

BEHAVIOR TO BE TAKEN BEFORE AN INFERTIOUS COUPLE WITH A VIEW TO MEDICALLY ASSISTED PROCREATION

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Abstract : In recent years, infertility disorders have continued to increase. One in six couples (16%) consult for an infertility problem and almost two-thirds will conceive spontaneously, or thanks to medical treatment. Infertility is a real public health problem, since around 14% of couples see a doctor at least once for an infertility problem. In about 33% of cases, a purely female cause is found, in 21% of cases a uniquely male cause, in 39% of cases both a female and male cause and 7% of cases no cause is found (unexplained infertility). AMP techniques have advanced a lot in recent years as well as their field of application. These techniques have a constant success rate.

I. Introduction

Infertility is the complete inability of a man, woman or couple to conceive at any given time. This incapacity can be temporary and reversible, or permanent and irreversible. We speak of primary female infertility when the woman has never been pregnant. Fertility is the ability to conceive. In practice, subfertility results in a longer conception period. The objective of this paper is to address the main causes of infertility in men and women, as well as the exploration of the infertile couple, in addition to the various techniques of medically assisted procreation.

II. Fertility disorders

➤ General factors influencing the fertility of the couple

Age: Female fertility peaks between 20 and 30 years, with an effective of 25%. This fertility drops from age 31, worsening more sharply from age 35 to exceed 50% from age 40, while the rate of spontaneous abortions is two to three times higher [1]. Male fertility, assessed on the characteristics of the sperm (count, mobility, morphology) reaches a maximum around 30, then signs of aging begin to appear on the testes.

Tobacco: Twice the risk of being infertile, decreased ovarian reserve, lower anti-Müllerian hormone (AMH) levels, short and irregular cycles and dysmenorrhea are also found in smokers (2). Studies have shown that smoking in men and women leads to a 40% decrease in the chances of AMP, and a three-fold higher ICSI failure rate in smokers [2].

Cannabis: Regular consumption of cannabis over 5 years results in decreased sperm volume, number of sperm, morphology and mobility with overactive sperm and decreased fertility [2].

Drugs: These are certain antihypertensives, chemotherapy, radiotherapy, treatments for neuropsychiatric conditions (antidepressants), or stomach ulcers [2].

Lifestyle: Oxidative stress occurs in about half of cases in infertile men. This stress targets, among other things, the DNA of gametes. Mineral and vitamin supplements may be offered to reduce the effect of oxidative stress [3].

Environmental and occupational pollutants: Recently the deleterious effects of heavy metals and ionizing radiations have been highlighted. Studies highlight the relationship between the exposure of certain professions (farmers, smelters, horticulturalists, soldiers, hairdressers, housekeeper, nurse) ; and the fertility problems that certain couples encounter [2].

Obesity: A real public health problem, plays a major role in female reproduction. The presence of obesity in adolescence is associated with a higher lifetime risk of nulliparity compared to women with a normal BMI.

➤ Main causes of infertility in men

Azoospermia: Is characterized by the absence of sperm in the ejaculate. This diagnosis is made after three successive spermograms taken three months apart. A distinction is made between secretory or non-obstructive azoospermia and excretory or obstructive azoospermia.

Teratospermia: The presence of an abnormally high level of abnormal sperm. These abnormalities can affect all parts of the sperm (head, flagellum) and are usually due to dysfunction of spermiogenesis [3].

Oligospermia: Insufficient number of sperm. It's the most common case of male infertility [4].

Asthenospermia: Lack of mobility of sperm. There is normally 40% motile sperm in semen.

Necrospermia: It's characterized by a high percentage of dead sperm (> 50%). Often due to infections. (Table 1)

Table 1: Main sperm abnormalities (1)

Volume	Hypospermia	Volume < 2ml
	Hyperpermia	Volume > 7ml
	Aspermia	Absence of ejaculate
Concentration	Polyspermia	> 200 × 10 ⁶ /ml
	Oligospermia	< 20 × 10 ⁶ /ml
	Cryptospermia	Rare spermatozoa requiring
	Azoospermia	Absence of sperm
Mobility	Asthenospermia	Mobility < 40%
	Akinetospermia	Absence of motile sperm
Morphology	Teratospermia	< 30% Typical shapes
Vitality	Necrospermia	< 50% live sperm

➤ **Main causes of infertility in women**

Ovulation disorders (anovulation, dysovulation): They affect 30% of female infertility. Ovulation disorders can be caused by dysfunction of the ovaries or the structures in the brain that control their activity. The possible etiologies are: hyperprolactinemia, hypothalamic-pituitary dysfunction, micro-polycystic ovarian dystrophy, ovarian failure.

Endometriosis: Is the presence of endometrial tissue outside the uterine cavity. It's a common disease affecting 6-10% of the general population. In women followed for infertility, the frequency is significantly higher (30 to 40%) [5].

Micro-polycystic ovaries: Polycystic ovary syndrome is defined by the presence of at least two of the following three criteria: oligo and/or anovulation; clinical and/or biological hyperandrogenism; the presence on pelvic ultrasound of at least 12 follicles per ovary, 2 to 9 mm in diameter and/or an increase in ovarian volume. Micropolycystic ovarian dystrophy is the most common cause of ovulation disorders.

Hyperprolactinemia: is found in 30% of women suffering from cycle disorders and in 20% of secondary amenorrhea of high origin. It is characterized by an increase in the level of circulating prolactin. Hyperprolactinemia in women when their level is greater than 30 µg/L [5].

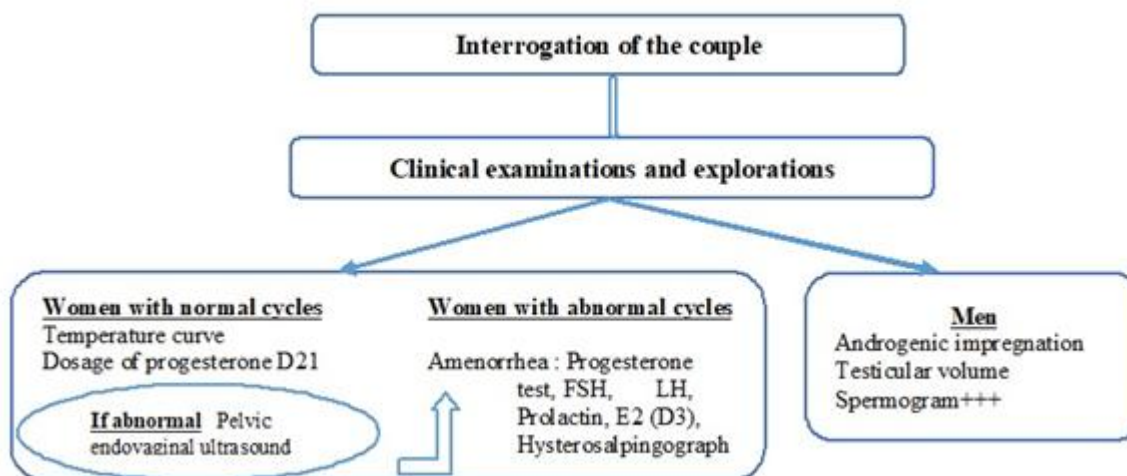
Genetic etiology: In anovulations of hypothalamic-pituitary origin, several genes have been identified: FGFR1, the prokineticin receptor and prokineticin, FGF8 and CHD7. In hypogonadotrophic hypogonadisms without anosmia, mutations of the GnRH receptor, GPR54, TAC3 and its receptor have been identified. In premature ovarian failure, there may be an abnormality in the number or structure of the X chromosome, deletions or translocations between the X and the autosomes.

III. Infertile couple exploration

➤ **First consultation**

A couple is infertile if they remain childless after two years of intercourse without any contraception. In more than a third of cases, the origin of infertility is mixed. The first consultation must therefore be taken care of by the couple. During this consultation, an interview and a clinical examination of each partner will help to establish a strategy for the additional examinations to be prescribed. The exploration of an infertile couple must therefore be carried out in parallel in both partners.

Figure 1: What to do during the first consultation [1]



➤ **Interrogation**

For couple: relates to the date of cohabitation, with or without contraception, regular and physiological sexual intercourse, scheduled preovulatory or not, the frequency of sexual intercourse (regular or episodic), previous or current treatments and explorations previously carried out.

For woman: the woman is questioned about her current treatments, sports activity, diet, the operative reports of the gynecological and obstetric interventions, blood group, serological status: rubella, toxoplasmosis, *Chlamydiae trachomatis*. In terms of medical (diabetes, arterial hypertension, thyroid pathology, phlebitis, psychiatric pathology...), in terms of surgical (abdomino-pelvic surgery), gynecology-obstetrics (age of first menstruation, regularity of cycles, dysmenorrhea, dyspareunia, premenstrual syndrome, taking contraception and type, pelvic infection, pregnancies and progress, pathology of the cervix). The questioning must be methodical and meticulous, because it often alone allows to identify a diagnostic orientation.

For men: The evaluation should include a complete medical and reproductive history, a physical examination and at least two semen measurements. The systematic questioning aims to find the reproductive history with the duration of infertility and the previous fertility of the both partners, age of the partner, childhood pathologies, diabetes, previous surgeries, sexually transmitted infections, exposure to deleterious factors (heat), family reproductive history and treatments (current and previous) [6].

➤ **Clinical examination**

In women: This exam assesses actual age and physiology. He also looks for height and weight, hair growth, blood pressure, appearance of the skin (acne). Breast exam is essential. Also assessed are vaginal trophicity, uterus, ovaries, presence and quality of cervical mucus, apparent condition of cervix, presence of uterine fibromyomas.

In men: The general physical examination is an integral part of the assessment of an infertile man. Hairiness, weight, size, blood pressure, examination of the penis, palpation of the testicles and their size, presence and consistency of epididymis, detection of varicocele, evaluation of secondary sexual characteristics with distribution of hair, distribution of fat, detection of gynecomastia, digital rectal examination is strongly recommended [6].

➤ **Woman's infertility assessment**

a. Hormonal assessment

Follicle Stimulating Hormone (FSH): The increase usually reflects ovarian failure, in association with increased estrogen levels and decreased ovarian reserve on ultrasound. The decrease usually reflects damage to the pituitary gland.

Luteinizing Hormone (LH): An increase early in the cycle is usually indicative of microcystic ovary syndrome. In this case, there's an increase in testosterone.

Estrogen: Estradiol levels > 80 pg/mL on day 3 of the cycle are indicative of decreased ovarian reserve. But this marker is mainly used to correctly assess the basal FSH because a high plasma estradiol level (> 70 pg/mL) can artificially normalize FSH by negative feedback effect [6].

Prolactin: A value > 200ng/mL indicates the presence of an adenoma. Factors can increase it: stress, postprandial period, estrogen therapy, pregnancy, thyroid insufficiency, kidney failure and medications

(antidepressants, antiemetics, antihypertensives...) [7]. It's therefore necessary to perform the dosage at the start of the cycle, in the morning at rest, on an empty stomach and after interruption of all therapy.

Anti-Mullerian hormone (AMH): This hormone is secreted by granulosa cells. AMH is currently considered to be the best marker of ovarian reserve, especially the quantity and activity of antral follicles. It has the advantage of non-variability during the menstrual cycle, making its dosage more credible, uniform and reproducible [8].

b. Ultrasound of the uterus and ovaries

It provides information on the uterine morphology, the ovaries (cysts), the existence of latero-uterine masses (hydrosalpinx). By endovaginal route, it allows to evaluate the count of the antral follicles which is considered a good marker of ovarian reserve, and the best for predicting a poor response to stimulation [7].

c. Hysterosalpingography

Hysterosalpingography is an essential examination for the exploration of the uterus and especially the tubes. It helps to appreciate the uterine cavity and tubal permeability.

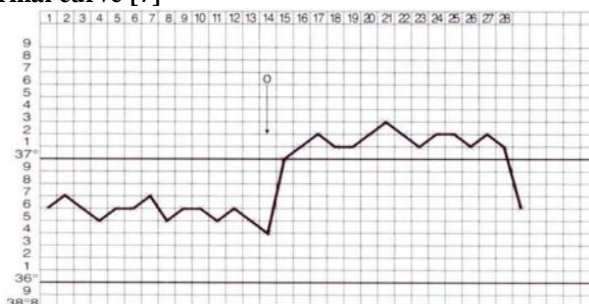
d. Laparoscopy

Laparoscopy is the examination of the abdominal cavity. It plays an essential role in the diagnosis and treatment of female sterility of organic origin and also functional sterility by allowing direct control of the ovaries and ovulation.

e. Temperature curve

Ovulation is accompanied by a body rise of 0.4 to 0.5 ° C. Establishing this curve helps assess the quality of ovulation. The temperature curve or menothermal curve (**Figure 2**) should be performed over at least two cycles. Hyperthermia of the luteal phase is caused by the action of a progesterone metabolite (pregnandiol) on the bulbar thermoregulation center.

Figure 2: Normal menothermal curve [7]



➤ **Assessment of infertility in men**

a. Spermogram

Fundamental examination in male, its realization is systematic. The three essentials parameters are: concentration, mobility and morphology of the spermatozoa. Different parameters are studied: volume, viscosity, pH, count, presence of round cells, agglutinates, vitality, mobility, morphological appearance (spermocytogram).

b. Hormonal blood test

Allows the evaluation of endocrine function, it is performed in case of abnormal spermogram with concentration less than 10 M/mL, sexual disorders or presence of other clinical symptoms suggesting endocrinopathy [6]. The minimum assessment involves testing for FSH and testosterone. Hyperprolactinemia should be investigated for iatrogenic origin, hypothyroidism, pituitary tumor [9].

c. Spermoculture

This is to check for the presence of possible infectious agents. The search for chlamydia and mycoplasma is done by culture on special media.

d. Survival migration test (TMS)

Consists of assessing the quantity and quality of motile sperm that can be extracted from the ejaculate. Their survival is evaluated after storage for 24 hours at room temperature. This test is used in the context of AMP where it can play an essential role in the therapeutic indications. The total number of motile spermatozoa available in the final preparation, their morphology and their survival influence the treatment decision [10].

Medical assistance for procreation

➤ **Artificial insemination**

Artificial insemination involves the instrumental introduction of spermatozoa into the female genital tract, possibly at the level of the cervix, but mainly into the uterine cavity to promote the meeting of male and female gametes [10]. The preliminary sperm assessment includes the performance of a spermogram, a sperm culture. The study of sperm movement allows an objective assessment, quantitative (% of mobile form) and qualitative (type of movement). The techniques select for "normal" spermatozoa either by upward migration (sedimentation migration) in a culture medium (swin-up from seminal plasma or after washing), or by filtration after passage

through a density gradient [11]. Intrauterine insemination in a spontaneous cycle has only been shown to be effective in two mechanical indications: isolated cervical sterility or the impossibility of having complete sexual intercourse.

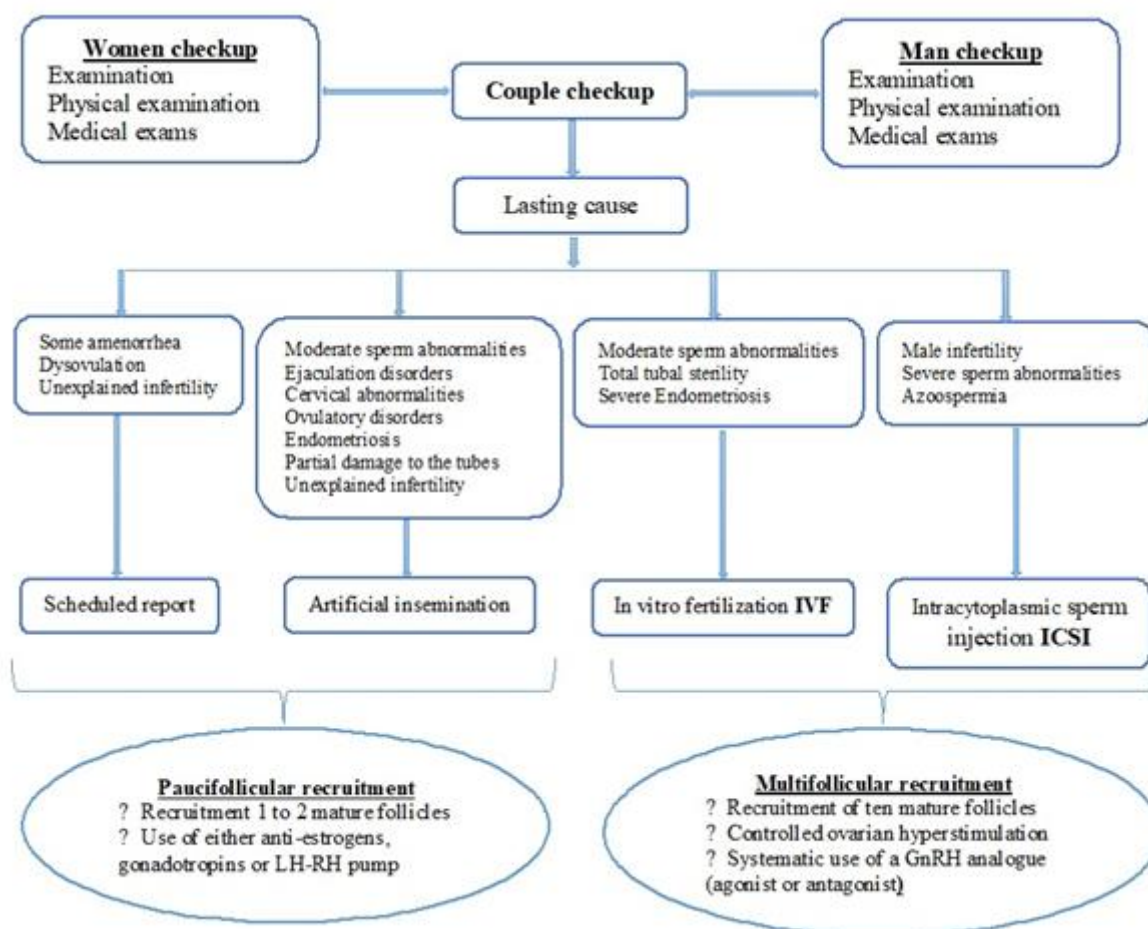
➤ **In vitro fertilization IVF**

IVF involves collecting the couple's gametes for extracorporeal fertilization, then transferring the resulting embryos into the uterus. The clinical part therefore mainly concerns women, and includes three essential steps: stimulation, oocyte puncture and embryo transfer [10]. The main indications for IVF are: tubal infertility, endometriosis, "idiopathic" sterility, second-line ovulation disorders, artificiels inseminations failures.

➤ **Intracytoplasmic sperm injection ICSI**

ICSI uses only a single sperm which is introduced into the ovular cytoplasm using a micropipette. ICSI can be used after failure of in vitro fertilization (lack of short fertilization). The main indication for ICSI is male infertility, especially in severe oligo-astheno-teratospermias, secretory and in most excretory azoospermias. ICSI may also be preferable when female and male factors are combined: poor response to ovarian stimulation (<5 matures oocytes) and sperm alterations reducing the chances of fertilization [12].

Figure 3 General diagram of the management of the infertile couple



IV. Conclusion

Medically assisted procreation is responsible for 20000 births per year, this trend is expected to increase with increasingly late childbearing and the resulting decline in fertility. When a curable cause of infertility is detected, the medical team will refer the couple to the most appropriate AMP technique.

Conflict of interest

The authors declare no conflicts of interest

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