Welcome to chapter 1.

The following chapter is called Female infertility: Definition, incidence and causes. The author is Professor Antonio Pellicer.

Please use the navigation bar at the bottom of the viewing panel in order to proceed through, pause or go back through the lesson and to adjust the narration volume.

Also please note the tabs above this panel which allow you to change the sidebar view and search for specific terms within the lesson text and narration transcript.
• After finishing this talk, the student should be familiar with the following important concepts:
  • Infertility, fecundity, and time to pregnancy
• Also, the student should be able to differentiate different degrees of infertility
• The student should be aware of the incidence of infertility in the western world
• And finally, the student should be able to classify, analyze, and define the different causes of infertility
• Infertility is a disease that is currently defined as 1 year of unwanted nonconception with unprotected intercourse in the fertile phase of the menstrual cycle. There are, however, 3 very important concepts that should be analyzed in the context of this definition:
  • First, the consideration of infertility as a disease
  • Second, the real meaning of the term “infertility” and whether or not this is a black and white situation, or whether there are degrees of infertility
  • And third, the moment in which a couple should be considered infertile, which is defined as “time to pregnancy” or “monthly fecundity rates”
• The American Society for Reproductive Medicine (ASRM) unambiguously defines infertility as a disease.

• The duration of the failure to conceive should be at least 12 months before an investigation is undertaken, unless medical history and physical findings dictate earlier evaluation and treatment, such as in the case of known tubal pathology, past problems with infertility, or amenorrhea, for example.

• However, there is reluctance to accept the term “disease” among governments and private health policy planners in many countries around the world.

  • This is a matter of cost, but it is important that national leaders fight at a local level to accomplish the recognition of infertility as a disease. This recognition would lead to the employment of public and private funds to assist affected individuals.
• The term “infertility” covers disorders ranging from sterility to nearly normal fertility. Thus, its uniform use is misleading
  • Often, the term subfertility is employed, but the definition is basically the same
• Typically speaking, an infertile couple is one that finds it impossible to conceive, or is unable to have a child. The antonym of the infertile couple is the fertile couple
• These definitions have been widely employed without gradations in between, which is what actually happens in clinical practice
• Habbema et al (2004) proposed a system of several prognostic categories into which infertile couples could be placed after an appropriate work-up has been performed
• These authors provide some examples to illustrate the grades of fertility concept
  • Case 1 is a couple with 36 months of primary nonconception and bilateral tubal occlusion. Since tubal occlusion is irreversible, it is obvious that this couple is classified as grade 4
  • Case 2 is a couple with 12 months of secondary nonconception and slightly impaired sperm quality. The chances of becoming pregnant can be considered to be between 40%–60% within 1 year, and therefore this couple is classified as grade 1
  • The last example that illustrates this classification is a couple with 50 months of unexplained infertility and obviously, because this couple has been trying to achieve pregnancy for a very long time, they are classified as grade 3
• A similar classification can be found on the next slide, in which Evers, in 2002, classified fertility into 5 different categories according to severity:
  • Superfertile
  • Normally fertile
  • Moderately subfertile
  • Severely subfertile
  • Infertile
• Although a 1 year threshold is necessary to fulfill the definition of infertility and has become the “gold standard” for clinical purposes in the last decade, the threshold was even longer in the recent past (World Health Organization, 1975)

• Today, organizations such as the World Health Organization define primary infertility as occurring “when a woman has never conceived despite cohabitation and exposure to pregnancy for a period of 2 years”

• The terms “fecundity,” “monthly fecundity rates,” “time to pregnancy,” and “cumulative probability of conception,” are of fundamental importance for finding suitable thresholds for the determination of the prevalence of subfertility grades
Although initial reports have calculated fecundity in humans as low as 20% as compared to baboons (80%) or rabbits (90%), more recent prospective studies have increased these expectations.

- The study of Gnoth et al (2003) showed a fecundity of 38%.
- The calculated "time to pregnancy" or "cumulative probability of conception" was 38%, 68%, 81%, and 92% after 1, 3, 6, and 12 months of unprotected intercourse, respectively.
• The degree of infertility and the monthly fecundity rate are interdependent. This table summarizes, in a hypothetical model, the cumulative probability of pregnancy according to the severity of the problem.

• This table also shows that some couples may attend infertility units without need if affected by a problem which is moderate in intensity, if the time considered optimal to visit a specialist is 6 months.

• For example, you can clearly see that in patients who have moderate fertility, the cumulative probability of achieving pregnancy is 46% after 12 months, and 71% after 24 months. That means if this couple attends a clinic and is treated with IVF, they may be overtreated.

• This table also shows that even in severe cases of infertility, time can solve the problem. In this sense, there are other factors that may sooner or later influence the decision to visit a fertility unit.
It is difficult to establish the incidence of infertility

- First, authors consider different numerators (i.e., some consider 1 year and others 2 years for defining the infertile couple)
- Second, the denominator also should be taken into account because in different populations the prevalence of infertility must be different
- As seen in the table, the prevalence of infertility ranges between 4%–15% when 1 year has been taken as the numerator, but in most of the studies published to date, 10%–15% of couples of reproductive age are infertile in western countries
In my experience, only 1 in 6 couples will ever attend an infertility clinic. This tendency is increasing for 3 main reasons:

- The first one, and probably the most important one, is due to social changes that have been happening in our society, such as a higher percentage of women in the workforce. This has resulted in a delay in childbearing, and age is a critical factor in fertility.
- The second reason is that several lifestyle factors affect fertility such as smoking, obesity, or stress.
- The third key reason is that there is a greater awareness about fertility clinics, and more information about treatment alternatives.
- There have also been better outcomes with new developments in infertility treatments.
As for the etiology of infertility in humans, we may say that the cause of infertility lies in both the male and female partners.

- In my clinical practice, the male partner is responsible for 30% of cases, the female another 30%, and in another 30% of the cases, there is a combination of male and female reasons for infertility. In 10% of my cases, the etiology remains unexplained.

- Since the introduction of assisted reproduction, we have found different situations in which the cause of infertility can be explained, reducing the actual incidence of couples with infertility of unknown etiology.

- Male infertility is a topic that would require a separate presentation; thus, we will focus on female infertility.

  - The ovary is responsible for up to 50% of the cases of female infertility for 2 main reasons: the age of the patients and the prevalence of polycystic ovarian syndrome.
  - The second potential cause is tuboperitoneal infertility, in which endometriosis is probably the main factor, altering the anatomy of the female reproductive tract and causing infertility.
  - There are also some cases involving the uterus as the main cause of female infertility.
  - Finally, some cases are the consequence of an altered passage of the sperm through the cervical channel due to a cervical factor or immunologic infertility.
• Age is the most important factor affecting female fertility. A complete chapter of this module is devoted to age, and another for polycystic ovarian syndrome and its consequences on fertility
• Ovarian cysts may affect the anatomy of the internal genitalia and cause mechanical infertility
• Endometriomas are the most frequent finding, and this is the topic of yet another separate chapter
• Anovulation of central origin is not as frequent as the other causes
• Measurement of different gonadotropic hormones and steroids helps to classify these clinical entities, as seen in the next slide
• In this slide, a classification of the most important causes of central anovulation is seen

• Central amenorrhea has been observed in the presence of low or normal levels of gonadotropins. In this case, it is important to observe the presence of factors that may alter the normal function of the hypothalamus–pituitary axis
  • Examples include athletes, women with anorexia nervosa, and other situations that may cause stress
  • Hypergonadotropism is associated with premature ovarian failure
    • It is important to rule out Turner's syndrome. Additionally, hyperprolactinemia is frequently associated with small pituitary adenomas that do not cause other symptoms
    • Iatrogenia should also be ruled out
Tuboperitoneal infertility is the second most frequent cause of female infertility. Two situations are especially relevant:

- The presence of endometriosis and
- A previous genital infection
  - Although *Chlamydia trachomatis* is not the only possible cause of damage to the fallopian tubes, raised chlamydia IgG antibody titres are a consistent finding in serum of women with tuboperitoneal infertility and a history of pelvic inflammatory disease
• The uterus accounts for approximately 15% of the cases of female infertility. The relationship between myomas and infertility is an important topic to be discussed in a full chapter of this module, but there is a general agreement that only submucous myomas cause infertility.

• Intrauterine adhesions are related to poor outcome. In fact, it has been reported that only 45% of these women will become pregnant, while 40% will have miscarriages, and 23% will have premature deliveries.

  • It is not known, however, whether intrauterine adhesions are the consequence of a history of repeated miscarriage in which the curettage induces Asherman’s syndrome, or the opposite. With reference to Müllerian malformations, the next slide shows a study that we published more than 10 years ago.
• In this manuscript we analyzed several uterine anomalies and their impact on reproduction

• The first key point is that the septate and the arcuate uterus are the most prevalent among the uterine malformation

• Second, the septate uterus as well as other major malformations such as the bicornuate, didelphys, and unicornuate uterus are associated with a high incidence of early abortion (as much as 25%), probably due to the fact that part of the uterus does not have enough vascularization. When implantation takes place in the uterine wall in which vascularization is diminished, it is associated with early pregnancy loss

• The third point is that preterm delivery is not a characteristic of the most frequent malformations (septate and arcuate), but is a feature of the others. The likelihood of a liveborn infant differs among the uterine malformations, and all these numbers should be kept in mind when advising our patients
Another possible cause of uterine infertility are endometrial polyps. Endometrial polyps are benign localized outgrowths of the endometrium commonly identified during the work-up of infertility. It has been suggested that endometrial polyps may affect sperm transport and implantation and may be a cause of uterine infertility.

However, there is only one randomized study in patients receiving IUI (intrauterine insemination) published by Perez-Medina et al in 2005 in which a positive effect of polypectomy on pregnancy rates was observed.

The truth is, today there is a lack of properly designed studies to answer the question as to whether endometrium polyps affect implantation and the mechanism of action of the polyps.

References
• The cervix is of paramount importance in human reproduction, since it is the checkpoint for sperm. Any difficulty entering the cervical channel at the right moment, or any inconvenience that may affect the quality of sperm, will result in cervical infertility.

• The most relevant issue, however, is whether sperm arrives at the cervical channel at the appropriate moment (i.e., the preovulatory phase, when mucus produced by the glands of the internal epithelium is abundant, clear, and viscous, allowing sperm to travel and to reach the endometrial cavity).

• When sperm is normal and the timing of the menstrual cycle is appropriate, the absence of sperm moving in the cervical mucus should be a sign of concern. Several causes should be analyzed:
  • First, there is the possibility of an anatomical alteration due to a very thin external cervical os and cervical channel, which will result in an impaired production of mucus.
    • The same is true when the patient undergoes a conization which removes many glands from the internal epithelium.
  • The presence of a cervicitis should be considered and the appropriate microbiological tests performed.
  • In addition, a possible immunologic factor should be considered.
• Immunologic infertility represents about 5% of all cases of female infertility, although antibodies against sperm can be produced by both men and women
• In men, antibodies can be detected in serum, semen, and sperm
• In women, antibodies are raised in the cervical epithelium and localized in serum, vaginal, and cervical secretions, as well as in follicular fluid
• The isotypes IgA, IgG and IgM have been identified
• Depending on the type of antibodies and their location, they can theoretically interfere with the process of human reproduction at different levels
• Antibodies that bind the sperm tail immobilize sperm, making it unable to meet the female genital tract
• If antibodies are in the sperm head and/or in the follicular fluid, they may interfere with the process of fertilization
• Also, immunological infertility has been associated with poor embryo development in IVF and implantation, although the mechanisms remain speculative
• When no cause of infertility has been found after appropriate infertility work-up, which is the topic of a different chapter in this module, the couple is classified as having “infertility of unknown etiology” or unexplained infertility.

• Since there is no known cause of infertility, the treatment will be empirical and usually begins with intrauterine insemination followed by IVF.

• If the couple does not succeed with the former but does succeed with the latter, the cause of infertility is believed to be an abnormal tubal function.

• The use of IVF has generated the discovery of new causes of infertility, such as failed fertilization, poor embryo development, and failed implantation.
  • This makes the percentage of couples classified as having infertility of unknown etiology smaller and smaller as empirical treatments are applied.
To finalize this first lesson, let me reinforce the main messages:

- Today we recognize that infertility is a disease, and is defined as 12 or more months of unwanted nonconception without achieving a pregnancy.
- There are several grades of severity, and it is important to establish a prognosis after a work-up (see last slide).
- The third main message is the monthly fecundity rates in humans is around 35%. For this reason, many specialists suggest starting the work-up after 6 months.
Another important message is that the prevalence of infertility is about 10% in couples of reproductive age, and that:

- Both men and women are equally responsible for human infertility, although 10% of infertility cases remain "unexplained"
  - This percentage decreases when assisted reproduction is employed

- This percentage decreases when reproduction assistance is employed
• The main causes of female infertility are:
  • The age of the patient
  • The high incidence of polycystic ovarian syndrome, which is related to anovulation and the presence of endometriosis
  • Other important causes such as pelvic infection, submucous myomas, uterine malformations, or a cervical factor should also be investigated
Recommended Reading


Question 1

One of the following sentences is correct:

a) Infertility is present in 20% of the infertile population and fecundity in human beings is 20%

b) Infertility is present in 10% of the infertile population and fecundity in human beings is 10%

c) Infertility is present in 10% of the infertile population and fecundity in human beings is 35%

d) Infertility is present in 20% of the infertile population and fecundity in human beings is 35%

Answer: C
Question 2

One of the following sentences is correct:

a) Major causes of female infertility are cervical factor, intramural myomas and endometriomas
b) Major causes of female infertility are male factor, submucous myomas and endometriomas
c) Major causes of female infertility are endometriosis, female age and PCOS
d) Major causes of female infertility are endometriosis, female age and submucous myomas

Answer: C
Question 3

Concerning the septate uterus, one of these sentences is NOT correct:

a) Is the most frequently diagnosed Müllerian abnormality
b) Associated with preterm delivery in 50% of cases
c) Associated with early miscarriage in 25% of cases
d) Associated with term pregnancy rate of 50%

Answer: B
Question 4

Antibodies against human sperm can be found in all the following biological specimens except:

a) Leydig cells
b) Male serum
c) Semen
d) Sperm

Answer: A