Editorial

Considerations on Clinical Assessment and Epidemiology of Fertility

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Introduction

Infertility is defined as unsuccessful reproduction after 12 months of unprotected intercourses or even a shorter time (6 months) when the woman is older than 37 years or in the presence of any risk factor. It is estimated to affect roughly 10-15% of the couples in developed countries and perhaps higher in underdeveloped countries, although this number could be a greatly imprecise estimation without considering continent, country or even regional specific evaluations [1].

Sterility on the other hand is a diagnosis of absolute infertility and impacts some less than 10% of the infertile population.

While in some countries the prevalence of sexually transmitted diseases (STD) still justify the high prevalence of tubal factor or obstructive male factor, in other areas of the world, environmental factors play a relevant role in the rate of secretory male factor or possible reduced women ovarian reserve. Furthermore the real estimation of the prevalence of infertility and its various etiologies suffer from biases such as the number of individuals that consciously decide not to have children and even not to have a stable relation, as shown by the growing number of 'singles' living in the large metropolis of western countries. Another element of confusion in the estimate that less than 50% of childless couples seek fertility consultations and even a smaller percentage of these couples access any type of treatment [2]. Based on a recent French National prospective cohort study of couples that reported having unprotected intercourse, using competing risk modelling, the frequencies of medical consultations for fecundity troubles was about 9 and 12% after 12 and 24 months of unprotected intercourse [3]. This is significantly lower than the prevalence of medical consultation due to involuntary infertility among couples who have sought a pregnancy for more than 12 months that varies in literature from 25% in the USA [4] to almost 50% in Copenhagen according to a Danish study [5].

Access to the Italian National ART Register (June 2013 reported data for cycles performed during 2011) revealed changes in the incidence of the various etiologies. Male factor represent 31% of indications to ART and 17% mixed male and female factor. Reduced ovarian reserve is reported as 7.2% of the diagnosis, unexplained infertility 14.6% and multiple female factors 6.6%, tubal factor 10.6%, endometriosis 6.6%. These data however do not clarify the real incidence of female and male aging as the main infertility factor or cofactor [6].

Aging

In 2013 the Eurostat [7] reported the 2010 delivery data in Europe, where Italy showed the higher female age in Europe (34 years), a 55% of deliveries in patients older than 35 years and a fertility rate of 1.41, where a total fertility rate of 2.1 is considered the level required to keep population size constant. These data include the rates of foreign-born or foreign-nationality mothers (healthy migrants) that in most countries in Western Europe exceeded 25% (19% in Italy). Moreover in Italy future estimations predict a 2% yearly decrease of the reproductive age population and need to be considered for future analysis.

Data-mining the Italian ART Register (June 2013 report) showed that in 2011 across the entire population of treatment cycles, female mean age was 36.5 years and male mean age was 39.9 years. Furthermore, 30.5% of the treatments were performed in women older than 39 years. Data from the Humanitas Fertility Center, (2,000 new couples referred

each year), the incidence of reduced ovarian reserve (FSH >10 IU/ml, less than 7 antral follicular count and <1 ng/ml AMH levels) for women younger than 40 years is over 20%. In addition, over 40% of these couples/females are themselves from older, single child and long 'time to pregnancy' parents.

Environmental Effects on Male and Female Fertility

In Western countries the epidemiology of male infertility seems conditioned by aging and by the potential role of endocrine disruptors on male reproductive axis. Many potentially harmful substances and products for the testes, epididymis and prostate have been reported to affect sperm motility, viability and sperm DNA. While the impact of endocrine disruptors in fertile men seems modest, the exposure to endocrine disruptors in men with a somewhat compromised sperm production is more obvious. The action of these potentially harmful factors may begin in the intrauterine environment by altering male reproductive tract development, including testis volume (low number of germ cells, Sertoli and Leydig cells) with subsequent low sperm production, higher incidence of testicular cancer, undescended testis and hypospadias. Studies on endocrine disruptors support an action on male brain and behaviour (a short anogenital distance is associated with a reduced masculine play in boys). Andrological workup should aim at recognizing these conditions, at avoiding unnecessary treatments and focusing attention on cancer risk and on the correction of unhealthy life-styles. Evidence is also accumulating that environmental chemicals (ECs) including endocrine-disrupting compounds (EDCs) can alter female reproductive development, fertility and onset of menopause. While not as clearly defined as in the male, this set of abnormalities may constitute an Ovarian Dysgenesis Syndrome (ODS) with at least some origins of the syndrome arising during foetal development. ECs/EDCs have been shown to affect trophoblast and placental function, the female hypothalamo-pituitary-gonadal axis, onset of puberty and adult ovarian function. The effects of ECs/EDCs are complex, not least because it is emerging that low-level, 'real-life' mixtures of ECs/EDCs may carry significant biological potency. In addition, there is evidence that ECs/EDCs can alter the epigenome in a sexually dimorphic manner, which may lead to changes in the germ line and perhaps even to trans generational effect [8].

New Risk Factors, Early Genetic Diagnosis and Interventions

Recent reports estimated that approximately 23% of patients

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Citation: Levi-Setti PE (2014) Considerations on Clinical Assessment and Epidemiology of Fertility. JFIV Reprod Med Genet 3: e111. doi:10.4172/2375-4508.1000e111

with premature ovarian aging have excessive triple repeats (>=30 CGG repeats) at the FMR1 gene locus on the X-chromosome and 55% abnormal autoimmunity [9]. If confirmed in larger samples the combination of autoimmune abnormalities and higher number of triple repeats on the FMR1 gene could be linked for a sizable number of cases of premature ovarian senescence and early genetic screening could potentially identify these at risk cases and offer them intervention as oocyte/embryo freezing. Additional genetic responsibilities for some causes of infertility discussed the role of pro-apoptotic genes Puma and Noxa as regulators of apoptosis in oocytes expressing TAp63 (a gene product implicated as a central player in oocyte apoptosis) and that women carrying BRCA1 mutation in addition to be at risk for breast a{Kerr 2012 [10], DNA damage-induced primordial follicle oocyte apoptosis and loss of fertility require TAp63-mediated induction of Puma and Noxa}{Titus 2013 [9], Impairment of BRCA1-related DNA double-strand break repair leads to ovarian aging in mice and humans} and other cancers, have deficiency in the DNA repair process also in oocytes and this might explain why mutation carriers often experience menopause at an earlier age compared to non-carriers. Concerning the association between cellular senescence and immunity/inflammatory modifications [10], Guo Zhang and co-authors in 2013, using several mouse models, demonstrated that the hypothalamus is important for systemic aging and for lifespan control. This hypothalamic role is mediated by IKK-b- and NF-kB-directed hypothalamic innate immunity involving microglia- neuron crosstalk. The underlying basis includes integration between immunity and neuroendocrine activity of the hypothalamus. The block of this immunity and the associated Gn-RH restoration could represent two potential strategies for combating aging-related health problems [11].

These few examples show how knowledge on early diagnosis of incipient premature ovarian senescence is improving and it is likely that in the near future, particularly with the advantage of genetic discoveries, many of the so-called unexplained infertility will find an explanationand accelerate appropriate clinical interventions and work more in general from best prognosis patients selection to ageing prevention and possible therapy efforts.

Conclusions

Clinical assessment of the infertile or sub fertile couple has been until recently focused in selecting, through a basic work-up of ovarian reserve, ovulatory and luteal phase function, tubal function and male sperm characteristics, couples with good or poor/ reduced prognosis to obtain a pregnancy/ child after medical, surgical or ART treatment. This process of selection (exclusion) from treatment and often from state/ insurance cost coverage continues from couple's epidemiology of fertility to oocyte, sperm, and embryo characteristics through yearly more expensive new tests and procedures. This process lead to a nearly 100% chance to obtain success only in a selected, small, lucky, rich population with a yearly growing number of childless couples excluded from homologous access to treatment. The process of population ageing, as shortly discussed in this paper, is changing the epidemiology and clinical assessment of infertility. Several changings in the main aspects of population healthcare are emerging: prolonged life span of older childless or with a reduced than desired children men and women, few

children at higher risk of epigenetic anomalies and probably carrying a sub fertile future, as a consequence to be conceived by older parents. We urgent need to really translate basic new knowledge in clinical application of methods fighting the ageing process. Not only longer life, but healthier, younger and fertile for a prolonged period as a new horizon of human rights. Since most of the environmental and genetic modifications act mostly in the prenatal period and many of these effects could be diagnosed during pregnancy and the perinatal period, only in these ages a primary prevention or therapy is a possible horizon. Nevertheless, cryopreservation of sperm and oocytes and consciousness of the actual need of a final divorce between sexuality and reproductive function, at least in higher risk men and women, is the only prevention strategy actually possible in clinical practice.

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