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Artificial insemination history: hurdles and milestones

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Abstract

Artificial insemination with homologous (AIH) or donor semen (AID) is nowadays a very popular treatment procedure used for many subfertile women worldwide. The rationale behind artificial insemination is to increase gamete density at the site of fertilisation.
The sequence of events leading to today's common use of artificial insemination traces back to scientific studies and experimentation many centuries ago. Modern techniques used in human artificial insemination programmes are mostly adapted from the work on cattle by dairy farmers wishing to improve milk production by using artificial insemination with sperm of selected bulls with well chosen genetic traits.
The main reason for the renewed interest in artificial insemination in human was associated with the refinement of techniques for the preparation of washed motile spermatozoa in the early years of IVF.
The history of artificial insemination is reviewed with particular interest to the most important hurdles and milestones.

Key words: **Artificial insemination, assisted reproduction, history, human, intrauterine insemination, semen.**

Introduction

The rationale behind artificial insemination is increasing the gamete density at the site of fertilization. Since many centuries different pioneers contributed to the history of artificial insemination, not only in humans but even more pronounced in farm animals. The primary reason for using this technique in farm animals was to speed up the rate of genetic improvement by increasing the productivity of food producing animals. This was accomplished by improving the selection differential wherein one highly selected male is mated with thousands of females. The AID industry was born.

For humans the situation is different: artificial insemination was originally developed to help couples to conceive in case of severe male factor subfertility of a physical or psychological nature. Nowadays artificial insemination with homologous semen is most commonly used for unexplained and mild male factor subfertility. In the previous century donor insemination was mainly used for male infertility due to azoospermia or very low sperm count and for inherited genetic diseases linked to the Y-chromosome. Nowadays donor insemination is more commonly used in women with no male partner (lesbians or single women).

Despite the extensive literature on the subject of artificial insemination with husband's semen, controversy remains about the effectiveness of this very popular treatment procedure, particularly in relation to IVF (in vitro fertilization) and ICSI (Intra-Cytoplasmic Sperm Injection) (Cohlen 2005; Ombelet, 2005; Bensdorp et al., 2007; Eshre Capri Workshop Group, 2009).

Milestones in the history of artificial insemination

Unofficial history claims that the first attempts to artificially inseminate a woman, were done by

Henry IV (1425-1474), **King of Castile**, nicknamed *the Impotent*. In 1455, he married Princess Juana, sister of Afonso V of Portugal. After six years of marriage she gave birth to a daughter, Joanna. Many contemporary historians and chroniclers assumed Henry was impotent. The possibility of artificial insemination was launched. Later on it was claimed that the princess was not the daughter of the king.

Spermatozoa were first seen and described by **Antoni van Leeuwenhoek** and his assistant **Johannes Ham** in 1678 in the Netherlands. In a letter to William Bounker of the Royal Society of London (Phil.Trans. Vol.XII, nbr. 142, 1678) he showed a picture of sperm cells of the human and the dog. van Leeuwenhoek described the spermatozoa as "zaaddiertjes" or "living animalcules in human semen ... less than a millionth the size of a coarse grain of sand and with thin, undulating transparent tails". He draws the conclusion that the tails must be operated by means of muscles, tendons and joints (Mol, 2006; Kremer, 1979). van Leeuwenhoek did not study Latin, the scientific language of the day. Nevertheless, his paper amazed and perhaps amused the reigning King of England.

More than 100 years later, in 1784, the first artificial insemination in a dog was reported by the scientist **Lazzaro Spallanzani** (Italian physiologist, 1729-1799). This insemination resulted in the birth of three puppy's 62 days later (Belonoschkin, 1956; Zorgniotti, 1975). It is believed that Spallanzani was the first to report the effects of cooling on human sperm when he noted, in 1776, that sperm cooled by snow became motionless.

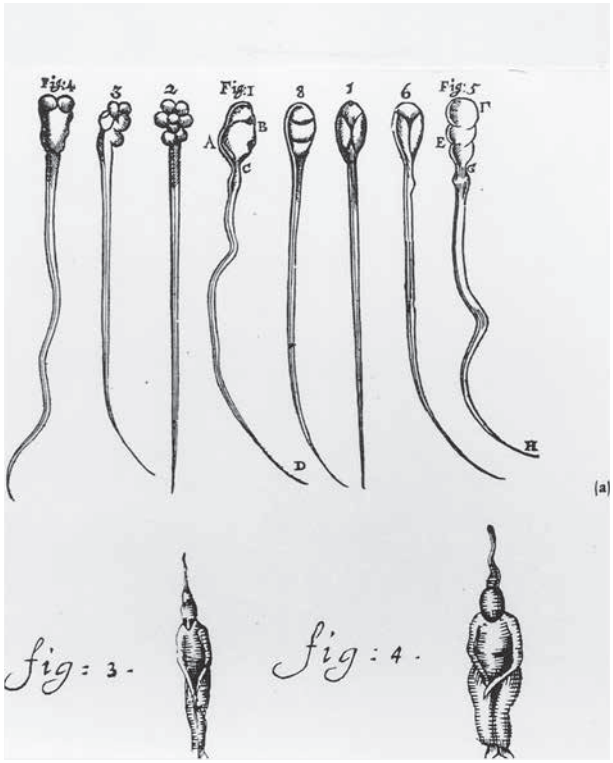

Fig. 2. — The 17th century conception of spermatozoa (A van Leeuwenhoek).

The first documented application of artificial insemination in human was done in London in the 1770s by **John Hunter**, which has been called in medical history the "the founder of scientific

Fig. 1. — Picture of Antoni van Leeuwenhoek (1632-1723).

Fig. 3. — John Hunter wrote the first report of artificial insemination in medical literature in 1790.

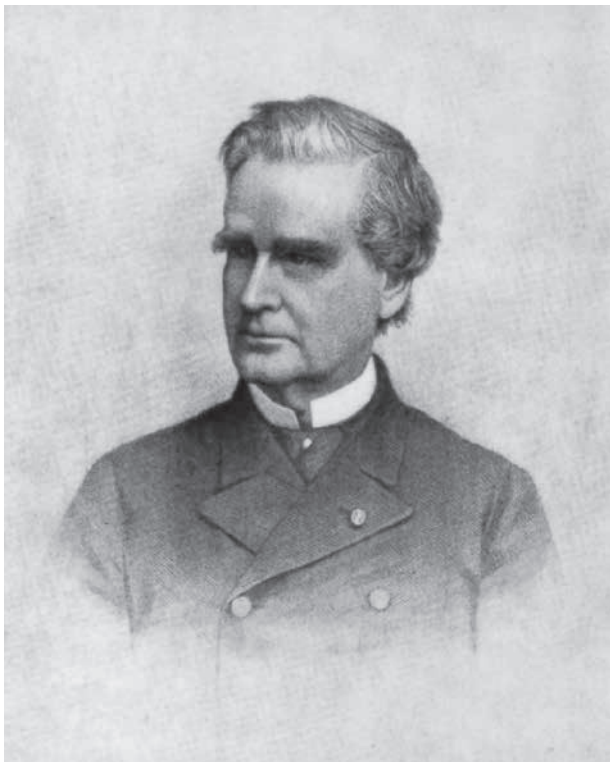

Fig. 4. — The first report of post-coital tests and the first description of 55 inseminations was done by JM Simms (US) in the 1850s (Source: South Med J, Lippincott, Williams & Wilkins 2004).

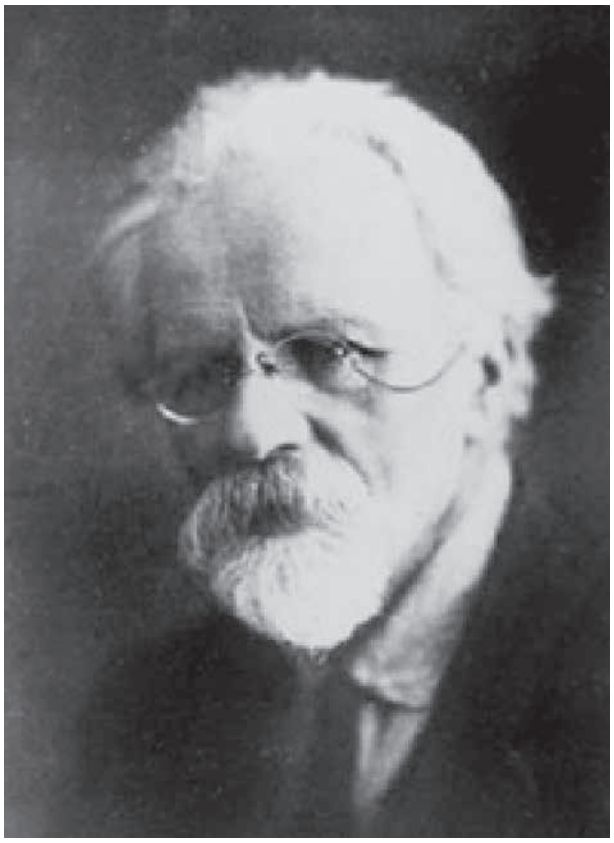

Fig. 5. — In 1922 Ilya Ivanovich Ivanov (Russia) developed the methods of artificial insemination as we know them today.

surgery". A cloth merchant with severe hypospadias was advised to collect the semen (which escaped during coitus) in a warmed syringe and inject the sample into the vagina.

J Marion Sims reported his findings of postcoital tests and 55 inseminations in the mid 1800s. Only one pregnancy occurred but this could be explained by the fact that he believed that ovulation occurred during menstruation. JM Simms was born in Lancaster County (USA) in 1813. In 1863 he began writing his innovative work *Clinical Notes on Uterine Surgery*, which was controversial but widely read. Its revolutionary approach to female diseases was refreshing and its emphasis on treatment of sterility, including artificial insemination, was ahead of its time.

In 1897 **Heape**, an outstanding reproductive biologist from Cambridge, reported the use of AI in rabbits, dogs and horses. Heape also studied the relationship between seasonality and reproduction, as a result of his research Cambridge became a world centre for reproductive studies.

In 1899 the first attempts to develop practical methods for artificial insemination were described by **Ilya Ivanovich Ivanoff** (Russia, 1870-1932). Although Ivanoff studied artificial insemination in domestic farm animals, dogs, rabbits and poultry, he was the first to develop methods as we know today in human medicine. He was a pioneer in the selection of superior stallions multiplying their progeny through AI. The work of Ivanoff was taken over by **Milovanov**, another Russian scientist. He published his paper on "Artificial insemination in Russia" in the Journal of Heredity in 1938. Milovanov established major projects for cattle breeding and designed the first artificial vaginas, very similar to those used today.

The innovating work in Russia inspired **Eduard Sörensen** from Denmark to organize the first cooperative dairy AI organization in Denmark in 1933, followed by the introduction of the first AI cooperative in the US in 1938 by **EJ Perry**, a dairyman from New Jersey. In the US and other Western countries the number of AI cooperatives increased rapidly. Nowadays more than 90 % of dairy cows are artificially inseminated in the Netherlands, Denmark and the United Kingdom. November 1, 1939, the first animal, a rabbit, conceived by artificial insemination was exhibited in the United States at the 12th Annual Graduate Fortnight at the New York Academy of Medicine. **Gregory Pincus**, an American biologist, removed an egg from the ovary of a female rabbit and fertilized it with a salt solution. The egg was then

transferred to the uterus of a second rabbit, which functioned as an incubator. Dr. Pincus conducted his experiments at Harvard University.

Considering humans, only after the introduction and availability of donor sperm, artificial insemination became very popular (AID). For many years homologous artificial inseminations were only indicated in cases of physiologic and psychological dysfunction, such as retrograde ejaculation, vaginismus, hypospadias and impotence.

With the routine use of post-coital tests other indications were added such as hostile cervical mucus and immunologic causes with the presence of antispermatozoal antibodies in the cervical mucus.

The first reports on human artificial insemination originated from **Guttmacher** (1943), **Stoughton** (1948) and **Kohlberg** (1953a; 1953b). It was the real start of a new era in assisted reproduction.

Other important research discoveries in animal studies undoubtly influenced the development of artificial insemination, also in human. **Phillips and Lardy** (1939) were the first to use egg yolk to protect bull sperm cells from temperature shock upon cooling. This protection was explained by the effect of phospholipids and lipoproteins in the egg yolk. **Salisbury et al.** (1941) improved the media by using egg yolk with sodium citrate, permitting the use of semen at 5° C for up to three days. **Polge and co-workers** (1949) were the first to freeze fowl and bull spermatozoa by using glycerol in the extender media. In 1950 Cornell University scientists (New York) discovered the benefit of antibiotics added to the sperm solution in artificial insemination processes. The so-called Cornell extender (**Foote and Bratton**, 1950) contained the antibiotic mixture of penicillin, streptomycin and polymyxim B and was used for many years as the standard. Antibiotics are still used for the protection against possible contamination.

In 1953 Dr. Jerome K. **Sherman**, an American pioneer in sperm freezing, introduced a simple method of preserving human sperm using glycerol. He combined this with a slow cooling of sperm, and storage with solid carbon dioxide as a refrigerant. Sherman also demonstrated for the first time that frozen sperm, when thawed, were able to fertilize an egg and induce its normal development.

As a result of this research, the first successful human pregnancy with frozen spermatozoa was reported in 1953. Considering the hostile climate for DI at the time (the Cook County Supreme Court ruled that artificial insemination with donor semen was contrary to public policy and good morals) it is not surprising that nearly a decade passed before the first successful birth from frozen sperm was announced in public, a major breakthrough in history.

Fig. 6. — Bob Edwards: IVF pioneer and winner of the 2010 Nobel Prize in Physiology or Medicine (speaker at the "Andrology in the Nineties" meeting in Genk, 1995).

Considering all these new developments, it could be expected that in the 1970s the sperm bank industry became very popular and commercialized, especially in the United States.

The IVF revolution

The main reason for the renewed interest in artificial insemination in human was undoubtly the introduction of in-vitro fertilisation (IVF) in 1978 by **Steptoe and Edwards**. In the early days the ejaculate of the husband was inseminated intrauterine without preparation resulting in uterine cramps and increasing the probability of tubal infections. With the arrival of IVF, semen preparation techniques were developed and IUI regained its popularity, being more safe and painless.

These washing procedures are necessary to remove prostaglandins, infectious agents and antigenic proteins. Another substantial advantage of these techniques is the removal of nonmotile spermatozoa, either leucocytes or immature germ cells. This may be an important factor in enhancing sperm quality by a decreased release of lymphokines and/or cytokines and a reduction in the formation of free oxygen radicals after sperm preparation. Sperm

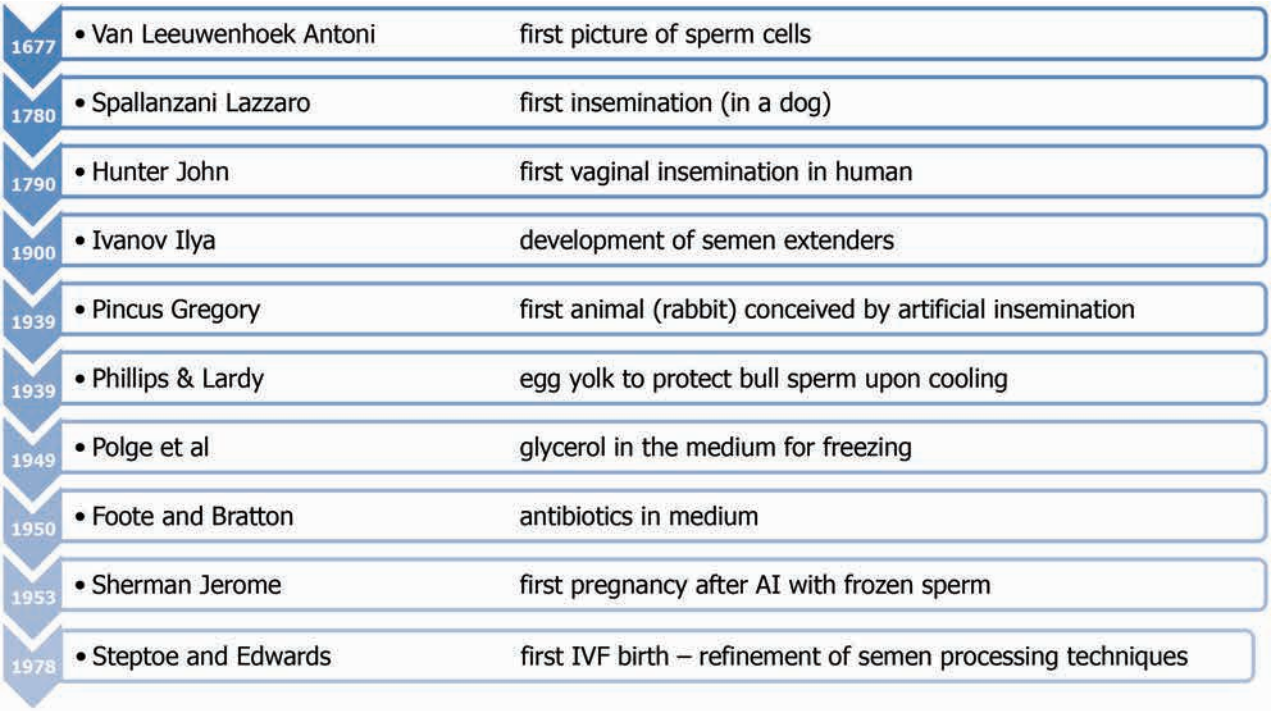

Fig. 7. — Most important milestones in the history of artificial insemination.

preparation techniques should isolate and select sperm cells with intact functional and genetic properties, including normal morphology, minimal DNA damage, and intact cell membranes with functional binding properties.

The final result is a better sperm fertilising ability in vitro and in vivo (Aitken and Clarkson, 1987) and an increasing number of motile sperm that are morphologically normal at the site of fertilization. Bypassing the cervix, which acts as a reservoir for sperm, increases the importance of adequate timing of the insemination.

Most popular are the swim-up procedure, the discontinuous Percoll gradient method, the mini-Percoll (small volume) gradient technique and the use of Sephadex columns.

Novel sperm selection methods (based on sperm surface charge or nonapoptotic sperm selection) show promising results. However, they have not yet established themselves in routine practice, and their purpose for AIH is unknown; more evidence is needed

Infertility care: the value of AIH anno 2015

As a consequence of these improved sperm selection techniques, the use of artificial insemination became very popular as a first line treatment procedure in case of unexplained and mild male factor infertility. At this moment AIH is probably one of the most applied assisted reproductive techniques worldwide. Nevertheless, there is still an on-going debate whether or not AIH is an effective treatment option for various indications. Controversy remains about its effectiveness, particularly in relation to IVF and ICSI (Cohlen 2005; Ombelet, 2005; Bensdorp et al., 2007; Eshre Capri Workshop Group, 2009).

The 2013 NICE guidelines were very clear with a message that couldn't be misunderstood: AIH should be abandoned in case of unexplained and moderate male infertility. Extended expectant management was recommended although the evidence-based data supporting this recommendation were not convincing at all. Recent studies, including a large prospective randomized multicentre study, have shown that AIH remains a useful and cost-effective first-line treatment in case of mild male infertility and unexplained infertility with an unfavourable prognosis as compared to the more aggressive techniques such as IVF and ICSI (Van Rumste et al., 2014; Bensdorp et al., 2015; Moolenaar et al., 2015). An increasing number of studies highlight the value of AIH and support the belief that artificial insemination with husband's semen will remain a widely used treatment option for many couples with cervical factor subfertility, physiologic or psychological sexual dysfunction, mild to moderate male subfertility and unexplained infertility with an unfavourable prognosis (Cohlen and Ombelet, 2014).

Legal, socio-cultural and religious considerations surrounding artificial donor insemination

The moral and social implications of artificial insemination were debated in both the medical and popular press in the United States since 1909, in Europe the debate started in the 1940s. The Catholic Church objected to all forms of artificial insemination, saying that it promoted the vice of onanism and ignored the religious importance of coitus. The main criticism was that artificial insemination with donor semen was a form of adultery ***promoting the vice of masturbation***. Other critics were concerned that AID could ***encourage eugenic government policies***.

Nevertheless, the demand for donor sperm increased tremendously. After the first successful pregnancy from frozen sperm, reported in 1953, the development of a thriving sperm-bank industry starting in the 1970s and the commercialization of AID became unavoidable. The growing number of AID's raised new concerns leading to new regulations. Because of the possible transmission of sexually transmitted diseases, including HIV, when using fresh sperm screening for infections of donors became mandatory. The use of fresh donor semen samples almost disappeared.

Another concern is the possibility to donate semen many times. In order to diminish the chances of unknowing marriage of biological siblings among AID children some government regulations tightly restrict the number of times a single donor's semen may be used and/or restrict the number of children by a given donor.

Sociocultural concerns with biological paternity and the maintenance of the heterosexual, married couple as the basis of the family remain important in many countries. A lot of countries all over the world have not approved the use of AI with donor semen for single women and lesbian couples yet. Another point of debate is whether the donor has to be anonymous or non-anonymous, and when to inform and what to tell AID children about their biological parentage, if non-anonymous donors are used. Is it possible and/or advisable to use sperm of relatives, such as brothers or the father? Whether or not to pay the donors and sexing of sperm by DNA quantification using flow cytometry instrumentation became a point of discussion.

Conclusion

The historical story of artificial insemination is a successful one; the worldwide acceptance of artificial insemination in animals provided the impetus for the innovation and development of many technologies which we are nowadays familiar with such as gamete cryopreservation, ovarian stimulation and cycle regulation, embryo freezing and cloning. Many of the principles nowadays used in human artificial insemination are adapted from domestic animal studies, especially from cattle. The use of frozen/thawed donor samples and the renewed interest in sperm washing procedures due to the introduction of IVF were the most important milestones in the history of human artificial insemination.

Intrauterine insemination with husband's sperm turned out to be a valuable first choice treatment before starting more invasive and more expensive techniques of assisted reproduction for many subfertile patients.

The increasing demand of lesbians and single women for AI with donor semen is another challenge in many countries worldwide. Many debates, socio-cultural and ethical, are to be expected in the near future. The issue of using anonymous and/or non-anonymous donors will be one of them.

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