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Review Article

EndoCompass project: research roadmap for reproductive and developmental endocrinology

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Abstract

Background: Endocrine science remains underrepresented in European Union research programs despite the fundamental role of hormone health in human wellbeing. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At national funding level, endocrine societies report limited or little attention of national research funding towards endocrinology. The EndoCompass project—a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges.

Methods: Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014-2020). Expert consultation was conducted to identify key research priorities, followed by broader stakeholder engagement including society members and patient advocacy groups.

Results: Research priorities encompass variations in sex development, hypothalamic–pituitary–gonadal regulation, and female and male reproductive disorders. Key areas include improving diagnostic capacity through (epi)genetic analysis, optimizing hormonal treatments, developing fertility preservation strategies. Special emphasis is placed on establishing pan-European registries, developing novel reproductive technologies, and exploring environmental impacts on reproductive health.

Conclusions: This component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into reproductive and developmental endocrinology pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of these disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of the highest potential impact in endocrine health.

Keywords: EndoCompass, reproduction, HPG axis (hypothalamic-pituitary-gonadal, funding, roadmap)

The following patient organisations were involved: Living with CAH, Turner Syndrome Support Society, Varia Suisse, MRKH Connect.

Significance

Reproductive endocrinology remains significantly underrepresented in EU research programs, despite the fact that millions of EU citizens face challenges with natural conception and suffer from comorbidities linked to impaired gonadal function. This chapter outlines the need for a strategic and systematic approach to identifying key clinical and research priorities related to the hormonal and genetic regulation of gonadal function—from early development to late adulthood, including menopause. It is emphasized that gonadal dysfunction has far-reaching implications beyond reproductive capacity. It can profoundly affect physical health, mental well-being, and overall quality of life. As a result of the increasing prevalence of gonadal dysfunction in the EU, up to 10% of all newborns are now conceived through Medically Assisted Reproduction (MAR), and despite its widespread use, significant research gaps remain, such as limited understanding of the underlying causes of impaired fertility and the potential long-term health consequences for offspring conceived through MAR. The chapter indicates research directions in reproductive endocrinology with the ultimate goal of informing policy, and improving care and long-term well-being of future generations.

Introduction

The development and function of the hypothalamic–pituitary–gonadal (HPG) axis and gonads underpin biological sex, influence gender identity, and are major determinants of our general health, quality of life (QoL), and reproductive capacity. Over 25 million people, or an estimated 1/7 couples in the European Union, are affected by infertility, which is due to congenital or acquired conditions of the genital organ structures or function, reproductive hormone imbalances, or a combination of these.[1]

Lifestyle factors, such as smoking, excessive alcohol intake, and obesity can affect fertility and the HPG axis. Exposure to environmental pollutants and toxins can be directly toxic to gametes (eggs and sperm), resulting in their decreased numbers and poor quality, and can affect the embryonic development of reproductive organs and/or the development or function of the HPG axis.[2,3] In addition, many individuals remain involuntarily childless for non-medical reasons.

The disease burden resulting from these conditions is high. Worldwide, age-standardized, disability-adjusted life years of infertility have increased between 1990 and 2017 by 0.396% per year for women and by 0.296% per year for men, with the highest increase in women living in high-income countries.[4] Infertility and its treatments reinforce gender inequalities and work capacity.[5]

Human sex development and variations in sex development

Epidemiology, societal impact, research state of the art

Human sex development is driven by genetic, epigenetic, and hormonal factors that are only partially understood. Numerical variations of the sex chromosomes are relatively frequent. Around 1/500 male fetuses have a 47,XXY karyotype (Klinefelter syndrome), many of which remain undiagnosed.[6,7] Around 1/2000 women have (partial) loss of an X chromosome (Turner syndrome).[8]

More rare differences/disorders of sex development (DSDs), estimated at 1/4000 live births, have been associated with the congenital absence of a uterus (Mayer–Rokitanski–Küster–Hauser syndrome), and with variations in multiple genes that result in disrupted gonadal differentiation into either a testis or ovary, with disrupted secondary sex organ differentiation due to sex steroid production defects, or with defects in androgen signalling.[9,10] Intra-uterine growth retardation due to placental insufficiency is associated with a 30% risk of genital variation and decreased reproductive capacity in males.[11]

Environmental factors and endocrine-disrupting chemicals (EDCs) have a major impact on both male and female sex development, mini-puberty, puberty, and fertility and are addressed in the chapter Environmental endocrinology.[12]

Many individuals who have conditions that negatively affect sex development need lifelong hormone replacement therapy and medical care for secondary conditions resulting from lack of sex steroid effects on peripheral target tissues, such as the cardiovascular and musculoskeletal systems, and the brain.[5,13] Mental health problems are reported by 80%, and most experience a need to receive psychosocial support. Lack of self-esteem may interfere with their social relationships.

Current research on conditions affecting sex development is focused on understanding the broad range of (epi-)genetic and environmental aetiologies, on advancing technologies for medically assisted reproduction, and on improving care, including psychosocial aspects, for affected individuals.

Future research priorities

Aetiology of DSDs

1. The diagnostic yield in DSDs remains relatively low. More research is needed to further unravel the (epi)genetic factors influencing male and female sex development. This requires extension of genetic analyses for DSDs to non-coding regions via whole genome sequencing, including long range sequencing with concomitant assessment of epigenetics.[14] Standardization of hormone measurements and of dynamic testing, and the establishment of reference values across ages will facilitate interpretation and promote equal healthcare around the world.[15,16]
2. There is emerging evidence that hormone dysregulation during embryonic development influences postnatal maturation of male gonadal Leydig and Sertoli cells and hence adult steroid hormone synthesis and fertility.[17] Thus, hormone-dependent sex development needs further research, in particular, the hormonal activation of genes that drive sex differentiation, including oestrogen action, which is still poorly understood.
3. The foetal–placental–maternal unit is pivotal in metabolising steroid hormones produced by the foetus and mother to safeguard hormonal balance, especially with respect to circulating androgens.[18] This system is out of balance in utero in some virilising conditions, shifting excess androgens towards recently proposed alternative pathways that

involve androgen production or metabolism and that play a role in health and disease. These pathways may affect pubertal development, gonadal function, and fertility.[19,20]
4. The gene regulatory networks governing gonad development and function are not evolutionarily conserved across all model organisms used in research and humans, making a bottleneck in research on aetiology and mechanism(s) of disease progression in DSDs. One way forward is the use of ex vivo, patient-derived cellular and organoid models,[21] which would also pave the way for personalized medicine approaches. Working towards this, successful cellular reprogramming of mouse and human gonadal cells has been achieved,[22] but their relevance to the clinical heterogeneity encountered in practice needs further exploration.

DSDs and the human brain

Both clinical and neuroimaging data obtained in patients with altered androgen levels/actions suggest an important role of androgens in inducing male-typical neural and psychosexual characteristics.[23] Studies investigating the neural and psychosexual functioning in DSDs characterized by low/absent oestradiol action can shed light on the role of oestrogens in the development of female-typical neural and psychosexual characteristics, including gender identity.

Comorbidities and risk factors for reduced QoL and long-term outcomes

1. Congenital extra-genital anomalies are often present in individuals who have a DSD,[24,25] as well as comorbidities, such as reduced bone mineral density,[26,27] early cardiovascular disease,[28] cancer,[29] neuropsychiatric disorders, developmental delay, and additional learning needs.[30,31] Some of these may be secondary to hormone deficiencies and some may be independent. Integrating results from lifelong in-depth clinical phenotyping studies and tissue-specific multi-omics research that provides mechanistic understanding is critical to reduce morbidity and mortality, provide realistic expectations, and improve QoL via appropriate risk analyses.
2. Individuals with a DSD and a Y chromosome are at increased risk for developing gonadal germ cell tumours (GCT).[32] Prophylactic gonadectomy to prevent GCT development should be targeted towards individuals who have the highest GCT risk and lowest chances for hormone production and fertility. Research on stratification of risk profiles has been descriptive so far.[33] Molecular genetic profiling of gonads and cell types is needed to understand the pathobiology of GCT in DSDs and to develop specific biomarkers for detection of premalignant cells. Such biomarkers are also required to support urgently needed surveillance programmes for preserved high-risk gonads.[34]
3. The case for standardized data collection across geographical borders is particularly strong in controversial areas such as DSDs, where the marked regional and sociocultural variation in care is based on minimal evidence of benefit.[35] Registries collecting real-world data such as the I-DSD registry will increasingly become important tools for pragmatic trials and, for this, there will be a need for greater interaction with regulators and healthcare policymakers. These trials should focus on:
   - Optimization of puberty induction and sex hormone replacement therapy in DSDs, such as improved formulations, route of administration, pubertal timing and progression, hormonal effects in conditions with reduced sex steroid end organ sensitivity and long-term outcomes for general health issues.[13,36] During adulthood especially, it is not clear which types of substitution with sex hormones are most efficacious.[37,38]
   - Optimization of fertility capacity and technologies.[39]
   - Optimization of sexual function, at all ages, considering functionality of genitalia, eventual genital surgery, hormonal status, psychological features, sociocultural background, and type of DSD.[40,41]
   - Development of effective psychosocial interventions in DSDs, aiming to facilitate acceptance, increase self-esteem, optimize social participation, and improve QoL of affected individuals.[39,42] Strategies should also target their caregivers, as empowered caregivers will pass their coping abilities to their children.[43] In parallel, measures to increase societal awareness of DSDs are urgently needed, to reduce stigma.[44,45]

Impact of living with atypical genitals on (gender) identity development, (gender) well-being and QoL

As childhood genital surgery has become strongly restricted following EU resolution 2191, an increasing number of children now grow up with a clear genital difference. Also, in some European countries, intersex or non-binary sex registration has recently become an option. Scientific evidence for successful outcomes with these approaches is currently not available. Systematic follow-up of the individuals concerned is urgently required, to understand the influence of genital ambiguity and non-binary sex registration on gender identity, gender comfort, and gender and body contentedness.[42]

Reproductive options for individuals who have a DSD

1. The natural history of the deterioration of gonadal function in DSDs is not understood and needs to be studied longitudinally through the collection of standardized data[35] from foetal life onwards, and with a focus on genomics and proteomics.
2. Expected cryopreservation options need to be integrated with the above research to be successful in DSDs.[46] Efficient strategies for fertility preservation need to be developed for individuals with (expected) limited gametogenesis.
3. The applicability of future options for medically assisted reproduction for these individuals needs to be explored, including the ethical, social, and moral acceptability of these methods.[47-49]
4. The technique of uterus transplantation for individuals with absent Müllerian structures has not gained wide uptake yet, in spite of its first application >10 years ago, and remaining barriers should be urgently identified and addressed.[50]

Figure 1 provides a visual representation of the content of this section.

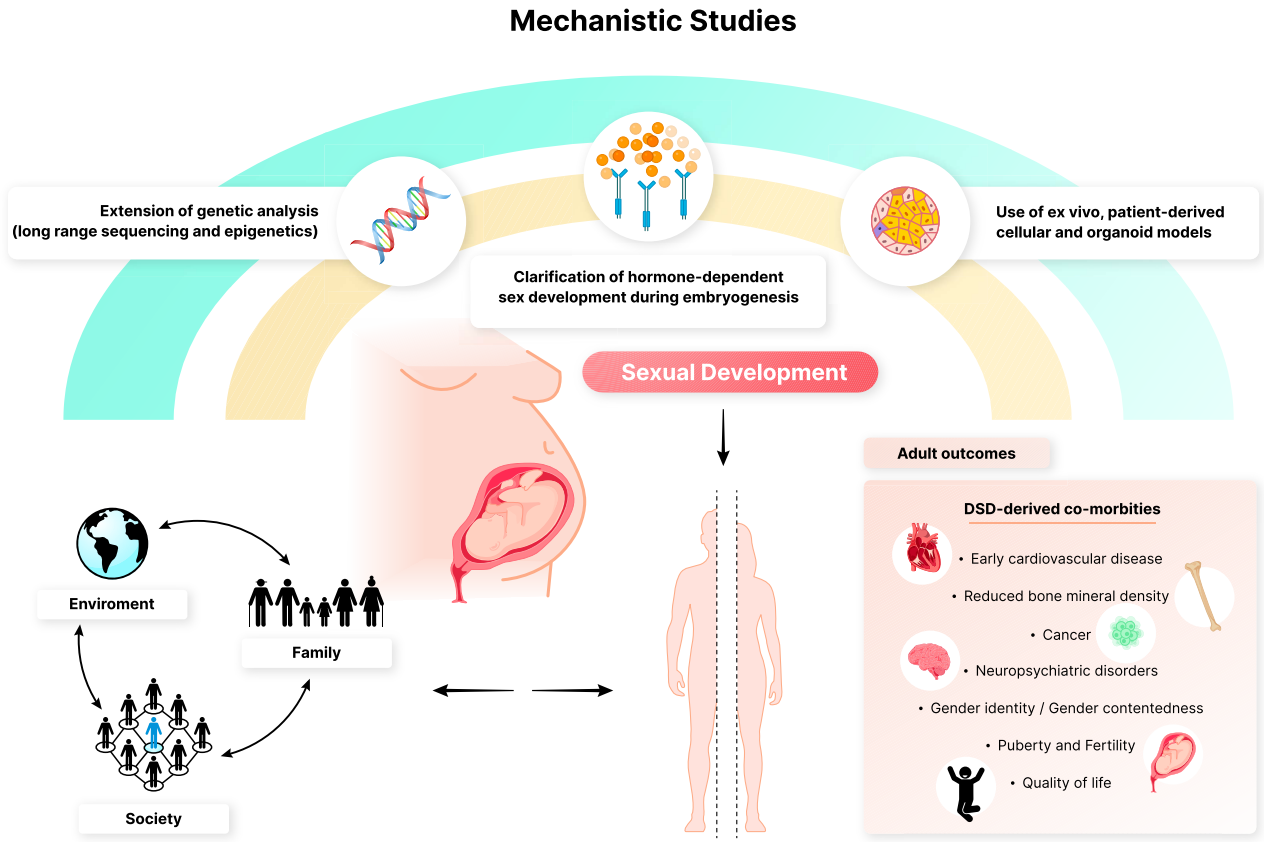

Figure 1. Mechanistic studies of variations in sex development.

Anticipated impact of future research

Improved diagnostic capacity will allow precision medicine, tailored to the needs of each individual, while at the same time avoiding unnecessary treatments, preventing comorbidities, and promoting healthy aging. Research on effective psychosocial therapies to address stigma and the burden of infertility, combined with societal research on ways to promote openness towards genital variation, and a better understanding of how gender identity development is influenced by variations in sex characteristics, will have a major impact on QoL of affected individuals. It will reduce the need for controversial types of surgery, in particular, genital surgery. The expansion of options for medically assisted reproduction, including uterus transplantation, to individuals who have a DSD has repeatedly been stated as a top priority by affected individuals.

Hypothalamic–pituitary–gonadal regulation across the lifetime

Epidemiology, societal impact, research state of the art

Incidence, economic and healthcare burden

The HPG axis plays a critical role in regulating reproductive function across the lifetime. Alterations in HPG axis function can lead to a range of conditions, including precocious puberty, hypogonadotrophic hypogonadism, and infertility, each with unique epidemiological profiles, economic and healthcare burdens, and wider societal impacts.

Observations from diverse geographic regions, including Denmark, Korea, and Italy, indicate a concerning rise in the incidence of precocious puberty in recent decades. This trend brings with it a host of associated sequelae, impacting upon not only metabolic health, but also fertility and psychosocial well-being. The burgeoning incidence underscores a pressing need for effective prevention strategies, genomic discovery and improved therapeutics to mitigate its broad-ranging consequences.

Central hypogonadotrophic hypogonadism (CHH) and primary ovarian insufficiency (POI), affecting 1% of women, stand as poignant examples of conditions underscored by their genetic foundations and profound effects on fertility and overall health. In accordance, primary hypogonadism in males due to sex chromosome anomalies like Klinefelter syndrome (47, XXY) or 45,X/46,XY gonadal dysgenesis, late onset hypogonadism, or sequelae to cancer therapy probably remain overlooked. Understanding the intricate genetic pathways underlying these conditions is pivotal for targeted interventions and improved patient outcomes.

The economic and healthcare burdens of these conditions are substantial. Direct costs, from diagnostic tests to ongoing management, place significant pressure on healthcare systems and families alike. These expenses are compounded by indirect costs, including loss of productivity and the profound psychosocial impacts experienced by those affected. Infertility, often driven by conditions like POI in women, presents its own set of challenges. Expensive interventions, such as in vitro fertilization and hormone replacement therapy, add layers to the financial burden. Meanwhile, the emotional toll of coping

with infertility further compounds the strain on individuals and families, amplifying the need for comprehensive support systems.

Wider societal impact

The societal impact of these conditions extends beyond the immediate healthcare implications. Early or delayed puberty can affect psychological development, social interactions, and academic performance, with potential long-term consequences on individual life courses. Recent Mendelian randomization studies indicate a causal link between pubertal timing and reproductive and general health, including incidence of type 2 diabetes and cardiovascular disease. Additionally, the psychosocial stress on families and caregivers, coupled with societal stigma, can exacerbate the challenges faced by affected individuals. Furthermore, infertility brings its own set of complex social and emotional challenges, often leading to significant distress and societal pressure.

Research state of the art

Current research directions are multifaceted, focusing on genomic discovery, clinical diagnosis, and therapeutic innovation.

Gonadal function is governed by the HPG axis. This neurohormonal system integrates 3 main groups of signals arising from: (1) the hypothalamus, where a scattered population of neurones produces the decapeptide gonadotrophin-releasing hormone (GnRH); (2) the pituitary, where gonadotroph cells, under the stimulus of GnRH, synthesize and release both gonadotrophins (luteinizing hormone, LH, and follicle-stimulating hormone, FSH); and (3) the gonads (testis and ovary), which respond to gonadotrophins by promoting gametogenesis and releasing hormones, including sex steroids. These elements are connected by feedback loops to ensure the dynamic regulation of the HPG axis along the lifespan.

While the main elements of the HPG axis are established before birth, the dynamic function of the axis and their interregulation undergo dramatic changes during pre- and postnatal maturation, heralded by specific features at mini-puberty, puberty and adulthood, which display divergent traits depending on the sex and nutritional status and are under the influence of a myriad of regulatory cues.

The quest to understand the triggers of puberty and the genetic landscape of CHH, POI, and primary male hypgonadism has led to significant advances, though many questions remain unanswered. Pathogenic variants in key genes and the exploration of novel diagnostic and treatment approaches, including the use of gonadotrophins and kisspeptin testing, represent the cutting edge of research in the field.

The importance of gonadotrophins for gonadal function has been known for decades. They are used today clinically to stimulate gametogenesis and/or modify gonadal hormone production in both sexes. The potency of FSH in stimulating spermatogenesis and folliculogenesis has been demonstrated in multiple studies. Today, FSH is still used during hyperstimulation of women undergoing assisted reproductive techniques and is also currently being tested as a novel treatment option for idiopathic male infertility, as previous attempts using anti-oestrogens, selective oestrogen receptor modulators, aromatase inhibitors and other agents have not been successful.

The effect of endocrine signals outside the HPG axis has also been investigated but, so far, none of these factors are used routinely clinically. For example, the influence of stress and adrenal homeostasis has only recently been noted. In recent years, however, there has been a greater research focus on factors influencing mineral homeostasis, including vitamin D, calcium and RANK ligand inhibitors, skeletal function and glucose homeostasis in functional hypogonadism due to obesity, and their possible role in infertility.

Moreover, environmental factors including nutrition or EDCs play a significant role in modulating the HPG axis. Conditions such as nutritional stress, including anorexia, can suppress pubertal maturation and gonadal function by inhibiting excitatory inputs to the HPG axis. Conversely, obesity seems to operate in a biphasic manner, initially over-activating the HPG axis, which can ultimately lead to suppressed gonadal function, particularly in males. This phenomenon, known as secondary hypogonadism due to obesity or obesity-induced hypogonadism, highlights the intricate interplay between metabolic and reproductive processes and underscores the importance of understanding external influences on the HPG axis for optimizing fertility and reproductive health.

However, despite these advancements, disparities in the availability of genetic testing, and the need for consensus on best practice management, underscore the ongoing challenges in optimizing care for populations affected by disorders of the HPG axis.

Future research priorities

Diagnostic challenges and the importance of early recognition

One of the foremost challenges in the field is the early recognition of clinical phenotypes associated with disorders of the HPG axis. The ability of general practitioners and paediatricians to identify these conditions in infancy and childhood is crucial for facilitating early diagnosis and management, as early intervention can significantly improve long-term health outcomes, psychological well-being, and fertility. Thus, dedicated research towards developing pragmatic investigative tools and pathways for these conditions is warranted.

Regarding adult patients, there is a need for stratification of patients experiencing infertility. Particularly in male infertility, where not all men can be treated with the same therapy, the selection must be based on careful clinical phenotyping, preferably in combination with genotyping for relevant variants modulating treatment response or specific factors measured in body fluids. Given the complexity of the regulation of the reproductive function, there is a paucity of controlled clinical trials that are testing different endocrine pathways, apart from androgens and gonadotrophins, and their response to treatment.

Mini-puberty: a critical window

Mini-puberty, a transient surge in the activity of the HPG axis during early infancy, represents a key period for growth and development, particularly in males. It is during this time that significant gonadal processes occur, impacting future fertility potential. Conditions such as CHH disrupt this critical period and may theoretically lead to several negative outcomes if left untreated. Questions regarding the timely identification of affected infants, the mimicking of mini-puberty physiology through hormone replacement, and the long-term outcomes on puberty, adult fertility and psychological well-being demand attention. The relevance of mini-puberty to female

fertility is much less clear. Also, the effects of exposure to EDCs during mini-puberty must be addressed. Such research could not only improve the QoL of individuals with disordered mini-puberty but also offer insights into the broader implications of hormonal deficiencies during developmental windows.

Unravelling genetic and environmental influences on pubertal timing

Puberty marks the transitional period resulting in the attainment of full adult reproductive capacity. Pubertal timing, influenced by genetic and environmental factors, poses a complex puzzle. While specific genetic variants are being identified, understanding their interactions with environmental factors like nutrition and EDCs remains elusive. Future research aims to clarify these interactions, identifying modifiable factors to mitigate adverse outcomes associated with early or delayed puberty.

Genetic diagnosis and precision medicine

High-throughput sequencing technologies have revolutionized genetic diagnosis for conditions such as CHH, POI, and primary male hypgonadism,[51] while whole genome association studies provided several novel genetic risk factors involved in these pathological conditions[52]; yet, a significant proportion of patients still lack a molecular diagnosis. Integrating genetic diagnostics with clinical management could greatly enhance patient outcomes, particularly in fertility and mental health. Precision medicine approaches are crucial, considering the diverse genetic forms of hypogonadism and the need for tailored therapies.

Advancing fertility preservation in CHH

Fertility preservation remains a critical concern for patients with CHH. Current treatments for CHH during adolescence and young adulthood, such as testosterone therapy and gonadotrophin replacement, offer some benefits, but also highlight the need for further research into more effective and physiologically congruent options. The potential for earlier diagnosis and intervention (eg, physiological replacement of mini-puberty), coupled with advancements in therapeutic strategies, underscores the importance of fertility as an outcome measure in research.

Exploring broader implications and emerging research areas

Beyond the direct impact on fertility and developmental outcomes, conditions affecting mini-puberty and puberty have broader implications for cognitive function, metabolic diseases and overall health. The interrelationship between reproductive and neurocognitive pathways, as demonstrated in studies involving Down's syndrome and GnRH replacement, presents an intriguing area for further investigation. Additionally, the effects of environmental factors, such as EDCs, and the impact of prematurity on developmental outcomes, warrant closer examination.

Moreover, there is an urgent need to collect prospective data on outcomes and side effects from replacement therapies in both infants and adolescents. This could be achieved by integrating data collection into international electronic registries, such as the existing SDM Registries and EuRRECa (the European Registries for Rare Endocrine Conditions). Prioritizing research in these areas will not only address current gaps in knowledge but also contribute to the advancement of science, environmental understanding, and societal well-being.

Anticipated impact of future research

Impact on disease management and healthcare

The trajectory of future research into HPG axis disorders suggests promising prospects for transformative impacts across multiple dimensions of healthcare, societal well-being, and environmental health. Targeted screening strategies for evaluating mini-puberty in male infants with bilateral maldescended testes or micropenis could significantly improve early detection and intervention strategies. This precision in early-life diagnosis and management has the potential to substantially alter treatment outcomes, particularly in fertility for males with CHH, by ensuring timely and physiologically appropriate hormonal replacement and timely gonadal development and maturation. Future research will unravel genetic, epigenetic, lifestyle and environmental factors responsible for the ongoing secular trend towards earlier pubertal onset. Identification of such risk factors, especially identification of the most deleterious EDCs, will enable future preventive initiatives. Appropriate diagnosis of late onset hypogonadism can be troublesome in the obese individual with low testosterone. Other emerging biomarkers like INSL3 may improve diagnostic evaluation.[53] Testosterone treatment to middle-aged or elderly men with low testosterone and signs of hypogonadism have been heavily debated. Age-specific ranges for testosterone levels still need to be defined in order to properly diagnose and treat late onset hypogonadism. In the recent TRAVERSE study, testosterone did not appear to cause cardiovascular disease[54] but was associated with higher incidence of atrial fibrillation, acute kidney injury, pulmonary embolism,[54] and fractures.[55] Thus, future studies are needed.

Revolutionizing fertility outcomes

Recent advances include the use of gonadotrophin replacement therapy during critical developmental windows, such as mini-puberty and puberty, to more closely mimic physiological development in males with CHH. This approach has demonstrated potential in improving long-term fertility in males with CHH but lacks robust evaluation and optimization.

Understanding novel endocrine signalling pathways and the clinical relevance of their defects has the potential to develop new evidence-based treatment options, with the ultimate advantage of a more efficient personalized therapy. This would increase the understanding of infertility in both sexes and ensure that women were less susceptible to being treated with assisted reproductive techniques when the male has impaired semen quality.

Improvement in non-reproductive health outcomes

Beyond its effects on fertility, hormonal replacement therapy during key developmental periods is anticipated to have a wide-ranging impact on general health outcomes. Specifically, the establishment of a causal link between pubertal timing and the risk of developing type 2 diabetes and cardiovascular diseases underscores the importance of correct pubertal management. Early intervention in cases of abnormal pubertal timing could potentially mitigate these risks, highlighting the need for comprehensive treatment plans that

consider both reproductive and non-reproductive health outcomes. Improved understanding and management of these links could revolutionize patient care, leading to better prevention strategies and health outcomes for individuals with disorders of pubertal timing.

Societal effects

Improving psychosocial and psychosexual development challenges faced by individuals with pubertal disorders can enhance social integration, relationship formation, and overall QoL, particularly during critical stages such as adolescence and young adulthood. By addressing these challenges through improved management and potential therapeutic interventions, future research stands to significantly enhance societal well-being and individual fulfillment.

Building supportive networks

The establishment of networks of centres in geographically diverse locations, for the equitable capture of patients and powering of studies, underscores the importance of collaborative research efforts. Such networks can facilitate comprehensive care and support for patients and their families, contributing to a more inclusive healthcare system. Additionally, the diverse origins and wide-ranging impact of disorders of reproductive function require broad collaboration between researchers across endocrinology, fertility, developmental paediatrics, metabolic health, genetics, and psychology.

Rationale for selected priorities

The prioritization of these research areas is driven by the need to address the comprehensive health challenges posed by HPG axis disorders. The potential to significantly improve patient outcomes, enhance QoL and reduce the healthcare and societal burdens associated with these conditions underscores the urgency and importance of these research directions.

In conclusion, the anticipated impact of future research into HPG axis disorders extends far beyond the immediate realm of healthcare, offering potential benefits that encompass societal well-being and environmental health. As we advance our understanding and treatment of these conditions, we move closer to a future where individuals with HPG axis disorders can lead fuller, healthier lives, supported by a more inclusive and sustainable healthcare system.

Female reproduction

Epidemiology, societal impact, research state of the art

During reproductive years, the hypothalamic–pituitary–ovarian (HPO) axis might be affected by various diseases, leading to the suppression of oestrogen secretion, development of chronic anovulation, and/or onset of hyperandrogenism. Hypo-oestrogenicity is often associated with the presence of hypothalamic amenorrhoea, which might be functional, organic, or drug-induced.[56] Functional hypothalamic amenorrhoea (FHA) affects approximately 1%-3% of the mature female population or, more specifically, 25%-35% of women with secondary amenorrhoea.[57]

Furthermore, hyperandrogenic conditions, such as polycystic ovary syndrome (PCOS) and non-classic forms of congenital adrenal hyperplasia (NCCAH), are common in adolescents and young women. They might be associated not only with chronic anovulation and reproductive failure but also with lifelong metabolic complications (eg, metabolic-associated fatty liver disease).[58-60] PCOS is the most prevalent cause of hyperandrogenism (70%) and the most common female endocrinopathy, affecting up to 13% of women of reproductive age.[61] Conversely, NCCAH occurs in between 1/200 and 1/1000 of the Caucasian population but is often misdiagnosed as PCOS, especially in women with long-lasting hirsutism.[62,63]

Diseases of the female reproductive system could harm both the individual and society, because of their high prevalence and long-term effects on metabolism, fertility, well-being, work capacity, morbidity, and mortality. Chronic hypo-oestrogenism associated with FHA might damage the skeletal system, cardiovascular system, nervous system, sexual function, and mental health.[57] Similarly, PCOS represents a major socioeconomic burden, considering its high prevalence and severe short- and long-term outcomes. Metabolic dysfunction is particularly common in women with PCOS who have excess weight and shows differences according to the PCOS phenotype.[64,65] Androgen excess may be partly responsible for the development of metabolic disorders in PCOS and, in turn, insulin resistance and metabolic status affect androgen synthesis and action. Moreover, women with PCOS are more susceptible to deterioration of oxidative stress and development of low-grade inflammation, subclinical cardiovascular disease and metabolic-associated fatty liver disease.[66,67] The usual treatment with combined oral contraceptives improves androgen excess and elicits regular menses but does not target the root cause and is off-label for adolescent patients.[68-70] Thus, the effects of different dietary and medication approaches (eg, insulin sensitizers and SPIOMET) should be investigated in various age groups.

Obesity and hyperandrogenism might be important factors predisposing to pregnancy complications. Gestational diabetes mellitus (GDM) is the most common medical condition in pregnant women,[71] and a diagnosis of GDM is linked to adverse maternal and offspring outcomes during pregnancy and in the future.[71] In mothers, GDM is the best predictor of type 2 diabetes, as women with previous GDM have a 7-fold-increased risk of the disease compared with women without GDM.[71] Other diseases are also more common after a diagnosis of GDM in pregnancy, including cardiovascular disease[72] and chronic kidney disease,[73] as well as psychiatric disorders.[74] The offspring of mothers with GDM have an increased risk of type 2 diabetes in adulthood,[75] and they also have more cognitive deficits compared to pregnancies without GDM.[75] Furthermore, there is an established link between GDM and obesity of offspring,[76] a path which is probably regulated through epigenetic mechanisms.[77] The prevalence of GDM varies greatly worldwide from 1% to above 30%,[78] depending on the characteristics of the population (ie, body mass index, age, ethnicity, PCOS status,[79] and genetics[71]).

An increase in blood pressure during pregnancy, within the pre-hypertension interval, doubles the risk of hypertension later in life.[80] Trajectories of maternal blood pressure might be associated with glucose levels in woman who are overweight and have GDM.[81]

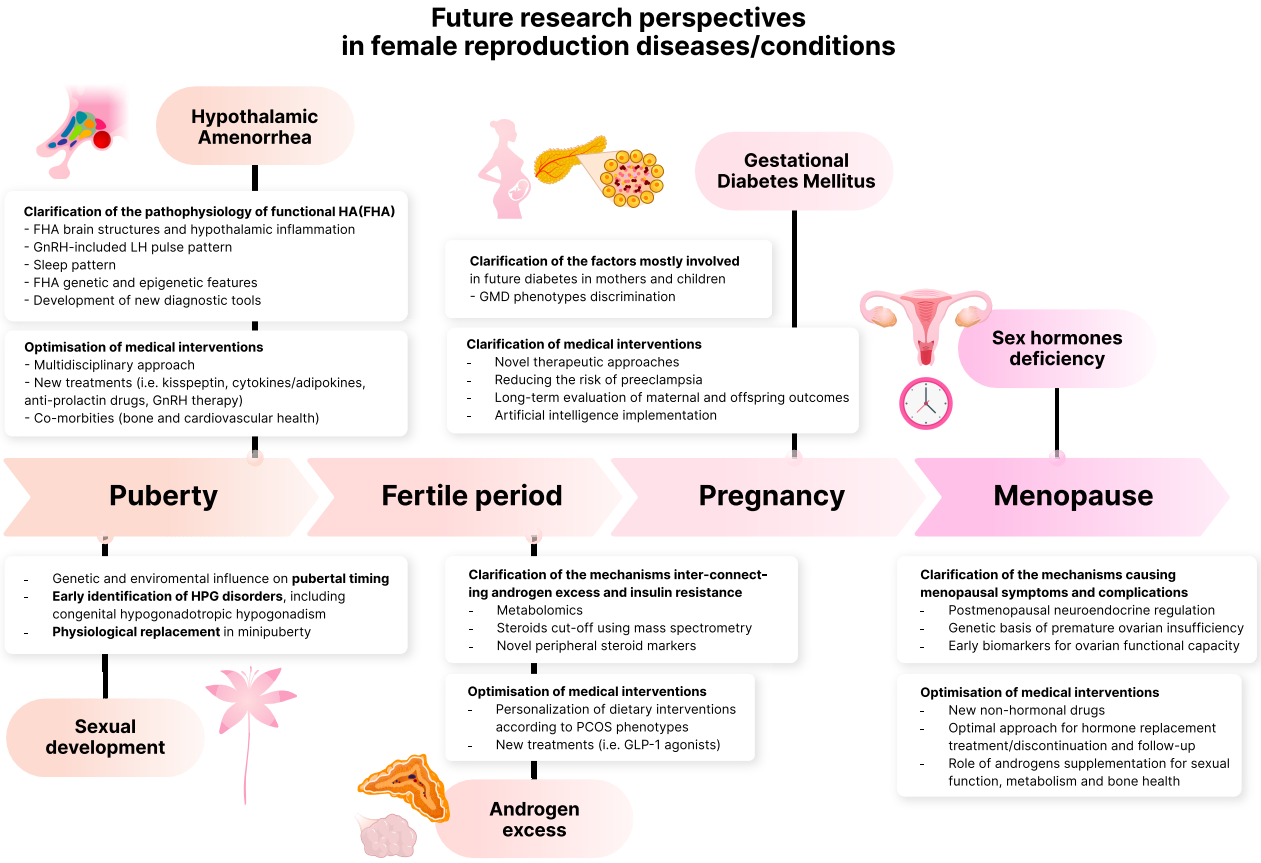

Figure 2. Future research perspectives in female reproduction diseases/conditions.

We treat pregnant women to reduce adverse obstetric outcomes as well as long-term health risks for mother and child, and the reduction of glucose levels is the main focus. However, minimizing the adverse outcomes of GDM must start early on, in combination with therapy during pregnancy and prevention of future disease in women and offspring with the highest risk.

In contrast to reproductive diseases, menopause is an inevitable change in every female individual and, on average, European women spend 30%-40% of their lifespan in menopause. However, the development of complications could lead to significant lost disability-adjusted life years, reaching 7.8 in patients with severe postmenopausal osteoporosis and prior bone fracture.[82] Recently recognized pathologic entities, such as menopause-related overweight and obesity, as well as metabolic derangements (ie, increased insulin resistance, hyperlipidaemia), necessitate extra effort in terms of understanding and management. Menopausal hormonal therapy has been recommended by multiple guidelines as a first-line option for vasomotor and vulvovaginal symptoms, osteoporosis prevention, and treatment of hypo-oestrogenism in hypogonadal women.[83-85] New therapies (eg, neurokinin-3 receptor antagonists) are also coming.[86,87] However, despite the abundance of therapeutic opportunities, the undertreatment of symptomatic women is common, even in the case of early surgically induced menopause and premature ovarian insufficiency (POI).[87-89] The undertreatment of peri- and postmenopausal women might be associated not only with pronounced individual clinical symptoms and complications but also with a substantial socioeconomic impact. Direct costs of the menopausal transition are related to medical consultations, laboratory analyses and over-the-counter and prescription drugs for multiple complaints, while indirect costs reflect decreased work productivity and motivation, prolonged sickness absence, and reduced work hours.[90-93]

Figures 2 to 4 provide visual representations of the content of this section.

Future research perspectives

Research priorities in hypothalamic amenorrhoea

In pathophysiology and diagnosis.

1. To study the central nervous system in women with FHA through functional magnetic resonance imaging, as well as possible correlates with metabolic and psychological parameters, and whether hypothalamic inflammation (activation of microglia) could be potentially linked to these associative processes.[94]
2. To study the genetic and epigenetic signatures of patients with FHA, markers predicting reversal of FHA (GnRH-induced LH pulse patterns and sleep patterns), as well as molecular imaging targeting opioid receptors, serotonin receptors, etc.
3. To further study co-existing FHA and PCOS in the same patients, and the role of GnRH pump therapy for short periods to unravel underlying PCOS phenotypes.
4. To establish diagnostic criteria for biomarkers of HPO axis function (dynamic tests of kisspeptin, GnRH, FSH,

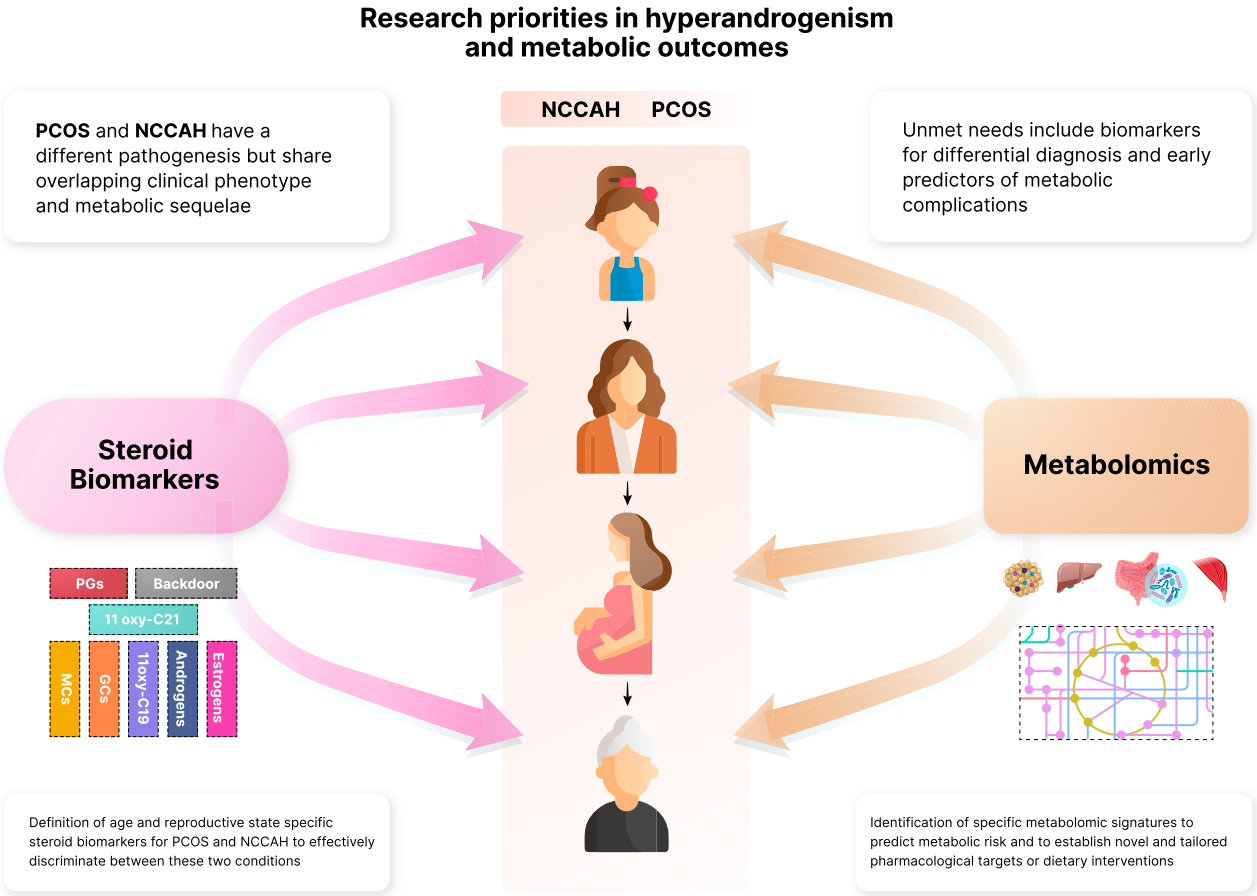

Figure 3. Research priorities in hyperandrogenism and metabolic outcomes.

LH, and oestradiol response), as well as markers of ovarian reserve for the study of fertility outcomes.

In clinical management.

1. To investigate optimal combinations of different nutritional, exercise, and psychological intervention modalities in managing FHA.
2. To study potential treatment modalities with molecules such as kisspeptin and various cytokines/adipokines for restoration of reproductive function in women with FHA,[95,96] proper oestrogenization (replacement therapy) in drug-induced hypothalamic amenorrhoea, the use of anti-prolactin treatments as well as fertility treatment strategies including GnRH pulsatile therapy and the relevance of in vitro fertilisation treatment in FHA.
3. To investigate the effect of hypo-oestrogenic conditions on peak bone mass and bone turnover markers in FHA,[97] long-term cardiovascular complications, hip fractures, and overall deleterious effects of FHA in society.

Research priorities in hyperandrogenism and metabolic outcomes

In pathophysiology, definition, and diagnosis.

1. To define early specific and sensitive biological and clinical biomarkers of insulin resistance at the level of liver and skeletal muscle, adipose tissue dysfunction, and association of specific metabolomic signatures encompassing alterations in ceramides, bile acids, short-chain fatty acids, branched-chain amino acids, and gut-derived metabolic pathways with defined PCOS phenotypes to predict the metabolic risk and to identify novel pharmacologic targets.
2. To set up large-scale studies using modern liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays for validating the steroid markers in different settings of PCOS and NCCAH. To identify and validate novel steroid markers analysing peripheral contribute to the steroid activation and inactivation (ie, in hypertrophic and dysfunctional adipose tissue). Determination of diagnostic cut-off levels for both ovarian and adrenal steroids.

In clinical management.

1. To perform randomized controlled trials to establish the specific short- and long-term impact of different dietary interventions as related to different PCOS phenotypes and metabolic comorbidities.
2. To perform randomized controlled trials to estimate and validate the short- and long-term effectiveness of different medications, either approved, such as the glucagon-like peptide-1 (GLP-1) agonists, or under development, such as low-dose SPIOMET, for specific subpopulations of patients with PCOS.

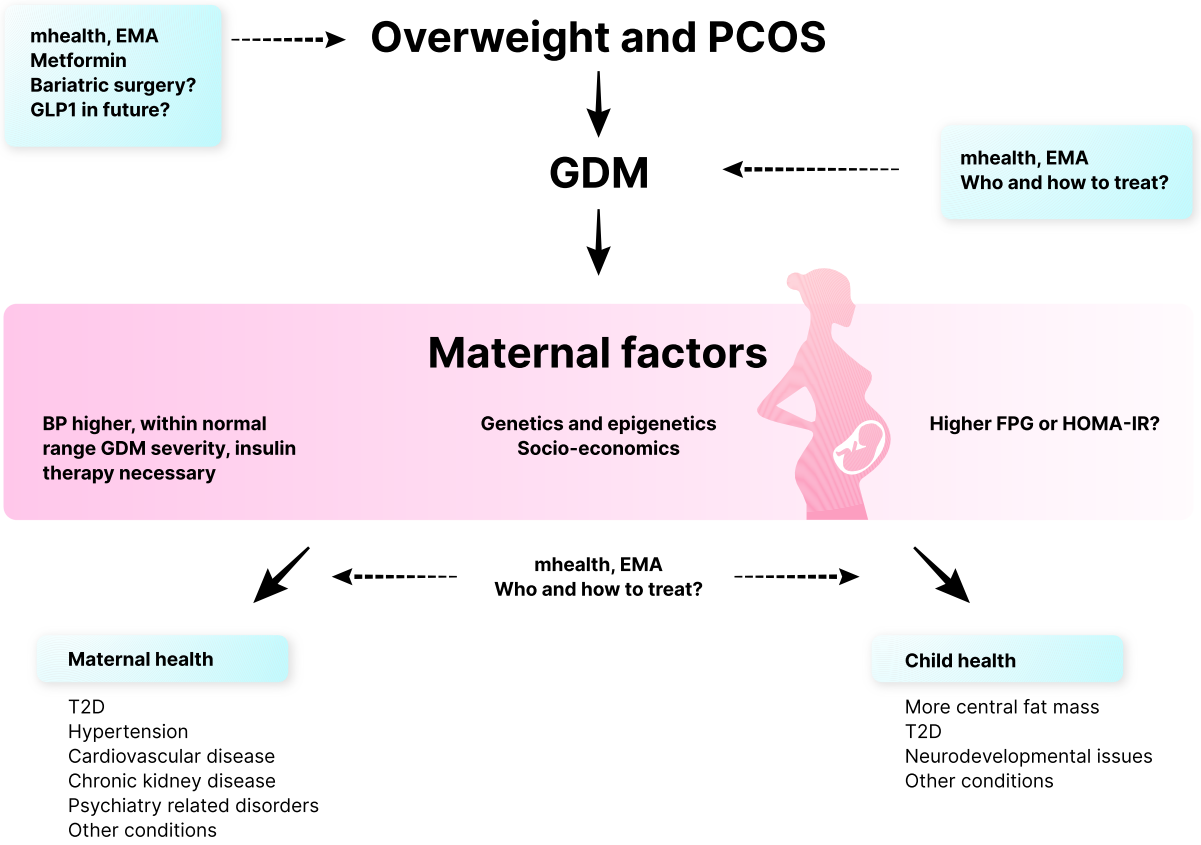

Figure 4. Future research perspectives in overweight and PCOS.

Research priorities in GDM, gestational, and offspring outcomes

1. To establish which maternal factors matter regarding risk of future diabetes in mothers and children after a pregnancy with GDM (ie, maternal age, pre-pregnancy body mass index, PCOS, severity of GDM,[73] and other pregnancy-related factors), as well as factors in offspring (ie, birth weight, abdominal circumference, and fat mass).
2. To investigate established and novel therapeutic approaches for GDM, including but not limited to metformin, sulfonylureas, insulin analogues, GLP-1 analogues, and related new drugs.[98]
3. To set up prospective studies to define the ideal normal cut-offs for systolic and diastolic blood pressure during every pregnancy trimester, based on ambulatory and continuous measurements adjusted for age and body mass index in women with GDM, to investigate optimal pharmacologic interventions, and to identify risk biomarkers for probable development of preeclampsia in women with GDM.
4. To assess the long-term effects on offspring related to glycaemic control through pregnancy, including obesity development and long-term neurological and psychological outcomes (neurodevelopment, evolution of IQ, autism, and attention-deficit hyperactivity disorder).
5. To apply cutting-edge methods, such as artificial intelligence (AI), to characterize distinct phenotypes of GDM and their relation to development of foetal life and evolution of offspring. To examine the role of mobile health (mHealth) in pregnancy affected by GDM and during follow-up of long-term outcomes, and to evaluate the role of ecological momentary assessment[99] in GDM and outcomes.

Research priorities in menopause and premature ovarian insufficiency

In pathophysiology and diagnosis.

1. To perform additional research on postmenopausal neuroendocrine regulation to develop new non-hormonal drug candidates beyond the serotonin and noradrenaline reuptake inhibitors, GABA modulators, and neurokinin receptor antagonists.[86]
2. To establish the more exact frequency of the POI worldwide and define reasons for the increased incidence of POI in some populations.[100,101]
3. To develop early biomarkers for ovarian functional capacity and implement screening programmes, which are crucial for fertility preservation in young women at risk, including those with premature ovarian follicular exhaustion due to genetic, immunologic and other causes,[102] or planning oncology treatments.[103,104]

In clinical management.

1. To perform clinical studies among healthy postmenopausal and women with POI, and patients with specific comorbidities to find the optimal dose, time for initiation, type of progestins and oestrogens, route of administration, and duration of menopausal hormonal therapy.[105-108] More

data are needed to determine the optimal approach for discontinuation and follow-up of menopausal hormonal therapy,[85] as well as the role of endogenous androgens and exogenous testosterone and dehydroepiandrosterone supplementation for sexual function, metabolism, and bone health in postmenopause.[109,110]
2. To carry out long-term studies, supported by AI, to target the efficacy and safety (eg, breast cancer risk) of non-hormonal therapies compared with hormonal drugs or placebo for vasomotor and other hypo-oestrogenic symptoms,[84,87,111] as well as their additional influence on the cardiovascular, neurological, and bone health of postmenopausal women and POI patients.[84,112]

Anticipated impact of future research

Future research focused on female hypo-oestrogenic and hyperandrogenic diseases would stimulate society to recognize these pathologic entities and their harmful impact on young women's lives. The establishment of units for management of FHA with other specialties (ie, psychiatrists and ergophysiologists) might help develop extensive epidemiological and physiopathological studies regarding the role of stress and excessive exercise in the development of the disease and, at the same time, provide multidisciplinary, organized care of these patients. Early diagnosis of FHA and promotion of aetiologic rather than symptomatic treatment approaches are also crucial.

So far, clinical studies have failed to identify clinical parameters that are able to differentiate between NCCAH and PCOS. The proposed research priorities could help in differentiating among the most common hyperandrogenic disorders, as well as improving clinical phenotyping for PCOS and NCCAH. Nonetheless, differential diagnosis, which relies on the laboratory, is necessary to establish the appropriate therapy. Steroid profiling can guide the opportunity to perform genetic tests to confirm the presence of 21-hydroxylase deficiency.[113] The broad implementation of LC-MS techniques will guide the diagnostic process and molecular testing through genome sequencing, or the application of microRNAs could confirm the diagnosis. From the therapeutic side, research outcomes could lead to targeted and tailored metabolic therapies for specific populations with PCOS. However, effectiveness, tolerability and safety are currently under investigation. Randomized controlled trials are needed of anti-obesity drugs, such as GLP-1 receptor agonists.

GDM is not a disease but a risk condition, which is an obstetric threat as well as a future maternal and offspring health risk. The steep increase in body mass index worldwide is an important factor for hyperglycaemia in pregnancy, but there are also correctable risk factors. Identifying and characterizing these factors may improve pre-gestational and obstetric healthcare, which may reduce the incidence of GDM or ameliorate its negative consequences for mother and child. Detailed knowledge regarding optimal therapy of hyperglycaemia and blood pressure, and prevention of preeclampsia, may have a substantial social and economic impact on society. Both mothers and offspring are resources for society and potentially contribute significantly.

Potential new therapies in pregnancy, like GLP-1 analogues, need to be examined in large European randomized controlled trials, as GLP-1 analogues have the potential to improve hyperglycaemia in pregnancy and future obesity and comorbidity in mother and child, and thus improve most adverse outcomes, but the safety of these drugs needs to be established. The use of mHealth and ecological momentary assessment may reach individuals who are unwilling to engage in standard follow-up programmes. Hopefully, we can also optimize their health outcomes (both GDM and related adverse outcomes) through information and treatment. Still, we need large clinical studies in Europe to establish the utility of these new tools.

Menopause is a natural physiological process. Nevertheless, the transition from reproductive to post-reproductive years is accompanied by health and social challenges for many women. Expanding knowledge about the pathophysiology and prevalence of menopausal symptoms as well as the postmenopausal disease burden may be beneficial for adequate counselling and support of aging women. The launch of interdisciplinary long-term pan-European clinical trials is paramount to exploring best practices regarding peri- and postmenopausal women, considering their risk profile and genetic and sociocultural background. Use of AI-assisted extensive dataset analyses could help develop individualized menopausal therapies and tools to alleviate personal symptoms, and reduce the impact of recently recognized pathologic entities. Timely diagnosis and use of new biomarkers and algorithms for early identification of women prone to developing POI is crucial for the implementation of targeted European programmes for the prevention and treatment of infertility.

In conclusion, the development of new diagnostic and therapeutic approaches for the management of reproductive disorders and menopausal transition, as well as the construction of a supportive work environment deprived of neglect and stigma, could improve the physical well-being, QoL and productivity of women, who will remain an essential part of the European workforce in the coming years.

Male reproduction, couple infertility and offspring health following medically assisted reproduction

Epidemiology, societal impact, research state of the art

Infertility concerns approximately 15% of couples worldwide, with a similar contribution from both genders. Both female and male infertility has a largely unexplored complex multifactorial origin. The 2 extreme infertile phenotypes are azoospermia (absence of spermatozoa in the ejaculate) in the male and POI in the female, both showing an incidence of 1% in the general population. Besides these extreme infertile phenotypes, many different infertile conditions are known (eg, altered semen parameters, impaired ovarian reserve, PCOS).

After a comprehensive diagnostic work-up, in about 50% of cases of male infertility the aetiology remains unknown; we refer to this condition as "idiopathic" infertility.[114] It implies that only limited numbers of infertile patients benefit from personalized rational treatment, while the majority will undergo medically assisted reproduction, mainly *in vitro* fertilization. These techniques present a significant challenge, with their relatively low success rates, forcing couples to undergo multiple treatment cycles. This imposes a heavy psychological and economic burden on the affected individuals and on the national health services. In azoospermic men, testicular sperm retrieval through testis biopsy (TESE) precedes *in vitro* fertilisation. TESE in an invasive procedure, with an average 50% success rate, and with no clinical/hormonal parameters able to predict its outcome.

A significant proportion of idiopathic male infertility cases are predicted to be due to as yet unidentified genetic anomalies (mainly a monogenic model) or to gene-environmental interaction (a polygenic model). While recent research efforts, based on massive parallel sequencing, have led to the discovery of several novel infertility-related genes, their clinical implications remain largely unexplored.[115,116] Some of the newly discovered genes are involved in DNA repair mechanisms, highlighting that mutations in these genes not only affect reproductive health, but also elevate the risk for cancer development. These findings support epidemiological studies, which have drawn connections between severe spermatogenic failure and higher risk of cancer development in azoospermic men.[117,118]

In parallel with the growing prevalence of couple infertility, the number of children conceived through medically assisted reproduction is steadily increasing, reaching 5%-10% of total newborns in many EU countries. In half of the cases, *in vitro* fertilization is performed in men with quantitative and/or qualitative impairment of spermatogenesis. Spermatozoa carrying genetic or epigenetic defects may lead to potential intergenerational inheritance of infertility, and even to somatic health defects in offspring.

There is a big knowledge gap concerning the health status of children conceived through medically assisted reproduction. An increased risk of adverse perinatal outcomes and congenital malformations in children conceived using *in vitro* fertilisation has been observed compared with children who were naturally conceived. It is still not clear whether this is due to the *in vitro* manipulation of gametes and embryos or, more likely, to the genetic/epigenetic quality of the gametes used or the techniques used for medically assisted reproduction (eg, *in vitro* culture). Data on the sperm parameters of children conceived using intracytoplasmic sperm injection (ICSI) are based on a few small cohorts and results are controversial.[119] Some studies have suggested poorer cardiovascular and metabolic profiles in children conceived with ICSI compared with those conceived naturally, but long-term data on large cohorts are missing, hence the long-term health consequences of medically assisted reproduction into adulthood remain unknown.

Fertility options for transgender and gender-diverse people (TGDP) are an emerging issue. Many TGDP remain involuntarily childless.[120] Those who (aim to) participate in existing fertility programmes or pursue medically assisted reproduction may experience multiple challenges.[121] Use of gender-affirming hormone therapies (GAHT) induces histopathological changes (testicular hyalinization, ovarian collagenization, and cyst formation) in the gonads of TGDP and impact gametogenesis.[122,123]

Like infertility, birth control is a major component of public health within the European Union. Despite the wide spectrum of contraceptive methods developed for females, the development of male contraceptive methods is lagging and, consequently, the burden of contraception falls primarily on women. Global surveys have reported that both women and men of different cultures, religions and social status support the development of reversible male contraceptives.[124,125] In recent decades, research has focused on the development of hormonal and non-hormonal methods. The androgen–progestin combinations[126] have provided highly encouraging results in terms of sperm suppression and safety. Most recently, the preliminary results of an ongoing phase 2b trial have suggested that the combination gel containing testosterone and segesterone acetate could provide rapid and profound sperm suppression and be highly acceptable to men.[127]

A number of promising novel testosterone molecules have also been developed and will be tested in combination with progestins in future clinical trials for male contraception. An alternative to hormonal contraceptives are those compounds that interrupt steps of male germ cell development required for fertility maintenance, including spermatogenesis, spermiation, and sperm motility. Several potential agents are in development; however, they may cause off-target effects that have hampered the development of some of these molecules. Therefore, each molecule will have to demonstrate not only effectiveness as a contraceptive but also safety and reversibility. The development of these molecules is still largely in the preclinical phase. Figure 5 provides a visual representation of the content of this section.

Future research priorities

Male factor infertility and the role of genetic factors involved in spermatogenic disturbances

1. Given the expected elevated number of genes involved in infertility, there is an urgent need for large-scale genomic studies, with the ultimate aim of providing precision molecular diagnosis and future successful targeted treatments.[115]
2. Standardized data collection and data sharing within large international consortia would substantially accelerate the translation of novel findings into clinical practice, both improving diagnostic capacity and allowing personalized treatments (eg, predicting TESE outcome and therefore avoiding invasive procedures or predicting fertilization failure avoiding ICSI procedure).
3. Integration of genomic data with other "omics" (transcriptome and proteomics) and epigenome sequencing data is necessary to advance our understanding of basic reproductive physiology and pathophysiology of testis function, and the risk of transmission of genetic/epigenetic alterations.
4. Comprehensive analysis of genetic variants in multiple genes (polygenic model) and their relationship with developmental, environmental, and lifestyle factors for preventive purposes would be valuable.
5. Multicentre efforts are needed to collect long-term follow-up data (especially morbidity and mortality) from large groups of genetically well-characterized infertile patients, in order to identify those genetic anomalies that also have implications for general health.

Health status of children born following in vitro fertilization

1. To improve the health status of children born after medically assisted reproduction, identification of the underlying cause of infertility is needed, with a specific focus on transmissible genetic defects. This implies a parallel improvement in the diagnostic capacity of genetic tests (see above). Reliable and easy-to-perform methodologies need to be developed to analyse the (epi)genomic integrity of spermatozoa of fathers undertaking ICSI.
2. A large, multicentre database is needed, containing standardized clinical and experimental information on the parents (aetiology of infertility, age, lifestyle, environmental exposure, sperm genome/epigenome integrity) and their children conceived using *in vitro* fertilization, including

Figure 5. Future research perspectives in male reproduction and couple infertility.

perinatal outcome (malformations), growth and development in childhood-puberty, reproductive (eg, semen parameters, reproductive success) and endocrine parameters, and general health status (with a specific focus on neurocognitive pathologies and cancer).

Fertility options for transgender and gender-diverse people

1. A dedicated research programme is needed in order to widen reproductive options for TGDP and to make existing programmes more accessible to them.
2. Fertility preservation strategies, such as follicle culture, cytoplasm rejuvenation, and *in vitro* maturation of immature cryopreserved stem cells need to be optimized in TGDP using GAHT. Gamete quality and embryo development in TGDP who have used GAHT need to be assessed.[128]
3. Dedicated research is needed to identify (personal, institutional, and societal) barriers to fertility preservation that TGDP may experience and to develop strategies to lower these barriers.
4. How to include the impact on fertility in the process of deciding to initiate medical treatments in transgender and gender-diverse adolescents and young adults is particularly challenging.[129,130] The development of tools to discuss the impact of their trajectory on fertility, assessing their level of understanding and capacity for informed consent, and the creation of age-adjusted decisional aids to support future-oriented reproductive decisions needs to be prioritised.
5. Long-term health outcomes and QoL of children born by use of preserved gametes and their transgender and gender-diverse parents need to be assessed.[131,132]

Male contraception

1. The objectives in this field are to achieve uniform sperm suppression in all men, a rapid suppression of spermatogenesis, and a rapid recovery of spermatogenesis after interruption of the treatment. For hormonal combinations that have provided the most promising results, larger efficacy trials need to be set up. Also, new molecules need to be developed, more potent in terms of sperm suppression but devoid of side effects. A few of these molecules are already being tested in small pilot studies.
2. Trials in men with subnormal sperm concentrations are also needed. Since hormonal male contraceptives will need to be available for all men, information on efficacy and reversibility in men with subnormal semen parameters are of fundamental importance.

Understanding the physiology of spermatogenesis and sperm function

Studies on basic physiological mechanisms of spermatogenesis and sperm function are urgently needed, using *in vitro* cellular models and testicular organoids. These studies will help to develop novel treatment options for patients with impaired spermatogenesis and optimal hormonal and non-hormonal male contraceptives.[133] The same models will be useful also in TGDP to mechanistically study eventual germ cell pool loss and damage induced by GAHT, along with the impact of clinical modifiers, such as age at start, duration, type, and dose of GAHT as stand-alone therapy or in combination with gonadal hormone-suppressing medications.

Anticipated impact of future research

Large collaborative genomic studies would allow a rapid advancement in the discovery of novel genetic factors and their translation into clinical practice. Integration of "omics" has the potential to provide a comprehensive evaluation of the fundamental mechanisms underpinning male fertility and acquire novel knowledge on testis physiology. It will have also a potential impact on the identification of those subjects who are predisposed to develop hypogonadism later in their life, allowing appropriate and timely intervention. The identification of genetic defects and their molecular consequences in the field of infertility would have a substantial impact on developing personalized treatment options, with an expected reduction in the psychological and economic burden on the concerned individuals and society. Understanding how specific genetic variations predispose to infertility and how they interact with environmental factors will enable early detection of individuals at risk and the implementation of targeted actions (personalized counselling on lifestyle factors, raising public awareness about environmental toxicants). Identifying genetic anomalies affecting not only spermatogenesis but also general health (especially predisposition to cancer) will allow timely actuation of preventive measures in the mutation carriers and their future descendants.

While registries report malformation rates in newborns, the long-term consequences of *in vitro* fertilization are largely unexplored. Comprehensive large-scale, prospective, well-controlled, follow-up studies will allow a realistic prediction of the consequences of different aetiologies of infertility on the health of children conceived using medically assisted reproduction, with adjustment for parental confounders. It is expected that genetic/epigenetic alterations causing infertility may also harm somatic health in both the father and his children. If such a correlation is demonstrated, timely intervention and prevention would represent one of the major benefits of these studies, at both the individual and the society level. These studies could identify specific individual lifestyle and environmental factors interfering with the sperm epigenome, and influence the health outcome of children conceived through medically assisted reproduction. Improving our knowledge about this relationship would allow preventive measures to be taken prior to medically assisted reproduction, with an expected higher probability of a healthy child.

The development of new male contraceptives could help bridge the gender gap in contraception. It will help achieve socially, ethically, and economically important goals such as re-establishing gender equity within a couple and providing men with the opportunity to contribute equally to family planning. It will help achieve the still unmet goal of preventing unwanted pregnancies and slow down population growth in overpopulated regions and its burden on the environment.

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Authors' contributions

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