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FONDAZIONE INTERNAZIONALE MENARINI

ABSTRACT BOOK

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GOLDEN COMMUNICATIONS

POSTER

Biologia della seduzione

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Non ci sono alternative: o la natura, e l'uomo, come oggi li vediamo sono stati creati oppure si sono evoluti. Se si aderisce alla prima possibilità, il testo di riferimento è una delle tante Genesi che si trovano in molte delle Sacre Scritture; se invece si pensa che tutto sia frutto dell'evoluzione il libro da consultare si chiama *L'origine della specie attraverso la selezione naturale* e l'ha scritto 150 fa Charles Robert Darwin.
La teoria dell'evoluzionismo darwiniano si basa su questi semplici concetti: piante e animali si evolvono grazie al caso che di tanto in tanto propone una mutazione nel patrimonio genetico. Se questa mutazione è svantaggiosa, la forma vivente soccombe e non lascia eredi con quel carattere; se invece permette di adattarsi meglio all'ambiente (selezione naturale) o di riprodursi di più (selezione sessuale), il suo carattere mutato si afferma e viene trasferito alle generazioni successive. E questo non vale solo per aspetti fisici come le pinne per nuotare o le penne per volare, ma anche per comportamenti-base, che nel loro insieme chiamiamo istinto.
Su queste basi è possibile stabilire come si siano evoluti i comportamenti adattativi che ci hanno portato a utilizzare le odierne strategie di seduzione.
Gli studiosi dibattono ancora sui vantaggi che rendono il sesso una strategia di così grande successo nell'evoluzione. È probabile che più fattori giochino un ruolo importante e tra questi si menziona spesso la maggiore velocità di adattamento delle specie sessuate, dovuta al fatto che il sesso permette, per mezzo della ricombinazione genetica, di unire in uno stesso genoma mutazioni vantaggiose originatesi in linee genealogiche diverse. Al contrario, nelle specie asessuate ogni mutazione vive e muore nella linea genealogica in cui si è originata, per cui l'accumulo di mutazioni benefiche è possibile solo se esse compaiono nella stessa linea genealogica (alcune specie asessuate, per esempio tra i batteri, possiedono comunque meccanismi di scambio genetico che permettono, su scala minore, l'incrocio di diverse linee cellulari). Questo ragionamento, tuttavia, si riferisce a vantaggi a lungo termine del sesso (la velocità di evoluzione della specie), mentre le forze più potenti nell'evoluzione genetica derivano dagli

effetti a breve termine dei geni, cioè gli effetti di un dato gene sull'individuo e non sulla specie nel suo complesso. Inoltre, la stessa ricombinazione genetica può avere conseguenze deleterie oltre che benefiche, per esempio separando geni che interagiscono favorevolmente tra loro. Non è quindi ovvio che la maggiore
velocità di evoluzione che il sesso conferisce alle popolazioni sia stata un fattore decisivo per la sua diffusione nel mondo biologico.
L'evoluzione ha prodotto sostanziali differenze nelle strategie sessuali dei maschi e delle femmine,
basate sulla loro disparità di investimento riproduttivo. Da una parte ci sono le femmine, che producono un numero limitato di gameti di grandi dimensioni e ricchi di nutrienti, e dall'altra i maschi, che producono un numero enorme di gameti di piccole dimensioni e con un costo energetico ridotto. La sessualità si è così trasformata in un conflitto che esprime la competizione mirata a garantire gli interessi dei due sessi. Ciò avviene attraverso i cosiddetti "ornamenti sessuali": decorazioni, la simmetria, e la bellezza stessa, che vengono scelti (cioè selezionati) perché indicano chiaramente la presenza di parassiti nel maschio e il derivante rischio che ha di trasmettere malattie. Tali ornamenti si si possono anche evolvere rapidamente nei maschi solo a causa del fatto che le femmine li scelgono. Se, infatti, un maschio possedesse un qualche ornamento che alle femmine piace, questo renderebbe il maschio di successo, e tale ornamento sarebbe trasmesso alla prole maschile, mentre alla prole femminile sarebbe trasmessa la preferenza per esso. Si produrrebbe così una rapida intensificazione degli ornamenti attraverso le generazioni, che si fermerebbe solo quando l'ornamento diventa troppo costoso per la sopravvivenza del maschio.
Anche nella nostra specie le femmine scelgono i partner sulla base di caratteristiche simili a quelle che si riscontrano tra gli animali.
È la teoria dell'handicap, in grado di spiegare molto delle strategie di seduzione adottate da maschi e femmine della nostra e di altre specie. Con questo strumento il sessuologo può delineare i meccanismi che hanno portato il maschio della nostra specie ad assumere un comportamento propositivo e che hanno affidato alla femmina il ruolo di disporre delle proposte maschili.

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Secondary Osteoporosis in Men and Women

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Osteoporosis can be classified into primary and secondary. While primary osteoporosis is related to osteoporosis caused by involutional bone loss associated with aging in both sexes and loss of estrogen production in women, secondary osteoporosis is due to endocrine, gastro-intestinal and autoimmune diseases, genetic disorders, cancer and medications which lead to bone loss, microarchitectural alterations and fragility fractures, even in clinical context, such premenopausal women or younger men who are usually not target populations for routine screening for osteoporosis. Secondary osteoporosis is more frequent in males as compared to females, and in young subjects as compared to the older ones (1). Hip and vertebral fractures occur respectively in 39% and 45% (2) of the men, a lower incidence if compared to women, but the relative risk of subsequent fractures (Center et al JAMA 2007) is higher in men, as well as the rates of morbidity , mortality, and hospitalization after an hip fracture (Amin et al Rheum Dis 2001). This is probably connected to the fact that osteoporosis in men commonly presents with vertebral body fracture or hip fracture, whereas in women it is often diagnosed by routine bone density screening. Moreover, in males osteoporosis is more frequently secondary to diseases which may have per se an impact on survival (3).

Apart from the more well-known endocrine disorders and glucocorticoid induced osteoporosis the emerging use of aromatase inhibitors (AIs) and androgen-deprivation therapy as adjuvant therapies in women with breast cancer and men with prostate cancer, respectively, have emerged as novel and important etiologies of secondary osteoporosis.

- Drug-induced osteoporosis

•Glucocorticoid-induced osteoporosis (GIO)

Oral corticosteroid have been widely used in medical practice for over 50 years and play a major role in the treatment of chronic obstructive pulmonary disease, inflammatory joint disorders, and other diseases affecting the gastrointestinal tract and central nervous system. Although often effective in these conditions, osteoporosis is one of the most serious complications of oral corticosteroid treatment and the most frequent form of secondary osteoporosis in males as well as in females (4). The central pathophysiological mechanism of bone loss during long-term use of glucocorticoids is impaired bone formation,

due to inhibitory effects of glucocorticoids on osteoblast differentiation and function. Moreover, early after exposure to glucocorticoid excess an increase in bone resorption generally occurs as effect of stimulation of RANKL production. This condition leads to a rapid bone loss occurring in the first months after starting glucocorticoid treatment with specific involvement of trabecular bone (5-6).

The major clinical manifestation of GIO are fractures which are most common in the vertebrae and hip, regions of the skeleton with large amounts of trabecular bone. Fractures occur in 30-60% of treated patients (7) with prevalence being higher in females as compared to males. The fractures occur independently of BMD values, and the risk is dose dependent (8), increase further during long-term glucocorticoid treatment (8) and tends to reverse sharply towards baseline after discontinuation of oral corticosteroids.

Incidence of non vertebral fractures rises exponentially with advancing age in women, while in men the incidence of non-vertebral fractures increases later after 65 years old (6).

Males and females with GIO are treated similarly after 50 years old with bisphosphonates or teriparatide, whereas in younger subjects the management is different between the two sexes mainly due to the clinical concerns deriving from using anti-osteoporotic drugs with potential teratogenic effects in fertile women (9).

•Aromatase inhibitors (AIs):AIs are widely used as adjuvant therapy in estrogen receptor positive breast cancer. They prevent androgen aromatisation, reducing circulating total estrogens levels with the result of an increased bone resorption, a reduction of the BMD and an increase risk of fractures (Mazziotti, AJM 2010). Most of literature data are derived from studies in which the skeletal effects of AIs were compared to those induced by tamoxifene, a drug with protective skeletal effects. From this point of view, the true fractures risk related to AIs therapy is still largely unknown. However, available data are convincing for clinically significant effects of AIs on the skeleton. AIs are classified in steroidal (exemestane) and non-steroidal (anastrazole and letrozole) and literature data do not provide evidence for differences in skeletal effects between these drugs (10-11). The skeletal effects of AIs are correlated inversely with baseline BMD and serum estradiol concentrations, and osteoporosis is more prevalent in women starting aromatase inhibitors early after menopause. There is only a partial recovery of BMD following the withdrawal of AIs (5).

The pharmacologic agents available for the prevention of AIs - induced bone loss in post-menopausal women are biphosphonates and Denosumab. In several randomized trials, biphosphonates like Risedronate (Greenspan SL et al JCO 2008), Ibandronate (Lester JE et

al Clin Cancer 2008) and Zoledronate (Z-FAST and ZO-FAST randomized trials) prevented or reduced bone loss in women receiving AIs. Denosumab increases lumbar spine, total hip and femoral neck BMD in AIs treated women (12). •Androgen-deprivation therapy(ADT): hypogonadism is an important cause of osteoporosis in men, accounting for 5-30% of osteoporosis (13) and with BMD values being 9-17% lower than those observed in eugonadal men (14).
Androgens directly regulate various aspects of osteoblastic lineage cells including proliferation differentiation, mineralization and gene expression, but most of the skeletal effects are mediated by estradiol produced by aromatization of testosterone (15-16) It seems that estradiol is essential in regulation of bone resorption whereas estradiol and testosterone are important in maintaining bone formation (17). Furthermore estradiol levels correlate with the frequency of osteoporotic fractures in males (18).
The use of GnRH agonists in men with prostate cancer is effective in reducing tumor growth and improving survival, but iatrogenic induced hypogonadism leads to the development of bone turnover and bone loss increasing the risk of fractures. In men with prostate carcinoma, BMD at hip, ultradistal radius, and lumbar spine decreases by 2-5% after 12 months of androgen deprivation therapy and the relative risk of vertebral and hip fractures increases by 40-50% (19-20). The risk of fractures correlates with the degree and rate of BMD decrease, patient age, and duration of therapy, but not with tumor stage. Compared to orchiectomy androgen deprivation therapy reduces the incidence of first fracture.
Since estrogen deficiency rather than testosterone deficiency seems to be primarily responsible for the adverse skeletal effects of GnRH agonists, SERMs have been used to prevent bone loss in this clinical context. Moreover, bisphopshonates were shown to be effective in improving BMD in patients undergoing treatment with GnRH agonists and more recently denosumab was shown to significantly decrease the risk of vertebral fractures in this clinical setting (21-25).

- Endocrine disorders

GH and IGF-1 are important regulators of bone homeostasis and are central to the achievement of normal longitudinal bone growth and bone mass (Giustina, Endocr Rev 2008).
•GH deficiency (GHD) in adult patients causes marked decrease of bone turnover with reduction of bone mass and increased risk of fragility fractures. The negative effects of GHD on the skeleton seem to be related to the age of the patients, the age of onset, the severity of the disease and concomitant others pituitary diseases.
Adult hypopituitary patients with GHD have a threefold increased of vertebral (Mazziotti JBMR 2006) and non vertebral (Rosen et al 1997

- Wuster et al 2001) fractures, without any significant difference between men and women and without correlation with gonadal status in males (Mazziotti, Pituitary 2008). As in GIO, also in GHD fractures occur even in presence of normal or slightly decreased BMD (Mazziotti, JBMR 2006). In males with untreated GHD, the prevalence of vertebral fractures was shown to be influenced by the dose of glucocorticoid used to replace secondary hypoadrenalism (Mazziotti, EJE 2010). Although there are no prospective data on the outcome of fracture risk in GHD, results from cross-sectional studies suggested that GH (rhGH) replacement therapy may be effective in decreasing the risk of vertebral fractures in adults with GHD, mainly if the treatment is started early after diagnosis of disease. There is evidence that males have more pronounced response to rhGH treatment in terms of increase in IGF-1 and improvement of BMD (Giustina, Endocr Rev 2008), whereas there is still unknow whether the outcome of fracture risk may be gender-dependent.

•Acromegaly: Although GH is an anabolic hormone for bone, patients with acromegaly have increased bone turnover, as determined by changes in biochemical markers, calcium kinetics, and bone histomorphometry. Data of BMD are rather controversial, with osteopenia and osteoporosis being demonstrated mainly at vertebral site in hypogonadal patients (Diamond et al Ann Intern Med. 1989, Scillitani et all Clin Endocrinol 2003) Over the recent years, it has become clear that acromegaly is associated with skeletal fragility (Ueland et al., Eur J Clin Invest 2002) which can lead to the development of vertebral and non-vertebral fractures. Indeed, our group and others reported that about 50% of patients with acromegaly may develop vertebral fractures (26,28). Males and females seem to have comparable risk to develop vertebral fractures (27-28) in relation to the activity of disease and comorbidities as hypogonadism (36) and diabetes mellitus (Mazziotti Endocrine 2011), but recently Wassenaar reported a gender difference in the prevalence of VFs with more men than women with one or more documented VF. Furthermore hypogonadal men has a significantly higher prevalence of VFs than eugonadal or hypogonadal women.

•Hyperprolactinemia: More than 50% of the pituitary adenomas are represented by prolactinomas. PRL is known to have important functions in the bone health, even during pregnancy. For many years prolactin induced oligo-amenorrhea has been considered the main factor associated with decreased BMD, although several studies have shown that hyperprolactinemia may be also directly responsible for the loss of bone mass, regardless of gonadal dysfunction. Data on osteoporotic fractures in hyperprolactinemia are limited. An increased prevalence of radiological vertebral fractures was recently observed in

post menopausal women and men with PRL-oma, but only in the male population risk of VFs was related to the BMD value, while in both the studies the duration of hyperprolactinemia was the most important risk factor.

•TSH and thyroid hormones: The detrimental effects of hyperthyroidism on the skeleton has been known since 1891. Traditionally, this has been considered a direct effect of thyroid hormones, but over the recent years there has been evidence for a direct effect of TSH on bone (29-30). Specifically, TSH was shown to exert anti-resorptive effects and low values of this hormone, as they occur in hyperthyroidism, may cause increase in bone turnover with bone loss. Regardless the underlying mechanisms, hyperthyroidism is associated with osteoporosis and increased risk of vertebral and non-vertebral fractures with effects being more pronounced in post-menopausal women and older males. Indeed, it was recently demonstrated that subclinical hyperthyroidism may impair the skeletal response to bisphosphonates in women with post-menopausal osteoporosis (Panico, Thyroid 2009).

- Conclusions

Male osteoporosis is frequently secondary to endocrine, non endocrine diseases and treatments but also in women secondary forms of osteoporosis are emerging causes of fragility fractures. While in this context glucocorticoids remain the major cause of drug induced osteoporosis in both sexes, other drugs used in breast and prostate cancers are differential causes of osteoporosis in men and women.

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Trunk Fat Mass in Obese Male Subjects Correlates with Bone Metabolism Alteration

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Obesity and osteoporosis are two global health problems with an increasing prevalence and high impact on both morbidity and mortality. Obesity has always been considered a protective factor for osteoporosis. However, recent clinical studies have shown that high level of trunk fat mass might be a risk factor for osteoporosis and fragility fractures in women. Aim of our study was to evaluate a potential interference effect of trunk fat mass on skeletal metabolism in obese men. The study included 86 men (mean age: 45±14 yrs; BMI: 33.8±6). Exclusion criteria were chronic medical conditions or use of medications affecting bone metabolism, hormonal and nutritional status, vitamin D supplementation, recent weight loss, and prior bariatric surgery. Patients underwent measurements of BMD (lumbar and hip) and body composition (lean mass, total and trunk fat mass) by DEXA and were evaluated for osteocalcin, inflammatory markers, hormonal profile. High trunk fat mass was inversely correlated with low BMD at lumbar ($p<0.01$) but not at hip sites; also, it was inversely correlated with testosterone ($p<0.01$) and osteocalcin serum levels ($p<0.0001$). Plasma Testosterone levels were directly correlated with BMD at lumbar and hip site ($p<0.0001$); also, estradiol levels were inversely correlated with lumbar ($p<0.001$) and hip ($p<0.01$) scores. Trunk fat in adult male individuals negatively correlates with bone mineral density, suggesting that obesity, as previously shown in women, cannot always be considered a protective factor for osteoporosis.

Physiopathology of Osteoporosis in Both Sexes

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Although osteoporosis has traditionally been considered a disease of women, men also incur substantial bone loss with aging, and elderly men have age-specific hip fracture incidence rates and vertebral fracture prevalence rates that are at least half those in women.

It has generally been held that estrogen and testosterone are the major sex steroids regulating bone metabolism in women and men, respectively. However, the description of several "experiments of nature" led to a reconsideration of this notion.

Early postmenopausal bone loss (which results in the syndrome of type I osteoporosis) is due to the direct skeletal consequences of estrogen deficiency, manifested by an increase in bone resorption without an adequate increase in bone formation. Even late postmenopausal bone loss in women may be due to estrogen deficiency. In particular, the late consequences of estrogen deficiency in elderly women result in abnormalities in calcium homeostasis and increases in parathyroid hormone secretion, leading to increased bone resorption and bone loss. Estrogen may play a significant role in bone metabolism in men, as several large epidemiologic studies have found that bone mineral density correlates better with serum estrogen than testosterone in aging men. Thus estrogen deficiency may lead to bone loss in men.

The estrogen-centric view is likely correct for cortical bone, which comprises over 80% of the skeleton and is the major structural determinant of fracture risk at most skeletal sites. By contrast trabecular bone loss begins in sex hormone-replete young adults of both sexes.

During growth, estrogen deficiency in females may produce increased bone size as a result of removal of inhibition of periosteal apposition, while failed endosteal apposition produces thin cortices and trabeculae in the smaller bone. In males, androgen deficiency produces reduced periosteal and endosteal apposition, reduced bone size, and cortical and trabecular thickness.

In midlife, in females, estrogen deficiency increases remodeling rate, increases the volume of bone resorbed, and decreases the volume of bone formed in each of the numerous BMUs remodeling bone on its endosteal (endocortical, trabecular, intracortical) surfaces so bone loss accelerates. In males, remodeling

rate remains slow and is driven largely by reduced bone formation in the BMU. Hypogonadism in 20% to 30% of elderly men contributes to bone loss. In both sexes, calcium malabsorption and secondary hyperparathyroidism may partly be sex-hormone dependent and contributes to cortical bone loss. Concurrent periosteal apposition partly offsets endosteal bone loss, but less so in women than in men. More women than men fracture because their smaller skeleton incurs greater architectural damage and adapts less by periosteal apposition. Sex hormone deficiency during growth and aging is pivotal in the pathogenesis of bone fragility.

All these findings will be presented and critically analyzed in the lecture.

Osteoporosis and biological drugs

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Bone remodeling is a complex, tightly regulated process carried out by two key cell types: osteoclasts and osteoblasts. Osteoclasts are the principal resorptive cell of bone and osteoblasts are specialized bone forming cells that synthesize bone matrix and regulate mineralization. An intimate cross-talk among bone resident cells, including osteoclasts, osteoblasts, osteocytes, bone lining cells, osteomacs, and vascular endothelial cells is tightly coordinated by regulatory proteins that interact through complex autocrine/paracrine mechanisms. In addition, T and B lymphocytes participate in the modulation of bone homeostasis.
An imbalance in the bone remodeling process, due to physiologic, drug-induced or surgical-dependent changes in the levels of hormones controlling bone homeostasis, leads to a number of clinical disease conditions including osteopenia and osteoporosis. Despite the exact mechanisms responsible for aberrant bone remodelling are still not completely understood, several paracrine or coupling factors, such as Receptor Activator for Nuclear Factor kappa-B Ligand (RANKL), sclerostin, insulin-like growth factor I (IGF-1), EGFL6 and semaphorin 4D, have been demonstrated to be crucial in bone homeostasis and will lay the foundation for drug development against bone diseases, possibly giving rise to a number biological drugs with better clinical profile.
Presently two biological drugs flank dietary supplementation strategies and older drugs (such as bisphosphonates) in the treatment of postmenopausal women with osteoporosis to decrease fracture risk: teriparatide and denosumab.
Parathyroid hormone plays an essential role in the regulation of calcium metabolism. When parathyroid hormone levels are continuously elevated, as seen in patients with hyperparathyroidism, there is a deleterious effect on bone, leading to loss of cortical bone. However, pulsatile administration of parathyroid hormone has a contrary effect, leading to anabolic effects on bone. Teriparatide is a peptide formed by 34 amino acids and is identical to the NH2-terminal portion of parathyroid hormone. Pharmacokinetic characteristics account for the anabolic effects of teriparatide given once a day. Teriparatide activates the parathyroid hormone-1 receptor, a G-protein-coupled protein, which leads to subsequent activation of cyclic

AMP-dependent protein kinase A and protein kinase C signaling pathways, both of which play key roles in regulating osteoblastogenesis and osteoblast function. Moreover, Teriparatide increases the production of IGF-1 by bone cells. Subsequently, IGF-1 acts primarily on differentiated osteoblasts by increasing osteoblast function and preventing apoptosis of differentiated osteoblasts. Teriparatide down-regulates the expression of sclerostin, a Wnt-β-catenin antagonist, which prevents Wnt signaling thus playing an important role in osteoblastogenesis.

Teriparatide could be combined with antiresorptive agents or used alone. Meta-analysis of 8 trials showed that teriparatide increases spine bone marrow density (BMD) by 8.1% and hip BMD by 2.5% compared with placebo (Johnson, 2012). Moreover, teriparatide reduced risk for vertebral and nonvertebral fractures. Teriparatide is generally well tolerated. Transient hypercalcemia, nausea, dizziness, headache, and leg cramps can occur in about 10% of patients; rarely rhinitis, or arthralgias can occur, but these are usually not severe enough to require discontinuation (Sikon and Batur, 2010). Antibodies to teriparatide have been detected in about 3% of women with long-term treatment, but hypersensitivity reactions or decreased efficacy has not been seen.

Denosumab is a novel antiresorptive agent that inhibits osteoclast-mediated bone resorption but works through a different pathway than bisphosphonates. In fact, denosumab is a fully human monoclonal antibody (IgG2) that inhibits RANKL with high specificity, mimicking the effects of OPG on RANKL. RANKL is essential for the formation, function, and survival of the osteoclasts. It binds to its cognate receptor RANK on the surface of precursors and mature osteoclasts, stimulating these cells to mature and resorb bone. Multiple preclinical models studying the effects of RANKL inhibition (for example, through OPG) showed that it leads to improved bone geometry and increased bone density and strength. In humans, a single subcutaneous dose of denosumab resulted in a dose-dependent, rapid, profound, and sustained decrease of bone turnover markers.

Meta-analysis of 25 trials showed that Denosumab reduces the risk of new vertebral fracture, as evaluated by radiography, by 68% compared with placebo ($p < 0.001$) and increases BMD at lumbar spine, total hip, and one-third radius more than alendronate and placebo (Silva-Fernández et al). Denosumab was in general well tolerated, but an increase in the incidence of urinary infections ($p = 0.012$) and eczema ($p < 0.001$) has been described.

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Sex and gender in cardiovascular diseases

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Sex and gender differences in frequent diseases have significant yet frequently underestimated consequences on the daily practice of medicine, on outcomes and on choice and efficacy of therapies. Using gender based approaches improves the quality of medical care. Understanding differences in symptoms of myocardial infarction and help seeking behaviour in women and men leads to a more efficient and faster therapy in both genders. Knowing, for example, that exercise ECG has different sensitivity in subgroups of women and men lowers the threshold to use additional imaging procedures in subgroups of women with suspected cardiac ischemia. The knowledge that a drug has more adverse effects in one gender will affect dosing and choice of therapy. Knowing that some prevention strategies are more voluntarily accepted in women or men will lead to the design of gender specific campaigns that are more efficient than global approaches.

Efficient pharmacotherapy is affected by pharmacokinetics, by resorption, metabolism, distribution and excretion of a drug. These depend, on body weight and composition, enzyme activities, organ perfusion and others, all of them differing significantly in women and men. In addition, efficacy and efficiency of drug therapy depends on underlying pathophysiology of a disease. Women and men are clearly similar in most of these parameters (as are mice and pigs and dogs to human) and therefore the majority of drugs that are developed in rodents work in humans of both sexes. Nevertheless, subtle and less subtle differences exist, in brain function, in ion channels of heart and kidney, in energy and bone metabolism, in immune responses and many more. They are due to the effects of sex hormones as well as to genes on X and Y chromosomes. The more and more we are advancing and refining drug therapy the more we have to adjust to these subtle differences. Therefore, optimizing drug therapy requires understanding of sex differences in pathophysiology. In addition to sex, age and related hormonal status play a role. In cycling animals and in cycling women, the phase of the cycle influences a number of physiological parameters outside the reproductive organs.

Gender differences in disease manifestations also determine pharmacotherapy. If a risk factor is underestimated in one gender or gender specific symptoms are not recognized, treatment may be delayed. Prescription habits depend on gender of patients and physicians and their interaction. Finally the estimated prevalence of a disease in the population influences attitudes in drug development and public health. Gender-based factors also determine the access to health care and the attitudes towards novel drugs.

Heart failure is one of the most common cardiac diseases that exhibits significant gender differences. Prognosis in heart failure in the Framingham Study improved over the last 50 years and was better in women than in men (Levy et al, 2002). In spite of higher mortality in men, the total number of heart failure deaths is higher in women due to the overall longer lifespan in women. In the EuroHeartFailureSurvey systolic heart failure was found predominantly in men, whereas women presented with heart failure with preserved ejection fraction. Major risk factor for heart failure in men is coronary artery disease, whereas in women hypertension and diabetes are most prevalent risk factors. Sex differences in pathophysiology are not well studied. Women have more frequently heart failure with normal systolic function whereas men present more frequently with heart failure with reduced ejection fraction. Survival is comparably poor in both forms.

Sex and gender differences in coronary artery disease are known since long. Women with coronary artery disease (CAD) are about 10 years older than men. Diabetes is a greater risk factor in women than in men. Genetic risk factors for chronic coronary artery disease differ in women and men. Men exhibit more main stem stenosis and more triple vessel disease. women present more frequently the single vessel disease, disturbances of the microcirculation and more angina with normal coronary artery disease. This phenomenon has been called syndrome X earlier. Recommended medical therapy does not differ in both genders; and percutaneous coronary intervention is successful in both. However, it is more often accompanied by bleeding complications in women than in men. Women do have a greater mortality after coronary bypass surgery (Regitz-Zagrosek, 2006). The FRISK Study has suggested that women respond less well to aggressive early revascularization in the case of acute angina or acute coronary syndromes.

Myocardial infarction is considered a disease of men, but it kills almost as many women as men (Rosamond et al, 2008). Women

experience the majority of myocardial infarctions about ten years later than men. Nevertheless, their longer life period leads to the fact that they experience a very similar absolute number of myocardial infarctions compared with men.
The incidence of MI declines worldwide in all parts of the population expect in young women. Nevertheless, young women do have a higher mortality after a first myocardial infarction than age matched men. Women and men differ in triggers for myocardial infarction. Psychological stress is more important in women; heavy exercise is more common in men. Women and men also differ in symptoms of myocardial infarction. Women appear to experience a greater variety of symptoms, more so-called “atypical Angina”. In contrast, there is a much higher likelihood for ischemic sudden death in men.
Thus, gendered approaches are important for both sexes.

Gender Differences and Hypertension

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The roles that both male and female sex steroids play in mediating or protecting against cardiovascular disease (CVD) and hypertension are controversial. For example, while animal studies have strongly implicated androgens as being mediators of CVD and hypertension, human epidemiological studies have shown that with chronic disease, including hypertension, serum testosterone levels are actually reduced. Thus whether androgens are truly causative of CVD is not clear. On the other hand, premenopausal women are typically protected from CVD and hypertension compared to men, and this has been hypothesized to be due to the protective effects of estrogens. The negative findings of HERS I and II and Women's Health Initiative (WHI) studies on hormone replacement therapy (HRT) in postmenopausal women have shaken our previous ideas that HRT was protective against CVD.

Mechanisms responsible for hypertension in women are several and may be different than in men. In recent studies, women have been shown to have poorer blood pressure control than in men despite the fact that women are typically more compliant with medications and see their care providers more frequently than men. In women, diabetes, both types I and II, are important factors responsible for hypertension in women. Other cardiovascular systems that may play a role in hypertension in women include the renin-angiotensin system (RAS), the endothelin system and activation of the sympathetic nervous system may also contribute to elevated blood pressure in women, particularly as they age.

Men have higher blood pressure than women throughout most of their lives and develop CVD at an earlier age than do women. These data support a role for androgens in mediating CVD in men. However, in epidemiological studies in which serum testosterone levels were measured in men with chronic CVD, such as hypertension, the levels are lower than in healthy age-matched men. These findings have lead investigators to presume that androgens could not be responsible for initiating and/or mediating CVD. However, it is also possible that the downregulation of androgen synthesis is a protective compensatory mechanism that occurs once the diseases are initiated. Animal studies

refute the hypothesis that CVD are not mediated by androgens in males. For example, in SHR, males develop higher blood pressure than do females. Removal of the testes in male SHR reduces blood pressure in the rats. Similar observations have been made in male Dahl salt-sensitive rats, as well as in models of non-genetic hypertension, such as DOCA-salt treated rats.

Potential mechanisms responsible for hypertension in men are not too dissimilar than in women: the RAS, endothelin, and activation of the sympathetic nervous system. However, there are sex differences, based on our animal studies: the cardiovascular response to androgens in males and females are different; the blood pressure response to increases or decreases in oxidative stress are different; the mechanisms responsible for sympathetic nervous system activation and blood pressure are different between males and females.

Additional clinical and basic translational studies will be needed to further elucidate sex differences in blood pressure in humans and thus develop gender-based treatment programs for both genders.

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Terapia anticoagulante e differenze di genere

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Abstract
A partire dalla metà degli anni ’90 si è sviluppata con forza la spinta verso la Medicina Basata sulle Evidenze, che ha contribuito alla successiva affermazione del concetto di medicina personalizzata, che vede nel gruppo “genere femminile” un’area di personalizzazione di estrema importanza, orfana però di ricerche specifiche.
Negli anni le evidenze si sono accresciute, anche se in modo non omogeneo nei diversi settori, e si è appropriatamente affermato il concetto di medicina personalizzata (una delle quattro P dell’attuale “4P Medicine”) in cui le evidenze da generali devono, per essere applicate al meglio, divenire specifiche del gruppo o della persona. Indubbiamente lo sviluppo della medicina personalizzata vede nel gruppo “genere femminile” un’area di personalizzazione di estrema importanza, che soffre però della mancanza di ricerche specifiche e, in particolare in medicina cardiovascolare, dell’avere per molto tempo, nei vari studi clinici condotti, acquisito dati che seguivano l’epidemiologia. Infatti, le evidenze si sono ottenute nel tempo senza particolare attenzione al genere, con gruppi di genere femminile sottorappresentati (spesso nel rapporto di 1 a 3 o 1 a 4 rispetto al genere maschile), e pertanto i dati specifici disponibili spesso non raggiungono per la quota femminile la numerosità necessaria per una valutazione robusta, costringendo ad estrapolare alla donna evidenze ottenute nell’uomo o raggiunte attraverso la combinazione dei dati dei due generi. (1,2).
In relazione al rischio emorragico connesso con i trattamenti antitrombotici esistono forti elementi a favore di differenze di genere in rapporto ai valori inferiori, nella donna, di massa corporea, di dimensioni degli organi e di funzione renale. Tuttavia, nei diversi studi l’attenzione alle differenze di genere si è sviluppata solo recentemente, pertanto per individuare il rischio emorragico specifico per i due generi, è necessario andare a ricercare in dettaglio i dati dei diversi studi e quelli delle ancora relativamente limitate metanalisi (10-18).
Per la terapia antiaggregante in prevenzione primaria il rischio di eventi emorragici gravi come l’emorragia cerebrale per le donne è inferiore a quello dell’uomo. Nelle situazioni acute, invece, in cui si impiegano contemporaneamente diversi farmaci antitrombotici il

rischio emorragico è maggiore per le donne; questo si osserva in particolare per l'associazione con l'eparina o l'eparina a basso peso molecolare o con farmaci trombolitici (2-9).
Per la terapia anticoagulante orale, numerosi sono gli studi disponibili in letteratura in cui l'incidenza di sanguinamenti, minori o maggiori, è stata analizzata in rapporto al genere: i risultati non sono del tutto omogenei e sembrano modificarsi nel corso degli anni (19-33).
In sintesi quindi esistono alcuni elementi di orientamento nel complesso quadro del rischio emorragico in rapporto ai trattamenti antitrombotici, con indicazioni di un rischio emorragico più contenuto rispetto all'uomo nel trattamento antitrombotico preventivo di lungo periodo con singoli agenti, anche se devono essere tenuti in precisa attenzione anche gli effetti del gioco ormonale e di altri farmaci di comune impiego al di fuori della prescrizione, ma in grado di determinare anch'essi significativi effetti sull'emostasi (3340).

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soggetti a basso rischio, 660000 pazienti-anno, 3554 eventi vascolari gravi) e 16 studi clinici di prevenzione secondaria (17000 soggetti ad alto rischio, 43000 pazienti-anno, 3306 eventi vascolari severi) che hanno confrontato la terapia a lungo termine di aspirina rispetto a placebo.

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Il TRITON-TIMI 38 è uno studio in doppio-cieco di fase tre, che ha confrontato su 13608 pazienti con sindrome coronarica acuta sottoposti ad angioplastica in elezione prasugrel (n=6813; 60 mg dose da carico, 10 mg/giorno dose di mantenimento) rispetto a clopidogrel (n=6795; 300 mg dose da carico, 75 mg/giorno dose di mantenimento).

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PLATO (NCT00391872) è uno studio prospettico, randomizzato, in doppio-cieco, condotto su 18624 pazienti ricoverati sia per sindrome coronarica acuta STEMI in previsione d'intervento di rivascolarizzazione o sindrome coronarica acuta NSTEMI, sottoposta a terapia invasiva o medica, volto a stabilire l'efficacia e sicurezza del nuovo antiaggregante ticagrelor rispetto al clopidogrel.

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Testosterone, phosphodiesterases and heart

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Cardiovascular disease (CVD) is the world's leading killer disease, and over 80% of deaths (Corona G et al. Best Practice & Research. Clinical Endocrinology & Metabolism 2011).
However, in all populations studied, CVD is more frequent and has a greater mortality risk in men than in women. In Europe, one in four men dies before the age of 75 years due to CVD, while the figure for women is only one in six (Rho RW et al. Circulation 2012). The reasons for such gender difference have not been completely understood. Sex hormones have been considered as a possible factor. A recent meta-analysis suggested that low testosterone levels have been shown to correlate significantly with CV risk factors but also with the incidence of coronary heart disease (CHD) and CVD events (Corona G. et al. European Journal of Endocrinology 2011). Testosterone deficiency and CVD are both associated with visceral fat accumulation, metabolic syndrome, type 2 diabetes, increased inflammatory cytokines, hyperlipidemia, and abnormalities of coagulation. And men with obesity and insulin resistance showed attenuated Leydig cell responsiveness to exogenous gonadotropin stimulation, probably due to direct effects of proinflammatory cytokines and adipokines on testes (Wan C. Diabetes Care 2011). Moreover, endogenous sex hormones may differentially modulate glycemic status, indeed there are evidences that men with lower testosterone levels had an higher risk of type 2 diabetes mellitus (DM) (Ding EL et al. JAMA 2006). Most epidemiologic studies, highlighted that the presence of DM increase the risk of developing incident heart failure, independently of overt coronary disease, providing evidence for the existence a specific diabetes related cardiomyopathy (Asghar O. et al. Clin Sci Lond. 2009). In particular in women, DM is considered the leading cause of heart failure (HF). It is well known that premenopausal women usually have a lower risk of cardiovascular diseases than age-matched men or post-menopausal women. Such advantage, however, disappear in the presence of diabetes mellitus. Heart diseases is twice more common in diabetic men, but five times more common in diabetic women. It seems that the female protective factors, is reversed in the presence of DM.
Most experimental and clinical studies on diabetes only induced male subjects and failed to address gender difference in diabetic heart complications. Furthermore, the clinical diagnosis is less accurate in

women as compared to men since HF in women is less closely associated with systolic LV dysfunction. The few studies addressing gender differences, have shown that female gender is associated with a more favourable myocardial adaptation to hemodynamic overload, including a better preserved contractile response and a greater adaptive hypertrophic reserve (Rho RW et al. Circulation 2012). These advantages that are partially related to an estrogenic effect and fall after menopause, are completely lost or even reversed in the presence of DM. It seems that female myocardium, when adequately estrogenized, is more resisted to developing hypertrophy, however, with advancing age and in post-menopause, a failing pattern rapidly develop. Several studies analyzed the cardiovascular effects of Testosterone replacement therapy in hypogonadal (Corona G et al. Best Practice & Research. Clinical Endocrinology & Metabolism 2011). But, if sexual difference with respect to cardiovascular risk decreased in diabetic population, we could hypothesize that hormonal replacement therapy is not the only therapeutic response. The currently recommended standard of HF therapy has been largely proven in male subjects and my not represents the optimal therapy for women. Cyclic-GMP-Phosphodiesterase (PDE5) protein is upregulated in myocardial hypertrophy. *In vitro* and *in vivo* studies in mice have shown that cGMP and its downstream protein kinase G (PKG) are signals common to most pathways activated in cardiac hypertrophy (Takimoto E. et al. Nat Med. 2005). Inhibition of phosphodiesterase-type-5 (PDE5) exerts a relaxant effect on the smooth muscle cells of the trabecular structures of the corpora cavernosa, resulting in improved erections in men and hypoactive sexual desire disorders in women (Blomers J et al. J Sex Med. 2012). More recently, PDE5 inhibitors (PDE5i) have been claimed to offer cardioprotective effects. The use of PDE5 inhibitors for HF has been assessed only in men. Whether these drugs could be used in women, or is influenced by the estrogen status, remains unknown. We documented (Giannetta E, Isidori AM et al. Circulation 2012) the early features of diabetic cardiomyopathy in large cohort of diabetic men showing that left ventricular concentric remodeling associated with altered myocardial contraction dynamics occurs in the absence of ischemic heart disease. We also showed that chronic PDE5 inhibition, at this stage, has a lusitropic effect resulting in improved cardiac kinetics and circulating markers, independently of other vasodilatory or endothelial effects, through a direct intramyocardial action**.** In this view, we are performing a large study to unravel the mechanisms involved in the onset of cardiac damage in diabetic patients and to determine whether chronic therapy with PDE5 induces an anti-remodeling effect by acting directly on the heart or peripherally on endothelial function and afterload. The aims of our project are to provide a better understating of the diabetic cardiomyopathy in women in order to offer a gender-oriented stratification of risk and personalized intervention strategy.

Gender medicine and epistemology

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La "medicina di genere" è un tema che viene alla luce negli anni Ottanta del secolo scorso, a partire da varie osservazioni, che mettevano in discussione l'adeguatezza dell'impostazione metodologica, ma in ultima istanza epistemologica, della medicina scientifica. Tra il 1983 e il 1989 l'FDA passava in esame la presenza delle donne nei trial clinici e giungeva alla conclusione che i risultati degli studi sperimentali sulla valutazione dei farmaci risentivano di un bias rilevante, poiché le donne non erano rappresentate adeguatamente in rapporto alla prevalenza della condizione clinica in oggetto e del trattamento studiato. Negli stessi anni veniva alla luce che la prevalenza delle malattie cardiovascolari aumenta significativamente nelle donne dopo la menopausa, che le manifestazioni disturbi cardiaci nelle donne sono diverse rispetto agli uomini e che c'è una sottovalutazione e un sottotrattamento della malattia cardiaca nella donna rispetto all'uomo.

Il fatto che sia stata l'appartenenza al genere femminile a dimostrarsi per la prima volta associata a diversi rischi di ammalare o a trattamenti meno efficaci, anche come conseguenza del fatto che i maschi sono stati i soggetti prevalentemente studiati e trattati dai medici, ha fatto sì che la "medicina di genere" sia oggi quasi sinonimo di "medicina della donna". I generi, in quando dipendono dai sessi, sono tendenzialmente due, e per entrambi, sul piano dell'impatto per la salute, sono in gioco sia i meccanismi biologici che determinano il sesso e quindi le funzionalità riproduttive, sia le variabili ambientali e culturali che incanalano i comportamenti in rapporto alle differenze sessuali. Quindi, senza sottovalutare le ragioni per cui nel passato e anche oggi le donne, per il fatto di essere donne, non godono delle medesime opportunità di salute degli uomini, è un fatto scontato che la salute dei maschi e delle femmine dipenda, sia messa a rischio e possa essere ripristinata da condizioni e interventi diversi. Anche a seconda dei momenti presi in considerazione nella biografia della persona. Le particolarità dei contesti sociopolitici quindi culturali e ovviamente le discriminazioni economiche e sociali legate al genere di fatto accentuano i rischi per la salute, condizionando gli stili di vita e le politiche di sanità pubblica.

In rapporto ai temi dell'epistemologia, la medicina di genere solleva diverse questioni, a seconda di quali istanze e orientamenti filosofici si

prendano in esame. In questo contributo, non saranno discusse questioni di epistemologia di genere in rapporti allo statuto conoscitivo della medicina. Invece, sarà affrontato il problema dell'adeguatezza dell'impianto epistemologico strettamente scientifico della medicina, sia sul piano della ricerca di base sia di quella clinica e sial dell'uso degli approcci *science based* nelle decisioni mediche e di sanità pubblica, nel tener conto dei fattori di genere che sono in gioco in medicina e sanità pubblica. Ora, il metodo scientifico va alla ricerca di spiegazioni il più possibile generalizzabili e di indicazione valide il più largamente possibile. Questo implica cercare di eliminare le differenze nei singoli casi, che si può assumere pesino di meno in una ipotetica catena causale. Questa opzione può funzionare quando si studiano sistemi naturali semplici, ma la fisiologia degli organismi umani è qualcosa di molto complesso. E complesso in un modo particolare. Si tratta di una complessità funzionale a un 'disegno' evolutivo, cioè alle logiche causali che hanno prodotto e alimentano l'evoluzione della vita sul pianeta. In questo quadro teorico, che è poi l'unico autentico, dove si ha a che fare con sistemi biologici in evoluzione, le differenze contano. Ovvero le differenza individuali, che includono anche quelle di genere, sono l'unica cosa che conta nella realtà dei fatti. Inclusi i fatti medici e sanitari.

L'epistemologia della medicina così come si articola attualmente, cioè considerata nel suo pluralismo metodologico che ruota intorno a diverse strategie di studio connotate come *sperimentali*, è riuscita e riesce a produrre conoscenze e strategie di intervento efficacia. Ma indirizza più a condizioni standardizzate che a capire la singolarità dei meccanismi fisiopatologico o a le terapie davvero sulle persone. Le pressioni quantitative esercitate dal flusso di dati genomici e le applicazioni o indicazioni delle correlazioni tra variabilità genetica individuale e rischio medico spingono inesorabilmente l'epistemologia medica a evolvere verso un impianto evoluzionistico generale anche per il pensiero medico. Almeno questa sarebbe l'inevitabilità teorica. Che deve fare i conti con dei pregiudizi ideologico-religiosi diffusi verso il modo di pensare evoluzionistico o darwiniano.

Il contributo inquadrerà i temi della medicina di genere come esempi dell'esigenza che la medicina faccia proprio, anche su un piano epistemologico, lo statuto biologico della differenza quale realtà di riferimento. I temi della medicina di genere saranno riesaminati ragionando a partire dall'influenza delle storie di vita individuali, condizionate dalla storia evolutiva della specie, sulle predisposizioni patologiche e le risposte ai trattamenti, e dall'analisi di come le

dissonanze tra l'ambiente dell'adattamento evolutivo e quello attuale influenzano i rischi di malattia.

La medicina di genere rappresenta uno stimolo fondamentale per il miglioramento della adeguatezza della ricerca e della pratica medica sul piano non solo della qualità dei risultati, ma anche della pertinenza della cornice epistemologica. I temi e i problemi della medicina di genere possono concorrere alla costruzione di un impianto di teorizzazione integrato ed efficiente del pensiero medico, cioè a una visione culturale unificante, fondata sul riconoscimento del fatto che l'impatto delle differenze di genere sulla salute non possono essere attenuate diffondendo valori egualitaristici di natura meramente ideologica. Solo un'impostazione culturale laica e pragmatica, che faccia riferimento a una medicina fondata sulle conoscenze scientifiche, cioè al pensiero biologico evoluzionistico, al metodo sperimentale e alle prove di efficacia, può rendere efficaci e utili le politiche sanitarie mirate a ridurre gli effetti negativi del genere sulla salute delle persone.

The Italian perspective

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Introduction

The relationship between women and science and the difficult acknowledgement of their leadership by the society, even in the more sensitive, advanced realms, has become one of the central issues that National and International institutions are facing with regards to job search policies, professional development, and health.
The ongoing debate between experts and public opinion has underlined the persistent difficulty women have in attaining high-level positions in the world of research and innovation.
This problem certainly exists in Italy; data on our situation and our prospects will be presented.

What are the future prospects?
Secondary school education is available to young men and women in equal measure, and the number of women enrolling in technical and scientific university departments is now equal to, if not greater than, that of men.
Both men and women possess the natural qualities required of a scientist, i.e., intelligence, intuition, the ability to work hard, and the capacity to endure the mental effort of extreme concentration.
Why, then, are there so few established female scientists?
Two elements play a fundamental role in the training and in the cultural background of a scientist: the importance of teachers and mentors as role models and the personal satisfaction and reconciliation with family life. Those women who want a lifestyle that includes both a family or personal relationships as well as a career in science may encounter difficulties given that in everyday life women can rarely dedicate all of their time to thought and study: they do not want to, nor can they, ignore the time and emotional demands placed on them by children, partners, and/ or elderly parents.

During that period of life when the foundation of one's career is being laid down, i.e., between the ages of 25 and 40, women's career advancement is limited, both because this is the time when women are likely to decide to have children and because of the problems related to two-career couples; these women are frequently married to men in important professional positions. The psychological impact they experience is therefore that of the widespread myth that all great discoveries are made before the age of 40.

But also for women that do not have family or children barriers exist to hinder their career.

What is the solution? While one can look for A *Room of One's Own* in the arts and in literature, science requires a laboratory and scientist colleagues, as well as the encouragement of society and of the scientific community.

We are facing a social evolution, with the number of women who are in the front lines increasing every day, even professionally. This inevitably leads to an increase in the number of stressful situations, added to psychophysical resources women expend in their family life.
The role of genes and hormones, which biologically determine gender, is only part of the problem. The way men and women deal with their health, their symptoms, with prevention, and with treatment stems from the conditioning of the society and the culture in which they grew up and/ or live in.
Women's two jobs (i.e., family and profession), their tendency to put the needs and health of others before their own, their interest in health issues that are for the most part limited to reproductive questions, and the limited participation of women in clinical trials of new drugs – these are all factors that demonstrate to what degree women are still at a disadvantage, compared to men, in terms of safeguarding their health.
In addition, as they live longer than men, women are also more subject to chronic disease. They take more medication, and they play an important role in the family in ensuring the appropriateness of their partner's and their children's treatment.
Women are also subject to various kinds of conditioning (family, work, mass media, and so on) which limit their freedom of action.
For a long time now, the health and sickness of a population have not made any distinction between men and women in terms of treatment, prevention, or research and development. Recent epidemiology has made us aware of the fact that disease incidence for men and for

women differ, as does the course of disease. The knowledge that there are important differences between men and women – for example, those that can been seen in the cardiovascular system as well as those in the variability of the hormonal regulation – and that these differences play a crucial role in medicine, dates back to the 1980s.
This is also true in oncology, where differences are seen in the incidence and mortality not only for those cancers that are typically male or female, but also for those that in theory are not gender-specific. An important epidemiological observation is that cancer mortality differs from country to country and between men and women.
According to the 2008 report from AIRT (Associazione Italiana Registri Tumori), the Italian population was over 59 million, with females counting just over 30 million. The demographic statistics produced by Istat highlight the fact that women live, on average, longer than men: the life expectancy for women is 84 years, while for men it is 79 years. Women's greater longevity contributes to determining some of the differences that are seen in chronic disease.
Cancer is the second leading cause of death in women after cardiovascular disease: every year, 119 women out of 10.000 over the age of 75 and 38 between the ages 55 and 74 die of cancer. In Italy, it is estimated that there are about 120.000 cases of cancer /year in the entire female population aged 0-84 years, about 38.000 of which are breast cancer.
The risk of dying of cancer is about 16.5% for men (1 death every 6 males) and 8.9% for women (1 death every 11 females). Women's risk is therefore lower, and this despite the fact that they live longer, which in theory should increase both the causes of cancer and the probability of mutations.
Prevention and early diagnosis have greatly increased survival for female tumours like breast cancer and cervical cancer, the incidence of which will decrease thanks to the vaccine.
Survival for breast cancer or colon cancer is longer in Italy, and especially in Emilia-Romagna, Tuscany, and in other Italian regions where screening programs have been implemented, than it is in England. The life expectancy of a woman in Emilia-Romagna is longer than the national average.

Objective
The mission is to pursue health-related objectives concerning the female population and gender medicine by strengthening and supporting the attention, research, assessment, and initiatives addressing especially the risk of complex diseases, the issues, and the areas pertaining to women's health and to gender medicine.

Methods
Efforts will focus on refining and consolidating the scope of research**,** dedicating analyses and specific project lines to the topic of promoting/ personalizing women's health and gender medicine, and enhancing the role of women in society and in the scientific community.

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The European perspective *La prospettiva europea*

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Research addressing sex and gender in biomedical sciences and clinical medicine is emerging as a promising field. 'Gender Medicine (GM)' is increasing the evidence on differences between women and men in pathophysiology and manifestation of many diseases and in received health care. There is an increasing recognition that both sex and gender affect the health for women and men. Sex refers to biological differences between women and men: genetic predisposition to diseases, body size and composition, drug metabolism. Gender refers to cultural and social attitudes that together shape "feminine" and "masculine" behaviour. Humans function in large and complex societies through learned behaviours. Gender is one aspect of these sets of behaviours and therefore gender based attitudes influence health. GM duly recognizes that sex and gender (S&G) influence each other and are inseparable in their relation to human diseases. Shorter life span and myocardial infarctions at younger age in men may be due to biological causes, such as a recently discovered gene variant on the Y-chromosome, but may also be related to stress or risk taking behaviours. Vice versa, gender based life style factors, smoking, toxins, nutrition and exercise modify DNA packaging and gene transcription by epigenetic mechanisms and thereby alter body composition. Adverse drug effects cause a large number of medical complications particularly in women which may be due to sex differences in drug metabolism as well as to gender related differences in prescription and drug use. Interaction of S&G related mechanisms leads to different manifestation of frequent diseases such as infarction, heart failure, diabetes, rheumatic disease and also infections in women and men. (1-6)

Given the wealth of evidence as described above it has become a matter of urgency to provide the research community with appropriate tools to address sex and gender in their research. The EU/US project Gendered Innovations in Science, Health& Medicine, Engineering and Environment, led by the FP7 Expert Group Innovation through Gender exactly aims for that. This project can be seen as following up upon earlier framework projects addressing the gender dimension of the research content, resulting from the EC policy framework of

mainstreaming gender equality in all EU activities including research policy (7,8).

Identifying gender bias and understanding how it operates in science and technology is important. But analysis cannot stop there: Designing sex and gender analysis into research stimulates new knowledge and technologies. From the start, sex and gender analyses act as additional "controls" (or filters for bias) to provide excellence in science, health & medicine, and engineering research, policy, and practice (9).

To achieve these goals, the GI project launched a website (http://genderedinnovations.eu) on 1st November 2011. The site highlights three elements:1) **Methods** of sex and gender analysis relevant to science, health & medicine and engineering; 2) **Terminology** defining key concepts used throughout the site; 3) **Case Studies** documenting specific gendered innovations and demonstrating how methods of sex and gender analysis are applied in specific examples. In seven international workshops, held in Europe and the US, materials have been developed and peer reviewed by 57 experts from different scientific fields (see contributors on the website) together with gender experts. The final results will be presented in a session in the European Parliament in early spring 2013.
By employing sex and gender analysis as a *resource* to create new knowledge and technology researchers can 1) add value to research and engineering by ensuring excellence in outcomes 2) add value to society by making research more responsible to social needs 3) add value to business by developing new ideas, patents and technology .

Some examples of Gendered Innovations

1. Sex analysis has revealed that the pathophysiology of CVD is different in men and women especially in younger women. It has led to better diagnostic techniques and symptomatology. Analyzing gender assumptions has improved the understanding of risk factors and prevention.
2. The inclusion of men in osteoporosis research has led to better diagnoses and treatments (in the past, osteoporosis was conceptualized as a disease of postmenopausal women).
3. Sex analysis in animal research has led to new knowledge about how sex hormones influence basic molecular pathways involved in immune system function (10).

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Sex differences in the cardiac myocyte

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Heart disease is the leading cause of death in the United States and Europe in both men and women**.** However, females have much better outcomes than males with heart disease when they are younger, and males have better outcomes than females when they are older. Males have increased mortality compared to females in response to a myocardial infarction as well as greater pathologic responses to aortic stenosis. Males with genetic cardiomyopathies also show 3-fold higher penetrance than females. Most of these differences are recapitulated in laboratory cell and animal models. Female mice have superior cardiac responses to exercise at any age. What underlies these potent sex differences? The roles that estrogen, and its two classical nuclear hormone receptors, ERα and β, play in regulating baseline cardiac function and these sexually dimorphic responses is still a topic of considerable debate. For example, while estrogen is essential for normal male physiology, excess hormone can be harmful; particularly in the cardiovascular system. Further, we and others have shown that estrogen is not always protective in females with heart disease, in contrast to widely held assumptions. Although men have low circulating levels of estrogen, there is local conversion of testosterone to estrogen which is functionally important. Further, men with mutations in either ERα or aromatase have profound phenotypes, including endothelial dysfunction, atherosclerosis, or excessive bone growth. We have taken a global approach to understanding the contribution of sex differences in the cardiac myocyte to these differences. We have found that female myocytes have much higher phosphorylation states of: receptor tyrosine kinases (RTK) and intracellular signaling cascades compared to male myocytes. Using agonists specific to each estrogen receptor (ER), we have also found sex-specific and receptor-specific effects on RTKs and downstream signaling activities. We found that ~2000 transcripts differ significantly between young males and female ventricles and will carry out RNA-Seq on male and female myocytes.

Diet and Hypertrophic cardiomyopathy (HCM).[1] HCM is more severe in male than female mice eating a soy-based diet. We determined that the detrimental effects are mediated by the phytoestrogens present in soy. A soy-free diet (casein based) supplemented with the predominant phytoestrogens in soy, genistein

and daidzein, recapitulated the fibrotic, proapoptotic and negative hemodynamic effects of soy in male hearts. As with the soy diet, the hearts of female HCM mice were not negatively affected by the phytoestrogen-containing diet. To determine the role of estrogen in the sex differences mediated by diet in HCM, gonadectomies were performed and estrogen was administered to male and female HCM mice on a casein- or phytoestrogen-supplemented diet. Somewhat surprisingly, estrogen was not protective in male or female mice with HCM and, in fact, was lethal in phytoestrogen-fed male mice with HCM. Because genistein is a potent tyrosine kinase inhibitor and tyrosine kinase inhibition has been associated with cardiotoxicity, we tested its effects in isolated adult cardiac myocytes. Genistein inhibited different tyrosine kinases depending on sex and, in combination with estrogen, resulted in apoptosis only in adult male cardiac myocytes. Finally, we show that phytoestrogens led to distinct programs of gene expression in hearts from males vs. females with HCM, suggesting mechanisms by which males are more sensitive to the detrimental effects of phytoestrogens and females are protected. These results implicate the phytoestrogen genistein in mediating cardiac pathology in males with HCM and, importantly, establish that estrogen is not protective in the setting of HCM.

The role of estrogen in females.[2] Although it is widely believed that estrogen is cardioprotective, there are contradictory reports, including increased cardiac events in postmenopausal women receiving estrogen and enhanced cardiac protection from ischemic injury in female mice without estrogen. We exposed aromatase knockout (ArKO) mice, which produce no estrogen, to both pathologic and physiologic stimuli. This model allows an investigation into the effects of a complete, chronic lack of estrogen in male and female hearts. At baseline, female ArKO mice had normal-sized hearts but decreased cardiac function and paradoxically increased phosphorylation of many progrowth kinases. When challenged with the pathological stimulus, isoproterenol, ArKO females developed 2-fold more hypertrophy than wild-type females. In contrast, exercise-induced physiological hypertrophy was unaffected by the absence of estrogens in either sex, although running performance was blunted in ArKO females. Thus, loss of estrogen signaling in females, but not males, impairs cardiac function and sensitizes the heart to pathological insults through up-regulation of multiple hypertrophic pathways. These findings provide insight into the apparent loss of cardioprotection after menopause and suggest that caution is warranted in the long-term use of aromatase inhibitors in the setting of breast cancer prevention.

Pregnancy and the heart.[3] Although the signaling pathways underlying exercise-induced cardiac adaptation have been extensively

studied, little is known about the molecular mechanisms that result in the response of the heart to pregnancy. The objective of this study was to define the morphological, functional, and gene expression patterns that define the hearts of pregnant mice, and to identify the signaling pathways that mediate this response. Mice were divided into three groups: nonpregnant diestrus control, midpregnancy, and late pregnancy. Pregnancy was associated with significant cardiac hypertrophy. The prosurvival signaling cascades of Akt and ERK1/2 were activated in the hearts of pregnant mice, while the stress kinase, p38, was decreased. We tested whether pregnancy-associated sex hormones could induce hypertrophy and alter signaling pathways in isolated neonatal rat ventricular myocytes (NRVMs). In fact, progesterone, but not estradiol treatment, increased NRVM cell size via phosphorylation of ERK1/2. Inhibition of MEK1 effectively blocked progesterone-induced cellular hypertrophy. Taken together, our study demonstrates that pregnancy-induced cardiac hypertrophy is mediated by activation of Akt and ERK1/2 pathways. Although the hypertrophic responses of the heart to pregnancy and exercise are both considered to be physiological processes, they occur in quite different hormonal and temporal settings. We compared the global transcriptional profiles of left ventricular tissues at various time points during the progression of hypertrophy in exercise and pregnancy. The following groups of female mice were analyzed: non-pregnant diestrus cycle sedentary control, mid-pregnant, late-pregnant, and immediate-postpartum, and animals subjected to 7 and 21 days of voluntary wheel running. Hierarchical clustering analysis showed that while mid-pregnancy and both exercise groups shared the closest relationship and similar gene ontology categories, late pregnancy and immediate post-partum were quite different with high representation of secreted/extracellular matrix-related genes. Moreover, pathway-oriented ontological analysis showed that metabolism regulated by cytochrome P450 and chemokine pathways were the most significant signaling pathways regulated in late pregnancy and immediate-postpartum, respectively. Finally, increases in expression of components of the proteasome observed in both mid-pregnancy and immediate-postpartum also resulted in enhanced proteasome activity. Interestingly, the gene expression profiles did not correlate with the degree of cardiac hypertrophy observed in the animal groups, suggesting that distinct pathways are employed to achieve similar amounts of cardiac hypertrophy. Our results demonstrate that cardiac adaptation to the later stages of pregnancy is quite distinct from both mid-pregnancy and exercise. Furthermore, it is very dynamic since, by 12 hours post-partum, the heart had already initiated regression of cardiac growth, and 50 genes had changed expression significantly in

the immediate-postpartum compared to late-pregnancy. Thus, pregnancy-induced cardiac hypertrophy is a more complex and dynamic process than exercise-induced cardiac hypertrophy and our data suggest that the mechanisms underlying the two types of hypertrophy have limited overlap.

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Gene-environment interaction in male (in)fertility

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Human fertility seems to continuously declining, especially in most industrialized countries. In these cases, the reduction in fertility rates might be regarded as consequence of economic and social factors, anyway the biological contribution to this phenomenon might not be disregarded. Indeed, clear evidence has shown that the fertility potential of men in western countries is progressively declining. Possible signs of such reduced fertility potential in couples of western countries are the continuous increase in assisted reproduction techniques, the reduction in sperm quantity and quality in last decades, and the increased incidence of congenital and acquired anomalies of the male reproductive tract. Although it is extremely difficult to clearly identify the relative role of environmental factors in these processes, it is nowadays well accepted that environmental pollution might contribute to decreased male fertility and poorer spermatogenesis. Dioxins, pesticides, heavy metals, cleaner components, plastic and paint additives are nowadays present everywhere in the environment and accumulate in food chain reaching the man through food and water. Such substances negatively influence the reproductive system and many considerable examples of the consequences of this pollution exist in animals living in particular areas. Many of these substances act as endocrine disruptors and therefore might affect not only fertility but also foetal development during pregnancy. Importantly, some evidence highlights that the environment is able to influence spermatogenesis mainly when acting on a specific genetic background, which in turn might regulate human fertility through different genes and genetic polymorphisms.
Nevertheless, male infertility represents one of the clearest examples of complex phenotype with substantial genetic basis. Numerous male mouse models, mutation screening and association studies performed in the last few years definitively demonstrate the high prevalence of genetic causes of spermatogenic impairment. Genetic causes account for 10%–15% of severe male infertility, including chromosomal aberrations and single-gene mutations. However, a large proportion of infertile males does not receive a clear diagnosis and are reported as idiopathic or unexplained, reflecting our poor understanding of the basic mechanisms regulating spermatogenesis and sperm function. Indeed, it has been suggested that up to 50% of infertility in humans can be attributed to genetic abnormalities. Although studies aimed at

identify gene mutations responsible for male infertility are numerous, actually little is known about the genetic control of natural fertility. A recent paper addressed this question. This study utilized a two-stage strategy to identify candidate genes for male fertility: it first performed a genome wide association study of two fertility traits (family size and birth rate) in 269 Hutterite men, and then significant polymorphisms were analysed in a validation study of 123 ethnically diverse men who underwent semen analysis. The Hutterites are a founder population of European descent that represents an ideal population in which to study the genetics of normal human fertility because they proscribe contraception and uniformly desire large families, and in which variation in non-genetic factors that affect reproductive practices is minimized between individuals. As a consequence, the Hutterites are among the most fertile human populations with only ~2% childless couples, median sibship size >10 persons and mean interbirth interval <2 years in the 1960s. The study included Hutterite men with at least one child and considered two quantitative measures of fertility: family size (number of births) and birth rate (calculated for couples with two or more children as the number of births per year of marriage). Genotyping of 248 210 autosomal polymorphisms$_{-4}$yielded 28 independent loci with a significant threshold of ≤ 10 for family size, 15 loci for birth rate and two regions for both phenotypes. The most significant polymorphisms were then selected and analysed in 123 men for validation and assessment for the functional or clinical effects on semen parameters. This analysis showed that alleles or genotypes for nine polymorphisms that were associated with reduced natural fertility in Hutterites were also associated with reduced measures of sperm count and/or motility in this cohort of men, representing therefore new potential loci for human male fertility. This study therefore identified new autosomal regions and genes with potential roles in male fertility and candidates as infertility genes.

On the other hand, standard semen analysis, although being able to give information on the probability of conception, cannot clearly distinguish fertile from infertile populations. This is particularly evident in cases of infertility or repeated assisted reproduction failure with normal routine semen parameters. In these cases, abnormal sperm function or unknown molecular defects can be hypothesized, making researches aimed at identifying new potential genetic markers of fertilizing ability and male fertility necessary. Recent studies therefore aimed at identifying gene markers able to provide information on the fertilizing potential of human spermatozoa in cases in which standard semen analysis does not detect any abnormality. In the near future therefore, research will probably clarify novel genetic

markers of natural fertility, effective spermatogenesis, idiopathic infertility cases, and reproductive potential during assisted reproduction technologies, including *in vitro* fertilisation and intracytoplasmic sperm injection cases with repeated implantation failure or pregnancy loss.

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Mutation rate and testicular aging: an other link to declining fertility?

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In developed countries, delayed parenthood is becoming a widespread phenomenon mainly due to various socioeconomic factors. While increased life expectancy would justify the trend of postponing childbearing, from the reproductive standpoint fertility might be affected in a negative manner. Although at a much lower extent than maternal age, it seems that paternal age also exerts a negative effect on fecundity (1, 2). The biological basis underlying this phenomenon is likely to be multifactorial and maybe related to changes in semen quality (sperm number, motility and morphology) and in genetic/epigenetic features of the aging male gamete. While the paternal age effect on some fecundity parameters such as fertilization rate, embryo quality, implantation rate is still controversial, there is a rather consistent association between miscarriage and advanced paternal age (3). This may reflect the higher frequency of numerical and structural chromosomal anomalies, DNA fragmentation and mutation rate observed in the male gamete of aged men. In fact, it can be hypothesized that the diffuse negative modifications observed in the sperm genome are probably the most relevant contributors to reduced fecundity.

Whether paternal age is associated with an augmented risk of aneuploidy in the offspring is still controversial. On the other hand, it has been estimated that 80% of structural aberrations detected during embryo development or at birth are of paternal origin. A relationship between men's age and the presence of sperm structural aberrations seems indeed plausible, since a higher frequency of acentric fragments, chromosomal breaks and rearrangements have been described in the elderly. Concerning a structural anomaly of the Y chromosome (AZFa deletion), we performed an estimate of the meiotic rate of this deletion in sperm-derived DNA of normozoospermic men aged from 20-67 years. All men carried an intact Y chromosome in their genomic DNA whereas the deletion was observed in their spermatozoa with a meiotic rate of the deletion ranging from 0.4 to 4.7 x 10^{-5}. The highest values were observed both in young and older men indicating the absence of a purely age-related effect on the deletion formation during spermatogenesis (personal data).

Concerning sperm DNA damage a higher levels of double-stranded DNA breaks were reported in older men and an inverse relationship

has been proposed between DNA fragmentation index and male age. Moreover, paternal age shows a positive correlation with increased DNA damage in sperm donors and in men of infertile couples.
Paternal aging not only affects the genomic integrity of spermatozoa in terms of DNA fragmentation and numeric and structural chromosomal anomalies, but it has been reported also in relationship with point mutations. A plausible explanation to such a phenomenon is that spermatozoa undergo many more germline cell divisions compared to oocytes. Furthermore, since sperm production occurs continuously throughout reproductive life, the advancement of paternal age will lead to an increased number of cell divisions and chromosome replications with the consequent acceleration of the mutation rate. By the age of 45 years old, 725 mitotic divisions would have occurred, with the possibility of a DNA copy error at every single replication (4). This could be due to several mechanisms: firstly, alterations of age-sensitive processes such as the DNA replication and repair might occur; secondly, the increased number of cell divisions might represent a compensatory event for cell death at old ages; finally, the accumulation of mutagens from either external or internal sources, which would certainly increase with age, might also contribute. Therefore, paternal aging is considered the major cause of new mutations in human populations leading to the accumulation of mutations that could possibly increase the incidence of recessive genetic disorders in the future (5). Advanced paternal age has been associated with an increased risk for spontaneous congenital disorders and common complex diseases (such as some cancers, schizophrenia, and autism). A small group of disorders, including Apert syndrome, achondroplasia, thanatophoric dysplasia and Costello syndrome, have been related to increased paternal age and are defined as "paternal age effect" (PAE) disorders. The direct quantification of PAE mutations in sperm and testes suggests that the common factor in the paternal age effect lies in the dysregulation of spermatogonial cell behavior, an effect mediated molecularly through the growth factor receptor-RAS signal transduction pathway. These PAE mutations, although arising rarely, are positively selected and expand clonally in normal testes. This phenomenon leads to the relative enrichment of mutant sperm over time -explaining the observed paternal age effect associated with these disorders.
Given that the trend toward older parenthood is an emerging issue, paternal age effect on fecundity definitely deserves substantial consideration especially concerning the genome of the aging gamete.

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Social age vs Biological age

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It is important to understand the factors that increase and limit fertility. While biological factors condition fertility, so do social expectations. These findings provide widespread evidence across Europe, social limits exist alongside biological ones and we can see that though both sets of factors are more binding for women. Aging is a normal biological process in human beings involving the gradual alteration of organ's structure, function, and tolerance to environmental stress. Since approximately age 30, effectiveness of various physiological functions begins a subtle decline that becomes more obvious around age 55-60. This condsideration is earlier for reproduction infact we can estimate a lower reproductive performance from 35 for women and 55 for men in western countries.
However, physiological aging does not occur at the same rate throughout the population. We may say that there is a biological and a chronological age: biological age focuses on senescent changes and physiological processes in eldrely , whereas chronological age focuses on elements of calendar time. Biological age may be reduced by regularly participating in a well-designed physical fitness program. As people age, there is no doubt that there are a certain number of well known changes that take place such as: reduction of lean muscle mass, increase in body fat due to loss of lean muscle mass and a slower metabolism, decline in maximal heart rate; decrease in bone density, increase in blood pressure, decrease in overall flexibility, decrease in cardiovascular output, decline in maximal oxygen uptake and gradual decline in motor skill function and coordination. Nowdays we are emphasizing biological age basing on lifestyle, medical history, and genetics. In other words, your body might be younger or older than you think, depending on how well you take care of it and your personal risk of accidents. All these considerations are more evident for reproduction: in western countries has been a separation between fertility age capacity and social age. Sometimes they match and sometimes they go in different direction. There is some part of this anti-aging idea that is totally genetic. However, most people have a great deal of control of how fast they age; by eating and exercising correctly. Social age deadlines for childbearing among women are likely to be driven, in part, by concerns about the health risks for both mother and child. But first we should consodr that ovarian aging is the first caue of fertility failure. After this point of view there are risks at

advanced maternal age include chromosome abnormalities foetal death, stillbirth and loss and other pregnancy complications (hypertension, diabates, growth fetus retardation…) Interestingly, there is evidence that for obstetric outcomes, increasing age is a continuum rather than a threshold effect. Recently advanced paternal age has captured the interest of physicians. It has been shown that also men's biological clocks affect hormone levels, fertility and sperm quality, despite a youthful appearance due to a healthy life. More over both advanced maternal and paternal age seems associated with the risk of autism spectrum disorders, miscarriage, lower success for IVF and higher occurrence of malformations. For these and other conditions, Authors suggest that the age of 43-45 is generally a turning point for Assisted Reproductive Technologies with own eggs.

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Differenze di Genere: Aspetti Bioetica

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La questione delle "differenze di genere" in *bioetica* non è una questione metafisica, ma una questione bio-medica. Pertanto, nel contesto di questa lezione non dovrei trattare direttamente argomenti sulla natura ontologica della sessualità umana, ma questioni cliniche.

Ho usato il condizionale, perché gli argomenti di questa assise scientifica che toccano la bioetica (osteoporosi, cardiovascolarità, fertilità, ricerca scientifica, medicina estetica) sono da una parte legati alla salute come questione terapeutica, ma dall'altra a trasformazioni del corpo che da "muto" forse parlerà linguaggi nuovi; questi linguaggi non sono neutrali e indifferenziati, ma parlano di nuove identità personali e nuove visioni della società.

Si pensi – solo per citare qualche caso – alle questioni biomediche (farmaceutiche e chirurgiche) legate al transessualismo; o agli ambiti della medicina riproduttiva dove i soggetti coinvolti (ad es. il nascituro) potrebbero, non per propria scelta, ritrovarsi con varietà parentali e genitoriali non date in natura (due genitori genetici in diverso utero; o l'embrione ottenuto per trapianto nucleare da un solo soggetto genetico che è anche il medesimo dell'utero).

Confermo, comunque, che non intendo trattare questioni metafisiche.

La bioetica studia sempre questioni cliniche e casi clinici, anche quando lo fa con riferimento allo statuto etico delle persone e degli altri soggetti coinvolti (animali e ambiente, per non "medicalizzare" l'intera salute umana). La bioetica "medica", in particolare, studia questioni sulla salute di carattere bio-sperimentale che toccano le opinioni morali delle persone e l'etica dei gruppi sociali. Non ci sono dubbi che la salute e la malattia sono profondamente segnate dai comportamenti e dagli stili di vita, quindi da questioni morali.

Ma quel che ci interessa in questa lezione sono le differenze sessuali, come fatto biologico, che segnano specificamente la chimica, la fisica, la fisiologia e l'anatomia umane. Il genere sessuale ha una dignità scientifica che deve essere bioeticamente "tracciata" perché possa segnare le scelte sia di chi fa ricerca scientifica, sia dei clinici,

sia degli amministratori della sanità o i pianificatori della biopolitica. Il genere sessuale è rimasto latente nello studio e nella terapia, ora occorre riorganizzare tutto il sapere e la gestione clinica in questa prospettiva: questo è un preciso compito e dovere bioetico.

La medicina è sostanzialmente chiamata ad essere medicina di genere, a meno che non si voglia procedere come fino ad oggi. Il genere sessuale segna ogni ambito biomedico con una caratterizzazione distintiva, tracciabile a livello ormonale, fisiologico, patologico. Di conseguenza anche la farmacologia deve essere farmacologia di genere, con un suo peculiare approccio al genere sessuale del soggetto in cura.

In particolare, alcuni temi bioetici che tratterò saranno segnati dalla distinzione fatta propria dalla WHO tra "sex" e "gender". "Maschio" e "femmina" sono categorie sessuali, mentre "maschilità" e "femminilità" sono categorie di genere. Alcune questioni bioetiche saranno, pertanto, proprie dell'ambito "sessuale", in quanto tocca dimensioni cliniche e biologiche specifiche; mentre altri argomenti bioetici si soffermeranno più sulla questione del "genere", quindi aspetti sociali, costumi e norme in quanto segnano profondamente la salute e la malattia sia a livello individuale che sociale. Proprio queste scelte bioetiche o biogiuridiche segnano in positivo o bloccano in negativo il progresso delle scienze biomediche.

GOLDEN COMMUNICATION

Sex-gender differences in autophagic and lysosomal markers

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Autophagy is a lysosomal degradative pathway involved in the intracellular turnover of proteins and cell organelles (1); this process participates to maintain the constitutive cell homeostasis and to respond to harmful conditions like nutrient starvation or oxidative stress (2). However, even if it is still poor known if autophagy and lysosomal function depend on sex-gender, it has been shown that spontaneous and induced autophagy diverges, among other organs, in rat vascular smooth muscle cells (VSMC) and in neurons (3-5). Sex-gender is a factor that largely influences health and diseases and numerous differences are emerging in many cell types, organs and apparatuses including the heart, the liver and the kidney (6); therefore, we aimed to detect sex-gender differences in then constitutive autophagic process in different rat organs. In addiction, we evaluated sex-gender differences in oxidative-stress related biomarkers.
In hearts, livers and kidneys obtained from male and female Sprague-Dawley, we studied the expression of some proteins involved in autophagy as Beclin-1 (7), LC3-I (cytosolic) and LC3-II (membrane bound) (8), these latter proteins ratio, and mTOR which plays a central role in the autophagic process (9); we also studied the expression of a lysosomial membrane protein, LAMP-1 (10). The oxidative stress biomarkers malondialdehyde and carbonylated group of protein (oxidation markers) were also evaluated.
In the heart, Beclin-1 and LC3-II/LC3-I ratio were significantly higher in males than in females suggesting that male heart have a major constitutive autophagy confirming and extending previous results (11). The higher level of autophagic markers in the cardiac tissue of male rats was linked with higher levels in carbonyl groups, indicating that protein oxidation could be of some importance. Interestingly, mTOR expression was higher in male, indicating a

plausible mTOR indipendent mechanism of autophagy, in fact, other mTOR independent mechanism has been already described (12).
In the liver, the autophagicbiomarkers such as Beclin-1, LC3-I, LC3-II, these latter proteins ratio, and mTOR were not sexually different as well as protein and lipid oxidation. Notably, although MDA difference did not reached statistical significance, it was about 26% higher in the female liver in comparison with male liver. One interesting finding is that the integral membrane protein LAMP-1 was significantly more expressed in males (about 60%) than in female. This, at our knowledge is the first time that such a difference is described in literature. Interestingly, it greatly colocalized with LC3 indicating a great number of autophagolysosomes. In these experimental conditions, the kidney is the organ that present less sex-gender differences because only MDA diverged between male and female being significantly higher in females than in males.
In conclusion, the above results suggest that sex and gender differences are organ specific and that the protein oxidation is more linked with autophagic processes in comparison with lipid peroxidation; In the liver, a more abundant number of lysosome has been found and, at our knowledge this is the first time it is described.

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Gender-related effect of rhGH supraphysiological doses on thyroid function in humans

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Abstract
rhGH non-therapeutic intake by athletes (i.e. as doping) is increasing and although GH-IGF-I hypothalamic-pituitary-thyroid (HPT) interaction have been widely described, it is still unclear whether rhGH could exert undesirable or noxious effect on thyroid function. We have reported that short-term administration of rhGH induced an early TSH suppression in healthy trained men, potentially inducing pathologic condition such as hypothyroidism – even though no thyroid function alteration was found (Sgrò et al. 2010). Herein we evaluated change occurrence of some HPT axis parameters in time in well-trained healthy women and men after rhGH (0.03 mg/kg body weight/day, *sc*) administration, 6 days/week for 3 weeks. Morning blood samples were collected immediately before and 3, 4, 8, 15, and 21 days after rhGH administration. A further set of blood samples were taken 3 and 9 days after drug withdrawal. Samples were analyzed for IGF-I, TSH, free T3 (FT3), free T4 (FT4). Whereas in men a significant TSH serum decrease was confirmed at each time point, no TSH changes were observed in women, except for a significant drop at day 4 of the treatment. Notably, each time-point values were significantly different between men and women ($P<0.05$). No differences were really found in FT4 and FT3 level. rhGH intake caused a significant increased in IGF-I serum level in men vs. baseline, while in women IGF-I peaks even over reference range only at day 21 of the treatment. In both groups, values returned to baseline 9 day after drug withdrawal. In conclusion, in women, differently from men, rhGH intake did not induce a constant TSH suppression and failed to increase IGF-I level, except for a peak at the 21st day of treatment. We can speculate that women's ability to "escape" to rhGH-induced changes in HPT-related parameters may be due either to estrogens or to higher basal plasma GH levels, as according to literature (Giannoulis et al. 2005, Veldhuis et al. 2011). Additional studies are necessary to further investigate gender-dependent response to rhGH also for a long-term abuse.

Osteoporosis lifestyle, risk factors and type of medical assistance

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Osteoporosis is a chronic non communicable disease, which is a pandemic disease with a worldwide extension and global health problem. This disease and the correlate bone fractures are an important cause of mortality and morbidity for millions of people. The loss of bone mass occurs from the fourth decade of age and it is progressive; in some subjects can be present an increased reduction of bone mineral content leading to osteoporosis and bone fragility more or less marked. The first sign of osteoporosis is quite often bone fracture and for this reason the disease is also called the "silent disease" **(1)**. Osteoporosis is characterized with a reduction of bone mineral density and an alteration of bone anatomical architecture, resulting in a greater fragility of bone and an increased risk of fracture, which occurs mainly at the level of the spine, femur, and forearm. Bone mineral density is expressed in g/cm^2 resulting mainly by two factors, the peak of bone mass reached at thirty years old and loss of bone mineral content starting from forty years old. Bone resistance to mechanical stress and trauma is given not only from the amount of bone mineral density, but also and mainly from its quality. The quality of bone is essentially depends on different factors such as remodeling, architecture, microtrauma, mineralization and bone matrix **(2)**. The gold standard for the diagnosis of osteoporosis is Dual energy X-ray absorptiometry (DEXA or DXA) analysis at the lumbar spine and proximal femur of non-dominant hand, which allows a precise measure of bone mass and bone mineral density (BMD) **(3)**.
The aim of the study has been to evaluate the lifestyle and dietary habits of patients that have done DEXA examination, to calculate how the degree of osteoporosis correlates to the nutrition habit. In addition, it has been investigated the presence of secondary osteoporosis and who is the leading specialist that is in charge of osteoporotic patients. The questionnaires were administered to 215 individuals during the period August-September 2012. All subjects underwent to the following evaluations: measurement of anthropometric data (weight, height, BMI), bone mineral density with DEXA Hologic 4500, Delphi

QDR Series, Food frequency questionnaire [4.5] to check the dietary habits and FRAX questionnaire which is a tool for assessing the risk of fracture in the next 10 years.
Patients had a mean age of 68 years (± 9.16 years), 203 females and 12 males. The population has been dived in 3 groups using the T-score value: 53 normal, 132 osteopenic subjects and 30 osteoporotic patients. In the group of normal patients were present 50 females and 3 males, with an average age of 59 years (± 9), 7 smoked and 15 took medications. In the group of people with osteopenia, 124 were female and 8 male. The median age was 63 years old (± 8), 19 smoked, 2 drank more than 3 drinks a day of alcohol and only 59 took medications. The last group was made up of 29 females and 1 male with osteoporosis. The average age was 67 years (± 9), only one drank more than three glasses of alcohol a day, and only 22 of them took medications. The habit of smoking was found in total 26 patients (12%) and 19 were osteopenic. Furthermore, in 96 individuals (45%) with osteopenia preventive therapy for osteoporosis was prescribed, in particular using bisphosphonate. The questionnaire (FRAX) revealed the presence of other diseases, which can correlate with the presence of secondary osteoporosis as already reported in recent studies, like type 2 diabetes mellitus (18 patients-8%), early menopause (8 patients-4%), inflammatory bowel disease (3 patients-1%) and celiac disease (3 patients-1%).
Body mass index (BMI) was calculated, this is a measure of body fat based on height and weight that can be applied to both adult men and women. Patients were divided into different categories like underweight (<19), normal weight (19-25), overweight (25-30) and obese (>30). One per cent of patients were underweight, 31% normal weight, 41% overweight, and 27% were obese. It is possible to observe how the majority of population were overweight or obese (total 68%); this is significant since the excess weight can have a negative effect on the osteoporotic process increasing the mechanical load on bones, despite the small number of sample. Analyzing the distribution of overweight (mean T-score -1.56) and obese (mean T-score -1.86) patients, it is possible to observe that higher levels of BMI are directly linked to increased bone fragility: 11% were normal, 63% osteopenic and 11% osteoporotic; differently three patients underweight were two osteopenic and one with osteoporosis.
FRAX questionnaire data analysis showed the following results: 1) 52 patients (24%) reported a previous fractures and after DEXA examination 15% were normal and 60% and 25% had osteopenia and osteoporosis, respectively; 2) 8 patients (4%) reported had rheumatoid arthritis, 1 was normal, 2 and 5 were osteopenic and osteoporotic, respectively. Then, 21 patients (9%) reported the use of

corticosteroids for period of 2-3 months and according to BMD were divided in 10% normal, 76% osteopenic and 14% osteoporotic
The FRAX algorithm allows to calculate the risk of fractures in the following 10 years according to BMD values at the femoral neck. In our sample, the average probability of major fractures were 3.86% (1.8% min-max 15%) in normal subjects, 7.94% (min 2.7% - max 28 %) in osteopenic patients and 17.5% (4.3% min-max 47%) in osteoporotic patients. In contrast, the average probability of hip fracture were 0.32% (min 0% - 1.7% max) in normal subjects, 2.08% (min 0.3% - max 115) in osteopenic patients and 7.87% (min 1.8% - max 30%)in patients with osteoporosis.
In addition, we asked to the patients who was the specialist for the cure and treatment of osteoporosis. In our sample only 17% normal individuals, 21% osteopenic subjects and 20% osteoporotic patients were already followed from an endocrinologist. The general practitioner had in care about 56% of individuals for all three groups. The reaming 30% of all three groups were followed from orthopedic, rheumatologist gastroenterologist, gynecologists and physiatrists specialist.
We can conclude that osteopenia was widespread and this condition can precede osteoporotic disease and it is usually asymptomatic. The early identification of high risk population will allow to implement preventive interventions, as a proper medication prescription or advice on diet and lifestyle. Therefore, interaction between different medical specialist, like endocrinologist with the other specialist, is important to ensure the best control and / or prevention of patients or osteopenic individuals and the combination of the two questionnaires can allow the identification of high risk population that should be evaluated using DEXA.

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Gender and Evolutionary medicine: how modern reproductive patterns of women may influence the role of fertility related genes

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Human fertility is regulated by a large number of genes acting in various different steps to establish both male and female fertility. Many polymorphic variants (alleles) have also been identified in fertility genes, but how these alleles affect human fertility remains unclear. According to the genetical theory of natural selection (1), different alleles at a locus should be associated only with small fertility differences (or no differences at all) and contribute very little to overall fitness, otherwise selection would lead to their fixation or elimination. However recent studies on fertility candidate genes have identified risk/ protective alleles involved in the occurrence of reproductive system diseases causing infertility or subfertility. In addition, some of these polymorphisms have been studied also in relation to their role in positive outcomes after in vitro fertilization (IVF) or other assisted reproductive technology (ART) procedures.

In recent investigations we were able to examine the way the variation of some fertility-related genes [ESR1 (estrogen receptor alpha, FSHR (FSH receptor), CYP19 (aromatase), P53 (tumor-suppressor p53), ACE (angiotensin I-converting enzyme)] may influence reproductive efficiency in natural (or near-natural) fertility populations (i.e. reproducing with premodern reproductive pattern and in absence of deliberate birth control) and could confirm the absence of a relevant effect of gene variants on total fertility (i.e., fertility of women at the end of their reproductive lifetime). We then compared these findings with those reported for the same fertility genes in clinical studies carried out on women reproducing with contemporary reproductive patterns (e.g., birth control, family planning, delayed childbearing, and spacing birth order) (Tab.1).

The overall analysis of the data led us to suggest that, according to Neel (2), fertility genes may represent a further example of genes "rendered detrimental by progress".

In line with this hypothesis some common variants of fertility genes may have become "detrimental", acquiring clinical relevance, following exposure to modern reproductive patterns and might therefore be now associated with reduced fitness and, hence, be under selective pressure (3). Set within an evolutionary framework, this process could lead to the selection of a set of gene variants fitter to

current reproductive behaviors as the shift to later child-bearing age in developed countries (Fig.1).

Table 1. Fertility related polymorphic genes which have been investigated for their role in populations with different reproductive patterns.

Gene	Phenotypes	
	Premodern pattern	**Modern pattern**
ESR1	fertility level	IVF outcome; POF[a]
FSHR	none	IVF outcome
CYP19	none	IVF/COH[a] ; POF[a]
P53	none	infertility; IVF outcome
ACE	none (see text)	recurrent miscarriages.

[a]POF:premature ovarian failure; COH: controlled ovarian hyperstimulation.

Fig. 1 - Some common variants of fertility genes, following exposure to modern reproductive patterns, may have become "detrimental" and associated with reduced fertility.

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Acute Coronary Syndrome: a gender/age-based difference study

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Background: ACS (Acute Coronary Syndrome) may occur in both men and women, but with different symptoms, risk factors or types at presentation. This leads to different clinical and pharmacological management and to the health outcome.
Aim: To analyze patients hospitalized for ACS during 2008 and to determine: population-based prevalence, in-hospital mortality, management of revascularization and non-revascularization, pharmacological treatment on discharge and adherence to it, potential cardiovascular risk factors all in a gender and age-based evaluation.
Materials and Methods: ULSS 16 is one of the local social services in Veneto Region with a population of 483,042 (232,899 men and 250,143 women) in 2008. We examined 1,204 ACS patients (760 men and 444 women) of the ULSS 16 visiting Saint'Anthony Hospital in 2008, their Sanitary demographics and hospital discharge forms. Therapy was determined utilizing hospital and territory medical distribution database. Methods used were overall the same of those of CINECA-study, but the gender and different age classes were considered.*
Results: The prevalence of ACS was 2.5 ‰ (3.26‰ were male patients and 0.92‰ were female patients). Of the ACS patients, 142 (11.8%) died in hospital without any gender and age difference. Thus, for further investigations a cohort of 1,062 ACS patients (688 male and 374 female patients) was considered. 40.12% of patients underwent a revascularization intervention and 48.1% were not revascularized. The over 65 years aged male patient was significantly more likely to have a revascularization than the female patient of the same age (age group: 65-79, OR=1.7 95%CI 1.2-2.5; age group >=80, OR=4.1 95%CI 2.2-7.6). A previous 12-month pharmacological treatment analysis showed that 77% of women and 69% of men (OR=0.7 95%CI 0.5-0.9) had an antihypertensive medication and 17% of women and 8% of men were treated at least once with an antidepressant. This may be potentially indicative of higher rates of hypertension and depression among ACS women. There was no difference in drug utilization for diabetes (21%M and F) nor for dyslipidemia treatment [37%M vs. 32% F, OR=1.3 95%CI 1.0-1.6].
Six months after hospital discharge antiaggregation therapy was analysed. 82% of the ACS population received at least one

antiaggregant the other remaining 18% did not receive any antiaggregant generally those were females (OR=2.8 95%CI 2.1-3.8). Revascularized and non-revascularized patients' therapy: Aspirin was used in 35% of the non-revascularized vs. 28 % of the revascularized patient prevalently in non-revascularized female patients; Thienopyridines were used in 8% of the non-revascularized vs. 5% of the revascularized patients prevalently in revascularized female patients and finally the dual antiplateletes therapy was prevalently used in revascularized patients (61% vs. 29%), prevalently in male non-revascularized patients. For the other non mentioned therapies male and female patients were treated equally. Regarding to therapy adherence, male patients were in general more adherent to Aspirin (92%M vs. 82%F, OR=2,4 95%CI 1.2-4.6) on the other hand, to Thienopyridines (87%M vs. 84%F, OR=1.3 95%CI 0.3-5.0) and to Dual-antiplateletes therapy (76%M vs.74%F, OR=1.1 95%CI 0.7-1.8) male patients were adherent equally as their female counterparts.

Conclusion: ACS occured more frequently in men than in women. There were no mortality rates difference between men and women after an ACS event. In general men were more revascularized than women. On discharge, female patients were usually treated without any antiaggregant therapy more often than their male counterparts. Revascularized patients comparing to non-revascularized patients usually did not have any gender difference in terms of therapy, but an evaluation between non-revascularized patients indicated an inequity between male-female patients use of antiaggregants. On the whole, both female and male ACS patients were adherent to therapy.

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POSTER

Sex-gender differences on human vein endothelial cell fate

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Sex-gender is an important determinant in health and diseases for example it has been evidenced numerous differences in cardiovascular system (1). Human umbilical vein endothelial cells (HUVECs) are widely used as an in vitro model to study physiology, pathology and the effect of therapeutics (2). However, only very few studies studied if HUVECs obtained from male babies (MHUVECs) and from female babies (FHUVECs) behave differently; here we evaluated the constitutive apoptotis and autophagic process in cells, at passage 3, obtained from cords of human healthy male and female newborns who were vaginally delivered at term by healthy non-obese and non-smoking mothers who were drug free with the exception of folic acid. The autophagic markers, beclin-1 expression and the ratio of LC3II/LC3I, are higher in MHUVECs than in FHUVECs. The biochemical results are confirmed by electron microscopy. The above results strongly suggested that MHUVECs are more autophagic than FHUVECs. In order to better understand this phenomenon we measure the most important checkpoint of autophagic process: mTOR (3, 4) and its associated protein Akt (4). The mTOR expression is not sexual divergent suggesting that the differences in autophagic processes is mTOR independent. The expression and activity of Akt is sex-gender dependent being significantly higher in female cells, these results are in line with previous results obtained in different tissues and cells (4, 5, 6). Notably, NOS3 expression was higher in female cells than in male cells. Finally, the expression of cleaved caspase 9, an indicator of apoptotic pathway, does not present a sexual disparity. These findings suggest that the studied parameters were selectively influenced by the sex of the cells indicating that some endothelial function is sexually determined and this could have important consequences a) the need to include male and female cells to reduce the time from bench to bedside b) the urgency of specific gender approach for individuation of innovative therapeutic approaches.

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Effect of maternal smoking on human vein endothelial cord cells (HUVECs): a sex-gender view

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Maternal cigarette smoking have associated with reduced birth weight, poor developmental and psychological outcomes, and increased risk for diseases and behavioral disorders later in life (1). Notably, reduction in birth weight is significantly lower in newborn boys than in newborn girls (2) such as the leptin modification induced on blood of cord (3). Remarkably, maternal smoking altered umbilical vein endothelial cells (HUVECs) for example it reduces NOS3 activity (4). However, it is not known whether it occurs in a sex gender specific way. Therefore, it has been studied whether maternal regular smoking differently affects some endothelial functions such as NOS3, apoptosis in HUVECs, at passage 3, obtained from cords of male (MHUVECs) and female (FHUVECs) babies vaginally delivered at term by healthy, non-obese, smoking mothers versus non-smoking mothers. Smoking and non-smoking mothers were drug free with the exception of folic acid. We evidence that maternal smoking reduces the NOS3 expression mainly in MHUVECs than in FHUVECs, indicating that MHUVECs are more susceptible versus cigarette smoking. Notably, the reduction in NOS3 expression could contribute to retarded fetal growth caused by the reduction of vasodilatory capacity, which could produce hypoxic situation (4). We also measure apoptosis evaluating Caspase 9, an initiator caspase involved in the apoptotic intrinsic pathway, which is triggered by cellular damages or stress (5). Cleaved caspase 9 is more expressed in female and male cells obtained from smoking mother than in cells obtained from non-smoking mothers. Relevantly, the cleaved caspase 9 is higher in MHUVECs obtained from smoking mothers than in FHUVECs obtained from smoking mothers, but the difference does not reach the significance.
In conclusion, these preliminary findings suggest that maternal cigarette exposure during pregnancy, may contributes to endothelial dysfunction and death, by a reduction of NOS3 and increase of cleaved caspase 9 expression in a sex-gender specific way.

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Women's Health Observatory – IRCCS-ASMN of Reggio Emilia, Italy
Equal but Different: The importance of gender-medicine in diagnostics and treatment

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Background
The Women's Health Observatory is part of the Department Infrastructure of Research and Statistics. This Observatory was set up in a context that is woman-oriented - the IRCCS-Arcispedale S. Maria Nuova of Reggio Emilia, one of the Italian hospitals that have received the Pink Seal of Approval.

The health and illness of a population never used to take into consideration gender differences in terms of treatment, prevention, or research and development.
Epidemiology has brought to light the fact that there are differences between males and females, both in disease incidence and in disease course. Therefore, gender medicine has recently been the focus of increasing attention, as it makes it possible to better understand gender-related health differences and thus to be able to provide gender healthcare.
Gender medicine stems from the awareness that men and women are different in terms of health and disease. Yet while this appears obvious, this branch of medicine has only recently been officially recognized. Indeed, the first world congress on gender medicine was held just a few years ago.
In what ways are men and women different? In many ways, for example, in terms of:

1) the incidence of a number of diseases
2) disease survival
3) longevity
4) drug response

5) pain
6) socio-economic factors

While advances in epidemiology and research have made health inequalities evident, no biological explanation for these differences has yet been unequivocally identified. Hormonal factors and the presence of two X chromosomes likely play a role, though they are not the only players. Further, men and women have attitudes towards health, symptoms, prevention, and treatment that are to some degree determined by social attitudes and by the culture they have grown up and/or live in.

The attention paid to women as patients leads to and includes thinking about women in healthcare professions and careers, for an authentic opportunity for gender equality and for raising awareness.

Objective

The aim of the Women's Health Observatory is to raise awareness in the hospital, the IRCCS, and among the population of Reggio Emilia concerning women's health and women in the healthcare professions. Events and initiatives, information, and awareness can lead to implementing gender medicine.

From this stems the need to progressively refine and consolidate the scope of scientific investigation and to dedicate analyses and specific projects concerning the promotion/ personalization of women's health, with the aim of enhancing the role of women in society and in the scientific community.

The Women's Health Observatory addresses those women who are active, aware, and in charge of their own health, even when they become ill over the course of their life.

The aim is to develop proposals for women who need to improve and maintain their health. The Women's Health Observatory thus involves those interested in pursuing the health objectives of the female population, strengthening and stressing the attention, research, assessment, and initiatives addressing primarily the risk of "complex" diseases and the issues and areas specific to women's health.

The mission of the Women's Health Observatory is to enhance, promote, support, educate, investigate, and inform, as well as to foster and support the assessment of the physical and psychosocial conditions of the female population in the catchment area of the IRCCS-Azienda Ospedaliera S.Maria Nuova and provincial hospitals of Reggio Emilia.

Our commitment is to:

- improving women's quality of life;
- fostering participation in research;
- investigating the field of gender medicine;

- promoting strategies addressing psychophysical well-being;
- promoting greater gender health equality;
- implementing strategies that allow women to voice their needs and desires and that enhance women's roles in science and in society;
- raising awareness/ informing by means of training, communication, information, and awareness.

Methods

In line with its objectives, the Women's Health Observatory proposes to develop studies in specific directions of research, training and dissemination initiatives/ activities. These activities will be integrated and coordinated by a work group – the "Gruppo O.S.D."–, which will be multidisciplinary and will involve different professional categories. The aim of this group is to support and stimulate a number of actions:

- support/ stimulate biomedical and psychosocial research projects, studies, and investigations in the areas of women's health and gender-based medicine;
- provide information about and promote prevention and early diagnosis;
- promote healthy lifestyle choices and education on physical and psychosocial well-being;
- organize events dedicated to the main issues in women's health (conferences, seminars, cultural events, exhibits, and so on).

Further, the Women's Health Observatory will avail itself of the collaboration a number of partners (Società Italiana Salute Medicina di Genere; Associazioni di volontariato del territorio reggiano; Forum Provinciale delle donne; Cooperativa Sociale Ambra R.E.; O.N.Da) and Institutions (the Municipality of Reggio Emilia).

Conclusions

In conclusion, the Women's Health Observatory aims to promote awareness, training, updating, and research by means of a 360° vision of women's health issues in relation to science and society and to dialogue with the general public, researchers, and other professionals in the areas of science, healthcare, and society and culture. Lastly, the Women's Health Observatory aims to organize seminars and debates, to publish research studies and material on its website, and to promote dialogue between science and society during the exhibits/ encounters proposed.

The influence of gender on atherosclerosis development in the Apolipoprotein E-deficient mouse

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Although several studies have investigated the impact of age as risk factor for atherosclerosis and cardiovascular diseases, the influence of gender on the development of atherosclerotic lesions still needs to be elucidated. Importantly, epidemiolodical studies indicate that women in the reproductive age are less likely to develop cardiovascular diseases, suggesting atheroprotective effects of circulating estrogens on the vasculature (1).
The apolipoprotein E (apoE) knockout mouse represents the most widely used murine model of atherosclerosis. The ApoE KO mouse shows increased levels of plasma cholesterol and spontaneous atherosclerosis that is accelerated by high fat diet (2, 3). Until a few years ago the majority of the studies in apoE KO mice confirmed the atheroprotective action of estrogens. However, more recent analyses have detected no significant differences in the abundance of atherosclerotic lesions between male and female apoE KO mice (3). Therefore, a better understanding of the influence of gender on atherosclerosis development requires further investigation.
Aim of the present study is to compare the effects of Aldosterone (Aldo) treatment on the aortic atherosclerosis in male and female apoE KO mice fed a high fat diet for 4 weeks. As observed in animal models and in clinical trials, Aldo has been shown to promote vascular inflammation, vascular remodeling, and atherosclerosis (4, 5, 6). Therefore, in our study, in addition to the high fat diet and the pro-atherogenic impact of apoE genetic defect, Aldo treatment was used as an additional source of stress for the vasculature.
Aldo was administered subcutaneously via osmotic minipumps. In the aortic root of male apoE KO mice, Aldo administration increased atherosclerotic plaque extension with respect to vehicle treatment. On the other hand, Aldo and vehicle treatments determined the formation of plaques of similar size in the aortic root of female apoE KO mice, suggesting a potential protective effect of circulating estrogens in females at least on this specific region of the aorta. Importantly, blood pressure of both males and females was not modified by Aldo treatment, excluding the impact of potential hypertensive effects of Aldo administration on atherosclerosis progression.
In ongoing experiments, we are investigating whether female apoE KO mice are also protected against the pro-atherogenic effects of Aldo in other aortic regions such as aortic arch and abdominal aorta.

Aldo and estrogens are both able to modulate gene expression in vascular cells resulting in promotion or protection from atherosclerosis respectively (7, 8). It is possible that Aldo and estradiol may exert opposite effects on the expression of vascular genes with established role in vascular function and disease.
Studies are ongoing to clarify the role played by estrogens in the development of atherosclerosis in different regions of aorta and investigate the molecular mechanisms mediating the supposed anti-atherogenic effects of estrogens on the vasculature.

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Determining the Role of Gender in a Context of Interculturality and Humanisation of the Cures

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The phenomenon of migration has assumed large, and also in Italy has changed in important ways the social and demographic context in which health services are now operating.
In particular, as the scientific literature, immigrants are persons who, at the time of departure from the country of origin, have a generally good state of health, which allows them to present itself as a viable workforce. In the host country, however, their "wealth of health" is often undermined by the conditions of insecurity and socio- economic and cultural disadvantage they face (unemployment, lack of protection in employment, housing deterioration, unbalanced diet, social exclusion, discrimination).
In addition, the existence of major legal, organizational and relational makes it the higher the risk of not receiving by the health care system the same services for the prevention, diagnosis and treatment of which the average of the population benefits .
In recent years, the incidence of foreigners resident population was also in the Veneto region in strong and growing. The community component was not until 2006 that dominant and fastest growing, accounting for 95% of the foreign population, in 2007 the entry of Romania and Bulgaria into the European Union has led to an enormous growth of foreign nationals Community currently account for about one quarter of the total foreign population in the Veneto. The characters of the territorial distribution of foreigners in the Veneto region are such that they have the highest concentrations in urban areas and foothills of the central part of the region. In Padua, in particular, the foreign resident population has increased from 6.64% in 2003 to 15.22% in 2011, alongside the regular citizens there is a high number of illegal immigrants who often have a picture of poor living conditions and of health.
Faced with this reality, the Padua's hospital has undertaken over the last ten years a path to take adequate action on the system of care capable of recognizing cultural diversity, in order to operate on the conditions that may preclude the provision of appropriate performance As shown in numerous studies, including epidemiological,

determinants called "distal" or socio- economic, are the ones at the base of the growing inequalities also on the use and quality of health services.
Among the factors essential to the health there is then the genre, because the state of health, the perception of the degree of well-being, the onset and course of disease, the therapeutic approach is different between men and women.
To understand the interaction between distal determinants and gender in immigrant population is one of the aims of the work on which the company is investing in research and planning. This path of knowledge is vital to really be able to put in place a structured set of appropriate measures to ensure access and fair treatment of migrants and to respond to their specific needs care and assistance, taking into account the different conceptions health, perception of illness, expectations of care and specific health problems.
With this in mind you are starting an observational study aimed to bring out the role of gender in determining the immigrant population. The assumption is that work on the gender dimension represents an effective tool to tackle health inequalities, related to membership of disadvantaged social classes, poverty and implement strategies for health -conscious dimension of the quality of effectiveness and equity, in view of intersectoral and inclusion as well as humanization. The Hospital of Padua was in fact, with Buzzi Hospital in Milan, the first company in Italy to join the health network of Health Promoting Hospitals - Health Promoting Hospitals (HPH). The idea behind the initiative was and still is to enable and support a process of re-orientation of organizational culture in order to add to the traditional healing activities a new approach to health , the implementation of an approach multidimensional and intercultural assistance.
Among the areas of activity that characterize the hospitals in the HPH Network, part of the implementation of an intercultural approach multidimensional and care, inside which gives centrality to the role of social determinants of health .
The research will be conducted with the involvement of all key stakeholders in the process of care delivery using the main instruments of quantitative and qualitative research in the social sciences: descriptive statistics, implicative analysis, focus groups and open interviews. The study includes the observation of several targets of population of different countries, including Italian, who access the services of the hospital over the following areas:

-Benefits and vulnerability resulting from the determinants of health ;

-Social integration and cohesion -related determinants of health and health inequities;

-The relationship between vulnerability, injustice and rapid social change ;

-The effect of gender in influencing the risks and opportunities for health.

The Role o Physical Activity i Young Volleyball Females Players o Bone Ultrasound Characteristics

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INTRODUCTION

An important risk factor strictly linked with osteoporosis (OP) onset in adults is the reaching of an adequate bone mass peak (PBM). PBM can be defined as the amount of bony tissue present at the end of the skeletal maturation and it is normally reached in the course of the third decade of life (1). Among the principal factors helping to optimize the bone mass, physical activity is crucially important. For this purposes, physical activity definition can be divided in two major categories: 1) aerobic activity, also said impact activity, or loaded exercise (i.e. running, football, basketball, volleyball, gymnastics), 2) resistance activity, or involving strength (weightlifting, swimming, cycling, usage of tools for static exercising) (2). The introduction of ultrasound apparels (QUS – Quantitative Ultra-Sound) to be helping in diagnosing OP, has enhanced a low cost, easy to access and radiation-free methodologies (3,4). The aims of our study are to be enumerated as follows: estimating the parameters detectable through a ultrasound measurement of the heel in female volleyball agonist players within the central Italy area, chosen within the age range when they normally reach the PBM. Evaluating the real influence of sport activities on PBM, comparing registered data with data gathered from a group of non sporty girls of the same age range.

MATERIALS AND METHODS

The study group included 31 girls (mean age 25.6±4.6 years; players since they were 11.8±4.2 years old). The control group consisted of 70 girls (same ethnical features and same area of residence) of an average age of 25.4±4.7 years, randomly enrolled and not being involved in any kind of agonistic sport (Table 1). Each participant involved in the study has been evaluated by an Hologic Utlrasound Sahara sonometer (Hologic Inc., Bedford, MA, USA). The parameters detected are the following: Broadband Ultrasound Attenuation (BUA, dB/MHz), Speed of Sound (SOS, m/S), Quantitative Ultrasound Index (QUI), Bone Mineral Density (BMD, g/cm^2). While BUA and SOS are parameters directly measurable through this device, QUI and BMD are calculated combining data for BUA and SOS.

RESULTS

Median values found within the volleyball players study group are the following: estimated BMD 0.675±0.144 g/cm^2, QUI 120.2±20.9, SOS 1590.4±32.3 m/S, BUA 95.5±20.1 dB/MHz. Each parameter referring to the volleyball players has resulted significantly higher ($p<0.05$-0.01) compared to the control group (Table 1). Particularly, QUI level shows an average of 15.5% highest, similarly to other studies on volleyball players, although measured with DXA methods, showing an increase of 13.2% on lumbar column and an increase of 15.8% on femoral neck (5).

DISCUSSION AND CONCLUSIONS

Physical activity represents a valid anabolic stimulus on the bone tissue with subsequent increasing of BMD in young subjects. Loaded sport activities performed against gravity impact (i.e. volleyball, basketball, football, running) are generally associated to a higher increasing of bone density, compared to sports that generate a mechanical load without additional weight given by the gravity force (i.e. swimming, horseracing) (6-13). Volleyball, as a loaded sport characterised by frequent jumps and quick direction changes, allows to reach a higher PBM compared to the people who do not do any sport. Data registered do not seem to be biased by the skeletal site or by the method followed. Volleyball, and supposedly all the sport activities with the same characteristics, positively influences the right PBM level achievement, widely balancing the hormonal, alimentary, behavioural and trauma derived risk factors, as gathered through the anamnestic questionnaire we used.

Disclosure:
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Table 1 – Clinical characteristics of the volleyball players and ultrasonometric data

Subjects *n. / mean age (years)*	**Duration of physical activity** *(years)*	**BUA** *(dB/MHz)*	**SOS** *(m/S)*	**QUI**	**BMD** *(g/cm^2)*
31 25.6±4.6	11.8±4.2	95.5±20.1	1590.4±32.3	120.2±20.9	0.675±0.144
		p<0.01	p<0.05	p<0.05	p<0.01
Control group (n.70)	-	75.5±18.2	1335.4±22.5	101.1±17.4	0.554±0.89

Legenda:
BUA, broadband ultrasound attenuation; **SOS**, speed of sound; **QUI**, quantitative ultrasound index;
BMD, bone mineral density

A multidisciplinary, non-pharmacologic approach to weight loss is associated with improvements in sexual and endothelial function in obese fertile women.

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Introduction: It is not clear whether obesity represents a risk factor for female sexual dysfunction (FSD). Aim of this study was to investigate the effects of weight loss on FSD complaints and endothelial function in young fertile obese females.

Material and methods: 44 fertile women (18-40 years) with sexual complaints at Female Sexual Function Index-6 $\leq$ 19 (FSFI-6 score) were enrolled into an 8-weeks intensive residential program with hypocaloric diet plus controlled physical exercise and at specialized clinic (Group A, N=23), or into a non-intensive outpatient clinic program consisting of hypocaloric diet and physical exercise (Group B, N=21). An 8-weeks follow-up period consisting of outpatient clinic controlled diet plus physical exercise was carried out. Primary endpoints were modifications of FSFI-6 scores and endothelial function as measured by reactive hyperaemia (RHI) with EndoPat2000. Secondary endpoints were modifications in body composition as measured by DEXA.

Results: After 16-weeks, FSFI-6 score and the frequency of sexual activity were significantly higher in Group A compared to Group B ($p<0.01$) and significant improvement in arousal, lubrication and satisfaction sub-domain scores were also found ($p<0.01$). Group A but not group B, showed improvements in RHI ($p< 0.01$). Finally, group A showed marked improvement in HOMA-IR ($p<0.001$) and anthropometric parameters as weight ($p<0.01$), BMI ($p<0.01$), fat mass ($p<0.0001$), percentage of fat mass ($p< 0.005$) and fat-free mass ($p<0.01$).

Conclusion: A multidisciplinary non-pharmacologic approach to female obesity appears to be superior to conventional outpatient clinic treatment and produces permanent improvements both in cardio-metabolic parameters and in several aspects of sexual dysfunction.

Regular smoking affects global DNA methylation, asymmetric dimethylarginine and monocytes-derived macrophages function in sex-gender manner

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Tobacco kills more then 5 million people which is much more than AIDS, tuberculosis, malaria combined. Cigarette smoking is more common among men (21.5%) than women (17.3%)[1] but women seem to be at significantly greater risk of developing a smoking related disease than men, as well as being susceptible to sex-gender specific health issues and pregnancy complications[2]. Furthermore, smoking is the most important modifiable risk factor for atherosclerosis in young women: 70% of women younger than 45 years with coronary artery disease are current smokers[3]. Despite that, few studies have been conducted to understand the bases of the differences. We therefore analysed a series of parameters to determine if they were influenced by the regular cigarette smoking. We selected young (median age of 27 years), adult and healthy volunteers. Women were analysed in the follicular phase of their menstrual cycle and were free from oral contraceptives in order to avoid any bias due to sexual hormones. Men and women were stratified according to their smoking habit, so that 28 males and 32 females were regular smokers while 55 males and 53 females were non-smokers.

Fasting blood samples were obtained and used for assessments of asymmetric dimethylarginine (ADMA, a marker of endothelial dysfunction), global DNA methylation, and monocytes-derived macrophages (MDMs) for TNF-alpha release determination[4]. MDMs were chosen because they play crucial roles in atherosclerosis and inflammation.

Regular smoking habit influenced in a sex-gender specific way global DNA methylation, plasma ADMA levels and MDMs function measured as TNF-alpha release.

Regular smoking reduces DNA global methylation either in men or in women but the reduction was bigger in females than in males. Although the results reported in the literature are not unique this finding suggests the importance of the inclusion of the gender variable

in studies on changes in DNA methylation as a marker of many diseases including breast cancer[5].

Secondly, smoker women during follicular phase have higher ADMA levels than smoker men and non-smoker women. Considering that endothelial dysfunction is related to an increased risk for adverse cardiovascular events, our results suggest that smoking is more dangerous for women than men also taking into account that the sex-gender differences in endothelial function may underlie the sex-gender differences in cardiovascular disease[6].

Finally, sex-gender and cigarette smoke regulated the basal release of TNF-alpha in MDMs, which was significantly higher in non-smoker males than in non-smoker females, while LPS-stimulated release of TNF-alpha was significantly higher in non-smoker females than in non-smoker males. These results suggest that regular smoking can also affect inflammatory response.

In conclusion, cigarettes smoke affects in a sex-gender specific manner the three studied parameters in a way that strongly suggests a greater danger for young adult women. Notably the obtained results are in line with the increased risk for cardiovascular diseases described in young women[7].

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Gender- and sexual orientation-dependence in facial preferences

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Abstract

Introduction: Differences between heterosexual men and women with respect to mating strategies are well documented. However, it is still a matter of discussion how differences in sexual identity or in sexual orientation may modify the mating strategies.

Aim: To investigate: 1. the differences in facial preferences between heterosexuals of both sexes, homosexual males, and male-to-female (MtF) transsexuals and 2. the influence of short-term and long-term relationship on facial preferences.

Methods: One hundred thirty-six subjects (30 heterosexual males, 64 heterosexual females and 42 homosexual males) were enrolled from university students and staff and at gay happenings (Gay Village, Rome, Italy). In addition were also enrolled seven patients with a male genotype who have been diagnosed as having MtF GID in our sexual medicine clinics. Diagnosis was based on formal psychiatric classification criteria (Standards of CareWorld Health Professional Association for Transgender Health, WPATH) and performed through a face-to-face interview. All subjects were shown a composite male or female face. The sexual dimorphism of these pictures was stressed or reduced in a continuous fashion through an open-source morphing program (gtkmorph).

Main outcome measures: The preference over a sequence of 21 pictures of the same face warped in a continuum from a feminized to a masculinized shape.

Results: Heterosexual males show a preference for hyper-feminine female faces and heterosexual females do not show a preference for hyper-masculine faces. The difference between heterosexual males and heterosexual females was statistically significant for long-term partners only, with no difference for short-term partners. In contrast,

homosexual males shown the same images demonstrated a preference for hyper-masculine male faces. Finally, we found for long-term relationship a female pattern of preferences in MtF subjects.
Conclusions: These data strongly suggest that homosexual and heterosexual males use the same mating tactics, preferring sexually dimorphic faces. This aspect is in line with the hypothesis that gender differences in sexual strategies are influenced by biological predispositions. On the contrary, heterosexual females and transsexuals showed for long-term relationship a preference for less dimorphic faces. Finally, the choices of the MtF subjects confirm that sexual preferences in transsexualism are innate and opposite from those of homosexual people for long-term relationship.

Short-Term Amiodarone Hepatotoxicity in Patients Over 70 Yr without Liver and Renal Disease: *Elderly* Gender?

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Introduction and Objective.
Amiodarone is one of the most effective antiarrhythmic drugs available and is widely prescribed despite several potentially life-threatening side-effects. Hepatotoxicity is the most frequent one during long-term oral therapy (1-2). Acute hepatic damage after intravenous amiodarone, which can be fatal, in elderly with normal renal and liver function is not well recognized.
Methods.
We describe three cases of acute hepatocellular injury after intravenous amiodarone administration (5 mg/kg in 250 cc glucose 5% as loading dose, followed by continuous infusion of 10 mg/kg for the first 72 hours for supraventricular tachyarrhythmias (HR > 180 bpm) in 3 elderly patients with dilated cardiomyopathy and without renal and liver disease.

Results.
Acute liver failure occurred in a 70-year-old woman within 72 hours of iv loading with amiodarone. The patients developed severe jaundice, acute renal disease, multi-organ toxicities and exitus after 24 hours.

Serum aminotransferase levels (> 4000 UI) and hyperbilirubinemia (3.80 mg/dl), nausea and vomiting occurred in a 75-year-old man within 72 hours of iv loading with amiodarone. These values were reversible after 48 hours cessation of iv amiodarone.

In other 78 year-old man occurred an increase of serum aminotransferase levels within 24 hours of iv loading with amiodarone and the patient had a rapid decline in symptoms and a return to his baseline status after 3 days of cessation of iv amiodarone.

Conclusion.
Identifying toxicity early and correcting it rapidly may prevent life-threatening sequelae associated with amiodarone toxicity. However, these observations show the necessity of hepatic monitoring of

patients treated with amiodarone in order to detect potentially severe hepatotoxicity, in particular in elderly patients without liver diseases.

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Post-traumatic stress disorder and coping strategies in diabetic patients: gender differences

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Introduction and Aim: Post-traumatic stress disorder (PTSD) is a complex psychopathological syndrome that is not easy to assess and treat, because its symptoms belong to the anxious and depressive spectrum and may have somatic implications. The main symptoms could be grouped into three clusters: intrusion, avoidance/numbing, and hyperarousal [1]. The exacerbation of PTSD generally occurs in people after personal or collective traumas. In this regard, there are some predictive factors for PTSD, such as coping strategies[2]. Coping strategies can be explained as the tendency of people to react and face a possible traumatic event. In addition, it is unclear if trauma, post-traumatic stress disorder and its related consequences have also a role in chronic organic pathologies such as diabetes[3]. Diabetes and PTSD are two clear pathologies where gender difference is most evident.
In fact, diabetes occurs more frequently in men than in women, while post traumatic stress disorder seems to have a higher prevalence within the female population.
Regarding PTSD, others studies [4] demonstrated that after the seismic event that occurred in L'Aquila, women showed more stress traumatic symptoms than men; other previous studies also revealed that women have a higher risk to develop PTSD after calamities or war.
The matter regarding gender differences in PTSD is more complicated when observing an unhealthy population with pathologies such as diabetes. Diabetes is itself a predictive factor of the exacerbation of a mental disease, and diabetic people are more vulnerable to develop anxiety, depression and also PTSD [5].
In consideration of the above, the aim of this study was to investigate gender differences in PTSD in diabetic patients who experienced the 2009 L'Aquila earthquake.
Methods: A group of 100 diabetic patients was sequentially recruited by our University unit in the Centre of Diabetology of San Salvatore Hospital in L'Aquila. We enrolled 54 men and 46 women with type 2

diabetes who were diagnosed with the illness for less than ten years and showing no significant clinical complications.
Patients who experienced the L'Aquila earthquake not suffering from other mental disorders were included in the analysis. To evaluate the prevalence and levels of PTSD, we used Davidson Trauma Scale, a well validated self-report test composed of 17 items with possible 4-likert scale, whereas to evaluate coping strategies we administrated Brief-Cope, a self-report test composed of 28 items.
Additionally, glycemia, hemoglobin, salivary cortisol and blood pressure were measured by physicians in San Salvatore Hospital and in the laboratory of our University.
Results: 29.6% (16/54) of males and 58.7% (27/46) of females suffered from PTSD, with a significant difference ($p=0.0001$). In particular, the means of DTS total score were 31.65 (SD=23.06) in males and 53.5 (27.01) with a p-value lower than 0.0001.
When observing and assessing the most traumatic event in the two groups, the resulting indication related to the earthquake was 33.3% (18/54) in the male group and 51.1% (24/46) in the female group, whereas 38.8% (21/54) of males and 8.7% (4/46) of females reported diabetes as the most traumatic experience. Also in these comparisons there existed significant differences between the two groups ($p<0.0001$).
The results at Brief-Cope showed some differences only in two scales: positive reframing and religion in the first one where the mean-score in men was 5.56 (SD=1.9) and in women 6.73 (1.46) ($p<0.0001$); in the second one men obtained 5.51 (SD=2.27) and women 6.52 (2.04), with a significant difference ($p=0.02$). Biological parameters comparison showed that the only statistically significant differences regarded the values of blood pressure. There were no differences in specific markers of diabetes as glycemia or glycated haemoglobin and BMI, although the trend of haemoglobin and salivary cortisol was higher in women than in men (data not showed).
Discussion and Conclusion: Our study revealed that diabetic women show higher PTSD levels than men and the prevalence of traumatic stress was higher in the female group. Additionally, after a natural disaster such as a seismic event, women consider the earthquake as the most traumatic event in their life, while men consider diabetes as the most traumatic one, therefore we could suppose that men give greater importance to personal health, while women to collective wellbeing. Additionally, we observed that the trend of glycemic control was more negative in women than in men, although there were no statistical differences.
We also found essential gender differences in the use of coping strategies. The use of positive reframing is more frequent in men,

whereas the religious coping is more frequent in women. As regards this aspect we highlighted the controversial role of religious coping in diabetic women. Religion did not seem to prevent PTSD exacerbation. Therefore, when treating diabetes it is fundamental to consider the evident gender difference in patients'mental health. In some cases a psychological support could be necessary for diabetic women who show PTSD symptoms. The role of the psychologist in treating diabetes is important either in terms of patient adherence to treatment or in terms of improvement of coping skills after traumatic events. Psychological trauma and glycemic control could have a gender-specific correlation [6, 7].

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Gender differences in sexual dysfunctions in a group of first-episode psychosis patients

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Introduction and aim: Patients with mental disorders and receiving psychopharmacological treatment often suffer from sexual dysfunctions. In most cases, pharmacological treatment causes sexual-dysfunction side-effects. The aim of this study is to investigate gender differences in sexual dysfunctions in people with first episode psychosis, while monitoring the effects of psychopharmacological treatment and the influence of prolactin levels.

Methods: A group of 40 males and 37 females with first episode psychosis took part in the study. We administered a psychiatric protocol that was composed of the PANSS (Positive and Negative Syndrome Scale), UKU (Side Effect Rating Scale) and SCID-DSM-IV (Structured Clinical Interview for DSM IV) diagnosis. We also considered the antipsychotic treatment and prolactinemia in the first three months of care.

Results: In men, 42.5% (17/40) had sexual dysfunctions while in women 37.8% (14/37). The logistic regression showed that the influence of drugs and prolactin levels on the sexual dysfunctions was not statistically significant.

The correlation between sexual dysfunctions and psychopathology did not reveal any association in the male group. In females instead, general psychopathology and positive symptoms are linked to the alteration of vaginal lubrication; ($r=.547$; $p=0.003$) and ($r=.485$; $p=0.011$), although orgasm alteration was also associated with general psychopathology ($r=.500$; $p=0.013$). Moreover, we found a significant link between alteration of vaginal lubrication with depression and disorder of volition ($r=0.627$; $p<0.0001$), ($r=0.600$; $p<0.001$) respectively.

Conclusion: These data suggest that the association between sexual dysfunctions and psychopathology regarded only the women. Additionally, in the initial phase of the treatment, prolactin levels and antipsychotic drugs did not influence sexual function. Therefore, during the patients taking charge it is fundamental to consider the evident gender-specific relationship between psychopathology and sexuality.

Escalation in alcohol drinking in female Sardinian alcohol-preferring rats

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Sardinian alcohol-preferring (sP) rats constitute one of the few rat lines selectively bred worldwide for high alcohol preference and consumption. When exposed to the standard, homecage 2-bottle "alcohol (10%, v/v) *vs* water" choice regimen with continuous access for 24 hours/day (i.e., the procedure under which sP rats had been bred), male sP rats consume daily approximately 6 g/kg alcohol. A recent study found that exposure of male sP rats to the intermittent (once every other day) access to 2 bottles containing alcohol (20%, v/v) and water, respectively, resulted in (a) marked increase in daily alcohol intake and (b) occurrence of signs of alcohol intoxication and "behavioral" dependence.

The present study was designed to assess alcohol intake in female sP rats exposed, under the 2-bottle choice regimen, to (a) 10% (v/v) alcohol with continuous access (CA10%), (b) 10% (v/v) alcohol with intermittent access (once every other day) (IA10%), (c) 20% (v/v) alcohol with continuous access (CA20%), and (d) 20% (v/v) alcohol with intermittent access (once every other day) (IA20%). Male sP rats (exposed to the CA10% and IA20% conditions) were included for comparison.

Over the 20 drinking-session recording-time, daily alcohol intake in female CA10% and IA20% rats averaged approximately 7.0 and 9.6 g/kg, respectively, with intermediate values in the IA10% and CA20% rat groups; the rank of the total amount of alcohol consumed over the 20 sessions was: IA20% > IA10% = CA20% > CA10%. Daily alcohol intake in male CA10% and IA20% rats averaged approximately 6.0 and 8.2 g/kg, respectively; the rank of the total amount of alcohol consumed over the 20 sessions was: female IA20% > male IA20% > female CA10% ≥ male CA10%.

These results (a) confirm in male sP rats and extend to female sP rats previous data demonstrating the capacity of the IA20% condition to markedly escalate alcohol drinking (in comparison to the standard CA10% condition), and (b) demonstrate that female sP rats consume more alcohol than male sP rats. This gender difference is more evident under the IA20% condition, suggesting that female sP rats may be highly sensitive to the promoting effect of the IA20% condition on

alcohol drinking. These data represent the first evidence of alcohol drinking behavior in female sP rats and contribute to the characterization of sP rats as a model of excessive alcohol consumption.

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PDE5 inhibitors in human bladder disorders: the role of L-cysteine/H2S pathway

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Abstract

Lower urinary tract symptoms (LUTS) affect countless individuals worldwide with a negative impact on patients' quality of life in both men and women. Typical symptoms include urinary urgency, frequency, incontinence and nocturia. Emerging data increasingly suggest that it is misleading to attribute individual symptoms to sex differences or to a specific underlying organ. LUTS are a non–sex-specific group of symptoms, which are age-related and progressive. The etiology of LUTS is highly complex and multifactorial then a need exists to increase education and awareness regarding LUTS, its causes, and associated comorbidities, and to assess and treat men and women for all LUTS, not just selected symptoms (1).

Traditionally, LUTS in men are related to benign prostatic hyperplasia (BPH), while in women are attributed to an overactive bladder or stress urinary incontinence (1). The current therapy for men includes α-blockers, 5-α-reductase inhibitors and anti-muscarinic agents, whose beneficial effects on LUTS are provided through different, albeit not perfectly defined, mechanisms of action (2). On the other hand for women, few treatments have been adequately studied and for example the α-blockers use is under discussion (2, 3).

Recently, several pre-clinical and clinical studies have shown that sildenafil, vardenafil and tadalafil, inhibitors of phosphodiesterase-5 (PDE5i), are effective in the treatment of LUTS associated to BHP, however their mechanism of action is still unclear (4). The phosphodiesterase 5 (PDE5) is the most abundant isoform expressed in the human bladder, its inhibition causes an increase of cyclic guanosinemonophosphate (cGMP) that mediates several pharmacological effects. In fact it has been hypothesized that PDE5i, in the lower urinary tract, can potentially modulate sensory signals, microvasculature dilation and smooth muscle cell relaxation in the prostate, urethra and bladder In particular it has also been reported that sildenafil relaxed human bladder detrusor strips through a not completely elucidated mechanism only partially dependent by nitric

oxide. Recently, it has been shown that hydrogen sulphide (H2S), a newly discovered gaseous transmitter, is involved in penile erection and lower urinary tract function. Indeed, H2S stimulates sensory nerves in rat isolated bladder (5) and is involved in the erectile mechanism and prostate function in humans (6,7). H2S is endogenously formed in mammalian cells from L-cysteine, mainly due to the action of both cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) (8). Many actions have been ascribed to H2S and recently H2S has also been identified as an endogenous inhibitor of PDE (9).

In the present study, we investigated the possible involvement of H2S as a mediator of sildenafil-induced relaxation in bladder detrusor dome obtained during surgical procedures of open prostatectomy in patients affected with BPH and bladder outlet obstruction. In order to address this issue, the presence of CBS and CSE enzymes was first assessed by a western blot. The enzyme activity was evaluated measuring H2S tissues production by a colorimetric assay. Moreover the modification of H2S tissues production in response to sildenafil (1,3,10 and 30μM) or two stable analogues of cGMP and cAMP i.e. 8-bromo–cGMP (100μM) and dibutyryl-cAMP (100μM) were investigated. A curve concentration-effect of NaHS, H2S donor (0.1μM- 10mM), L-cysteine (0.1μM-10mM) and sildenafil (0.1-10μM) was performed on pre-contracted detrusor dome strips. In order to confirm that H2S signaling is involved in sildenafil effect, CBS and CSE inhibitors were also used.

We demonstrated that CBS and CSE are present in human bladder dome and efficiently convert L-cysteine into H2S as shown in figure 1A and 1B respectively. Indeed, L-cysteine adding significantly increased H2S production and this effect was significantly reduced by DL-propargylglycine (PPG; 10mM) and/or aminooxyacetic acid (A0AA) CSE and CBS inhibitions respectively (Fig 1B).

Figure 1A: CBS and CSE protein expression

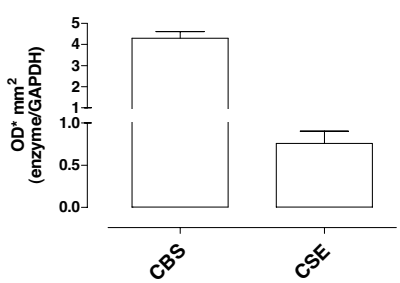
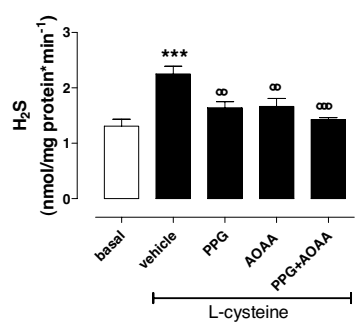


Figure 1B: CBS and CSE enzyme activity



*** versus basal
¤,¤¤ versus vehicle

L-cysteine and sildenafil relaxed human strips in a concentration-dependent manner and this effect was significantly inhibited by CBS and CSE inhibitors. Similar relaxation effect was observed with NaHS too.
Interestingly, sildenafil caused a concentration-dependent increase in H2S production that was reverted by
CBS and CSE inhibition (Fig. 2; **p<0.01 vs vehicle; °,°°p<0.05 and 0.01 vs sildenafil). Similarly to sildenafil,
both 8-bromo–cGMP or dibutyryl-cAMP caused an increase in H2S production (Fig 3; *p<0.05 vs vehicle).

Figure 2: sildenafil causes an increase in H_2S production

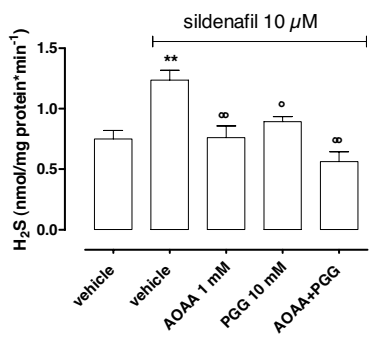
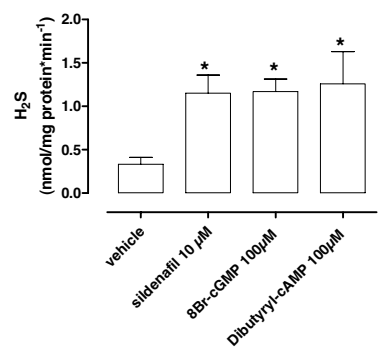


Figure 3: CBS and CSE enzyme activity



Our results clearly showed i) the involvement of the L-cysteine/H2S pathway in the man human bladder and ii) the H2S signaling contribution in sildenafil's effect on human bladder. However, we cannot exclude that Lcysteine/ H2S pathway could be present and have a functional role in woman bladder too.
In conclusion, the H2S signaling may have a pathophysiological role in human (man/woman) bladder and may open new possible therapeutic approaches for the efficacy of PDE5i on LUTS not even in man but also in woman besides the development of new medicaments for the treatment of lower urinary tract dysfunctions.

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Accuracy of introital ultrasound in predicting vaginal orgasm and female ejaculation

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Purpose. A clear anatomical structure of the urethrovaginal space (UVS) that adequately stimulated can lead to vaginal orgasm has not been fully described yet. This study sought to identify which differences were present between women with or without experience of female ejaculation on the basis of thickness of UVS

Method: Introital ultrasound was performed to examine the thickness of UVS in a cohort of 100 women. For ultrasound analysis the measurement of UVS was obtained along a line between the border of the smooth muscle and mucosa-submucosa layer of the urethral wall and the border of the vaginal wall at 90th (distal) percentile of the urethra length.

Results: Forty-four women out of 100 had no experience of vaginal orgasm (Group 1), 34 women had vaginal orgasm (Group 2), and 22 women had both vaginal orgasm and ejaculation (Group3). The UVS was significantly different among the three groups as showed using ANOVA test (p=0.0001). Post-hoc analysis showed an higher UVS in Group 3(11.2±1.7mm) compared to Group 2 (6.9±2.0mm; p=0.0001) and Group 1 (4.0±1.6mm; p=0.0001). UVS in group 2 was also significantly different compared to group 1(p=0.0001) and 3 (p=0.0001). ROC-curve analysis identify the best cut-off to predict the vaginal orgasm in women without ejaculation as 5.2mm, while the best cut-off to predict the vaginal orgasm in women with ejaculation as 8mm.

Conclusions: The presence of female ejaculation was associated with the higher thickness of UVS. ROC curve methods were useful to determine cut off values for thickness of UVS concerning women with vaginal orgasm and women with female ejaculation by a simple ultrasonography.

Analysis of sex-gender differences in gene expression for human umbilical artery smooth muscle cells

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Males and females not only have phenotypic differences but also show differences in health, life span, cognitive abilities, responses to drugs, coronary heart disease and hypertension. The umbilical cord is a useful source of human vascular smooth muscle cells (VSMC) and can be easily obtained just after birth, but umbilical arteries live in a medium completely unique from the point of view of hormones, characterized by high levels of estrogen, progesterone and cortisol [1–3]. Simmons et al.[4] found that in male umbilical cord blood testosterone and estradiol were significantly higher than in female. A ligand needs to bind its receptor(s) to exert its effects, so we used real time PCR to estimate the sex-gender differences in gene expression for receptors which have a special relevance in VSMC physiopathology: Estrogen Receptor "ER" alpha and beta, Estrogen-related receptor alpha "ESRRA", G protein coupled receptor "GPER", Androgen receptor "AR", Cysteinyl-leukotriene receptor 1 "CYSLTR1"and Angiotensin II Receptor "AGTR" 1 and 2**.** They were normalized on the geometric mean [5] of the values measured for β2 microglobulin and ribosomal protein L30, whose expression was found to be not different between male and female cells. Importantly, only ER-alpha and ER-beta gene expression diverged between sexes being more present in male VSMC than in female ones, thus suggesting the importance of these estrogen receptors in determining sex-gender differences**.** Furthermore these results strongly suggest that sex-gender differences start at the very beginning of life**.** Behind the difference in gene expression for ERs in VSMC cultures, there is still need for investigations on tunica media implications in physiopathology in a sex-gender perspective. These results suggest that these cells could be a good model for studying sex-gender differences in cardiovascular physiopathology.

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Gender differences in pain treatment among terminal oncological patients

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Background. In oncological patients pain treatment is a serious health problem worldwide. Recent studies have demonstrated gender differences in pain perception and an influence of sex hormones in modulating the pharmacologic response to analgesic therapy.
Objectives. The aim of the present study was to analyse possible gender differences in a cohort of cancer patients admitted to the local Hospice for evaluating the rate of hospitalization in the structure, the degree of pain perception and the pharmacological treatments before and during the period in Hospice.
Materials and Methods. Data were extracted from all medical records of cancer patients admitted to the Hospice "Paul VI" ULSS 16 of Padova in the time interval 2008-2009. Pain perception [measured with the Numerating Rating Scale (NRS)] and pharmacological therapy were screened in the following observational periods: before admission to the Hospice (T0), the day after admission (T1), the tenth day of stay (T2) and the day before discharge from the Hospice (T3).
Results. The medical records relating to 343 patients [49.9% males (mean age: 71.3 years), 50.1% females (mean age: 70.6 years)] were analysed. For the age group of ≥ 65 years (n = 264) data showed that male patients were more likely to be admitted to the Hospice than females [2.55 ‰ vs. 3.89 ‰; OR = 0.7 , 95% CI 0.5 to 0.8]. However, there was no difference between males and females in the length of stay in the structure (20 vs. 23 days) and the internal mortality (97% vs. 94%). In general, at T0 pain was perceived by 72% of patients. Among the younger ones (age <65 years) it was significantly more frequent in females (77%) than in males (50%) [OR = 3.4, 95% CI 1.2 to 9.4]. To ensure complete analgesia, 3/4 of these female patients (78%) at T0 were taking major opiates, apparently used in inadequate doses. At T1 opioid rotation was performed in 54% of patients with a higher frequency for females (59%) than for males (50%) [OR = 1.4 (0.9 - 2.4)]. During the Hospice stay a gradual replacement of analgesic drugs in use occurred, especially at T3. Most of the patients (88%) were treated with major opiates, usually parenteral morphine. Change of analgesics administered at home and/or dose adjustment provided a rapid pain relief in both sexes after the first day of

admission to the Hospice [NRS value: 3.76 (T0) vs. 0, 87 (T1), P <0.001).

Conclusions. Pain control still remains a serious problem in terminal cancer patients. On access to the local Hospice younger women were more likely to have a higher pain perception than their male counterparts, despite the administration of major opiates, probably due to inadequate use. During stay in the Hospice, the rotation of major opiates and dosage adjustments of same analgesics in use have provided a fast and effective pain control in most of the patients.

Infertility Differently Bears on the Risk of Development of Sexual Dysfunction Between Females and Males

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Introduction: Literature data regarding the sexual quality of life of infertile couples are frequently discordant.
Aim: to investigate the prevalence of sexual dysfunctions between infertile females and males and between infertile couples attempting to the adoption path.
Materials and methods: sexual function of 61 infertile couples (Clinical group) and 35 infertile couples attempting to the adoption path (Control group) was measured with the International Index of Erectile Dysfunction (IIEF-15) and with the Female Sexual Function Index (FSFI). The association level between the presence of sexual dysfunction and the variables "infertility" and "infertility with adoption" was measured with the Relative Risk (RR). The differences in continuous and dichotomous variables were measured with T Student test for unpaired data and with Chi-Squared or Fisher's test, respectively. P values <0.05 were considered statistically significant.
Results: the prevalence of female sexual dysfunctions was statistically different between women of Clinical [49.2% (30/61)] and Control group [17.1% (6/35)] (p=0.004). The prevalence of moderate (p=0.065) and severe (p=0.249) erectile dysfunction (ED) was not statistically significant: 18% (11/61) of men in Clinical group were affected by moderate ED and 21.3% (13/61) by severe ED. In Control group 3% (1/35) were affected by moderate ED and 34.3% (12/35) by severe ED. Females of Clinical group had nearly three-time higher probability (RR=2.87; 95%CI 1.32 to 6.20; p=0.0074) to develop a clinically significant sexual dysfunction respect to females of Control group. No association was found in males between moderate/severe ED and infertility.
Conclusions: The higher risk to develop a significant sexual dysfunction between infertile females, but not between infertile males, may be partially due to the presence of depressive symptoms that can also worsen sexual desire.

Female alopecia: medicines used for its treatment and analysis of the suspected adverse drug reactions recorded in the Italian Pharmacovigilance Database

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Introduction.
Androgenetic alopecia is the most common form of hair loss in women. Its clinical manifestation determines a reduction in hair density and may lead to serious psychological implications in the affected woman. Moreover, this condition is currently increasing among women.
Minoxidil topical solution (from 2 to 5%) is the most commonly used treatment in female androgenetic alopecia. As therapeutic alternatives oral finasteride, flutamide, ethinylestradiol/drospirenone and cyproterone acetate/ethinyl estradiol associations are also administered. The use of finasteride, flutamide and of the association ethinyl estradiol/drospirenone in the treatment of alopecia in women is an off-label use, but supported by published studies.
Finasteride is an inhibitor of the 5 alpha-reductase, the enzyme which mediates at receptor level the conversion of testosterone to dihydrotestosterone; this hormone shows a greater activity than its precursor. Finasteride, first introduced in the clinical use in the treatment of benign prostatic hypertrophy, was subsequently studied in cases of cutaneous androgenization. Estroprogestinics can improve the clinical signs of hyperandrogenism by reducing circulating androgens. This effect is achieved both by a reduction in the production of ovarian androgens and an increase in circulating hepatic globulin SHBG. Finally, flutamide is used in women in the treatment of androgenetic alopecia and hirsutism generally at a low dose (125 mg / day while the authorized dosage in prostate cancer is 250 mg three times a day).
A recent systematic review by the Cochrane Collaboration on studies performed with these treatments, however, has shown that the experimental evidence does not support the clinical effectiveness of these drugs in the treatment of androgenetic alopecia in women. The purpose of this study is the retrieval and analysis of all the suspected adverse drug reaction (ADR) recorded into the Italian Pharmacovigilance Database (Rete Nazionale di Farmacovigilanza or RNF) and associated with the use of medicines used in the treatment of alopecia in women.

Materials and methods
An analysis of the reports of suspected adverse drug reactions recorded in the RNF of AIFA and associated with the use of medicines used in the treatment of alopecia in women was conducted. The data refer to the period 01/01/2002 - 20/11/2012.

Results
Thirteen reports of suspected ADR, 6 of which severe, occurring after the administration of drugs used to treat alopecia in women have been retrieved in the Italian Pharmacovigilance Database. The table below shows the associated ADRs and the relative seriousness.

Active ingredient	**Indication for which the drug was administered**	**ADR**	**Seriousness**
Minoxidil	Alopecia	Hypertricosis	non serious
Minoxidil	Alopecia	Dermatitis, pruritus	non serious
Minoxidil	Alopecia	Conctact dermatitis	serious
Minoxidil	Alopecia	Pathology of the skin, abnormal structure of the hair	non serious
Minoxidil	Alopecia	Urticaria	non serious
Minoxidil	Alopecia	Periorbital edema, erythema	serious
Finasteride	Alopecia	Disturbance of attention, fatigue, weight decreased	not reported
Finasteride	Alopecia	Hemorrhagic cystitis, breast tenderness, breast induration	non serious
Flutamide	Alopecia	Fatigue, hepatic enzyme increased, hepatocellular trauma	serious
Flutamide	Alopecia	Fulminant hepatitis	serious
Flutamide	Alopecia	Acute hepatitis, jaundice	serious
Ethinyl estradiol + drospirenone	Alopecia	Deep Venous Thrombosis	serious
Ciproterone acetate + ethinyl estradiol	Alopecia	Generalized edema	non serious

Serious ADRs are mainly associated with the use of flutamide and of the association ethinyl estradiol/drospirenone. In particular, for the 3 cases of suspected ADRs associated with the use of flutamide the drug has been taken for 4 months in two cases and for 3 months in the other case; deep venous thrombosis occurred after 2 months of therapy with ethinyl estradiol/drospirenone.

Conclusions

Although currently there is no clinical evidence in the effectiveness of the treatment with finasteride and other drugs used in androgenetic alopecia women, and these drugs are not authorised for the use in women, the presence of records of suspected adverse reactions with these drugs in women and in this indication in the RNF demonstrates their use in the treatment of female alopecia. The lack of exposure data to these drugs in women as well as the likeliness of ADRs under-reporting does not allow, at present, the evaluation of the risk associated with the use of these drugs in the treatment of androgenetic alopecia in women.

Gender-disparities in the quality of diabetes care in Italy: Results from the AMD Annals

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Inside a nonstop national initiative kept on by the Italian 'Associazione Medici Diabetologi' 'AMD', we evaluated the 'quality of care' offered by one third of Italian diabetes units, to a population of type2 diabetic patients split for gender.
PATIENTS & METHODS We analyzed data of 415.294 patients, of whom 188.125 (45.3%) females and 227.169 (54.7%) males, visited in 2009, coming from an electronic medical record systems (Eurotouch), shared by 236 diabetes clinics.
In particular, we studied patients' rate with at least one HBA1C value/year as **PROCESS MEASURE,** the prevalence of patients reaching **'Favourable'** (HbA1c ≤7% BP ≤ 130/80mmHg, LDL - C <100mg/dl) or **'Unfavourable' Targets** (HbA1c >8%, blood pressure 'BP' ≥140/90
mmHgLDL - C ≥130mg/dl) as **INTERMEDIATE OUTCOME MEASURES,** and the rate of patients under **PHARMACOLOGICAL TREATMENT** (any hypoglycemic, antihypertensive or lipid-lowering treatment). Moreover, the quality of care summary score **'Q score'** (0-40**)** was calculated on the basis of HbA1c, BP, LDL-cholesterol and microalbuminuria levels. The higher is the score, the better is the quality of care. **Statistics** Multilevel logistic regression analyses were applied. All models were adjusted for age, diabetes duration, BMI and clustering effect.
RESULTS: Women were older (68.4±11.4 vs. 65.7±11.1 years) and less smokers (11.8% vs. 21.5%) than men, with a higher BMI (30.2±5.9 vs. 29.1±4.6 Kg/m2) and a longer diabetes duration (11.1±9.7 vs. 10.0±9.1 years)
PROCESS INDEXES, M vs F: **HbA1c** 92,6 & 92,2%, **BP**, 79,1 vs 74,1%, **Lipid profile** 78,4 vs 72,4%. **FAVORABLE OUTCOMES M vs F**: **HbA1C≤7%:** 45,5 vs 41,6%, **BP≤130/80**mmHg 15,4 vs14,9%, **LDL - C <100:** 44,6 vs 38,4%. **UNFAVORABLE OUTCOMES M vs F: HbA1c >8%**: 26,9 vs 29,1%, **BP≥140/90**mmHg 56,1vs 58,1% & **LDL-C ≥130**: 23,6 vs 28,9%. **TREATMENT: M vs F: Any hypoglycemic treatment**: 29,3 vs 33,8%, **≥2 antihypertensive agents** 36 vs 33%. **Lipid-lowering agents** 41,2 vs 41,3%. Finally, a **GLOBAL 'Q SCORE'<15** was found in:7,2 M & 8,5% F , whilst a **Q SCORE >25** in 38 vs 34,2%.
C**ONCLUSIONS** Mild/moderate sex disparities were observed in favour of male patients. Despite similar/even more aggressive treatment, women reached less targets for the main CVD risk factors.

Social Integration of Ethnic Groups: the Case of Intellectual Women

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In the controversial debate in Italy regarding, on one hand, the possibility/impossibility of migrants' integration and, on the other, the complexity of the integration process, most scientific works focus either on the legal aspects in a merely juridical or economic perspective or on the integration of the more "disadvantaged" migrants in a sheer perspective of human rights defence. The intervention will focus on an aspect which has been completed neglected until now, that is the study of the integration processes of migrants from another point of view, that of the migrant women. This paper will overcome all previous studies about immigration and integration in Italy through a more mature analysis of the migrants' integration process taking into consideration its highest manifestations, that is the study of the integration strategies enacted by intellectual migrant women in Italy.
Most scientific works focus on gender migration in Italy from a paternalistic point of view,
taking into consideration only the most disadvantaged ones, that is those carrying out menial jobs. This approach is not enough in order to demolish the stereotypes and prejudices which are commonly associated to migrant women.
The hypothesis is that intellectual migrant women do not follow "traditional" strategies to integrate into the Italian society, but they go beyond the learning of the hosting country language and of the learning of cultural habits through the achievement of a deeper awareness which allows them to overcome the daily problems in order to participate in cultural and social activities at a higher level.
Therefore, it will be argued what strategies are enacted by intellectual migrant women to integrate into the Italian society through the analyses of a certain number of interviews and writings produced by migrant women residing in Italy.
Ingrid Stratti: Ingrid Stratti holds a DPhil (PhD) in International Affairs and is president of the International Research Centre for Intercultural Studies. Her main research and teaching interests are in the areas of human development, equality policies, human mobility and the historic interlinks of gender, nation and culture, as categories of social inclusion and exclusion.

HPV model: from women to gender medicine

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Her name was Henrietta Lacks, but scientists know her as "HeLa".
Henrietta Lacks "perceived" early her cervical lesion. But her cervical lesion, unrecognized by gynaecologists, progressed to cancer. She was 31 years old! [1]
There were the days of Apartheid. Johns Hopkins in Baltimore was the only choice for a hospital, since it was the only one that treated black patients. But, also in the "colored" ward of Johns Hopkins Hospital, empathy and listening attitude of a white doctor towards a black women were scarce.
Why do we speak about Henrietta Lacks? Henrietta Lacks is the woman of the immortal cells known as "HeLa". HeLa cells, taken from Henrietta cervix during a biopsy, and cultured without her permission, reproduces boisterously in most research laboratories in the world, starting from 1951, the year of Henrietta death [1]. They were the first human cells ever to do so.
HeLa helped build thousands of careers (i.e. five Nobel Prize for Medicine), not to mention more than 60,000 scientific studies, with nearly 10 more being published every day. They gave profound benefit to medical research. revealing the secrets of everything, from aging and cancer to polio vaccine, from drugs against cancer, AIDS, Herpes, leukaemia, influenza and Parkinson's disease to many other scientific pursuits. HeLa helped in understanding atom bomb's effects and allowed important advances, like in vitro fertilization and human genome mapping.. HeLa even "flown" in the space!
These cells have a modal chromosome number of 82 possess and are carriers of a mutation of telomerase gene. This mutation was induced by Papillomavirus. The same virus that broke off the life of Henrietta, makes her immortal! [1]
George Papanicolaou, before Henrietta death, already published his "Diagnosis of Uterine Cancer by the Vaginal Smear" (1943); few years later, the National Cancer Institute and the American Cancer Society promoted the introduction of Pap test into clinical practice (1948).
Earlier, in 1842, the Italian Rigoni-Stern reported the unusual high rate of cervical cancer among prostitutes and the very low incidence

among nuns, thus hypothesizing the sexual transmission of cervical cancer.
Pap test: one of the milestones of the modern medicine and the turning point towards the preventive oncology. A test that saved hundreds of thousands of women, could also save Henrietta. Thanks to Pap test and to the " HPV model " the paradigm of medicine, "tested on men, valid on the entire population" has been subverted. Women, indirectly, allowed researchers to know the natural history and the epidemiology of one of the most common viruses, and to find the ways to prevent one of the most prevalent cancer.
Which kind of diseases are HPV-induced in men? Certainly penile cancer. Most recently, HPV infections have been found in more than half of oropharyngeal cancer. The incidence of oropharyngeal cancer is increasing, especially among men [2]. Anal cancer, frequently observed among men who had sex with other men, is also increasing in its incidence.
More and more frequently, male issues often disregarded due to "intellectual androcetrism" are, de facto, linked to women's health. In this context, it is growing the need to support the modern andro-sexuological knowledge with the old gynecological knowledge. In this context women indirectly put the basis for gender medicin.
Nowadays, we know that about 30% of male whose partners are HPV positive are carrying HPV in their ano-genital tract, and that frequently men are responsible to HPV transmission to women. Then, it is now the time to start to prevent HPV infection also in male population.
In many Western countries, HPV vaccination was introduced on women. The European Commission recently approved the use of quadrivalent vaccination also on male volunteers..
Since we may use the same preventive tool for both men and women , why we should not use on men the same validated diagnostic tool which are currently used on women, optimizing them according to gender?
In female population, molecular technologies assessing the presence of HPV-DNA (HPV-DNA test) and the expression of HPV oncogenic protein (HPV E6/E7 mRNA test) are essential to characterize cervical lesions. These techniques can be used in cytological specimens from various body districts.
In Cytopathology Unit of “G. d’Annunzio” University we carried out several studies on men. The common aims of all these studies was to evaluate the prevalence and the incidence of HPV infection and related neoplasia and to evaluate the diagnostic performances that molecular tests, which have been already used in the diagnosis of uterine HPV infection, would have in male management.

Study 1) "cytologic versus virologic analyzes of specimens collected from different genital area in asymptomatic male population"
Methods: We selected 314 symptomatic males who were partners of women with cervical disease. Exfoliated cells were taken from their different genital's areas (internal and external preputial surfaces, glans, coronal sulcus, penile shaft and distal urethra) and placed in Thin Prep ® medium. Results: cytological signs of viral infection have been reported in only 17.8% of cases, but HPV-DNA positivity was detected in 25.2% of men. Viral oncogenic expression was found in 50% of cases with positive cytology and in 50% of cases with negative cytology. Conclusions: Both, HPV-DNA test and HPV mRNA test would be useful in monitoring genital men infection, particularly in the absence of clinical lesions.
Study 2) "HPV-related Head and Neck Cancer: the experience of an Italian multidisciplinary team. Preliminary data ".
Methods: starting from June 1, 2012, all patients referring to otorhinonolaryngology outpatient department and having a suspect oropharyngeal lesion were included in this prospective study. Until now, we enrolled 21 patients. Oropharyngeal cytological specimens were then taken. All samples were collected into PreservCyt LBC media. For each patient, cytological Papanicolaou slide was prepared. Residual cytological specimen was tested for the presence of HPV-DNA, and for the expression of HPV E6/E7 oncoproteins. Finally, from symptomatic patients, incisional or excisional biopsies were obtained. Hystological diagnosis was regarded as gold standard. Results: 57% of the patients were male. In 100% of symptomatic patient, atypical squamous cells in favour of malignancy has been detected. 81% of patients showed HPV-DNA positivity (among them, 60% were male). Among these, 2 cases showed the oncogenic expression of HPV-16; both patients were male. Conclusions: The incidence of head and neck HPV-related cancer is increasing, especially among males. Since HPV-related neoplasia shows better response to chemo-radiotherapy and overall better clinical outcome, biomarkers which are able to verify the presence of HPV-DNA and to detect HPV oncogenic expression would be useful in both treatment and therapeutic management of such patients.
Study 3) "Molecular tools in anal pathology: preliminary data".
Methods: starting from June 2011 and until now, we included in this prospective study 22 homosexual asymptomatic men. Each patients underwent to HPV-DNA test and HPV-mRNA test. Results: HPV-DNA of oncogenic types was detected in 100% of patients. E6/E7 oncoproteins were detected in 41% of cases (HPV-16: 89%, HPV-18: 11%). Conclusions: Molecular studies from anal brushing, are

promising in the early diagnosis of HPV-infection and in the evaluation of carcinogenic risk in homosexual patient.

In conclusion, with our studies we would to promote advanced research on Papillomavirus infection field as a useful tool for the evaluation of clinical appropriateness and as an integral part of gender medicine.

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