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REVIEW

The model of "genetic compartments": a new insight into reproductive genetics

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Abstract

Currently, we are witnessing revolutionary advances in the analytical power of genetic tools. An enormous quantity of data can now be obtained from samples; however, the translation of genetic findings to the general status of individuals, or their offspring, should be done with caution. This is especially relevant in the reproductive context, where the concepts of "transmission" and "inheritability" of a trait are crucial. Against this background, we offer new insight based on a systemic view of genetic constitution in the compartmentalized organism, that is, the human body. This model considers the coexistence of "different" genomes in the same individual and the repercussion of this on reproductive efficacy and offspring. Herein, we review the major differences between somatic, germinal, embryonic, and fetal/placental genomes and their contribution to the next generation and its reproductive efficacy. The major novelty of our approach is the holistic interaction between microsystems within a macrosystem (i.e., the reproductive system). This panoramic model allows us to sketch the future implications of genetic results in function of the origin (compartment) of the sample: peripheral blood or other somatic tissues, gametes, zygotes, preimplantation embryos, fetus, or placenta. We believe this perspective can be of great use in the context of reproductive genetic counseling.

Keywords Reproductive genetics · Offspring · Systems biology · Inheritance · Genetic · Compartments

Background

Reproductive genetics studies the relationship between genotype and reproductive capacity (ESHRE definition: https://www.eshre.eu/Specialty-groups/Special-Interest-Groups/Reproductive-Genetics.aspx). This discipline analyzes how genetic material is transmitted, the effect of genetic abnormalities on reproductive efficacy, the genetic "normality" of the offspring, and the consequences of epigenetic modifications for reproductive function.

Human reproductive incompetence is referred to as "infertility" or "subfertility." This is a trait of overlapping etiological causes and heterogeneous phenotypic presentation. Anatomic dysmorphisms, functional disorders, hormonal disbalance embryo lethality, and among other factors can coexist, masking the biological basis of the reproductive inefficacy in question. Genetic dysfunctions could also underlie these failures. Moreover, confounding factors related to the nature of genetic studies must also be taken into account. Aspects such as representativity of the results, the biological pathways analyzed, and the inferential, predictive, or diagnostic power of obtained data must all be taken into account.

From the genetic point of view of reproduction, we can distinguish two main typologies of patients using reproductive services and counseling. On the one hand, there are asymptomatic patients with an elevated risk of producing genetically abnormal embryos; these include women of advanced age, men with sperm chromosome alterations, and couples with balanced chromosomal rearrangements or single-gene disorders. Such asymptomatic cases can be represented in functional fertile and infertile couples. On the other hand, we treat infertile patients whose infertility is caused by a genetic disorder, i.e., azoospermic men carrying pathogenic variants in the *CFTR* gene, causing congenital absence of the vas deferens, or women with ovarian insufficiency caused by

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pathogenic expansion of the *FRM1* gene. The etiology of the reduced fertility in each group is completely different.

The aim of this paper is to introduce a new approach so as to better understand the genetic etiology of reproductive dysfunctions. In our view, the genetic defect triggering the "infertile trait" can be located in any of the different "genetic compartments" that make up the reproductive system. This approach is inspired the general systems theory, which was first expounded by Ludwig von Bertalanffy in the 1960s to explain organismic systems [1]. This pioneering systemic view introduced concepts such as "open systems," "organismic interactionism," "dynamic equilibrium," and the "steady state". Using this framework, we aim to define four interacting genetic compartments in the reproductive system: the somatic, germinal, embryonic, and fetus-placental compartments. We want to point out that, conceptually, each compartment has its "own" genetics that play their role in an open system of interactions (Fig. 1). Concurrently, a virtual fifth compartment represents the epigenesis of the human genome (epigenetics), understood in terms of interactions that rise above the level of the gene as a sequence of DNA (see review [2]). Epigenesis is permanently and transversal, and is crucial to specific compartments, as we will discuss further later on. Below, we describe the particularities of each "genetic compartment."

Somatic compartment

Usually, the contents of the "somatic" genome are deduced from the DNA extracted from peripheral blood (lymphocytes), saliva, the oral epithelium (buccal cells). or other tissues. The results of molecular or cytogenetic analysis provide extremely valuable information concerning the somatic genetic status, which represents the "inferred" genetic condition of the individual. Data obtained from somatic tissues permit us: (i) to confirm a clinical diagnosis (phenotype); (ii) to determine the carrier status of an individual with genic or chromosomal disorders; or (iii) to establish a predisposition or susceptibility to develop a certain trait. This information allows us to anticipate genetic risk in the first group of patients mentioned above, and to confirm the genetic causes of a specific phenotype in the second group. In both cases, this inferred information can be used to drive reproductive decisions.

However, it is important to note that defining an individual's genetic status based on the somatic genetic compartment, and extending it to future offspring, should be done with caution. Critical aspects such as genetic heterogeneity, genetic variability, or reduced penetrance should be taken into account in order to infer the inheritability of a trait in the reproductive context [3]. For example, there are individuals without clinical manifestations of severe Mendelian childhood-onset diseases, despite harboring completely penetrant pathogenic variants [4]. It is likely that genomic interactions which are not fully understood (or are even totally unknown) could play a role in these "resilient" individuals, thus conferring a protective genetic effect. Several mechanisms have been proposed in order to explain this resilience: the cis/trans conformation of the variants [5, 6], somatic mosaicism [7], genetic modifiers [8], or enhancers and drivers [9] could mediate the theoretical inheritability of a feature. Indeed, cryptic gene regulation most probably underlies the fertile capacity of our species.

Germinal compartment

In terms of germinal genetics, human germ cells (spermatozoa and oocytes) are radically different from each other, and the germinal compartment is very different from the rest of the genetic compartments. Its origin, timing, morphology, and contribution to early developmental stages are distinctive. Both type of gem cells come from the same primordial germ cells (PGCs), which migrate and colonize the rudimentary gonad, and differentiate into male or female stem germ cells (spermatogonium or oogonium, respectively) during organogenesis, very early on during fetal development.

No obvious sexual differences have been observed during the initial specification and proliferation phases. However, male and female germ cells assume distinct paths of differentiation during embryogenesis. Thus, meiosis in humans can be considered a gamete-specific process, and so we prefer to refer to "gametogenesis" sensu stricto: spermatogenesis and oogenesis.

Male gametogenesis

Male gametogenesis is a continuous and epithelium-dependent (Sertoli cells) process that culminates in motile and mature cells with a specific genetic composition. Genetically, the sperm genome is composed of a highly twisted, packed and DNA with drastically reduced histone, with fragile sites affected by single- or double-strand ruptures, most probably caused by the protamination process. In addition, the testis plays a homeostatic role by eliminating defective cells and maintaining the right Sertoli to germ cell ratio. This balancing mechanism implies apoptotic-like subroutines that cause DNA damage and aneuploidies (reviewed in [10]). In addition, reproductive function in men is a highly coordinated process involving many genetically regulated pathways: development of the urogenital system; differentiation of the spermatogonial stem cells; formation of the spermatid acrosome and flagellum; acquisition of motility and the chemotactic response to oocyte-corona-cumulus complex arrival; chemical, enzymatic and mechanical equipment to penetrate the oocyte membranes and eventually induce activation of genomes (see embryonic compartment). In parallel, the endocrine regulation of gonadal function and the physiological

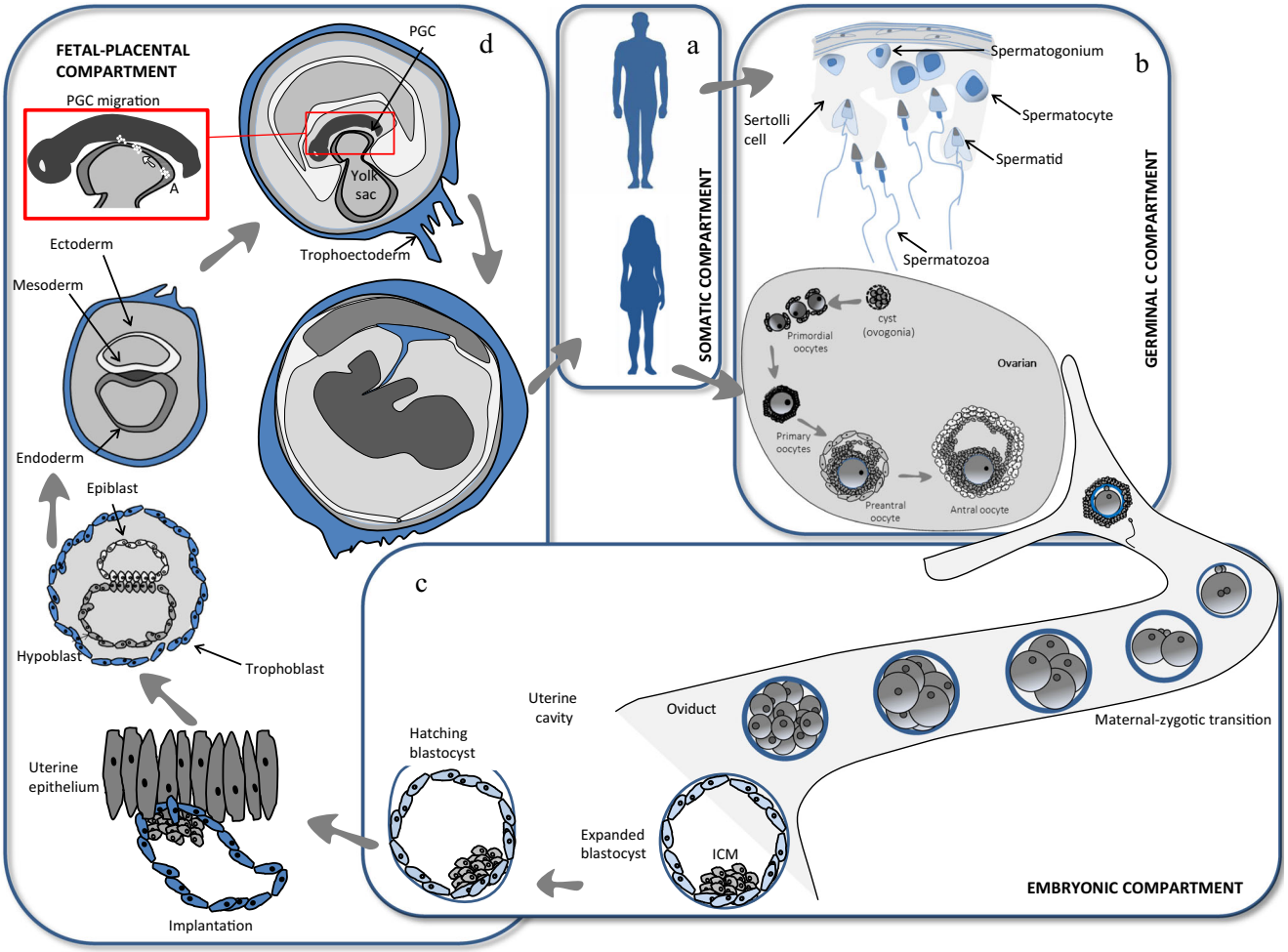

Fig. 1 The picture represents a schematic view of the proposed model of genetic compartments. A: The somatic compartment corresponds to male and female somatic genomes, represented by DNA from organs, tissues, blood, and other organic fluids. This compartment exemplifies the constitutional genetics of an individual. B: The germinal compartment includes haploid genomes from gametes with very specific genomic particularities. A summary of spermatogenesis and oogenesis is provided. The intermediary steps of gamete-specific meiotic division are highlighted. C: The embryonic compartment's box represents a schematic view of preimplantation embryo development. The resumption of oocyte meiosis, fertilization, and maternal-to-zygotic transition are key steps that trigger the activation of the embryo genome, which regulates the following phases that culminate in uterine epithelium invasion and generation of the next compartment. D: The fetal/placental compartment contains the genomes of the offspring. Fetal (the future somatic genome of the new individual), maternal, placental, and gametic genomes coexist in this compartment. The main steps of early fetal development, placentation and primordial germ cell migration, and differentiation are represented

mechanisms of erection and ejaculation are also genetically directed (reviewed in [11]).

On the other hand, sperm cells undergo a paradoxical transformation; surprisingly, it is the only human cell reported to exhibit longer telomeres in older age, which translate into longer leukocyte telomeres in the offspring [12]. This is a poorly understood phenomenon probably caused by biological mechanisms operating in the germinal tissue during a male's lifetime. It increases the differences between the male germ compartment and the rest of the compartments, conferring exclusive characteristics to the male germ genome. Finally, current hypotheses introduce new ideas concerning the transgenerational role of male genome. Nowadays, several groups are focusing their efforts on the study of the biological function of stable sperm RNA transcripts which can contribute to very early embryogenesis and regulation of embryo gene expression [13, 14]. These potential epigenetic markers illustrate the interaction between genetic compartments following the systemic view. Thus, the genetic information revealed by sperm analysis allows a prognosis to be made concerning male reproductive capacity. It is especially valuable for inferring gamete DNA injury, zygotic activation, and preimplantation embryo viability.

Female gametogenesis

On the female side, oogenesis is a discontinuous process whose phases are separated by long intervals (years) and

which spans from the primary oocyte to the competent mature oocyte. Oogenesis includes initial germinal epithelium–dependent steps and final stages occurring out of the ovary. The diplotene arrest of oogenesis is practically simultaneous in the primordial follicles of all primary oocytes during fetal stages. However, the resumption of oogenesis and germ cell division and maturation are separate processes occurring one at a time and producing a single non-motile immature cell. The oocyte undergoes nuclear and cytoplasmic maturation prior to achieving developmental competence. Nuclear maturation implies a chromatin remodeling and a new arrest in metaphase II, during which it waits to be stimulated by fertilizing spermatozoa.

The oocyte's cytoplasmic maturation relies on the regulation of many transcripts generated during the previous stages of oogenesis (particularly during the early oocyte growth phase), the silencing of new transcriptional activity, and a selective mRNA degradation (review in [15]). The oocyte's cytoplasmic competence enables it to further decondensed and remodel the sperm's head (exchange of protamine by maternal histones) to orchestrate a passive paternal DNA demethylation and to form a new pronuclear paternal envelop. The oocyte's maturation continues with a reductive division by an unequal diakinesis, rendering a DNA-containing microstructure, i.e., the first polar body. Oogenesis eventually culminates in the development of a mature metaphase II oocyte, containing all the machinery and molecules necessary to direct the subsequent post-fertilization steps.

The contribution of the female germ compartment to further developmental stages is crucial. In vertebrates, critical phases are orchestrated by the molecular products of the oocyte. Key processes, such as fertilization, maternal and paternal genome fusion and remodeling, and first mitosis control, depend on the molecules, mRNA and proteins accumulated inside the oocyte during the prolonged prophase I arrest, and oocyte maturation phases. These "maternal molecules" exercise their function prior to activation of the complete embryo genome (eight-cell stage, in humans) and are codified by oocyte genes named "maternal effect genes," which were first described in mammals at the beginning of this century (reviewed in [16]). When preimplantation embryos activate their own genome (detailed in the "Embryonic Compartment" section) these genes stop exercising their function. Most of these maternal genes make a unique contribution in these initial phases of development. They do not participate in later processes, but are responsible for regulating early embryogenesis in the next generation. Gaining knowledge about these genes is radically important to our understanding of complex adult processes, such as species' preservation, successful fertilization, and correct preimplantation embryo development; in other words, reproductive competence and fertility. The special characteristics of oogenesis make it environment- and age-sensitive process. The "maternal age" effect conditions the normality of the oocyte genome and can potentially have deleterious effects on the next generation.

On the other hand, recombination represents an exclusive and essential phenomenon occurring in the germinal genetic compartment. Both male and female germ genomes recombine in this compartment, rendering a new and unique genome. Recombination creates new combinations of alleles with more or less biological success, conferring genetic variability along the way. Aberrant recombination, with little or excessive rates of chromosomal exchanges, can result in aneuploidy or chromosomal rearrangements, many of which have been associated with diseases or low reproductive success [17]. Interestingly, the rate of chromosomal crossing-over varies drastically between male and female germ compartments. There are fewer crossovers and genetic variations among individuals in the case of males. On the contrary, an enormous variation has been described in the number of crossovers among oocytes from the same female [18]; too many or too few can be discarded early on in the perinatal stages, during oocyte attrition [19]. However, the arrest of oogenesis occurs after crossovers and is completed once fertilization occurs, several years later. Aggressions to the biomechanical meiotic machinery during this interval can determine reproductive competence. Genetic studies of the female germ compartment are scarce, and they are not used routinely in clinical practice. The great transformations of the maternal genome that can impact on female fertility, or the offspring, take place in the germinal compartment. However, genetic tests of the female germ compartment are not usually performed in clinical practice due their invasive nature, and it is not always possible to draw conclusions about female reproductive capacity simply by studying the somatic compartment.

Embryonic compartment

The embryo genome differs in some aspects from the germinal and somatic genome. The maternal-to-zygotic transition is regulated by maternal effect genes, as explained above. The genetic information responsible for early development is transcribed and stored as RNA or protein in the ooplasm during oogenesis. The synthesis of mRNA is absent in the final stages of oocyte maturation until the first mitotic divisions take place. Thus, the genetic regulation of maternal-zygotic transition occurs at the post-transcriptional level. This fact is crucial to understanding the embryonic compartment and the generation of a "novel" genome.

Sperm-oocyte fusion results in the unloading of sperm chromatin and centriole into the ooplasm. This fusion triggers the resumption and completion of oocyte meiosis and programmed zygotic genome activation (ZGA, also referred to as "minor" embryonic genome activation), which occurs during the two-cell stage in humans [20]. Several post-

transcriptional mechanisms in accumulated maternal products are responsible for male genome processing, the elimination of maternal RNAs and proteins, and the activation of the embryo genome [21–23]. Subsequent events are known globally as "activation" of the zygote genome, which acquires totipotent capacity (reviewed in [24–26]). The first epigenetic modifications, known as "genome reprogramming," occur immediately after the encounter between maternal and paternal genomes: modification of DNA-linked proteins, methylation, acetylation, ubiquitination and phosphorylation [27]. The male genome is decondensed, deprotaminated, and repacked with maternal histones. Paternal DNA is destabilized, restructured, and repaired during this replacement process, which is regulated by maternal genes (reviewed in [16, 28]). The paternal chromatin undergoes an active, rapid, and drastic DNA demethylation over the course of the prolonged G1-phase of the first cell cycle, prior to the first DNA replication. All these modifications result in a "new" paternal genome located in the embryonic compartment. In murine models, it has been described that the maternal chromatin exposed in the same cytoplasm is resistant to active demethylation and remains highly methylated [29–31].

Therefore, both gametes regulate embryo development in different ways; firstly by activating and modulating oocyte transcription over the first cleavage stages that follow fertilization and then by triggering full embryonic genome activation, which occurs during the four-to-eight cell stage [20, 32, 33], or on day 3 of development [34, 35], producing the largest onset of de novo gene expression. In addition, the correct developmental pattern of gene expression is imperative for successful embryo development (effective activation of the zygotic and embryonic genome).

The embryonic genome governs the next developmental phases. The synthesis of embryonic proteins begins slowly and the maternal products (mRNA and proteins) are quickly degraded. The embryonic transcripts now take control of development. The complete activation of the embryonic genome is conditioned by transcription factors (proteins regulating the transcription of specific genes). After remodeling, the embryo genome is accessible to activation by these transcription factors. Some of these key factors are codified again by maternal-effect genes. It is important to remark that some of these genes play a key role during oogenesis, and their mRNA continues to be present in two-cell stage mammal embryos. This persistent (residual) maternal function during early preimplantation phases, after zygotic genome activation, plays a role alongside de novo embryo products and is crucial for normal development and achievement of the blastocyst stage [36]. All these phenomena conclude in a new diploid genome in undifferentiated cells which divide by means of mitosis.

One of the particularities of the embryonic compartment is the kinetics of cell cycle. Whereas the first cell cycle is extended due to remodeling and reprogramming of both genomes, the G1 phase of the human embryonic cell cycle—during which the first cleavage divisions take place—is extremely short [24, 37]. The shortening of the G1 phase has been related to the absence of appropriate genetic checkpoints during early stages [38] and aberrant chromosomal segregation. High rates of chromosomal instability in human preimplantation embryos [39] and elevated levels of chromosomal missegregation have been reported. Aneuploidy is one of the main causes of cell death during pre- and post-implantation stages, but not all abnormal cells die or are detained, with high rates of whole chromosome and segmental aneuploidy having been detected during preimplantation embryo development [40]. Aneuploid cells are involved in the growth of the embryo, and turn into mosaic embryos and blastocyst [41, 42]. A depletion of aneuploid lineages has been described during early embryo development [43]. However, an elevated grade of "abnormal" chromosomal segregation is compatible with embryo development until the blastocyst stage. In fact, a trophectoderm-confined aneuploidy has been described, and the representativity of analytical results with trophectoderm samples has been questioned [44, 45]. This aspect is crucial to preimplantation genetic testing for aneuploidies. In this sense, whereas whole-chromosome aneuploidy seems to be related to disturbances in the segregation machinery during meiosis—clearly related to maternal age [46, 47]—mosaicism can probably be explained by abnormal segregation of whole chromosomes, which is related to anaphase lag, mitotic non-disjunction, accelerated diakinesis, endoreplication, cell fusion, or multipolar division [47–50]. Thus, there is an apparently paradoxical grade of what we have named "mitotic permissiveness" towards aneuploidy in these very early stages of human development, which confers the embryo genome radically different features to those of the somatic genome.

Fetal/placental compartment

The placenta is the first complex organ formed in eutherian mammals. Evolutionarily, viviparity has permitted the development of an intricate maternal-fetal relationship. The placenta mediates an endocrine and metabolic control of the fetus and transmission of environmental signals, nutrition, immunological components, and gas exchange between mother and fetus. In this sense, it is functionally difficult to dissociate fetal from the placental environment. However, from the genetic point of view, a "parent-offspring conflict" theory has been proposed (reviewed in [51]). In short, fetal trophoblast and maternal decidua serve their own genetic interests in a homeostatic way during pregnancy. In addition, parental genes exert antagonistic pressure. Paternally expressed genes promote the growth of the fetus, whereas maternally expressed genes constrain fetal growth. Genomic imprinting is the key process

modulating the selective silencing of parental genes and contributes to the generation of the "new" fetal genome [52, 53]. Thus, the role of the placenta is crucial. The epigenetic modification of the human placenta is vastly different to that of all somatic tissues and regulates monoallelic inheritance, which has a direct relation with offspring phenotype [54]. In addition, placental DNA is extremely hypomethylated and acquires a pseudo-malignant nature. The "controlled" malignancy of the cytotrophoblast permits the migration of the extravillous trophoblast, and the invasion and remodeling of the maternal decidual [55]. This has a bearing on the chromosomal constitution of tissues in the placenta, where there is a relaxation of mitosis checkpoints that usually ensure a correct chromosomal segregation. This results in a phenomenon known as "confined placental mosaicism" [56]. Conclusively, despite the embryonic origin of the placenta, there are clear variations between embryonic, placental, fetal, and somatic genomes. The coadaptation of all genetic compartments during in utero development is crucial and exclusive of this developmental process. In fact, during pregnancy, three transgenerational genomes coexist: the maternal genome, the fetal genome, and the genome of the developing gamete inside the rudimentary gonads [57].

This systemic model emphasizes the interaction between compartments. In this sense, transgenerational epistasis should be taken in account. A non-Mendelian phenotype transmission has been suggested in animal models [58]; accordingly, genetic variants present in one generation affect phenotypes in successive generations. This epistasic inheritance explains the transgenerational segregation of traits and helps to understand the "missing heritability" phenomenon. This model implies interaction between genomes, key signaling pathways, chromatin remodeling mechanisms, methylation, RNA editing, and microRNA biology [59]. These putative routes and mechanisms may help us to understand "fertility success" as an imbricated trait.

Final remarks

In conclusion, the reproductive function of humans is a highly coordinated process involving many genetically regulated pathways. Our "genetic compartments" model aims to conceptualize inter-genome variations in the same individual. We suggest the coexistence of somatic, germinal, embryonic, and fetal-placental genetic microsystems. There are significant chromosomal, structural, functional, and timing differences between compartments. The contribution of these "genomes" to individual reproductive capacity varies. The systemic view considers a holistic interaction between microsystems within a macrosystem, in this case, the reproductive system. Additionally, this conceptualization has a practical application. This panoramic view could help non-experts in reproductive genetics to better understand the scope of genetic tests performed as part of reproductive medicine. This model allows us to define the significance of analytical results in function of particular tissues: peripheral blood, ejaculate, germ tissue, preimplantation embryos (blastomeres or trophectoderm), amniotic fluid, chorionic villi, or cell-free DNA. In light of this, it would not seem to be accurate to automatically infer clinical conclusions based on genetic data for a specific compartment. Such projections should be carried out with caution, and compartment particularities taken into account in order to establish the limits of extrapolation. In our view, these considerations are crucial in the context of reproductive genetic counseling.

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