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Testicular Vulnerability to Early-life Stress and High-fat Diet

Vulnerabilidad Testicular Frente al Estrés Temprano y a la Dieta Alta en Grasa

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SUMMARY: The sustained decline in fertility rates and the rising prevalence of male infertility have increased interest in understanding how environmental and biological factors act across development to shape reproductive function. Among these factors, early-life stress induced by maternal separation and high-fat diets represent two highly relevant conditions capable of persistently altering endocrine, metabolic, and testicular physiology. Evidence in humans indicates that adverse childhood experiences are associated with disruptions in the hypothalamic–pituitary–gonadal (HPG) axis, reduced semen quality, and altered pubertal timing. Complementarily, overweight and high intake of saturated fats are linked to oxidative stress, sperm DNA damage, and impaired spermatogenesis. Experimental models of maternal separation and high-fat diet exposure in rodents have helped elucidate underlying cellular and tissue mechanisms, including reduced numbers of sustentacular cells, disorganization of the germinal epithelium, disruption of the blood–testis barrier, decreased testosterone levels, and the establishment of a pro-inflammatory testicular microenvironment. Although both factors have been extensively studied independently, their interaction remains an emerging field. Early adversity increases metabolic vulnerability and preference for fat-rich foods, suggesting that their combined exposure may produce cumulative deterioration of testicular morphofunction. This manuscript critically reviews the available evidence and highlights the need for integrated experimental designs that simultaneously examine the impact of postnatal stress and nutrition on testicular maturation and fertility, providing a more comprehensive perspective for understanding male reproductive programming within the Developmental Origins of Health and Disease framework.

KEY WORDS: Early-life stress; High-fat diet; Testis; Male fertility.

INTRODUCTION

The sustained decline in birth rates is a global phenomenon with multiple determinants. According to the United Nations World Population Prospects (United Nations, 2022), the global fertility rate has decreased from 3.2 children per woman in 1990 to less than 2.3 in 2021. This trend is partly attributable to social and demographic factors, such as delayed parenthood, increased female workforce participation, shifts in family structure, and the rising costs associated with childrearing (OECD, 2023; UNFPA, 2023). However, alongside these sociocultural drivers, environmental and biological conditions are emerging as contributors to the decline in actual fertility. Infertility currently affects approximately 17.5% of the global adult population, and in nearly half of cases, the male factor plays a direct role (Carlsen *et al*., 2003; WHO, 2022).

Several human studies have demonstrated that adverse childhood experiences, such as neglect, maternal separation, violence, or chronic poverty, are associated with persistent alterations in the HPG axis and reduced reproductive function in adulthood. A meta-analysis by Zipple *et al*. (2021) showed that early-life stress correlates with a significant reduction in serum testosterone levels and with disruptions in male pubertal maturation. Longitudinal studies in European and North American cohorts have further shown that men who experienced childhood adversity present a higher risk of hypogonadism and lower semen quality, regardless of adult lifestyle factors (Lawn *et al*., 2018; Boynton-Jarrett *et al*., 2022).

Complementarily, high-fat diets and male overweight are recognized as factors that reduce fertility. In a cohort study including more than 700 participants, Attaman *et al*. (2012) demonstrated that high intake of saturated fats is associated with lower sperm concentration and motility. Similar findings were reported by Dadkhah *et al*. (2017),

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who observed reduced normal sperm morphology in men consuming hyperlipidic diets. Likewise, obesity and insulin resistance are associated with testicular oxidative stress, sperm DNA damage, and hormonal dysfunction (Funes *et al*., 2019; Jarvis *et al*., 2020).

Taken together, these findings suggest that both early-life stress and acquired dietary habits can induce long-lasting alterations in male endocrine and reproductive function. This relationship has been interpreted through the lens of the Developmental Origins of Health and Disease (DOHaD) paradigm, which proposes that environmental stimuli acting during critical developmental windows program adaptive biological responses with structural and functional consequences in adulthood (Barker, 2004; Sánchez-Garrido *et al*., 2022).

The maternal separation paradigm and its impact on testicular morphology and function

The study of early-life stress effects on male reproductive function has been extensively addressed through experimental models that reproduce disruption of the mother–offspring bond during the postnatal period. Among these, the maternal separation (MS) model and its more recent variant, Maternal Separation with Early Weaning (MSEW), constitute well-established paradigms for evaluating the consequences of psychosocial stress during critical developmental windows (George *et al*., 2010; Choe *et al*., 2024; Choe & Jones, 2025). These models are supported by evidence showing that the loss of maternal contact disrupts regulation of the hypothalamic–pituitary–adrenal (HPA) axis and the HPG axis, inducing sustained hyperactivation of the stress system that impacts endocrine, metabolic, and reproductive function.

In its original formulation, George *et al*. (2010) proposed the MSEW model, which combines daily separation of the pups (4 h/day between postnatal days 2 and 16) with early weaning on day 17, instead of the standard day 21. This protocol produces, in adult mice, a phenotype characterized by stress-axis hyperactivity, elevated basal corticosterone, anxious behaviors, and metabolic alterations, establishing a reproducible condition of mild chronic stress. Subsequently, Choe *et al*. (2024) refined the model by demonstrating that factors such as the lipid composition of the post-weaning diet significantly influence the magnitude of the corticosterone response, underscoring the need to control nutritional variables when studying the effects of early-life stress on peripheral physiology. Finally, Choe & Jones (2025) systematized the methodological recommendations for the model, standardizing critical variables, separation duration and timing, ambient temperature, nesting materials, and weaning age, thereby enabling consistent reproduction of its neuroendocrine effects and facilitating its application to the study of reproductive and testicular programming within the DOHaD paradigm.

Functional studies have shown that chronic stress induced by MS leads to significant disruption of the gonadal axis. In a murine model, Khodamoradi *et al*. (2019) reported decreased serum testosterone levels, reduced sperm motility and concentration, and increased testicular oxidative stress and inflammation, accompanied by upregulation of pro-apoptotic genes (Bax and caspase-3) and downregulation of Bcl-2. These findings suggest an imbalance between cell survival and cell death within the germinal epithelium. In a subsequent study, the same authors demonstrated that parental MS experience is also associated with poorer sperm morphology and viability in male offspring, indicating a potential intergenerational effect of early-life adversity on reproductive function (Khodamoradi *et al*., 2020).

At the histological and cellular levels, several studies have shown that early-life stress or corticosterone exposure during the postnatal window directly affects testicular architecture and supporting cells. Miyaso *et al*. (2021, 2022) administered corticosterone between postnatal days 1 and 10, observing a reduction in the number of sustentacular cells, increased expression of p27 (a cell-cycle inhibitor) decreased testicular weight, and reduced sperm count in adulthood. They also reported a reduction in seminiferous tubule diameter and an enlargement of the interstitial area, suggesting limited spermatogenic capacity due to diminished structural and functional support from sustentacular cells. Similarly, Abdelmoez *et al*. (2024) described, in rats subjected to neonatal MS, disorganization of the germinal epithelium, reduced epithelial thickness and tubular diameter, and widening of the interstitium, accompanied by lower expression of Ki-67 (proliferation) and iNOS (oxidative stress). These histological changes reflect a persistent alteration in the balance between cellular proliferation and degeneration, consistent with the endocrine effects described in functional models.

High-fat diet as a postnatal modulator of male reproductive function

Experimental evidence in rodents shows that exposure to a high-fat diet (HFD) during juvenile stages or adulthood consistently compromises testicular architecture and function. In C57BL/6 mice, Fan *et al*. (2015) fed 6-week-old males an HFD for 10 weeks and identified disorganization of the germinal epithelium, vacuolization of sustentacular cells, desquamation of germ cells, and foci

of tubular atrophy, along with reduced epithelial thickness and dilated tubules with sparse cellular content. In parallel, a marked reduction in sperm motility and an increase in teratozoospermia were observed, linking seminiferous architectural disruption to impaired fertility. Funes *et al*. (2019), using C57BL/6J mice fed for 16 weeks with a diet enriched with 22% chicken fat, described predominant ultrastructural alterations in spermatozoa, head defects, acrosomal irregularities, and abnormalities of the nuclear envelope, that affect late stages of spermiogenesis, even when the tubular epithelium does not exhibit the pronounced atrophy seen in the Fan *et al*. (2015) model.

In Wistar rats, hyperlipidic diets show a clear dose–response gradient in structural damage. Tarragó Castellanos *et al*. (2025) exposed 3-month-old males to diets containing either 10% fat (overweight) or 60% fat (obesity) for four weeks, observing reduced seminiferous tubule diameter, decreased germinal epithelial thickness, increased interstitial space, and alterations in gonadosomatic indices, along with lower sperm viability and a higher proportion of abnormal spermatozoa; the effects were more pronounced in the 60% fat group. Zhang *et al*. (2023) showed that in obese mice fed an HFD, switching to a normolipidic di*et al*lows partial recovery of tubular organization, germ cell density, and blood–testis barrier integrity, indicating some degree of structural plasticity in response to dietary normalization, although with incomplete reversibility.

Beyond morphological damage, HFD exposure renders the testicle an immunologically vulnerable organ. Under physiological conditions, testicular immune tolerance is maintained by the blood–testis barrier, cytokine modulation, and the activity of regulatory immune cells (Hedger, 2010). Obesity induced by HFD establishes a state of low-grade chronic inflammation that erodes this balance (Hedger, 2010; Fomichova *et al*., 2024). In Wistar rats exposed to a high-lipid diet for 14 weeks, Pencheva *et al*. (2022) reported increased levels of C-reactive protein, serum amyloid A, IL-4, and angiotensin-converting enzyme, accompanied by histological and morphometric changes consistent with an inflamed microenvironment. In another HFD-induced obesity model, Moradi-Ozarlou *et al*. (2021) found overexpression of HSP70-2a and HSP90, reduced PCNA expression, decreased total antioxidant capacity and serum testosterone, along with mRNA and DNA damage, creating a scenario of oxidative and genotoxic stress in which cellular stress responses are insufficient to protect the germinal compartment.

Susceptibility to HFD-induced damage is particularly pronounced during immature stages. Zhang *et al*. (2017) exposed male mice to an HFD from the post-weaning day (PND21) for 45 days, finding a significant reduction in testicular IL-1b, alterations in sexual maturation, lower sperm quality, and reduced fertility. This pattern suggests that early HFD exposure induces an immunometabolic dysfunction that interferes with germinal epithelium maturation and the establishment of adult spermatogenesis. Complementarily, Matuszewska *et al*. (2020) observed that brief exposures (2 - 4 weeks) to hyperlipidic diets in juvenile rats generate epithelial disorganization, tubular dilation, changes in cellular density, and early signs of tissue stress in both testis and ovary before reaching full sexual maturity. Compared with adult-rat models such as that of Tarragó Castellanos *et al*. (2025), these findings indicate lower damage thresholds during early postnatal life.

At the endocrine and functional level, HFDs reduce spermatogenic efficiency even when tubular architecture is not fully collapsed. Fan *et al*. (2015) demonstrated in C57BL/6 mice a significant decrease in plasma testosterone, accompanied by reduced motility and a higher proportion of abnormal spermatozoa, effects associated with loss of blood–testis barrier integrity. Funes *et al*. (2019) described sperm head defects that compromise fertilizing capacity despite the absence of extreme epithelial degeneration. In Wistar rats, Nematollahi *et al*. (2019) reported that HFD-induced obesity markedly reduces serum testosterone, sperm concentration, and motility, along with tubular diameter changes consistent with reduced spermatogenic efficiency; furthermore, they showed that the functional impact depends on prior metabolic status. In the model by Tarragó Castellanos *et al*. (2025), sperm viability and the proportion of normal sperm decreased in direct proportion to the lipid content of the diet, indicating that even moderate degrees of overweight measurably impair semen quality.

Interaction between early-life stress from maternal separation and high-fat diets: a dual-impact perspective

The accumulated evidence shows that both early-life stress caused by MS and high-fat diets are capable of negatively modulating male reproductive function through distinct but potentially convergent mechanisms. However, their possible biological interaction remains an underdeveloped area within the literature. Several studies suggest that early adversity alters appetite regulation, feeding behavior, and sensitivity to hypercaloric foods later in life. In this regard, da Silva *et al*. (2014) reported that rats subjected to MS develop a marked preference for high-fat foods and alterations in satiety sequencing, whereas Mela *et al*. (2012) demonstrated that maternal deprivation exacerbates the metabolic response to hyperlipidic diets in a sexually dimorphic manner.

These findings are complemented by studies that combine early adversity with exposure to palatable or hypercaloric diets in other physiological systems. Maniam & Morris (2010) observed that rats with a history of neonatal stress exhibit hyperreactivity to HFDs, using them as a strategy to buffer anxious behaviors. Convergently, Yam *et al*. (2015) demonstrated synergistic effects between early-life stress and hyperlipidic diets on metabolism, with exacerbated alterations in glucose homeostasis, lipid profile, and endocrine regulation. Sasaki *et al*. (2020) reinforced this framework by showing that the combination of perinatal stress and energy-dense diets amplifies stress reactivity and alters metabolic parameters in adulthood.

Although some studies have explored the interaction between early-life adversity and hyperlipidic diets in metabolic and behavioral parameters, the morphological and functional evaluation of the testis under the combined influence of both factors remains poorly documented and not systematically addressed. This gap is particularly relevant considering that MS affects key processes in testicular development, such as sustentacular cell proliferation, germinal epithelium maturation, and regulation of the HPA axis, whereas HFDs impair steroidogenesis, blood–testis barrier integrity, and sperm quality. The convergence of these factors on shared physiological nodes suggests that they may produce cumulative, or even synergistic, deterioration in male reproductive function.

From this review, a clear need emerges for studies that integrate both conditions within a single experimental design, incorporating histological, stereological, endocrine, and immunological evaluations together with semen-quality analyses. Addressing this gap would help clarify whether HFD exposure in later stages amplifies the damage induced by early-life stress, or whether it modifies the trajectory of testicular maturation and functional capacity in adulthood. This gap represents an opportunity to advance toward a more comprehensive model of reproductive programming, in which the impact of adverse experiences and nutritional environments can be assessed jointly and systematically.

CONCLUSIONS

The analysis of the evidence shows that early-life stress due to MS and HFDs affect male reproductive function through distinct yet potentially convergent mechanisms. MS disrupts early processes of testicular maturation and stress-axis regulation, whereas hyperlipidic diets impair steroidogenesis, blood–testis barrier integrity, and sperm quality.

Although some studies have combined early-life adversity and HFDs in behavioral and metabolic contexts, their joint impact on testicular morphofunction remains poorly documented. Given that early adversity increases the preference for high-fat foods later in life, it is plausible that both factors may potentiate one another. Therefore, studies that simultaneously evaluate these conditions through morphological, functional, and endocrine analyses are needed to gain a more integrated understanding of how early-life experiences and later-life lifestyle factors shape male reproductive health.

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RESUMEN: El descenso sostenido de la fecundidad y el aumento de la infertilidad masculina han motivado un creciente interés por comprender cómo los factores ambientales y biológicos actúan a lo largo del desarrollo para modular la función reproductiva. Entre ellos, el estrés temprano por separación materna y las dietas altas en grasa representan dos condiciones de gran relevancia, capaces de modificar de manera persistente la fisiología endocrina, metabólica y testicular. La evidencia en humanos indica que las experiencias adversas en la infancia se asocian con alteraciones del eje hipotálamo-hipófisis-gonadal, menor calidad seminal e inicio puberal alterado. De manera complementaria, el sobrepeso y el consumo elevado de grasas saturadas se relacionan con estrés oxidativo, daño en el ADN espermático y deterioro de la espermatogénesis. Los modelos experimentales de separación materna y de dietas altas en grasas en roedores han permitido caracterizar mecanismos celulares y tisulares subyacentes, incluyendo reducción del número de células sustentaculares, desorganización del epitelio germinal, alteración de la barrera hematotesticular, disminución de testosterona y establecimiento de un microambiente inflamatorio testicular. Aunque ambos factores han sido ampliamente estudiados por separado, su interacción constituye un campo emergente. La adversidad temprana aumenta la vulnerabilidad metabólica y la preferencia por dietas ricas en grasa, lo que sugiere que su combinación podría generar un deterioro acumulativo sobre la morfofunción testicular. Este manuscrito revisa críticamente la evidencia disponible y destaca la necesidad de diseños experimentales integrados que evalúen simultáneamente el impacto del estrés posnatal y de la nutrición sobre la maduración testicular y la fertilidad, aportando una perspectiva más completa para comprender la programación reproductiva masculina dentro del paradigma de los Orígenes del Desarrollo de la Salud y la Enfermedad.

PALABRAS CLAVE: Estrés temprano; Dieta alta en grasas; Testículo; Fertilidad masculina.

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