

Neurovascular Regulation of Male Reproduction: Associations Between Blood–Brain Barrier Integrity and Semen Quality

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Abstract

Background:

Male fertility is regulated by the hypothalamic pituitary gonadal (HPG) axis, which depends on the integrity of the blood–brain barrier (BBB) to maintain neuroendocrine homeostasis. Disruption of BBB integrity may permit inflammatory mediators and stress-related signals to interfere with hypothalamic function, potentially impairing spermatogenesis. Despite growing evidence linking neurovascular health to endocrine regulation, the relationship between BBB dysfunction and male reproductive outcomes remains poorly characterized.

Objective:

To investigate the association between biomarkers of BBB dysfunction, neuroendocrine hormonal alterations, and sperm quality in men planning parenthood.

Methods:

A cross-sectional study was conducted among 100 Indian men aged 24–45 years intending conception within 12 months. BBB integrity was assessed using circulating biomarkers of permeability, including S100 calcium-binding protein B (S100B) and matrix metalloproteinase-9 (MMP-9). Neuroendocrine function was evaluated by measuring serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone, and cortisol using ELISA-based assays. Semen analysis was performed in accordance with the WHO Laboratory Manual for the Examination and Processing of Human Semen (6th edition). Associations between BBB markers, hormonal profiles, and seminal parameters were analyzed using Pearson correlation and independent t-tests.

Results:

Men exhibiting elevated levels of BBB permeability markers demonstrated significantly reduced sperm concentration, progressive motility, and normal morphology. BBB dysfunction markers showed a positive correlation with serum cortisol and a negative correlation with testosterone and sperm motility ($p < 0.05$). Elevated cortisol levels were associated with suppressed androgen status and poorer semen quality.

Conclusion:

BBB dysfunction is associated with altered neuroendocrine regulation and reduced sperm quality in men planning conception. These findings suggest that BBB integrity may represent an upstream determinant of male reproductive health and a potential target for early preventive interventions.

Key Words: blood–brain barrier; neuroendocrine regulation; sperm quality; male fertility; preconception health

Introduction

Male reproductive function depends on tightly coordinated regulation of the hypothalamic–pituitary–gonadal (HPG) axis, which governs

spermatogenesis through pulsatile secretion of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone

(FSH), and testosterone. Maintenance of this endocrine balance relies in part on the blood–brain barrier (BBB), a specialized neurovascular interface that regulates molecular exchange between the central nervous system and the peripheral circulation [1,2]. BBB dysfunction has been implicated in neuroinflammation, dysregulated stress responses, and altered hormonal signaling. Increased BBB permeability may allow peripheral inflammatory mediators and glucocorticoids to influence hypothalamic neurons, thereby disrupting gonadotropin release and downstream reproductive hormone production. While BBB impairment has been extensively studied in neurological and metabolic disorders, its potential contribution to male reproductive dysfunction has received limited attention. In low- and middle-income settings, including India, increasing psychosocial stress, metabolic disease burden, and environmental exposures may adversely affect BBB integrity. Understanding the role of neurovascular health in male fertility is therefore particularly relevant in the context of preconception care. This study aimed to evaluate the relationship between BBB dysfunction, neuroendocrine regulation, and sperm quality in men planning parenthood [3,4].

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted at a reproductive health research center. A total of 100 men aged 24–45 years who were planning conception within the following 12 months were enrolled.

Exclusion criteria included a history of diagnosed infertility, neurological or endocrine disorders, varicocele, chronic infections, or substance abuse.

Assessment of Blood–Brain Barrier Integrity

BBB function was assessed using circulating biomarkers associated with BBB permeability:

- S100 calcium-binding protein B (S100B)
- Matrix metalloproteinase-9 (MMP-9)

| Parameter | Normal BBB Markers | Elevated BBB Markers | p-value |
|----------------------------------|--------------------|----------------------|---------|
| Sperm concentration (million/mL) | 58.6 ± 19.2 | 36.4 ± 16.8 | <0.01 |
| Progressive motility (%) | 41.2 ± 8.5 | 29.8 ± 9.1 | <0.001 |
| Normal morphology (%) | 6.1 ± 1.6 | 4.3 ± 1.4 | 0.02 |

Correlation Analysis

S100B levels were negatively correlated with sperm motility ($r = -0.49$). Serum cortisol showed a negative correlation with testosterone ($r = -0.52$). Testosterone levels positively correlated with sperm concentration and motility.

Discussion

This study provides evidence linking BBB dysfunction with neuroendocrine alterations and impaired sperm quality in men planning conception. Elevated markers of BBB permeability were associated with increased stress hormone levels and reduced androgen status, suggesting suppression of the HPG axis and compromised spermatogenesis.

These findings support the concept of a neuro–reproductive axis, in which central neurovascular integrity indirectly influences male fertility. Chronic stress, systemic inflammation, and metabolic dysregulation may impair BBB function, thereby contributing to endocrine imbalance and reduced semen quality. Incorporating neurovascular health into reproductive risk assessment

Elevated serum levels were interpreted as indicative of compromised BBB integrity.

Neuroendocrine Hormonal Assessment

Fasting venous blood samples were analyzed for:

- Luteinizing hormone (LH)
- Follicle-stimulating hormone (FSH)
- Total testosterone
- Serum cortisol

All hormonal measurements were performed using standardized ELISA methods.

Semen Analysis

Semen samples were collected following 2–7 days of sexual abstinence and analyzed according to the WHO Laboratory Manual (6th edition) [5]. Parameters assessed included semen volume, sperm concentration, total and progressive motility, and normal morphology.

Statistical Analysis

Data are presented as mean ± standard deviation. Independent t-tests were used to compare groups with normal versus elevated BBB markers. Pearson correlation coefficients were calculated to assess associations between BBB biomarkers, hormonal parameters, and semen quality. Statistical significance was defined as $p < 0.05$.

Results

BBB Biomarkers and Hormonal Profiles

Participants with elevated S100B and MMP-9 levels demonstrated: Significantly higher serum cortisol concentrations. Reduced total testosterone levels. Mild suppression of LH and FSH secretion.

Association with Semen Quality

may enhance current models of male fertility evaluation, particularly in preconception settings.

Conclusion

Compromised blood–brain barrier integrity is associated with neuroendocrine dysregulation and reduced sperm quality in men planning parenthood. Integrating biomarkers of BBB function with hormonal and seminal assessments may provide a novel and comprehensive approach to evaluating male reproductive health.

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