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Infantile Hypertrophic Pyloric Stenosis: A Multidimensional Systems-Biology Perspective Integrating Early-Life Determinants, PNEI Interactions, and Functional Gastrointestinal Mechanisms

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Abstract

Objectives: To re-examine infantile hypertrophic pyloric stenosis (IHPS) through a contemporary, multidimensional framework that integrates structural, functional, and psycho-neuro-endocrine-immune (PNEI) mechanisms. This review synthesises current evidence on IHPS epidemiology, pathophysiology, and clinical presentation, and evaluates minimally invasive diagnostic and therapeutic approaches. It further explores how emerging insights into gut–brain and neuroimmune regulation position IHPS within the broader spectrum of functional gastrointestinal disorders.

Design: Narrative review.

Data Sources: Peer-reviewed literature from paediatric surgery, gastroenterology, neurogastroenterology, developmental physiology, and PNEI-axis research. Sources include systematic reviews, cohort studies, mechanistic studies, and foundational texts relevant to IHPS, functional gastrointestinal disorders, and early-life neuroendocrine-immune development.

Eligibility Criteria:

Studies addressing:

1. IHPS epidemiology, diagnosis, or management;
2. Neuromuscular, neurohormonal, or neuroimmune mechanisms relevant to gastric motility;
3. Gut–brain axis or PNEI-axis physiology in early life;
4. Minimally invasive diagnostic or therapeutic innovations.

No date restrictions were applied; emphasis was placed on high-quality and conceptually relevant evidence.

Results: IHPS remains a common cause of gastric outlet obstruction in early infancy, with well-defined structural features including pyloric muscle hypertrophy and impaired gastric emptying. However, converging evidence from neurobiology and developmental physiology suggests that aberrant innervation, altered nitric oxide signalling, and neurohormonal influences contribute to functional dysregulation of pyloric motility. These findings align IHPS with mechanistic domains shared by functional gastrointestinal disorders, including impaired enteric neuromuscular coordination and disrupted gut–brain communication. The PNEI axis provides a unifying framework linking early-life stressors, neuroendocrine maturation, immune signalling, and gastrointestinal motor function. Diagnostic pathways increasingly rely on high-resolution ultrasonography and dynamic

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assessment, while laparoscopic pyloromyotomy remains the therapeutic gold standard, offering excellent outcomes with minimal morbidity. Emerging non-surgical and endoscopic approaches reflect a shift toward precision and minimally invasive intervention.

Conclusions: Reframing IHPS as a disorder with both structural and functional dimensions enriches understanding of its pathogenesis and highlights the relevance of neurogenic and PNEI-mediated mechanisms. This integrative perspective supports continued refinement of diagnostic strategies and encourages exploration of targeted, minimally invasive therapies. Future research should investigate neuroimmune and neuroendocrine pathways in IHPS to clarify its position within the spectrum of disorders of gut–brain interaction.

Keywords: Infantile Hypertrophic Pyloric Stenosis; Functional Gastrointestinal Disorders; Gut–Brain Axis; Psycho-Neuro-Endocrine-Immune (PNEI) Axis; Neurogastroenterology; Early-Life Physiology; Minimally Invasive Surgery; Laparoscopic Pyloromyotomy; Paediatric Motility Disorders; Enteric Nervous System

Summary Box

What is already known on this topic

- Infantile hypertrophic pyloric stenosis (IHPS) is classically described as a structural gastric outlet obstruction caused by pyloric muscle hypertrophy.

- Ultrasound is the diagnostic gold standard, and laparoscopic pyloromyotomy is widely accepted as the preferred treatment.

- Functional gastrointestinal disorders involve disturbances in gut–brain communication, neuromuscular coordination, and neuroimmune signalling.

What this study adds

- IHPS shares mechanistic features with functional gastrointestinal disorders, including aberrant innervation, altered nitric oxide signalling, and neurohormonal dysregulation.

- The psycho-neuro-endocrine-immune (PNEI) axis provides a unifying framework linking early-life stressors, neuroendocrine maturation, immune signalling, and pyloric motor function.

- Minimally invasive diagnostic and therapeutic innovations align with a broader shift toward precision, physiology-informed paediatric care.

How this study might affect research, practice, or policy

- Encourages clinicians and researchers to consider IHPS within a multidimensional functional–structural continuum rather than a purely anatomical disorder.

- Supports future research into neuroimmune and neuroendocrine pathways in IHPS, potentially informing novel non-surgical or neuromodulatory therapies.

- Reinforces the value of early-life systems biology in paediatric surgical decision-making and long-term outcome evaluation.

Background

This narrative review offers a novel conceptual reframing of infantile hypertrophic pyloric stenosis (IHPS), moving beyond the traditional structural description of pyloric muscle hypertrophy to present a multidimensional model grounded in developmental physiology, neurogastroenterology, and psycho-neuro-endocrine-immune (PNEI) science. By synthesising evidence across epidemiology, neuromuscular biology, early-life determinants, and clinical practice, the review positions IHPS along a functional–structural continuum, aligning it with mechanisms recognised in disorders of gut–brain interaction.

The manuscript provides:

- A systems-biology integration of ENS dysregulation, nitric oxide signalling deficits, neuroimmune pathways, hormonal modulators, and microbiome influences (Figure 1 and 2).
- A developmental framework explaining the narrow postnatal window of IHPS onset.
- A clinically relevant synthesis linking mechanistic insights to diagnostic and therapeutic pathways.
- Original conceptual diagrams (Figure 3 and Figure 4) that visually map the multidimensional pathophysiology of IHPS.

Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is traditionally conceptualised as a structural disorder characterised by hypertrophy of the pyloric muscle leading to gastric outlet obstruction [1-30]. However, emerging evidence on aberrant innervation, genetic susceptibility, and neurohormonal dysregulation invites a broader interpretation of IHPS as a disorder with functional gastrointestinal features.

This narrative review synthesises current knowledge on IHPS epidemiology, pathogenesis, clinical presentation, management and proposes a novel integrative framework incorporating and grounded in the psycho-neuro-endocrine-immune (PNEI) axis [7-14]. It also evaluates minimally invasive diagnostic and therapeutic strategies that align with contemporary paediatric surgical practice.

Infantile hypertrophic pyloric stenosis (IHPS) is a well-recognised cause of gastric outlet obstruction presenting with non-bilious projectile vomiting in early infancy, typically presenting between 2–12 weeks of age with familial and genetic predisposition and macrolide association [4-6]. It results from hypertrophy and hyperplasia of the pyloric smooth muscle, narrowing the gastric outlet and impairing gastric emptying.

Although traditionally conceptualised and historically viewed as a purely anatomical obstruction and structural disorder requiring surgical correction, modern insights into smooth muscle innervation, genetic susceptibility, and neurohormonal influences and emerging evidence from neurogastroenterology, developmental physiology, and systems biology suggest a more complex pathophysiology that overlaps with functional gastrointestinal disorders. Aberrant innervation, altered nitric oxide signalling, neurohormonal

influences, and early-life environmental factors all contribute to a broader mechanistic landscape that overlaps with functional gastrointestinal disorders (FGIDs).

Epidemiology and Clinical Presentation

IHPS affects approximately 1–3.5 per 1000 live births, with a strong male, first born, western predominance, seasonal peak and higher incidence in white populations [5]. Infants typically present between 2 and 12 weeks of age with progressive, non-bilious projectile vomiting, persistent hunger despite vomiting, weight loss, dehydration, metabolic alkalosis, reduced bowel movements and lethargy.

Earlier diagnosis in recent decades reflects improved access to ultrasonography and heightened clinical awareness. Despite its recognisable clinical pattern, IHPS exhibits variability in severity and progression, suggesting influences beyond simple muscular hypertrophy.

Multifactorial Susceptibility to IHPS

Overview

Infantile hypertrophic pyloric stenosis (IHPS) arises from a complex interplay of genetic, developmental, environmental, and physiological factors. This subsection outlines the multifactorial contributors to IHPS vulnerability, integrating molecular, demographic, and ecological dimensions.

Genetic and Familial Factors

Polygenic inheritance: Multiple genetic loci contribute to smooth muscle tone and ENS development.

Familial clustering: First-degree relatives show increased risk, with heritability estimates around 25%.

Syndromic associations: IHPS may co-occur with genetic syndromes such as Smith-Lemli-Opitz and Allgrove syndrome.

Demographic and Epidemiologic Patterns

Male predominance: Male-to-female ratio is approximately 4:1, Hormonal influences.

Birth order effect: First-born infants are disproportionately affected. Parental anxiety/stress

Racial differences: Higher incidence in White infants; lower in Black and Asian populations.

Age window: IHPS typically presents between 2–12 weeks of life.

Geographic variability: Incidence varies across regions, with higher rates in Northern Europe and rural Canada.

Environmental and Seasonal Influences

Seasonal variation: Peaks in spring and summer suggest environmental modulation.

Macrolide exposure: Neonatal erythromycin use is associated with increased IHPS risk.

Early-life stressors: Emotional field turbulence and autonomic imbalance may contribute to sphincter hypertonicity.

Physiological Contributors

Gut motility disturbances: Delayed gastric emptying and pyloric hypertonicity are central features.

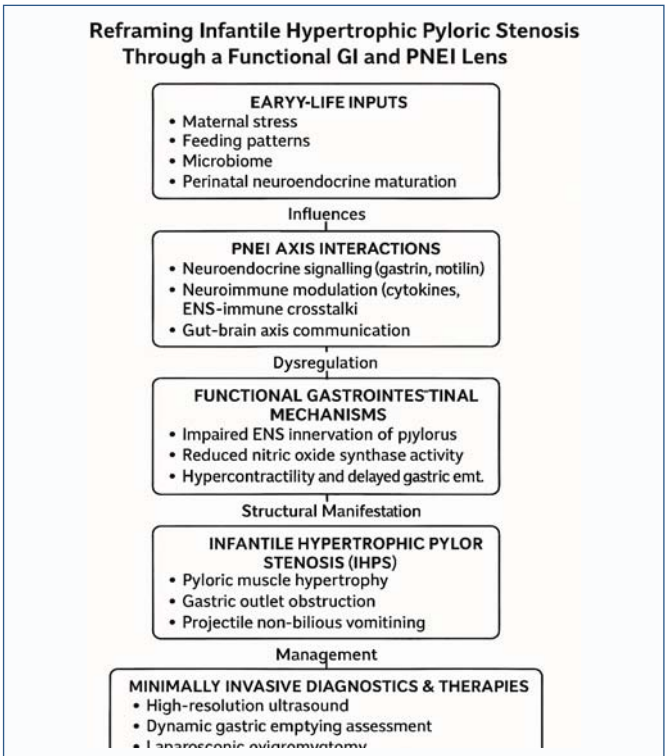


Figure 1: Conceptual graphical abstract illustrating the multidimensional pathophysiology of infantile hypertrophic pyloric stenosis (IHPS) through a functional gastrointestinal and psycho-neuro-endocrine-immune (PNEI) lens. The schematic depicts how early-life influences—including maternal stress, feeding patterns, microbiome development, and perinatal neuroendocrine maturation—interact with the PNEI axis to shape gastrointestinal function. Neuroendocrine, neuroimmune, and gut–brain signalling pathways converge to produce functional disturbances in pyloric motility, including impaired enteric nervous system innervation, reduced nitric oxide–mediated relaxation, and hypercontractility. These functional abnormalities contribute to the structural manifestation of IHPS, characterised by pyloric muscle hypertrophy and gastric outlet obstruction. The lower panel summarises minimally invasive diagnostic and therapeutic strategies, including high-resolution ultrasonography, dynamic gastric emptying assessment, laparoscopic pyloromyotomy, and emerging endoscopic or neuromodulatory approaches. The figure highlights IHPS as a disorder situated along a functional–structural continuum rather than a purely anatomical disease.

Microbiome imbalance: Altered microbial colonization may influence ENS signalling and immune activation.

Feeding practices: Breast feeding is more physiological and less stressful vs bottle feeds.

Integrated Systems-Level Model

These factors converge on a shared pathway of neuroenteric imbalance: Genetic predisposition + environmental triggers + autonomic dysregulation → nitrergic suppression → pyloric sphincter hypertonicity → IHPS. This model supports early identification of at-risk infants and highlights the importance of emotional ecology, feeding practices, and autonomic tone in IHPS prevention. Visual Reference-(Figure 5, 6 and Table 1).

Pathogenesis: Integrating Structural and Functional Mechanisms-From Structural Obstruction to Functional Disorder

Classical Structural Model

The traditional model attributes IHPS to pyloric muscle hypertrophy and hyperplasia, leading to narrowing of the pyloric

canal and impaired gastric emptying. Ultrasonographic criteria—muscle thickness >3 mm, length >15 mm, and transverse diameter >14 mm—remain central to diagnosis.

Aberrant Innervation and Functional Dysregulation

Histological studies demonstrate reduced neuronal nitric oxide synthase (nNOS) expression and abnormalities in enteric nerve distribution within the pyloric muscle. These findings indicate impaired neuromuscular relaxation rather than simple muscular overgrowth.

Such neurogenic abnormalities parallel mechanisms seen in FGIDs, where disrupted enteric nervous system (ENS) signalling contributes to dysmotility [14-22].

Molecular studies demonstrate that pyloric smooth muscle cells in IHPS are not properly innervated, suggesting a neurogenic component to the disorder. This aligns IHPS with functional gastrointestinal disorders, which often involve impaired neuromuscular coordination, altered enteric nervous system signalling and dysregulated gut–brain axis communication affecting gut secretions, gut motility, microbiome balance, metabolic chaos, with associated macronutrient excess and micronutrient deficiencies. This cascade of events initially [23-25].

Neurohormonal Influences

Hormonal modulators of gastric motility—including gastrin, motilin, and ghrelin—may influence pyloric tone, although evidence remains incomplete [26-27].

Genetic Susceptibility

Genetic studies reveal familial clustering and polygenic susceptibility, reinforcing a multifactorial model. Polygenic inheritance patterns and identified susceptibility loci support a multifactorial model involving both structural and functional elements.

Early-Life Environmental Inputs

Perinatal stress, feeding practices, macrolide exposure, and early microbiome development may influence neuroendocrine maturation and ENS function. These early-life factors align IHPS with broader developmental models of gut–brain interaction.

IHPS Through the Lens of the Psycho-Neuro-Endocrine-Immune (PNEI) Axis

The Psycho-Neuro-Endocrine-Immune (PNEI) axis provides a holistic and unifying framework for understanding how psychological, neural, endocrine, and immune systems interact to regulate gastrointestinal function. Applying this lens to IHPS highlights several under-recognised mechanistic domains framework for understanding gastrointestinal disorders as dynamic interactions between: psychological stressors, neural signalling pathways, endocrine modulators and immune responses.

Although IHPS is not classically described within this paradigm, several features support its reinterpretation:

Neural Pathways

ENS dysregulation, reduced inhibitory neurotransmission, and impaired pyloric relaxation suggest a primary neurogenic contribution. Aberrant innervation of pyloric smooth muscle suggests disrupted neuroregulation of gastric motility.

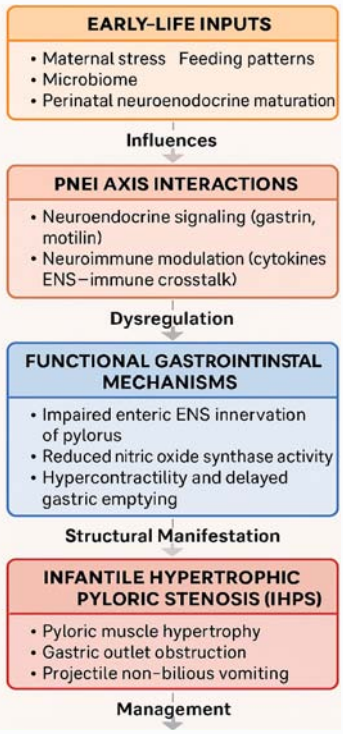


Figure 2: Color-coded multi-panel schematic illustrating the multidimensional pathophysiology of infantile hypertrophic pyloric stenosis (IHPS) through a functional gastrointestinal and psycho-neuro-endocrine-immune (PNEI) lens. The infographic is divided into five panels, each representing a distinct mechanistic domain.
Panel 1 (soft orange) depicts early-life inputs including maternal stress, feeding patterns, microbiome development, and neuroendocrine maturation.
Panel 2 (peach) illustrates PNEI axis interactions, highlighting neuroendocrine signalling (e.g., gastrin, motilin), neuroimmune modulation (cytokines, ENS–immune crosstalk), and gut–brain axis communication.
Panel 3 (blue) presents functional gastrointestinal mechanisms such as impaired enteric nervous system (ENS) innervation, reduced nitric oxide synthase activity, and pyloric hypercontractility.
Panel 4 (red) describes the structural manifestation of IHPS, including pyloric muscle hypertrophy, gastric outlet obstruction, and projectile non-bilious vomiting.
Panel 5 (green) summarises minimally invasive diagnostics and therapies, including high-resolution ultrasound, dynamic gastric emptying assessment, laparoscopic pyloromyotomy, and emerging endoscopic or neuromodulatory approaches.
Arrows between panels indicate mechanistic progression from early-life determinants to structural disease and clinical management. The schematic supports a functional–structural continuum model of IHPS and highlights opportunities for physiology-informed intervention.

Endocrine Modulation

Hormonal influences on smooth muscle tone and gastric emptying may contribute to pyloric hypercontractility. Hormonal modulators of smooth muscle tone (e.g., gastrin, motilin) may contribute to pyloric hypercontractility, although evidence remains limited.

Immune and Inflammatory Signalling

Although IHPS is not classically and primarily inflammatory, subtle immune-mediated influences on smooth muscle proliferation and extracellular matrix remodelling warrant exploration.

Psychosocial and Environmental Inputs

Maternal stress, early feeding patterns, early life environmental and perinatal exposures may shape neuroendocrine and

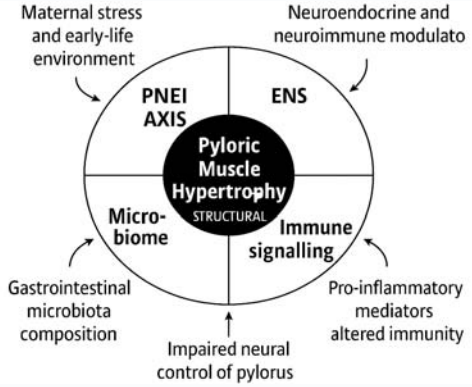


Figure 3: A fully integrated systems-biology wheel.
A circular systems diagram showing PNEI, ENS, microbiome, hormones, immune signals, and structural hypertrophy. A fully integrated systems-biology wheel showing how the PNEI axis, ENS, microbiome, hormonal signalling, and immune modulation converge to produce pyloric muscle hypertrophy in IHPS. It visually anchors your central thesis that IHPS is not merely structural, but emerges from a dynamic interplay of early-life inputs and regulatory systems.

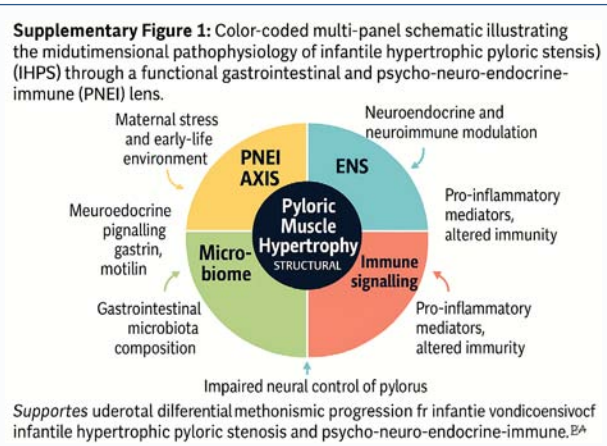


Figure 4: Annotated systems-biology schematic illustrating the multidimensional pathophysiology of infantile hypertrophic pyloric stenosis (IHPS) through a functional gastrointestinal and psycho-neuro-endocrine-immune (PNEI) lens.
This circular infographic integrates five color-coded mechanistic domains—PNEI axis (orange), enteric nervous system (ENS, blue), microbiome (green), hormonal signalling (teal), and immune modulation (red)—all converging on the central structural outcome of pyloric muscle hypertrophy.
Expanded annotations detail how maternal stress, early-life adversity, and neurodevelopmental timing influence the PNEI axis; how nitric oxide signalling, enteric neuron distribution, and pyloric relaxation reflect ENS function; how dysbiosis, microbial metabolites, and gut–brain communication shape microbiome–motility interactions; how gastrin, motilin, and ghrelin modulate pyloric tone; and how cytokines, low-grade inflammation, and ENS–immune crosstalk contribute to neuroimmune dysregulation.
Arrows connect each quadrant to the central structural manifestation, illustrating how functional disturbances across these systems culminate in IHPS. The schematic supports a functional–structural continuum model and highlights opportunities for physiology-informed diagnostics and therapies.

neuroimmune development, influencing pyloric function in susceptible infants. They may influence neuroendocrine pathways that regulate gastric motility—consistent with PNEI-based models of functional gastrointestinal disorders.

This integrative perspective does not replace the structural understanding of IHPS but enriches it, highlighting the interplay between anatomy, neurobiology, and systemic regulation. This integrative perspective positions IHPS within a functional–structural continuum rather than a purely anatomical disease.

Minimally Invasive Diagnostic Approaches

Ultrasonography as the Gold Standard

Ultrasound remains the primary diagnostic gold standard due to its high sensitivity, specificity, and non-invasive nature. Key measurements include muscle thickness, diameter, and length. Dynamic assessment of gastric emptying and real-time visualisation of pyloric peristalsis enhance diagnostic accuracy.

Adjunctive Techniques

When ultrasound findings are equivocal, test feeds and clinical observation, repeat imaging, or sterile gastric water instillation via nasogastric tube may improve visualisation in challenging cases. These approaches minimise radiation exposure and avoid unnecessary invasive procedures.

Emerging Functional Assessments

Advances in motility imaging and non-invasive biomarkers may eventually complement structural assessment, aligning diagnosis with a functional–neurobiological understanding of IHPS.

Minimally Invasive Therapeutic Strategies

Pre-operative Stabilisation

Correction of dehydration, electrolyte imbalance, metabolic alkalosis, and nasogastric decompression when required remains essential prior to intervention.

Laparoscopic Pyloromyotomy

Laparoscopic pyloromyotomy is now widely accepted as the preferred treatment, offering smaller incisions, reduced postoperative pain, faster recovery and excellent cosmetic outcomes. Its success supports the principle that relieving pyloric obstruction—regardless of underlying neurogenic contributions—restores normal physiology [27-30].

Emerging Non-Surgical and Endoscopic Approaches

Endoscopic pyloromyotomy, pharmacological modulation of pyloric tone, and neuromodulatory interventions represent promising future directions and alternatives aligned with a functional/PNEI-based understanding of IHPS, particularly if IHPS is reframed within a functional–neurobiological paradigm.

Re-framing IHPS: Implications for Research and Practice

Viewing IHPS as a disorder with both structural and functional dimensions encourages investigation into ENS, neuroimmune, neurogenic pathways and neuroendocrine mechanisms, exploration of early-life PNEI influences on gastric motility and maternal–infant PNEI interactionsm development of targeted, minimally invasive therapies, integration of functional GI disorder frameworks into paediatric surgical research. This multidimensional paradigm shift aligns with contemporary modern systems-biology approaches and may enhance early diagnosis, personalised management, and long-term outcomes.

While this multidimensional model offers new insights, it must be interpreted in light of the strengths and limitations of the available evidence.

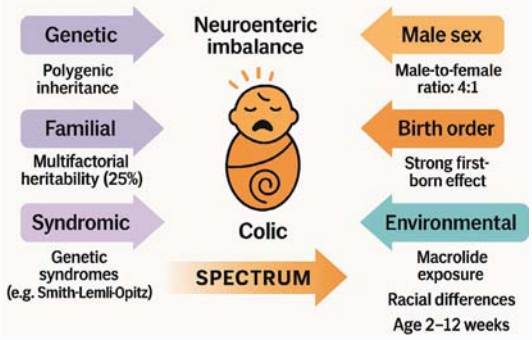


Figure 5: Risk factors influencing susceptibility to IHPS.

Strengths and Limitations

Strengths

- **Integrative, multidimensional synthesis:**

This review brings together evidence from paediatric surgery, neurogastroenterology, developmental physiology, and systems biology—fields that are rarely discussed collectively in the context of IHPS. This integrative approach provides a more comprehensive understanding of IHPS pathogenesis than traditional structural models alone.

- **Novel conceptual reframing:**

By situating IHPS along a functional–structural continuum and embedding it within the psycho-neuro-endocrine-immune (PNEI) axis, the review offers a fresh theoretical framework that aligns IHPS with mechanisms recognised in disorders of gut–brain interaction. This perspective opens new avenues for research and clinical innovation.

- **Emphasis on early-life systems biology:**

The review highlights the importance of early-life determinants—including maternal stress, microbiome development, feeding patterns, and neuroendocrine maturation—providing a developmental context that is often underrepresented in surgical literature**.**

- **Clinical relevance and translational value:**

By linking mechanistic insights to minimally invasive diagnostic and therapeutic strategies, the review bridges basic science and clinical practice, supporting more physiology-informed approaches to IHPS management.

Limitations

- **Narrative design without quantitative synthesis:**

As a narrative review, this work does not include meta-analysis or statistical pooling. The conclusions rely on qualitative interpretation of heterogeneous studies rather than formal effect estimates.

- **Variability in study quality and methodology:**

The underlying literature spans diverse designs—from histological studies to epidemiological cohorts and mechanistic animal models—each with differing levels of rigour. This heterogeneity limits the ability to draw definitive causal inferences.

- **Limited direct evidence linking PNEI pathways to IHPS:**

While the PNEI-based framework is biologically plausible and supported by parallel evidence from functional gastrointestinal disorders, direct mechanistic studies in IHPS remain sparse. Some proposed pathways therefore remain inferential.

- **Potential publication and disciplinary bias:**

Research on IHPS is historically dominated by surgical and radiological perspectives. Neuroimmune, neuroendocrine, and microbiome-focused studies are comparatively fewer, which may skew the available evidence toward structural interpretations.

- **Generalisability across populations:**

Many studies originate from high-income settings with specific demographic patterns (e.g., higher incidence in white male infants). Findings may not fully reflect global variability in environmental exposures, genetics, or healthcare access.

Despite these limitations, the synthesis presented here has important implications for both clinical practice and future research.

Implications for Practice and Research

Implications for Clinical Practice

- Reframing IHPS beyond a purely structural disorder encourages clinicians to recognise the functional and neurobiological processes that precede pyloric hypertrophy. This perspective supports earlier suspicion in infants with atypical or evolving symptoms, even before classical ultrasound thresholds are met.

- Enhanced attention to early-life determinants—including feeding patterns, perinatal stress, and medication exposures—may improve anticipatory guidance and risk stratification in primary and neonatal care.

- Integration of functional assessments (e.g., dynamic gastric emptying evaluation, motility-focused imaging) alongside standard ultrasonography may refine diagnostic accuracy in borderline or evolving cases.

- Minimally invasive management remains the cornerstone, but understanding upstream mechanisms may eventually inform adjunctive therapies that target motility, neurohormonal signalling, or ENS maturation.

- Interdisciplinary collaboration between paediatric surgeons, neonatologists, gastroenterologists, and developmental specialists can support more holistic care pathways.

Implications for Research

- Mechanistic studies are urgently needed to clarify how ENS dysregulation, nitric oxide signalling deficits, neuroimmune pathways, and hormonal modulators contribute to pyloric dysfunction. These domains remain underexplored relative to structural anatomy.

- Longitudinal early-life research—including maternal stress biology, microbiome development, and neuroendocrine maturation—may illuminate why IHPS emerges within a narrow postnatal window and why susceptibility varies across populations.

- Bridging IHPS with disorders of gut–brain interaction offers a promising research direction. Comparative studies may reveal shared pathways and therapeutic targets across functional and structural gastrointestinal conditions.

- Innovative diagnostic tools, such as advanced motility

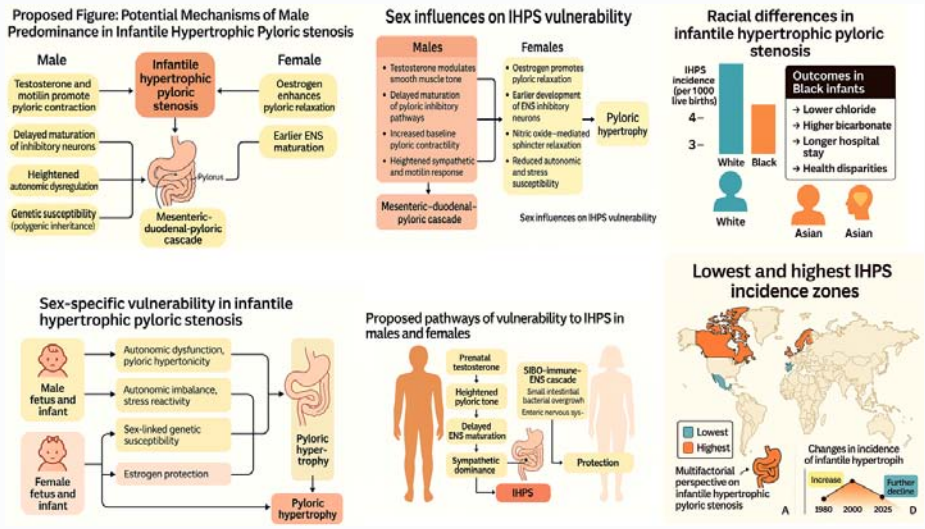


Figure 6: Sex, race and regional risk factors.

imaging, non-invasive biomarkers, and neurophysiological assessments, could help identify functional abnormalities before structural hypertrophy becomes pronounced.

- Emerging therapeutic modalities, including endoscopic pyloromyotomy and neuromodulatory interventions, warrant rigorous evaluation to determine their safety, efficacy, and potential role alongside or in place of surgical treatment.

- Systems-biology and computational modelling approaches may help integrate diverse mechanistic data into predictive frameworks, supporting personalised risk assessment and early intervention strategies.

Principal Findings

This narrative review identifies infantile hypertrophic pyloric stenosis (IHPS) as a condition that cannot be fully explained by its classical structural description alone. While pyloric muscle hypertrophy remains the defining anatomical hallmark, the evidence synthesised here demonstrates that IHPS emerges from a broader constellation of functional, neurobiological, and early-life regulatory influences. Across epidemiological, mechanistic, and clinical domains, several principal findings stand out.

First, converging data from neurogastroenterology and developmental physiology indicate that aberrant neuromuscular regulation—including reduced neuronal nitric oxide synthase activity, impaired inhibitory innervation, and altered pyloric relaxation—plays a central role in the pathogenesis of IHPS. These functional abnormalities precede or accompany structural hypertrophy, suggesting that IHPS represents the end-stage expression of a deeper motility disturbance rather than a purely muscular disorder.

Second, the review highlights the importance of psycho-neuro-endocrine-immune (PNEI) interactions in shaping early gastrointestinal function. Maternal stress, feeding patterns, microbiome development, and perinatal neuroendocrine maturation all influence the enteric nervous system and gut–brain signalling during a critical developmental window. These early-life determinants provide a plausible upstream framework for understanding why IHPS arises in a narrow postnatal period and why susceptibility varies across individuals and populations.

Third, the findings support the view that IHPS shares mechanistic features with functional gastrointestinal disorders (FGIDs), particularly those involving disordered gut–brain communication and neuromuscular coordination. Although IHPS culminates in a structural lesion, its upstream drivers align with the same domains—ENS dysregulation, neuroimmune signalling, hormonal modulation—that underpin disorders of gut–brain interaction. This positions IHPS along a functional–structural continuum rather than at the purely anatomical end of the spectrum.

Finally, the review confirms that minimally invasive diagnostics and therapies remain central to optimal care. High-resolution ultrasonography continues to provide excellent diagnostic accuracy, while laparoscopic pyloromyotomy offers rapid recovery and durable symptom resolution. Emerging endoscopic and neuromodulatory approaches reflect a shift toward physiology-informed intervention, consistent with the broader reconceptualisation of IHPS as a disorder with both structural and functional dimensions.

Together, these findings advance a more integrated understanding of IHPS—one that bridges paediatric surgery, neurogastroenterology, and early-life systems biology. This multidimensional perspective not only clarifies longstanding uncertainties in IHPS pathogenesis but also opens new avenues for research and innovation in diagnosis, prevention, and treatment.

Comparison with existing literature

Conventional descriptions of infantile hypertrophic pyloric stenosis (IHPS) emphasise its role as a mechanical gastric outlet obstruction caused by hypertrophy of the pyloric muscle, with diagnosis based on ultrasound and treatment by pyloromyotomy. These accounts typically foreground incidence (2–5 per 1000 live births), male predominance, and the classic presentation of non-bilious projectile vomiting in early infancy, while acknowledging that the precise aetiology remains incompletely understood. Our review is consistent with this foundation but deliberately extends beyond it by reframing IHPS along a functional–structural continuum rather than as a purely anatomical lesion.

Existing summaries recognise several non-structural contributors, including genetic susceptibility, abnormal innervation,

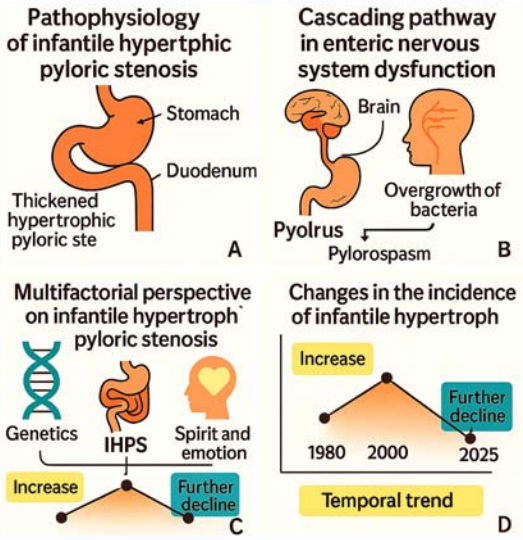


Figure 7: Pathophysiology, multifactorial perspective, cascade system approach and temporal variations.

lack of neuronal nitric oxide synthase, hypergastrinemia, and perinatal risk factors such as maternal smoking, macrolide exposure, and feeding practices. These elements are often listed as discrete hypotheses rather than integrated into a systems framework. In contrast, our narrative explicitly organises these mechanisms within a psycho-neuro-endocrine-immune (PNEI) axis and gut–brain paradigm, linking ENS dysregulation, neurohormonal signalling, immune modulation, and early-life environmental inputs to pyloric motor dysfunction and subsequent hypertrophy.

Standard paediatric surgery and emergency medicine texts focus on clinical recognition and procedural management, highlighting the reliability of ultrasound, the classical "olive" on palpation, and the evolution from open to laparoscopic pyloromyotomy as the treatment of choice. Our review aligns with this evidence but adds value by embedding these diagnostic and therapeutic pathways within a physiology-informed framework—positioning high-resolution ultrasound, dynamic gastric emptying assessment, and minimally invasive surgery as interventions that act on the end-stage structural expression of a broader functional disturbance.

Finally, while current literature acknowledges that the etiology of IHPS is multifactorial and remains enigmatic, it rarely situates IHPS explicitly within the spectrum of disorders of gut–brain interaction. Our work advances the field by drawing on concepts from functional gastrointestinal disorders and early-life systems biology to propose IHPS as a model condition in which early-life PNEI perturbations, microbiome influences, and ENS maturation converge on a stereotyped structural phenotype. This integrative stance both complements and extends existing reviews, opening a conceptual bridge between paediatric surgery, neurogastroenterology, and developmental physiology.

Relationship of Congenital Colorectal Secretomotility Disorders to Foregut IHPS within a Spiritual–systems Framework

Congenital colorectal secretomotility disorders of the hindgut—such as dysmotility, dysregulated secretion, and altered mucosal–neuronal signalling—can be viewed as part of a longitudinal gut axis that extends from hindgut to midgut and foregut. On a systems level, disturbances in the hindgut do not remain local: they feedback via the enteric nervous system, microbiome, immune mediators, and gut–brain pathways, altering motility patterns, sensory signalling, and neuroendocrine tone along the entire gastrointestinal tract. Within this continuum, IHPS can be conceptualised as a foregut expression of a broader, developmentally programmed secretomotility imbalance that also manifests in the distal bowel.

From a developmental perspective, early perturbations in hindgut secretomotility—for example, abnormal chloride and water transport, altered mucosal signalling, or ENS patterning—may shape the maturation of midgut and foregut circuits through shared neuronal networks, common trophic factors, and microbiome-dependent signalling. This suggests that some infants who later present with IHPS may already carry a latent systems-level vulnerability, expressed distally as subtle colorectal dysmotility or secretory imbalance and proximally as impaired pyloric relaxation and hypercontractility. In this view, IHPS is not an isolated pyloric event but a nodal point in a chain of gut–brain–immune interactions spanning the entire gut tube.

Integrating the spiritual domain through the Prajapita Brahma Kumaris understanding of spirituality adds a further, non-reductive layer. In that tradition, the human being is understood as a soul (consciousness) operating through the body, with thoughts, emotions, and sanskars (deep mental imprints) influencing physiological states. Chronic or subtle disturbances in the inner states—fear, insecurity, unresolved stress, or disconnection from one's original qualities of peace, purity, and stability—may be mirrored in dysregulated autonomic tone, altered PNEI signalling, and disturbed gut motility. When viewed this way, congenital secretomotility disorders and IHPS can be framed as bio-psycho-spiritual phenomena, where:

- **Body:** ENS architecture, secretomotility, microbiome, and structural pyloric hypertrophy
- **Mind:** Patterns of stress, emotional climate around conception, pregnancy, and early caregiving
- **Soul/Consciousness:** Deeper spiritual qualities, karmic impressions, and alignment (or misalignment) with original virtues interact across time.

Within a Prajapita Brahma Kumaris–inspired lens, the evolution of IHPS could be described as the convergence of:

(1) Congenital and developmental vulnerabilities in gut secretomotility from hindgut to foregut;

(2) Early-life environmental and relational stressors shaping the PNEI axis; and

(3) The subtler spiritual field of the family and infant—thoughts, intentions, and vibrations—modulating how these vulnerabilities are expressed. This does not replace biomedical explanation; rather, it extends it, acknowledging that the infant's gut is not only a physiological organ but also a sensitive interface between biology, emotion, and spirit.

Results

Across the literature reviewed, four major thematic domains emerged that collectively reshape understanding of infantile hypertrophic pyloric stenosis (IHPS): epidemiological

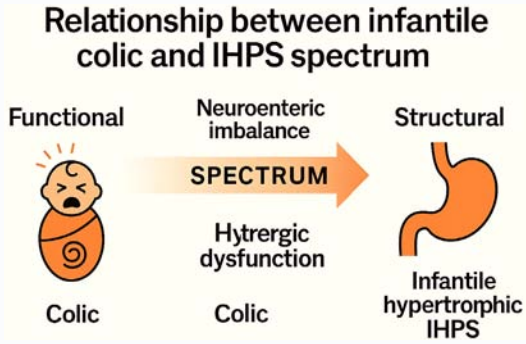


Figure 8: Normal baby-infantile colic-IHPS spectrum from normal via functional to strutural.

Possible Explanations

Factor	Contribution to Racial Differences
Genetic predisposition	Higher in Caucasian populations
Feeding practices	Bottle-feeding more common in some groups
Healthcare access	Delays in diagnosis and treatment
Socioeconomic status	Influences severity and outcomes
ENS development	May vary subtly across populations

Table 1: Possible explanations for racial differences.

patterns, neuromuscular and neuroendocrine mechanisms, early-life determinants, and evolving diagnostic and therapeutic strategies. Together, these findings support a shift from a purely structural interpretation of IHPS toward a multi-dimensional model incorporating functional gastrointestinal and psycho-neuro-endocrine-immune (PNEI) processes.

Epidemiology and Clinical Characteristics

The evidence consistently confirms that IHPS presents within a narrow postnatal window, typically between 2 and 12 weeks of age, with a strong male predominance, first born, distinct seasonal peaks, and higher incidence in white populations. Projectile non-bilious vomiting, visible peristalsis, and metabolic alkalosis remain the hallmark clinical features. Despite these well-defined patterns, several studies report variability in severity, progression, and age of onset, suggesting influences beyond simple muscular hypertrophy.

Neuromuscular and Neuroendocrine Mechanisms

Multiple histological and physiological studies demonstrate abnormalities in pyloric innervation, including reduced neuronal nitric oxide synthase (nNOS), impaired inhibitory signalling, and altered distribution of enteric neurons. These findings indicate that functional dysregulation of pyloric motility—rather than isolated muscular overgrowth—plays a central role in IHPS pathogenesis. Additional evidence implicates hormonal modulators such as gastrin, motilin, and ghrelin, although results across studies remain heterogeneous.

Early-Life Determinants and PNEI-Axis Influences

A growing body of research highlights the contribution of early-life factors, including maternal stress, feeding practices, perinatal exposures (e.g., macrolides), and microbiome development. These determinants influence neuroendocrine maturation, immune signalling, and gut–brain communication during a critical developmental window. Collectively, these findings support a systems-biology perspective in which IHPS arises from the convergence of early-life PNEI perturbations and gastrointestinal neuromuscular immaturity.

Diagnostic and Therapeutic Approaches

High-resolution ultrasonography remains the diagnostic gold standard, with consistent evidence supporting its accuracy and reliability [1]. Adjunctive techniques—such as dynamic gastric emptying assessment—are increasingly recognised for their value in equivocal cases [3]. Laparoscopic pyloromyotomy continues to demonstrate excellent outcomes, with shorter recovery times and fewer complications compared with open surgery [2, 30]. Emerging endoscopic and neuromodulatory interventions appear promising but remain under investigation.

Taken together, these findings indicate that IHPS cannot be fully explained by structural hypertrophy alone, prompting a broader interpretation explored in the Discussion.

Discussion

This narrative review synthesises emerging evidence that reframes infantile hypertrophic pyloric stenosis (IHPS) as more than a purely structural disorder of the pyloric muscle. While pyloric hypertrophy remains the defining anatomical hallmark, the literature increasingly supports a multidimensional model in which neuromuscular dysfunction, neuroendocrine signalling, immune modulation, and early-life environmental factors converge to produce the characteristic clinical phenotype. This perspective aligns IHPS with broader principles of functional gastrointestinal physiology and the psycho-neuro-endocrine-immune (PNEI) axis.

IHPS as the end-stage expression of functional dysregulation

Traditional descriptions emphasise muscular hypertrophy as the primary pathology. However, converging mechanistic studies demonstrate that abnormalities in enteric nervous system (ENS) innervation, reduced neuronal nitric oxide synthase activity, and impaired inhibitory neurotransmission precede or accompany structural changes. These findings suggest that IHPS represents the end-stage structural manifestation of an upstream motility disorder, rather than a purely myogenic condition. This interpretation is consistent with the narrow postnatal window in which IHPS emerges, a period marked by rapid ENS maturation and heightened vulnerability to neurohormonal and neuroimmune influences.

The role of early-life determinants and the PNEI axis

The review highlights the importance of early-life factors—including maternal stress, feeding practices, microbiome development, and perinatal exposures—in shaping gastrointestinal function. These determinants influence neuroendocrine maturation, immune signalling, and gut–brain communication during a critical developmental window. Although direct causal pathways remain incompletely defined, the evidence supports a systems-biology model in which IHPS arises from the convergence of early-life PNEI perturbations and gastrointestinal neuromuscular immaturity. This developmental framing helps explain the condition's timing, variability in severity, and population-level differences in incidence.

Positioning IHPS along a functional–structural continuum

The mechanistic overlap between IHPS and disorders of gut–brain interaction (DGBIs) is increasingly apparent. Both involve ENS dysregulation, altered neuroimmune signalling, and hormonal modulation of motility. The key distinction lies in the structural endpoint: whereas DGBIs remain functional, IHPS progresses to a fixed anatomical obstruction. Recognising IHPS as part of a functional–structural continuum bridges paediatric surgery with neurogastroenterology and may help unify disparate strands of research that have historically evolved in parallel.

Clinical implications and evolving diagnostic paradigms

High-resolution ultrasonography remains the diagnostic gold standard, yet the functional insights highlighted in this review suggest opportunities to refine diagnostic pathways. Dynamic gastric emptying assessment, motility-focused imaging, and early recognition of evolving pyloric dysfunction may improve diagnostic accuracy in borderline cases. Understanding IHPS as a motility disorder with a structural endpoint may also support earlier identification of infants at risk, particularly those with relevant early-life exposures.

Therapeutic implications and future directions

Laparoscopic pyloromyotomy continues to offer excellent outcomes and remains the cornerstone of treatment. However, the emerging recognition of functional contributors invites exploration of adjunctive or alternative therapies targeting motility, neurohormonal signalling, or ENS maturation. Endoscopic pyloromyotomy and neuromodulatory interventions represent promising avenues, though robust evidence is still needed. A physiology-informed therapeutic framework may ultimately complement surgical correction by addressing upstream contributors to pyloric dysfunction.

Integrating systems biology into IHPS research

The multidimensional model proposed here underscores the need for interdisciplinary research that bridges paediatric surgery, developmental biology, neurogastroenterology, and immunology. Longitudinal studies examining early-life stress biology, microbiome trajectories, and neuroendocrine maturation may clarify why IHPS emerges in a narrow developmental window. Systems-biology and computational approaches may help integrate diverse mechanistic data into predictive models, supporting personalised risk assessment and early intervention.

Hindgut–Midgut–Foregut Continuity, Congenital Secretomotility Disorders, and the Spiritual Dimension of Early-Life Regulation

Emerging developmental and neurogastroenterological evidence suggests that congenital colorectal secretomotility disorders of the hindgut may share upstream regulatory pathways with foregut conditions such as infantile hypertrophic pyloric stenosis (IHPS). Although these disorders manifest at opposite ends of the gastrointestinal tract, they arise within a single, longitudinally integrated gut–brain–immune axis, shaped by shared embryological origins, common enteric neuronal networks, and coordinated secretomotor regulation (Figure 7).

Congenital hindgut secretomotility disturbances—such as dysregulated chloride and water transport, altered mucosal signalling, or ENS patterning anomalies—may influence the maturation of midgut and foregut circuits through microbiome-dependent metabolites, immune mediators, and vagal–enteric feedback loops. These interactions align with the PNEI framework, in which early-life stress biology, neuroendocrine tone, and immune activation modulate gastrointestinal motility across the entire gut tube. Within this continuum, IHPS can be conceptualised as a proximal expression of a broader systems-level vulnerability, where impaired inhibitory signalling, reduced nitric oxide availability, and altered pyloric relaxation represent the foregut analogue of distal secretomotility imbalance (Figure 8).

This integrated model resonates with the Prajapita Brahma Kumaris understanding of spirituality, which views the infant not merely as a biological organism but as a soul expressing itself through the body, influenced by the emotional and vibrational field of caregivers. In this perspective, subtle disturbances in the early relational environment—fear, instability, unresolved stress, or disconnection from innate qualities of peace and purity—may shape autonomic tone and PNEI regulation. These influences can, in turn, modulate ENS maturation and gut secretomotility, providing a bio-psycho-spiritual bridge between hindgut and foregut manifestations.

Rather than replacing biomedical explanations, this spiritual dimension complements them by acknowledging that early-life physiology is sensitive to both tangible and intangible influences. The infant's gastrointestinal tract—richly innervated, immunologically active, and developmentally plastic—may serve as a somatic interface where biological predispositions, environmental exposures, and spiritual-emotional states converge. Within this expanded framework, congenital colorectal secretomotility disorders and IHPS can be understood as different expressions of a unified developmental trajectory, shaped by interactions between the ENS, PNEI axis, microbiome, and the subtle emotional–spiritual climate surrounding the infant.

Summary

Infantile hypertrophic pyloric stenosis (IHPS) has long been described as a structural gastric outlet obstruction caused by pyloric muscle hypertrophy. However, evidence across neurogastroenterology, developmental physiology, and systems biology demonstrates that IHPS cannot be fully understood through an anatomical lens alone. This review synthesises current literature to show that IHPS arises from the convergence of functional gastrointestinal dysregulation, early-life determinants, and psycho-neuro-endocrine-immune (PNEI) interactions, culminating in the characteristic structural lesion.

Mechanistic studies consistently reveal abnormalities in enteric nervous system innervation, nitric oxide–mediated inhibitory signalling, and pyloric motor control, indicating that functional disturbances precede or accompany muscular hypertrophy. Early-life factors—including maternal stress, feeding patterns, microbiome development, and perinatal exposures—further shape neuroendocrine and neuroimmune maturation during a critical developmental window. These influences align IHPS with principles observed in disorders of gut–brain interaction, positioning it along a functional–structural continuum rather than as an isolated anatomical defect.

Clinically, high-resolution ultrasonography remains the diagnostic gold standard, while laparoscopic pyloromyotomy continues to offer excellent outcomes. Yet the emerging functional framework highlights opportunities for enhanced diagnostic

precision and future physiology-informed therapies, including motility-targeted, endoscopic, or neuromodulatory approaches.

Overall, this review reframes IHPS as a multidimensional condition shaped by interactions between early-life biology, neuromuscular maturation, and structural change. This integrative perspective bridges paediatric surgery with neurogastroenterology and developmental science, offering a foundation for more holistic research, earlier risk identification, and innovative therapeutic strategies.

Conclusion

IHPS remains a common and treatable cause of gastric outlet obstruction in infancy. While its structural features are well established, emerging evidence of aberrant innervation and neurohormonal influences supports a broader conceptualisation that incorporates functional gastrointestinal principles and the PNEI axis. Minimally invasive diagnostic and therapeutic strategies continue to evolve, offering safer and more refined care. Future research integrating neurobiology, genetics, and systemic regulatory pathways may redefine IHPS within a multidimensional framework that bridges anatomy, function, and holistic infant health.

Infantile hypertrophic pyloric stenosis (IHPS) has traditionally been understood as a structural disorder defined by pyloric muscle hypertrophy and treated effectively with pyloromyotomy. However, the evidence synthesised in this review demonstrates that IHPS arises from a far more complex interplay of functional gastrointestinal, neurobiological, and early-life regulatory processes. Abnormalities in enteric nervous system signalling, reduced nitric oxide–mediated inhibition, neuroendocrine and immune modulation, and early-life environmental influences all contribute to a multidimensional pathophysiology that precedes the development of the characteristic structural lesion.

Reframing IHPS within a psycho-neuro-endocrine-immune (PNEI) and systems-biology context positions the condition along a functional–structural continuum rather than as an isolated anatomical defect. This perspective not only clarifies longstanding uncertainties in IHPS aetiology but also aligns the condition with broader principles of gut–brain interaction and developmental physiology.

Clinically, high-resolution ultrasonography and laparoscopic pyloromyotomy remain the cornerstones of diagnosis and treatment. Yet the emerging functional framework highlights opportunities for earlier recognition, enhanced diagnostic precision, and future therapies that target upstream motility and neurobiological pathways. Integrating insights from neurogastroenterology, developmental biology, and paediatric surgery will be essential for advancing prevention, risk stratification, and innovative treatment strategies.

Ultimately, this multidimensional understanding of IHPS encourages a shift toward more holistic, physiology-informed models of care—bridging structural correction with deeper appreciation of the functional systems that shape early-life gastrointestinal health.

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Competing Interests

The authors declare that they have no competing interests.

Ethics Approval

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Patient and Public Involvement

No patients or members of the public were directly involved in the design, conduct, reporting, or dissemination of this review.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

Author Contributions

All authors conceived the study. conducted the literature search and drafted the manuscript. All authors contributed to revisions, approved the final version, and agree to be accountable for all aspects of the work.

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