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Tuberculosis control in Italy and gender phthisiology

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Abstract. Worldwide, TB cases' notification is higher in men than in women. In 2015, the male/female ratio among adults was 1.69. Epidemiologists believe these differences consequence of socio-economic and cultural barriers that could restrict women's access to health services resulting in underreporting TB. In many countries, TB rates, among women, are higher in those of childbearing age. As a general rule, females exhibit more robust immune responses to infection than males and this is mediated to a large extent by sex hormones, in fact the male bias does not arise until puberty. Estrogens, androgens and progesterone profoundly affect the immune response, but such biological considerations do not clarify why active TB is more common in women of childbearing age, when estrogens set up their protective role. The female symptomatology is not identical to that of men. In pulmonary TB, general symptoms are more common in women than in men, whereas respiratory symptoms are more common in men than in women. With this background, the control of TB, based only on the recognition of symptoms, could lead to underreporting of active TB cases, particularly among women. Italy is a country with increasing female immigration from high TB risk regions and it should be interested in a gender oriented TB diagnosing.

Key words: tuberculosis control, sex, gender differences.

Controllo della tubercolosi in Italia e tisiologia di genere

Riassunto. Nel mondo, il numero di casi tubercolari notificati è maggiore tra gli uomini; il rapporto maschi/femmine, relativo al 2015, è stato 1,69. Nella maggior parte dei paesi, le età più colpite sono quelle giovanili, con una moda di 35 anni per gli uomini e di 25 per le femmine. Tra le ultracinquantenni le statistiche sono meno omogenee, mentre le età pediatriche non mostrano differenze statistiche tra maschi e femmine. In epidemiologia si addebitano tali difformità a sottonotifica dei casi di tubercolosi tra le donne a causa di barriere socioeconomiche e culturali, ma è possibile anche una spiegazione biologica. Le donne infatti mostrano una più efficace risposta immunitaria, rispetto agli uomini, nei confronti delle malattie infettive. In particolare gli estrogeni e gli androgeni sono considerati, rispettivamente, inibitori e stimolatori della risposta immunitaria anti-tubercolare Th1. Tuttavia, la maggior frequenza di tubercolosi nelle donne si registra in età fertile, quando gli estrogeni dovrebbero esercitare la maggior protezione. Anche la sintomatologia differisce nei due sessi, in particolare per quanto riguarda la tubercolosi polmonare: nelle donne sono più comuni i sintomi generali mentre negli uomini sono più comuni i sintomi respiratori. Con queste premesse, il controllo della TB, basato esclusivamente sulla raccolta dei sintomi, potrebbe condurre a una sottodiagnosi dei casi di malattia attiva nelle donne. L'Italia è un paese a immigrazione femminile crescente dalle regioni ad alta endemia tubercolare. Un efficace controllo della malattia non può prescindere da un approccio di genere alla sua diagnosi.

Parole chiave: controllo tubercolosi, sesso, differenze di genere.

Starting back to 1900

In recent years, in Italy, reported tuberculosis (TB) cases among migrants have increased from 39.4% in 2004 to 63% in 2013[1]. This trend is related to the increase in the number of refugees and asylum seekers, recorded also in Italy (Figure 1). This population in fact comes normally from countries at high TB-risk.

It is known that an economic recession fosters tubercular infection and for this reason, mathematical models anticipate an increase in mortality due to TB in the next decades. Nevertheless, the economic recession that started in 2008 has induced many European countries to reduce or abolish their programs for the control of infectious diseases[2].

WHO statistics on TB are fragmentary since: 1) there is a high gap among the expected and reported cases; this discrepancy, in 2015, was estimated to be 4.3 million cases, half of which "unrecorded" since they were not reported from India, Indonesia and Nigeria, 2) part of the data is not broken down by sex and age[3].

In 2016, for the first time, WHO published some charts related to new cases of TB whose smear is positive to AFB (acid fast bacilli), breaking them down by sex and age[3]. In the 191 states that were examined, a graphic representation of the disease broken down by sex and age allows for the identification of a mode = 35 years for men and 25 years for women, more spaced out in older ages. This situation is reminiscent of what was

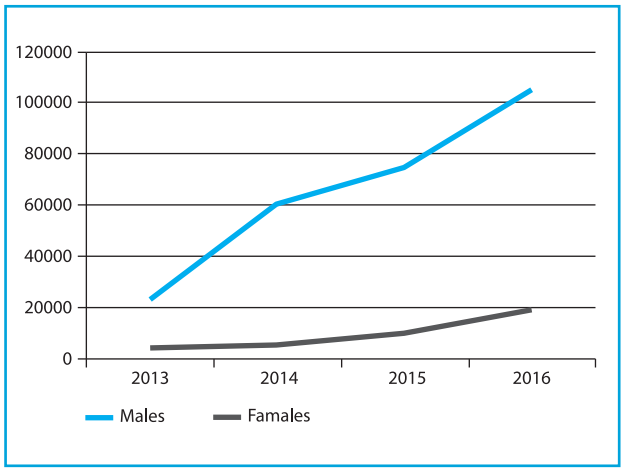

Figure 1. Total asylum requests ♂+♀: 2013 = 22,966+3,654; 2014 = 59,870+5,016; 2015 = 74,250+9,720; 2016 = 105,006+18,594. Source: Ministry of the Interior (www.interno.gov.it > data and statistics).

happening in the 1930-1950 period when TB was more frequent in women before the age of 40, and in men, after the age of 40[4].

Thirty years later, in Italy, a social and epidemiological structure is becoming comparable, in many aspects, to that of New York city during the tuberculosis epidemic of years 1975-1993[5] when the migration of 7 million people, the consequent overcrowding, economic instability, disintegration of the social and family fabric and the lack of attention paid to tuberculosis, erroneously considered fully eradicated, produced an outbreak[6]. In 1979, TB was declared out of control by the NY TB Control Bureau and in 1993 was considered a "Global Emergency" by WHO.

In this scenario, the disease and infection control in countries with a low endemic risk, like Italy, requires a further effort because of the increased flow of migrants from high TB-risk countries.

Moreover a careful and timely diagnosis of the disease (in particular of the pulmonary forms) is desirable in order to counteract the growing number of TB cases among the migrants (who are often paucisymptomatic and sometimes affected by MDR-TB), and the consequent increased risk of contagion also among the native population[7].

In view of this objective, the main responsibility is political.

However, the medical community may contribute by improving its phthisiological practices. In fact, in the 1st edition of the "General status of tuberculosis", held in 2011 in the Senate of the Republic, the first critical issue identified in the tuberculosis control system in Italy was the "lack of preparation of doctors in terms of this disease which has been eliminated from the studies in medical schools for years". It was concluded that there was an absolute need to reinstate an adequate training of the entire medical staff[8].

This training must also include gender differences especially in consideration of the progressive increase in migrants arriving in Italy (Figure 1). It is known, in fact, that the clinical symptoms suggestive of pulmonary TB are reported less frequently by women and this is significantly associated with a delay in the diagnosis of pulmonary TB in women[9].

A proteiform epidemiology

The number of reported tuberculosis cases is greater among men. In 2015, the male/female ratio among adults was 1.69 and in Europe 2.01, with an estimated 10,400,000 new cases, 5,900,000 men and 3,500,000 women. To these figures, an additional 1 million cases of children must be added[3].

Despite the mentioned fragmentation of the statistics, this data is accepted by the scientific literature. The possible explanations for the overall male predominance of the disease are the following:

1. socio-cultural differences: health literacy, stigma, income, different opportunity of accessing healthcare services;
2. different exposure to risk factors: smoke, occupation, indoor air pollution, protective factors: diet, concentration of vitamin D;
3. biological differences.

However, individually, each of these factors cannot fully explain this epidemiological data.

This work will address primarily the clinical aspects of the issue and will only summarise some aspects of biological nature, such as the role of sexual hormones in the immune response, which may explain the different TB incidence between men and women, abstaining from socio-epidemiological explanations for which it would be necessary at least to correlate the 2016 WHO charts with the pyramids of the population ages of the individual countries, as well as all related socio-economic conditions and levels of health literacy[10].

A partial gender susceptibility

If the TB reports are more numerous in males, must we assume that men are more susceptible to the disease than women?

This is probably true, but only partially.

In fact, in the '60s, it was clear that "active" pulmonary tuberculosis was three times more frequent in girls than boys, especially in the first few years after the menarche[11] whereas the first evidence of greater susceptibility to TB in pregnant women goes back to 1922[12].

Unfortunately, there are no WHO data on TB and pregnancy, and the New York "TB Control Bureau" itself, which defeated the tuberculosis epidemic of the years 1975-1993, has never included data on pregnant women, and since 2009 has ceased to breakdown the cases also by age.

The endobronchial TB (EBTB) "prefers" young women, with a male/female ratio up to 0.33 in the Asian population[13].

The inclusion of women's life phases, like pregnancy, in the collection of the global data on TB may, in the future, improve our understanding on disease susceptibility and explain several apparent contradictions: 1) auto-immune diseases are more frequent in women and the TB incidence is greater in patients with autoimmune diseases. We should therefore presume that women are the prevailing ones in TB cases among patients with auto-immune diseases. However, men are, with a male/female ratio around 2:1[14]; 2) the WHO data have confirmed a greater incidence of women affected by TB in the countries where HIV prevalence is high (>1%). In some cases, as in Pakistan, Lebanon and Cyprus, where, inter alia, the access by women to health services is extremely limited and the HIV prevalence is very low, the male/female ratio is reversed: ≤1[3,15]. What is the real reason? A study, carried out in 2011, has compared the TB AFB+ incidence between Pakistani and Indian women. The data was expected to be overlappable because of the similar socio-economic and cultural conditions. Surprisingly, the results were the opposite: the incidence male/female was <1 in Pakistan and >1 in India. This has supported the hypothesis that the hypovitaminosis D, repeatedly confirmed in the Pakistani and not Indian women, was playing a role[15]. But other factors, for example, the ethnic origin, may also come into play. These contradictions clarify how differences between men and women in the incidence and pathogenesis are due to biological differences related to sex, determined for instance by sexual hormones or other genetic and epigenetic factors, and by cultural norms related to the gender. Therefore, future research for tuberculosis control will need to adopt a global approach where the biological and socio-cultural aspects, which are still for the most part unexplored, must be taken into consideration[16].

Biology and tuberculosis

Immune response to Mycobacterium tuberculosis

Innate immune response represents the first line of defence against tubercular infection[17]. The cells of the innate system that *Mycobacterium tuberculosis* meets in the pulmonary alveoli are: i) macrophages that phagocytose it, acquire microbicide capacities and produce inflammatory cytokines ii) dendritic cells responsible for presenting mycobacterial antigens to T lymphocytes iii) NK cells which produce IFN-γ[18]. The acquired antitubercular immune response requires the contribution of multiple lymphocyte populations: i) CD4+ T lymphocytes with Th1 profile, responsible for the production of IFN-γ, TNF-α and IL-2, essential cytokines for the amplification of the cellular response and the activation of the macrophages, ii) CD4+ Th17 lymphocytes which recruit the neutrophiles in the infection site, iii) CD8+ T lymphocytes which lyse the infected cells. The anti-mycobacterial pro-inflammatory response is regulated or inhibited by anti-inflammatory cytokines, such as IL-10 and IL-4, produced by regulatory T lymphocytes and lymphocytes with Th2 profile[19]. Non-conventional T cells, such as γ/δ +T lymphocytes, CD1-restricted α/β + T lymphocytes and MAIT (mucosal-associated invariant T cells) contribute to the anti-mycobacterial response recognising primarily non protein antigens of the mycobacterium[20,21].

The humoral immune response contributes to attenuate the spreading of infection and the tissue inflammatory response through the production of antibodies that opsonise the mycobacterium[22].

Sexual hormones and immune response

The immune cells express hormonal receptors and their phenotype, and their functions are modulated by the sexual hormones[23]. In general, estrogens, in particular the 17-β estradiol (E2), act as drivers at least of the humoral immunity, and the progesterone and testosterone as natural immuno-suppressors[24]. Sexual hormones have different effects according to their concentration, but also to the target cell and the subtype of the receptor expressed on a specific type of cell. At the concentrations reached around the ovulation and pregnancy phases (500 pg/ml-50ng/ml), E2 has mainly anti-inflammatory effects, inhibiting the production and the function of pro-inflammatory cytokines such as TNF-alpha, IL-1β e IL-6 and the activation of NK cells, and inducing the expression of anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β. Therefore, at the indicated concentrations, E2 favours a Th2 and regulatory T cell phenotype. At lower concentrations, E2 stimulates NK cells and the production of TNF-alpha, IFN-γ, IL-1β. Finally, both at low and high concentrations, E2 increases the production of antibodies. Progesterone stimulates the switch from a pro-inflammatory immune response to an anti-inflammatory response, by promoting the differentiation of regulatory T lymphocytes and inhibiting NK cell function. Testosterone blunts the immune response by inhibiting pro-inflammatory cytokine and antibody production and Th1 cell differentiation, while increasing anti-inflammatory cytokine synthesis.

Therefore, it is obvious that many of the cells of the immune system involved in the anti-mycobacterial response are affected by a hormonal milieu. The stimulating and inhibiting effect on the Th1 immune response by estrogens and testosterone, respectively, would make one assume that, as in other infectious diseases, the anti-mycobacterial response is more effective in women. In support of this hypothesis, two studies carried out in the USA[25] and in Sweden[26], the first on 297 psychiatric patients who were castrated and the second one on 142 ovariectomized young women, documented how the removal of gonads, in men, has reduced mortality due to TB from 20.6 to 8.1% while in women it has increased it from 0.7% to 7% compared with the controls.

However, the anti-mycobacterial immune response among men and women not only differs due to sexual hormones but, as a recent study has demonstrated, the genetic polymorphisms of the toll-like receptor 8, located on the X chromosome, may have gender-specific effects on the development of the disease[27].

In conclusion, a more in depth study about gender differences in the anti-mycobacterial immune response should investigate the role of genetic and epigenetic variants in the two sexes and should take into account the gender-specific differences also in those non-conventional lymphocyte populations such as γ/δ +T lymphocytes, CD1-restricted α/β + T lymphocytes and MAIT, which are still little explored from this point of view.

Other possible causes for gender-related differences in the susceptibility to tuberculosis

Although these biological considerations may explain the high male/female ratio in adults, they do not clarify why the "active" TB, including the EBTB, is more frequent in child-bearing women, already two years after the menarche, when the estrogens should have assumed their protective role, nor do they clarify why it is less frequent in menopause when the "estrogenic activity" should be reduced. Similarly to the epidemiological ones, they produce an unclear phenomenology of the TB in the various female ages and recently estrogenic concentrations, even higher in post-menopause women with tuberculosis, compared with the control groups have been documented [in a group of 38 women in post-menopause affected by TB, with average age = 61 ± 11 years, the TB diagnosis has coincided with estrogen levels significantly higher (26.3 ± 14.3 pg/ml) compared with the control groups (19 ± 6.5 pg/ml)[28]].

It was observed that the hormonal fluctuations of the menstrual cycle entail changes in the number and function of the immune cells and this may exacerbate some diseases[29].

It is therefore plausible that susceptibility to TB responds also to a similar mechanism.

In addition, the greater prevalence of the EBTB, so far attributed to the socio-cultural inhibition of women to freely expectorate, which prolongs the contact of the infected sputum with the bronchial mucosa, may have a hormonal justification: the estrogens reduce the airway epithelium liquid layer and the progesterone reduces the beat of cilia which both contribute to reduce the clearance of the mucus from the airways[30].

Therefore the biological mechanism for understanding the male/female ratio of TB remains unclear. Finally, as regards the greater incidence of TB in patients with auto-immune diseases, in particular men, it is possible that the bacterium itself, through molecular mimicry induces or promotes auto-immunity, and it is possible to hypothesize a male gender-related genetic association in this mechanism.

Susceptibility to tuberculosis during pregnancy

The epidemiology of TB data about pregnant women, although limited, are more linear and indicate a greater susceptibility to the disease.

In pregnancy the immune response shows a Th2 profile and Th1 and NK cell responses are inhibited to guarantee the immunological tolerance to foetal antigens[31]. However this immunological milieu could potentially reduce the protective immune response against mycobacterial infection[32].

Progesterone, produced by the corpus luteum and subsequently by the placenta to prepare the uterus for the implant, stimulates the apoptosis of the monocytes, through the progesterone-induced blocking factor (PIBF) and the Glycodeline A, preventing the differentiation in macrophages. The E2, produced by the ovaries and subsequently by the placenta in order to increase the blood flow to the uterus and stimulate the growth of the mammary glands, attenuates the expression of many genes. The human chorionic gonadotropin (HCG), produced by the syncytiotrophoblast to facilitate the implant and ensure nutrition to the foetus, causes the formation of the vacuoles in the monocytes. It is also possible that the α-fetoprotein may interfere with the monocytes thus reducing the production of TNF-α[31].

The result is that the estimate of the prevalence of the disease ranges from 60 to 11,000 cases out of 100,000 pregnant women, if at a low or high tuberculosis risk, and with a negative or positive HIV[33].

A comparison with the incidence recorded in South Africa in 2015: 834/100.00[3], the highest worldwide, helps to understand the potential statistical weight of TB during pregnancy.

In addition, TB during pregnancy may often go undiagnosed and can be challenging to recognize, because

the typical TB symptoms are sporadic, as we will see at the end of the next paragraph.

The clinical approach

Female and male symptomatology are not identical. The male symptomatology is normally used as an example in the medical text books.

In a recent study carried out in South Africa, 73% of women with a culture positive TB did not exhibit any of the symptoms (cough, fever, night sweating and weight loss) indicated by the WHO four-part symptom screen, and of these, less than 3% turned out to be by smear microscopy[9].

In fact, in the pulmonary TB, the general symptoms (fever, tiredness, anorexia, headache) are significantly more common in women, while respiratory symptoms (cough, sputum and hemoptysis) are more common in men[9].

In the extra-pulmonary TB, the symptoms more often reported: fever, fatigue, arthralgia and the signs more often highlighted: anaemia, leukopenia, positivity for ANA and anti-histone antibodies, alteration in liver cytolysis examinations, pleural and/or pericardial effusion, arthritis, are the same that, in women, may suggest an autoimmune disease, such as systemic lupus erythematosus[34]. Again, among women, the smear microscopy is less frequently positive and the chest radiological lesions are less severe[9].

Given the above, the TB controls based on the recognition of the symptoms by the patient who should report them to the doctor (passive case-finding) or by the doctor (case-finding through questionnaire analysis) leads to a under-reporting of active TB among women with an increased risk of infection[35,36].

Even the EBTB, especially when not associated with parenchymal symptoms, may elude a diagnosis. Its main symptom, and often the only one, the chronic cough (typically defined "barking cough") and the frequent evidence of bronchostenosis at auscultation (although localised) make it easy, sometimes, to confuse it with asthma or even simply attribute it to cigarette smoking. The consequences occur in 90% of the cases and they affect both the patients (severe bronchostenosis, complicated with atelectasis and bronchiectasis) and the population (risk of contagion).

It is important to consider that the female genital TB, often associated with active pulmonary forms, is particularly difficult to diagnose.

But what deserves more attention is the TB diagnosis during pregnancy. It must start from the tuberculosis risk calculated according to the country of origin of the woman and her clinical history.

In fact, the pregnancy physiological symptoms, such as fatigue, dyspnea, sweating, cough, tachycardia and temperature alteration, coincide with the symptoms of pregnant women with TB, to the point that the clinical screening of HIV-positive pregnant women can identify the disease only in one woman out of four women with tuberculosis. Even some laboratory exams, such as the increase in ESR, anaemia, hypoalbuminemia coincide in the two conditions, while only the weight gain and hypertension, more typical of a pregnancy, are offset by weight loss and hypotension, typical of the TB.

Conclusions

The increased migratory flows from high TB endemic countries entails that a growing number of TB cases are diagnosed in women and men resident, both permanently and temporary (CARA and SPRAR), in Italian migrant centers as well as in the national territory[1]. In 2016, compared with 2013, the number of people requesting asylum, increased by 4.6 times for men and by 5.1 times for women (Figure 1). The data from the Ministry of the Interior concerning the migration flows of February 2017, show an increase compared with the previous month, by 30% for males and 40% for females.

In the USA, Australia and Europe, most TB patients come from high TB-risk countries. The current programs for TB control at the borders provide for the identification of people with active TB, often through questionnaires that investigate the "TB male symptoms".

Epidemiology uncertainties, incomplete understanding of biological differences between men/women and the complexity of a safe clinical practice entail that also Italy, a country with a low incidence but with increasing immigration, has a strong interest in developing a gender approach for the diagnosis of tuberculosis, especially among pregnant women, in order to prevent, especially in women and their children, the complications of a delayed or lack of TB diagnosis, and to reduce the risk of contagion within the native population.

Hence the need to develop case-finding programs in groups at high TB risk and among pregnant women (without a chest XRay), especially if migrants[37]. Consistent with the above, TB control programs at the borders should be "gender sensitive".

This is also in line with the "End TB Strategy" launched by WHO for the purpose of eliminating tuberculosis by the year 2050, though it is clear that, in a globalized world, TB will not be sustainably eliminated in any country until it is globally eliminated.

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Key messages

- Worldwide, tuberculosis case notification rates are usually higher in men than in women.
- Underreporting TB cases among women is only one of the possible explanations for differences in active TB incidence between men and women. Hormonal status is another possible explanation for these differences. Surprisingly, in many countries female TB is more common in women of childbearing age.
- The female TB symptomatology is not identical to that of males.
- Undiagnosed active TB is reported to be common among pregnant women because immunity in pregnancy could facilitate the growth of intracellular organisms such as *Mycobacterium tuberculosis* and TB symptomatology is similar to that of pregnancy itself.
- Italy is a low TB incidence country with increasing female immigration and should be interested in a gender oriented TB diagnosing.

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