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Editorial

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The present special issue of *Metabolism* is dedicated to Reproductive Endocrinology. The endocrinology of the gonads and the placenta constitutes the most rapidly evolving topic in Endocrinology and Metabolism, with many practical applications, especially in the field of human reproduction. *Metabolism* during the last two years has repeatedly published key papers in relevant topics, such as polycystic ovary syndrome (PCOS) [1–5], vitamin D deficiency [6–10], and pregnancy [11,12]. Nevertheless, a collection of papers that highlight the current diagnostic and therapeutic trends in Reproductive Endocrinology has not been attempted until today.

When C.M. Mantzoros, editor-in-chief of *Metabolism*, had the idea of this special issue, the editorial team had to confront two main concerns. The first was the selection of the topics. We decided to include all main fields of Reproductive Endocrinology, namely "Reproductive Physiology", "Female Reproductive Endocrinology", "Male Reproductive Endocrinology", "Endocrinology of pregnancy" and "Pediatric Reproductive Endocrinology", in an attempt to cover every possible aspect (basic, translational, clinical) and age (embryo, child, adolescent, adult and aging). We had also to take under consideration different tissues (testis, ovary, adipose tissue, placenta), special situations (pregnancy), prevalent diseases (PCOS, hypovitaminosis D, thyroid disease, metabolic syndrome, hypogonadism, hypertension), special procedures (ovarian stimulation) and different treatments (testosterone replacement), not ignoring environmental issues (endocrine disruptors) and transitional ages (Kallmann, Klinefelter, and Turner syndromes during adolescent transition).

The second was the selection of the authors. We find it exciting to form "mentor - mentee" pairs, where senior scientists with overwhelming contribution to their special fields of research would join forces with younger colleagues, who already have proved their research interest. The main idea was this *Metabolism* special issue to have an educational aspect for the younger colleagues, supporting the development of their career.

Having these two main principles in mind, we organized the contents in such a way that every main field of Reproductive Endocrinology is represented in this *Metabolism* special issue with two or three papers for a total of thirteen review articles.

In **Reproductive Physiology**, A. Kaprara and I. Huhtaniemi discuss "The hypothalamus-pituitary-gonad axis", especially the factors that influence the migration of GnRH neurons in all species, narrating "tales of mice and men" [13]. Several GnRHs have been found from protochondrates to vertebrates, the pulsatile manner of GnRH secretion being essential for optimal gonadotropin secretion. H. Mathew, V.D. Castracane and C.M. Mantzoros explore the complex association between "Adipose tissue and reproduction" [14]. Adipose tissue is an endocrine secretory, which influence reproductive health. Leptin, adiponectin and other adipokines have physiologic roles in reproductive health, as well as involvement in conditions such as hypothalamic amenorrhea, anorexia nervosa, lipodystrophy syndromes, PCOS and reproductive malignancies. The evolving understanding of the relationship of adipose tissue and reproduction suggest potential avenues for therapeutic agents.

In **Female Reproductive Endocrinology**, P. Anagnostis, B.C. Tarlatzis and R.P. Kauffman in their review on "PCOS: long-term metabolic consequences" [15] remind us that polycystic ovary syndrome (PCOS) is associated with a plethora of cardiometabolic consequences, such as glucose intolerance and diabetes mellitus, atherogenic dyslipidemia, systemic inflammation, non-alcoholic fatty liver disease, hypertension and coagulation disorders. These metabolic consequences lead to a potential increased risk for subclinical atherosclerosis. In addition, G. Mintziori and D.G. Goulis review the evidence on "thyroid function during IVF/ICSI procedures" [16], discussing the association of subclinical hypothyroidism and thyroid autoimmunity to adverse reproductive outcomes after IVF, and suggesting universal screening for thyroid function and autoimmunity before IVF.

In **Male Reproductive Endocrinology**, Ch. Dimopoulou, D.G. Goulis, G. Corona and M. Maggi, critically appraise "The complex association between metabolic syndrome and male hypogonadism" [17] as there is accumulating evidence from animal and human studies suggesting that metabolic syndrome is involved in the pathogenesis of hypogonadism in males as well as the other way around. Ch. Tsametis and A. Isidori focus on "Testosterone Replacement Therapy", trying to answer the question "for whom, when and how?" [18]. They clarify that testosterone replacement therapy should only be offered to men with documented androgen deficiency and that men with late-onset hypogonadism should be treated on an individualized basis. Finally, S. Lymperi and A. Giwercman discuss that, despite extensive research on endocrine disruptors (EDs) the last few decades, the epidemiological data on "Endocrine disruptors and testicular function" [19] are still controversial. EDs are capable of transgenerational inheritance, suggesting that their effects may be manifested in next generations. Furthermore, prenatal exposure to EDs seems to be deleterious to the male reproductive system and increased awareness of pregnant women is necessary.

In **Endocrinology and Metabolism of Pregnancy**, E. Kintiraki and D. G. Goulis present "multi-disciplinary treatment approaches for Gestational Diabetes Mellitus" [20], the most common metabolic disease of pregnancy. They provide evidence that multi-disciplinary management,

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consisting of diet, physical exercise and pharmacological agents, constitutes the most effective therapeutic approach. Ch. Antza, V. Kotsis and R. Cifkova propose that ambulatory blood pressure monitoring is a useful tool to diagnose "Hypertensive complications of pregnancy" [21] compared to office blood pressure measurements. Biomarkers, carotid artery intima media thickness, pulse wave velocity, augmentation index and arterial wall tension are new tools to predict preeclampsia, whereas antihypertensive medication should be used only when diagnosis is certain to prevent small-for-gestational age infants. Concluding the discussion on very prevalent pregnancy complications, S. Karras, C.L. Wagner and V.D. Castracane wonder whether "Vitamin D deficiency constitute a pandemia or an epi-phenomenon" [22]. Vitamin D has been considered as a significant regulator of both innate and adaptive immunity. It manifests striking differences during pregnancy as compared with the non-pregnant state to provide optimal intrauterine development of the fetus and systemic and local maternal tolerance to paternal and fetal alloantigens. Hypovitaminosis D has been associated with pregnancy-related disorders.

Finally, in **Pediatric Reproductive Endocrinology**, M. Stamou and N. Georgopoulos present the archetypical disease of hypogonadotropic hypogonadism, the Kallmann syndrome, in an attempt to describe its "phenotype and genotype" [23]. Isolated GnRH deficiency (IGD) and normosmic idiopathic hypogonadotropic hypogonadism (nIHH) are characterized by a wide genotypic spectrum, with more than 35 genes implicated in their pathophysiology. Those genes act in neurodevelopmental and neuroendocrine pathways of GnRH development, rendering genetic screening in patients with IGD a crucial diagnostic procedure. G. Kanakis and E. Nieschlag review the archetypical disease of hypergonadotropic hypogonadism, the Klinefelter syndrome, suggesting that it is "more than an infertility syndrome" [24]. Klinefelter syndrome is the most frequent chromosome disorder in males, with as many as 70% of cases may to remain undiagnosed throughout life. The patients present several comorbidities that increase morbidity and mortality by 40%, such as verbal processing, attention and social skill deficits that may impair socioeconomic status. In the last review, I. Kosteria and Ch. Kanaka-Gantenbein expand on Turner syndrome, specifically on the crucial period of "transition from childhood to adolescence" [25]. A structured, personalized transition plan is crucial in girls with Turner syndrome, including growth, sex hormone replacement and cardiovascular morbidity. Although new fertility options are provided, careful planning and follow-up of pregnancies is essential.

We do hope that this special issue of *Metabolism* constitutes an updated, comprehensive and clinically-oriented collection of review articles in the field of Reproductive Endocrinology that will remain on your virtual (electronic version) or actual (printed version) desktop for a long time.

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