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Editorial

Special Issue Featuring Papers for Celebrating the Third Year since the Founding of *Reproductive Medicine*

Stefano Palomba

Unit of Gynecology, University "Sapienza" of Rome, Sant'Andrea Hospital, 00191 Rome, Italy; prof.stefano.palomba@gmail.com

It is a great pleasure to introduce this Special Issue celebrating the third year since the founding of *Reproductive Medicine*. After an intense and competitive reviewing process, ten interesting papers have been selected for publication. They consist of many original studies, but also case report and reviews. The geographical origin of the published works is very varied and involves all continents. Indeed, the headquarters of affiliations include the United States, France, Japan, India and Ghana.

Fertility preservation is an important and debated concern for young cancer patients, and especially for patients with hematopoietic and lymphoid tissue tumors, because the time to chemotherapy is crucial [1]. In the study by Akino et al. [2], data of fertility preservation treatment in these cancer patients were retrospectively reviewed in a small but well-selected sample. All patients received ovarian stimulation (OS) using a GnRH antagonist random start protocol with double triggering, oocyte pick-up and cryopreservation. Of note, cancer patients received OS after first-line e/o consolidation chemotherapy. Reproductive data demonstrated that fertility preservation in patients with hematopoietic and lymphoid tissue tumors is a feasible procedure, although the outcomes are inferior to those observed in breast cancer patients.

The development of genital structures is controlled by several interconnected biological mechanisms, including alterations at genetic, endocrine, structural and/or environmental levels [3]. Thanks to chromosomal microarray analysis (CMA) being used to uncover copy number variants (CNVs), the smallest regions of overlap (SROs) have been characterized and defined. These SROs may identify candidate genes with clinical relevance for a specific disease. For the first time, Amukamara and Amarillo [4] constructed a chromosome map consisting of SROs, retrospectively using a database for genomic regions containing recurrent duplications and/or deletions in patients with atypical development of female external and internal genital structures and investigated such regions for genes that may be associated with the development of atypical female genitalia. One hundred and eighty unique SROs, variable from 7.95 kb to 45.34 Mb, were intercepted. The most frequent SROs were found in chromosomes X, 17, 11 and 22, whereas none were found in chromosome 3. Twenty-two new genes were identified as potential candidates; only one was associated with ambiguous genitalia, whereas almost half of these genes were previously considered to be implicated in the development and/or function of the reproductive system [4].

Genetic causes of male infertility in humans are not totally known, even if the male factor of infertility involves more than half of infertile couples [5]. Specific gene mutations and sperm DNA damage have been identified [5]. Genotyping may help to identify genetic factors, and the variants can be explored with single nucleotide polymorphism (SNP) array, NGS next-generation sequencing (NGS), microarrays and comparative genomic hybridization-array (array-CGH) to understand rare variants and disease etiology on a molecular level. Salvi et al. [6] used the Genome Wide Associations Studies (GWAS) platform to identify potential SNPs related to male infertility. They performed an Identify Candidate Causal SNPs and Pathway (ICSN Pathway) analysis using a genome-wide association study (GWAS) dataset, and an NCBI-PubMed search which included 632 SNPs

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in GWAS and 451 SNPs from the PubMed server, respectively [6]. The study aim was to elucidate and characterize the genetics of male infertility, and to study the association between genetic pathways and biological mechanisms. The authors demonstrated that multiple genes related to inflammation and metabolism might predispose to male infertility susceptibility, interacting with functional pathways, and that the genetic contribution to male infertility is pivotal. In fact, the knowledge of these SNPs and their associated pathways can help the clinician to screen infertile patients and to improve the prognosis thanks to the immediate use of advanced strategies for treating infertility [6].

Anti-Mullerian hormone (AMH) is a biomarker to evaluate ovarian reserve. The clinical usefulness of the AMH assay has been tested to predict ovarian responses to OS for in vitro fertilization (IVF) treatments and to diagnose polycystic ovary syndrome (PCOS) [7,8]. Moreover, scientific data have not completely proven its efficacy for optimizing OS and for diagnosing PCOS. In addition, fewer data are available on Black patients, and comparative analysis has demonstrated differences among different races [9]. The association between AMH levels and age was prospectively assessed by Mawusi et al. [10] in a large sample of infertile patients scheduled for IVF cycles. As expected, AMH levels were very low and high in patients older than 40 years and in younger patients (from 20 to 25 years) and were inversely related to women's ages. Unfortunately, AMH levels did not produce a distinctive result for other classes of women's ages, specifically from 25 to 40 years. These data confirm that AMH is probably one of the best endocrine biomarkers for predicting age-related decline in ovarian reserves in healthy women, even if more research is needed for identifying intermediate categories of age [10].

Anxiety is a very common condition, especially during pregnancy and the postpartum period [11]. Anxiety interferes with daily activities, is associated with lower maternal self-confidence, and can have adverse effects on child development [12,13]. In a survey-based cross-sectional study including 64 women, Olson et al. [14] assessed the relationship between postpartum pain and anxiety. At hospital discharge for delivery and 24 h later, each woman completed specific tools for assessing general anxiety and pain control. Moderate-to-severe scores for anxiety were found to be directly related to severe scores of pain during the postpartum period [14]. On the other hand, preexisting psychiatric disorders such as anxiety, depression or both were not associated with anxiety and/or higher rates of severe pain in the immediate postpartum period. This study underlines that in the postpartum period, pain perception may be strongly modified by anxiety, and thus interventions for anxiety may affect pain perception. This is particularly true and important considering that severe pain in the postpartum period may predict persistent pain and adverse mental health outcomes. Specifically, patients who had severe acute postpartum pain had a 2.5-fold increased risk of persistent pain at 8 weeks after delivery and a 3.0-fold increased risk of postpartum depression compared to those with mild postpartum pain [15].

Ovarian tissue cryopreservation and autograft is the only option available for prepubertal girls and young patients who cannot delay their cancer treatment [16]. To improve the efficacy of these strategies, in vitro systems have been developed to support the growth and maturation of follicles from the immature to the final stage. In vitro folliculogenesis has been successfully obtained in an animal model [17–19]. In proper culture systems, the addition of activin A, a dimeric glycoprotein belonging to the transforming growth factor beta superfamily that acts on a specific receptor expressed in primordial, primary, and secondary follicles, seemed to activate the primordial follicles and to initiate follicle growth [16–19]. An experimental study by Jovet et al. [20] evaluated the efficacy of a new compartmented chitosan hydrogel microbioreactor ["three-dimensional (3D)-structure"] to activate the in vitro folliculogenesis of human ovarian fragments from transgender men, with or without activin A. Five fresh ovarian human tissues were cultured in vitro, and the follicular morphology, density and quality were evaluated, as well as estradiol production. Proliferation and apoptosis were also assessed. Spontaneous folliculogenesis was observed regardless of the presence of the 3D structure or activin A [20]. The final data demonstrated that activin A did not play a crucial role in the in vitro folliculogenesis and supported the

efficacy of the use of the 3D structure to induce a more physiological folliculogenesis, and to prevent its deleterious, excessive and hasty activation [20].

Maternal marital status, alone or in combination with educational and income levels, is an important factor closely associated with adverse pregnancy and neonatal outcomes [21]. The relationship among marital status, maternal and neonatal complications and placental abnormalities has also been studied by Zhang et al. [22]. A large sample of 3724 placentas from single pregnancies was studied and their histology analyzed according to several clinical data, and especially to marital status. Marital status, categorized as married, single, divorced, life partner, or others (including unknowns and declined to respond), demonstrated a significant association with maternal age, race/ethnicity, maternal body mass index at delivery, neonatal birth weight, preeclampsia, and preterm delivery [22]. Of note, the fetal/placental ratio, altered fetal vascular perfusion due to avascular villi and chronic villitis also resulted in a significant relationship to marital status. The logistic regression model analysis confirmed those differences among marital status categories [22]. This study suggests that knowledge of the specific relationships between different marital states and specific pregnancy-related complications may help clinicians to administer more specific and closer monitoring during pregnancy and the postpartum period, reducing maternal and neonatal mortality and morbidity.

The current Special Issue also included an interesting case report regarding a mother who received a single embryo transfer (SET) and developed a dichorionic diamniotic twin pregnancy. SET is a strategy widely used in IVF treatments to reduce the number of twin/multiple pregnancies and the obstetric risks associated [23]. To date, five other cases with mothers who underwent SET have been reported [24–27]. Here, the authors present a sixth case of a dichorionic, diamniotic twin pregnancy with sex discordance. The postnatal genetic testing confirmed 46, XX, and 46, XY karyotypes in offspring and placentas [23]. Unfortunately, no zygosity testing was performed to diagnose monozygotic or dizygotic pregnancy. The case report underlines that, as with the SET use, it is possible to have a twin pregnancy due to concurrent natural conception, via breakthrough ovulation at the time the procedure or due to the discordant postzygotic nondisjunction of a single embryo transferred. In fact, monozygotic twins may have phenotypic and genotypic differences due to the modification of the original zygotic genome via various mechanisms such as blastomere allocation and postzygotic genetic, epigenetic or environmental events [28,29]. In addition, the report highlights that twin pregnancies should not be excluded during patient counseling and informed consent in cases of infertile patients scheduled for SET in IVF cycles.

PCOS is a common endocrine disorder affecting a large proportion of women of reproductive age and associated with increased risks of infertility [30] and pregnancy complications [31], risks probably due to an impaired oocyte/embryo [32] and endometrial [33] competence. An increased cardio-metabolic risk has been also suggested [34]. Less is known about the psychosocial aspects of PCOS, and the inter-relationships between these and the clinical risks are still unclear. Based on these considerations, the psychological co-morbidities potentially present in women with PCOS, such as depression, anxiety and eating disorders, as well as a decrease in self-esteem and quality of life, have been discussed in the review by Simon et al. [35]. The authors underline that the first step is to perform a correct diagnosis, that the time-to-diagnosis should be short, and that clear information should be provided. However, the authors report solid data on the difficulty of performing a PCOS diagnosis, and that the diagnosis is made at an average age of about 30 years, and only little and unclear information is given at consultation. Very interesting are findings on the psychological effects of receiving a diagnosis of PCOS, which seem to have positive as well as negative effects. In fact, the diagnosis of PCOS is associated with specific treatment and lifestyle changes, but also with the fear of being infertile and of developing some chronic pathologies, such as diabetes mellitus [35]. Thus, four specific conditions should be always searched in women with PCOS, including anxiety, depression, reduced quality of life and eating disorders [36], using specific questionnaires that should

be self-administrated at first visit and then re-assessed during treatments. Unfortunately, data on the effect of available treatments on psychological co-morbidities are very few to date.

The last paper is a comprehensive review article aiming to discuss the use and the role of the hypo-osmotic swelling (HOS) test for the assessment of the male factor [37]. In that review, Check et al. [38] discuss the functional integrity of the sperm membrane as an important factor in the acrosome reaction, sperm capacitation, sperm metabolism and the binding of the sperm to the zona pellucida, and whether the HOS test may be a useful tool to evaluate the sperm membrane integrity. The authors detail the mechanisms and principles of the HOS, the historical evolution of this test, its para-physiological alterations (for example, with advancing age of the male) and the high predictive value to detect male subfertility with regard to the specific alterations in the semen parameters and compared with the other functional tests [38]. In consideration of its low cost, ease of performance and stability over short time periods, the HOS test has several clinical applications in specific situations, all well-documented by the authors.

In conclusion, I believe that this Special Issue is interesting not only for the quality of the works presented, but also for their variety, ranging from frankly experimental to clinical studies and from topics regarding infertility to pregnancy.

Conflicts of Interest: The author declares no conflict of interest.

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