal function, the prostate may receive aberrant signals during key phases of development, which could result in an elevated risk of malignancy.^{179,180} Maternal nutrition is known to affect fetal growth and birth weight, which interferes in fertility rates and prostate cancer risk.^{11,179} However, mechanisms linking prostate cancer to male infertility remain largely hypothetical, and, given the somewhat conflicting nature of current data, identifying a causal relationship between these two disease processes remains a challenge for future studies.

Final considerations

The role of maternal low-protein diets in the development of phenotypes in offspring has been studied extensively. Progress in

this field has benefited from integrated analyses combining knowledge gained from studies of human cohorts, animal models and cell systems. Moreover, strong evidence has shown that improvements in healthy aging require better nutrition of girls and young women. Today in the Western world, many fetuses are malnourished because their mothers are chronically malnourished.¹⁸¹ Maternal undernutrition has been described as one of the most neglected aspects of nutrition in public health globally.¹⁸² Ensuring a healthy nutritional status and lifestyle before and during pregnancy is one of the best ways to help support the healthy growth and development of the unborn child. Protecting maternal nutrition and health will not only prevent chronic disease, but will also produce new generations with better health and well-being through their lives.

In addition, attention must be given to the effect of maternal obesity on offspring health. To our knowledge, no study has examined the effect of quantity and source of protein consumed during pregnancy in obese mothers on both mothers' health and their children. Moreover, cohort studies covering the whole life course, focusing on critical windows of exposure and the time course of exposure to disease (birth cohorts, adolescent cohorts and young adult cohorts), should be considered. It is particularly important because there is consistent evidence that overweight is associated with increased risks of several types of cancer.

Studies presented in this review provide evidence that a mother's diet during pregnancy can exert major effects on the short- and long-term health of their children. It is important to remember that diet is shaped by many factors such as traditions, knowledge about diet, food availability, food prices, cultural acceptance and health conditions. It is also critically relevant to consider the fact that any change in protein content or source of maternal diet will influence embryonic/fetal development in multiple ways. In this sense, adequate nutritional status is crucial for both prostate morphogenesis during early life as well as homeostasis of the gland throughout the lifespan.

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