Introduction

A couple that cannot conceive within a year of regular unprotected sexual intercourse is generally considered infertile. A small percentage of couples succeeds in having a child only after 2 years of attempts; therefore many prefer to speak of infertility only after 24 months. Conversely, if a couple has already had children but cannot have others, it is said to have secondary infertility. As a whole, infertility affects about many couples and it has many and diverse causes, among which are those due to thyroid dysfunction which can lead to effects on the neurodevelopment of the infant, various complications in pregnancy, and even spontaneous abortion (1, 2). Few description of the couples ability to conceive a pregnancy exist in non-selected groups of the general population. Strictly defined, sterility occurs when couples have a precise irreversible disease or
remain infertile even after a diagnostic approach and exhaustive therapy. When sterility is a permanent condition, all that remains to be done is to resort to more sophisticated medically assisted procreation techniques.

Estimates of the infertility rate in a given population can be either direct or indirect. An indirect estimate takes into consideration the overall number of childless couples of childbearing age. The lack of children, however, at least in some cases, is a matter of choice and not an effect of infertility; therefore there is a risk of overestimating the data. Direct estimates of infertility are certainly more reliable in that they are based on specific demographic surveys conducted on an entire population or, more often, on sample groups (3, 4).

Subfertility means having a fertility index of 3 to 4 times lower than normal: this means that some couples will take longer to conceive. A major contributing factor to subfertility is the woman’s age. According to both the results of Medically Assisted Procreation and to demographic studies investigating the percentage of new sterile couples and reporting a progressive increase in sterility with age, the ability to conceive decreases with age.

It is very difficult to assess the impact of the various factors causing infertility. A reliable estimate, although regarding only one part of the population, comes from data on couples going to assisted procreation centers. The Italian Register on Medically Assisted Procreation collected the following data: male infertility: 29.3%; female infertility: 37.1%; female and male infertility: 17.6%; Idiopathic infertility: 15.1%; genetic cause: 0.9% (5, 6).

Furthermore, complex psychosocial phenomena like lifestyle, seeking the first child later in life, drug use, alcohol abuse, smoking, working conditions, and pollution stand out increasingly as possible causes of infertility in the medical literature.

Female infertility

Italian women are having children later and later (7). They get married at an average of 28 years, give birth to their first child at 30. The reasons compelling couples to postpone parenthood are entirely understandable. First, economic security must be achieved, then there must be sufficient family organization to manage the children. The most fertile period for a woman is between 20 and 25 years old, with fertility staying relatively high until age 35, and then it dipping considerably from 35 to 40, beyond which it drops to very low levels (8). Female gametes age as women age and the risk of diseases involving infertility and sterility increases. These are often common diseases that can arise over the years, such as pelvic inflammatory diseases, diseases involving the fallopian tubes, development of uterine fibroids, and endometriosis.

The aging of eggs is a particularly relevant cause of sterility. The eggs of women who are no longer young often have genetic abnormalities which, if fertilized, can lead to deformed embryos, often aborted spontaneously. Natural selection, in fact, eliminates most malformed embryos and this explains the high rate of spontaneous abortion in older women: the abortion rate is 18% for women between 30 and 39 years old, 34% at around 40, compared to only 10% in women under 30. Therefore, factors reducing fertility are both quantitative and qualitative: there are fewer eggs in number and they are of worse quality (9). The age of the uterus, by contrast, is of much less importance. Nevertheless, statistics show a correlation between the age of the uterus and an increase in the percentage of spontaneous abortions of chromosomally normal embryos and a higher incidence of cases of placenta previa, difficult labor, uterine diseases, such as endometrial polyps and uterine fibroids. There also seems to be an increase in sclerotic lesions in uterine arteries, which, despite a lack of direct impact on fertility, are correlated with obstetric complications such as placental detachment, cesarean section birth, malpresentation of fetus, etc. (10).

Male infertility

Even male fertility has seen a significant drop. Many studies show that average sperm count has plummeted by nearly half over the last 50 years. This is why 35% of infertility cases are attributed to a male cause. The age of the man is a much less significant determinant of infertility (11). However, the quality and quantity of the ejaculate is reduced in older men. There are fewer sperm cells, with less motility, and more frequent chromosomal abnormalities. Male infertility certainly has a large social component, as environmental conditions and lifestyle (including stress) add up to individual pathological conditions. Finding conclusive answers, however, is harder than it might seem. Many and heterogeneous factors have been investigated; moreover, there is a great variability in sperm count (not only from person to person, but also from ejaculate to ejaculate), in terms of morphology and motility. Among other things, the sperm count in and of itself is not a proven fertility index, in that there is no correlation between the number of sperm and fertility, except in the cases of oligozoospermia or azoospermia. There is, instead, a stronger body of evidence regarding specific risk factors. Some working conditions exposing the worker to radiation, toxic substances, or to microtrauma, increase the risk of infertility (12). Exposure to pollutants also have a negative impact. Cigarette smoking also harms sperm: smokers often have increased abnormal sperm morphology. Even lifestyle, if excessively stressful, can reduce fertility.
Among medical causes of male infertility are all of the diseases that may alter the structure and function of the testicle or the penis (like cryptorchidism and hypospadias). Testicular cancer, in particular, is a risk factor in and of itself and as a consequence of chemotherapy or radiotherapy (only 40% regain reproductive function). To overcome reproductive difficulties encountered by men who must undergo treatment for testicular cancer, sperm can be collected and cryopreserved before any intervention or risky therapy. Lastly, one known factor, although not always a determining factor for male infertility, is varicocele. Hypothyroidism can also lead to reduced libido and erectile function (13). Genetic factors also have their effect: for example, it is theorized that an alteration of the long arm of the Y chromosome leads to a risk of oligozoospermia (14). Thyroid gland previously supposed not have any impact on spermatogenesis and male fertility, are now being recognized as having important role in male reproductive functions (15).

Thyroid and fertility

The hypothalamus is an area of the brain involved in regulating various organs, in particular the pituitary gland. In fact, the hypothalamus produces a series of substances that inhibit or stimulate the anterior pituitary: gonadotropin releasing hormone (GnRH), which stimulates synthesis of follicle-stimulating hormone (FSH) and of luteinizing hormone (LH), thyrotropin-releasing hormone (TRH), which stimulates production of thyroid-stimulating hormone (TSH); GHRH (growth hormone releasing hormone), which stimulates production of GH; CRH, which stimulates synthesis of ACTH (adrenocortico tropic hormone); PRH, which stimulates synthesis of prolactin (PRL). If the hypothalamus controls hormone secretion by the anterior pituitary it is also true that anterior pituitary hormones exert feedback control on the hypothalamus itself. Triiodothyronine (T3) and tetraiodothyronine (T4) thyroid hormones are among the most important regulators and controllers of general homeostasis of the human body. In humans, T3 and T4 also play a central role in reproductive function at the onset and progression of pregnancy, in intrauterine fetal growth, and breastfeeding. Meta-analysis studies show, however, that the prevalence of couple infertility correlated only with abnormalities of thyroid function is about 1% and therefore is much lower than the prevalence of abnormalities of thyroid function. Epidemiological studies show that thyrotoxicosis has a prevalence of 1.0-1.5% and that hypothyroidism, especially in its subclinical form (SCH, subclinical hypothyroidism), is the most prevalent thyroid disease in the general population aged 18 and over, and is more frequent in women and in the elderly (1.4 vs 1.4 per 1000 women per year at ages 20-25 and 75-80 years old, respectively). On average 10% of the general population is calculated to be affected by hypothyroidism. As for pregnant women, 1% has overt dysfunction, 2-3% has an undiagnosed subclinical form, 5 to 15% has anti-thyroid peroxidase (anti-TPO) antibodies, often associated with a pregnancy or postpartum disease and 10 to 30% is iodine-deficient. Epidemiological studies show that in the infertile population, the main cause of thyroid dysfunction is chronic autoimmune thyroiditis, followed by iatrogenic hypothyroidism secondary to definitive treatment for thyrotoxicosis. Specific risk factors for progression from SCH to clinical hypothyroidism are anti-TPO antibodies and anti-thyroglobulin (anti-TG) antibodies and very high thyroid stimulating hormone (TSH) values (16).

Thyroid and gonadal axis interactions

Most T3 and T4 is transported in serum bound to thyroxin binding globulin (TBG), to transthyretin, and to albumin. TBG has an elevated affinity for T4 and transports about 75% of it. During pregnancy TBG levels markedly increase T4-binding sites. Among other changes that arise in pregnancy is increased glomerular filtration rate (as well as increased iodine clearance) and increased human chorionic gonadotropin (HCG) in the first trimester. During application of assisted reproductive technologies (ART), when ovarian hyperstimulation is performed, estradiol concentrations are very high and these levels further tax the hypothalamic–pituitary–thyroid axis, which may even alter thyroid hormone kinetics. Other effects that may arise are hyperprolactinemia – due to increased thyrotropin releasing hormone (TRH) output – and subsequent altered secretion of gonadotropin releasing hormone, which leads to delayed luteinizing hormone response and to inadequate formation of the luteus body. High prolactin levels inhibit side chain cleavage (SCC-450) in the ovary (an enzyme which converts steroid hormone precursors) directly inhibiting steroi-dogen activity and exerting an inhibitory effect on LH ovarian receptor recycling. A direct effect of thyroid hormones on the gonads arises from T3 modulation of FSH and luteinizing hormone. Lastly, it should be remembered that specific T3 and TSH receptor sites have been found on eggs (17). Thyroid hormones also stimulate liver synthesis of sex hormone binding globulin (SHBG), therefore in hyperthyroidism there is increased SHBG associated with high levels of total testosterone (T) but with reduced levels of free T; low free T is associated with increased levels of gonadotropins. Hypothyroidism can conversely be associated with low SHBG levels, leading
Thyroid autoimmunity associated with infertility

Many studies have looked into the prevalence of women with thyroid autoimmunity (TAI) in infertile women. The prevalence of hypothyroidism in women of childbearing age varies from 2 to 4% and it is often due to TAI. Hypothyroidism, even when subclinical, is often associated with recurrent abortion; hyperthyroidism is less frequent and therefore its role in recurrent abortion is lower (19).

Interpreting the results of the many studies done is difficult because of their many differences: selection bias and infertility causes (one vs multiple), different contexts (such as retrospective vs prospective), controls, number of cases, and type of test used to measure anti-thyroid antibodies. In one study (20), after 552 pregnant women were screened for the presence of anti-thyroid antibodies in the first trimester, twice as many spontaneous abortions occurred in TAI-positive women than in those who were TAI-negative. The increase in abortions was independent of TSH, T3, and T4 serum concentrations, of the auto-antibody level, of the history of obstetric disorders, and of maternal age.

Finding a correlation between TAI and spontaneous abortion does not involve finding a cause and effect relationship; rather, abortion could be attributable to a combination of factors that may potentially lead to it.

With that in mind, 3 theories have been put forth:

1) The first is that abortions are actually linked with various factors especially involving immunity; for example women who have had multiple abortions have a higher number of CD5/20+ cells compared to women who have had 1 or no abortions (21). Despite that, T cell function is normal. Lastly, mice immunized with thyroglobulin were found to have antithyroglobulin antibodies and a lower placental weight.

2) In the second theory, the presence of TAI is associated with low thyroid hormone levels for the gestational date, simulating a picture of hypothyroidism. This theory still fails to set pregnancy reference ranges for TSH, T3, and T4. One publication found that TSH values tended to be high in the first trimester in women with TAI. The risk of hypothyroidism increases if the TSH is over 2.5 mIU/L when there is a high level of antiperoxidase antibodies and the thyroid gland appears to be hypoechogenic. In other studies only TAI-positive women who experienced abortion showed different TSH and T4 levels compared to those without TAI.

3) The third theory concerns the age of the woman. Women with TAI tended to be older than the controls. This theory actually does not contradict the others.

In the event of TAI, if a normal thyroid status is restored through a pharmacological treatment, the risk of abortion tends to decrease.

One study found a 16% prevalence of TAI in women who had gone to a fertility clinic, 5% of whom only had anti-Tg antibodies, 4% only had anti-TPO Ab, and 8% of the cases presented both types. The group with anti-Tg Ab was associated with TSH values of over 2.2 mIU/L. After treatment with L-thyroxine abortion values and other complications were similar to those in women without TAI. Both the NHANES and the Strieder (22, 23) studies showed a positive correlation between anti-TPO Ab and thyroid function and Strieder found a positive correlation between anti-TPO Ab and TSH levels (but not with anti-Tg Ab). This data, regarding the correlation between Ab and TSH, is associated with thyroid infiltration by lymphocytes and therefore with thyroiditis. This observation suggests the theory that hypothyroidism is then developed and that this later interferes with ovulation, pregnancy, and its outcome.

Thyrotoxicosis and hyperthyroidism

Elevated serum levels of thyroid hormones, such as with thyrotoxicosis/hyperthyroidism, bring about increased blood levels of sex hormone binding globulin (SHBG). It should be recalled that SHBG is a glycoprotein whose synthesis, essentially hepatic, is regulated by the estradiol to androgens ratio and by IGF-1 (insulin-like growth factor) produced by the pituitary and which exerts an inhibitory action on the liver. SHBG has a high affinity for dihydrotestosterone and for testosterone (T). Only free T has proven to be usable by cells; that bound to SHBG only works as a reserve. Women with thyrotoxicosis/hyperthyroidism also present estradiol (E2) serum levels 2-3 times those found in women with a normal thyroid (23). Based on the literature, it is not entirely clear whether the increase of E2 is attributable to an increase of the SHBG or not. In favor of the first theory, one study has reported that the meta-
Interaction of the thyroidal and gonadal axes and infertility. A brief overview

Hypothyroidism

Studies in the literature report that women with hypothyroidism have reduced metabolic clearance of A and E1, increased peripheral androgen aromatization, reduced SHBG and therefore increased T and E2 free fractions (27). The causal relationship between hypothyroidism and altered metabolism of sex hormones is demonstrated by the fact that in most cases restoration of normal thyroid function leads to normalization of sex hormones (28). Serum gonadotropin levels are usually normal in women with hypothyroidism while prolactin (PRL) levels can prove to be increased due to a greater pituitary response to TSH releasing hormone (TRH) leading to an increase not only in TSH but also in PRL. It is reported in the literature that 50-60% of women with hypothyroid of childbearing age present alterations of the menstrual cycle with a frequency of about 3 times greater than in women with a normal thyroid. Menorrhagia, metrorrhagia and polymenorrhea are frequently found (29). The correlation between clinical hypothyroidism and female infertility is evident in that clinical hypothyroidism can lead to hyperprolactinemia and therefore to oligo-anovulation. Conversely, the literature is inconsistent and inconclusive about the correlation between SCH and natural female fertility and SCH and the efficacy of MAP techniques. Hypothyroidism is more closely associated with abortion or complications for the delivery or the newborn, while it has lesser impact on fertility. It is important that it can also result in cognitive damage in the child (30).

Hypothyroidism, even when subclinical, is frequently associated with recurrent abortion. Do not underestimate that in iodine deficient areas you may experience an even subclinical hypothyroidism that certainly favors infertility (31). IQ level and cognitive performance of children born to LT4 treated hypothyroid mothers is similar in those whose mothers have subclinical hypothyroidism during pregnancy compared with those whose mothers have normal serum TSH concentration during pregnancy (32,33).

Conclusions

To date, the mechanisms responsible for alterations in fertility remain incompletely defined. A factor of vital importance is undoubtedly the increasing age at which conception occurs. Another relevant cause is also the high prevalence of iodine deficiency in women which can lead to hypothyroid and can easily be prevented. Thyroid disease only accounts for 1% of the cases of infertility and therefore it must be assumed that there are other co-factors, hormonal or otherwise. Recently, pesticides have been confirmed to exert a negative role on thyroid function and fertility. Despite that, thyroid hormones play an important role in reproductive function both by way of direct effects on the ovaries and by way of multiple interactions with other sex hormones. Thyroid function should be screened in infertile women, especially if they also present endometriosis or ovarian dysfunction. The American Thyroid Association also recently issued a reminder that the TSH value in pregnant women in the first trimester should not exceed 2.5 mIU/L.

Thyroxtine treatment can improve fertility when a diagnosis of clinical or subclinical hypothyroidism is made. For women treating hypothyroidism is an essentially part of any effort to correct infertility. If infertility remains after hypothyroidism has been corrected, other intervention to treat infertility remains may be needed.

Thyroid autoimmunity does not always jeopardize conception but women with chronic autoimmune thyroiditis are at a higher risk for abortion. Thyroid dysfunction adversely affect fertility. Many studies imply a role for immunology, including thyroid autoimmunity in conception failure.
References


