Welcome to chapter 1.
The following chapter is called "An Historical Review of in Vitro Fertilization (IVF)".
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It is a universal tenet that, in order to fully understand a subject, one should be familiar with its history and background. For this reason, the originators of this educational series have rightly decided that students of Assisted Reproductive Technologies (ART), who wish to follow the Global Fertility Academy program, should first be made aware of the history of in vitro fertilisation (IVF) and ART.

There follows in this first module a brief outline of the history of human ART, which, hopefully, will "set the scene" for the student’s further studies, and stimulate him or her to read more about the background of our fascinating specialty.
The history of IVF is long and interesting. It began with many theories, and continued with research on in vivo and in vitro fertilisation in a number of different animal species. Finally in the 1960s the research progressed to human IVF, which culminated in the birth of Louise Brown on 25 July 1978 in England - the World’s first “Test-Tube Baby”.

This chapter will present an overview of the early research by pioneers in the field leading up to 1978. This is followed by a review of some of the “milestones” in IVF since then.

At this point a full list of references cannot be provided, but study of the abbreviated list will lead the Student to many fascinating other references, which should be read in order to fully understand human IVF as it is practised today.
Human reproduction has fascinated man since the beginning of time. This can be seen in very early cave drawings, through to Egyptian tomb inscriptions and early Greek texts. Aristotle, some 300 years BC, believed that it took “seed” from both a man and a woman to create children; but it was not for another 1200 years that any further progress was made in the understanding of procreation – animal or human.

Aristotle (384-322 BC) proposed the theory that children are a product of “the mingling of male and female seed”. This opposed the prevailing theory that children were from the male seed and women were merely the “receptacle for the child”.

William Harvey (1578-1657) studied the fertility of the King’s herd of deer, and wrote: “De generatione animalium” in 1651, in which occurs the well known phrase: “Ex ovo omnia” – “from the egg is everything”.

Antonij van Leeuwenhoek (1632-1723) carried out the first studies on human sperm with the newly invented microscope.

Report of homunculus, a miniature human within a sperm, by Dalenpatius (1699), which turns out to be a hoax!

When the key discoveries were made of the existence and importance of the female’s egg and the function of sperm in the seventeenth century, the science of human reproduction really advanced. This was also, for obvious reasons, closely associated with the discovery of the microscope.
The early work on male and female gametes, and later embryos, was carried out on a number of different animal species.

Spallanzani (1729-1799), an Italian Scientist, studied semen in mammals. He performed artificial insemination (AI) in a spaniel bitch – the first recorded instance of AI. He is also credited with the first freezing of sperm in 1776.

John Hunter in c.1790 performed the first successful human AI for a man with hypospadia.

Karl von Baer’s work on the ovaries and oocytes of bitches in 1825 was probably the most important research up until that time, which is why he is often referred to as “the father of modern embryology”.

Nelson (1852), Newport (1853), van Beneden (1854) and Hertwig (1876) report the process of fertilization in ascaris, amphibians and mammals, respectively.
Some 40 years later, Walter Heape was credited for creating the first mammalian embryos (in rabbits), but reported no pregnancies, and it was 60 years later, in 1959, that Chang was able to achieve pregnancies and births of live rabbits following IVF.

Pincus and Enzman (1934) postulated that mammalian and human oocytes could develop normally \textit{in vitro}.

Polge in 1949 reported the first practical freezing of animal sperm using glycerol.

Bunge and Sherman (1953) reported the first successful AI with frozen/thawed sperm in humans.

Chang (1959) reported the first rabbit young to be born as a result of \textit{in vitro} fertilized oocytes.

Yanagimachi and Chang (1963) reported the first mammalian (hamster) IVF with sperm capacitated \textit{in vitro}.

Whittingham (1972) reported the first successful freezing of mouse embryos.
Once the basic research had been done in animal species, scientists and clinicians were ready to move the science on to the treatment of human infertility.

The main problem in applying the animal research successfully to humans was the difficulty in obtaining human oocytes. Up until the introduction of laparoscopy, pioneered by both Palmer and Frangenheim, oocytes were collected by laparotomy.

The real advances in human IVF were made due to the much simpler technique of laparoscopy. This enabled the gynaecologists to see ovaries and developing follicles clearly and later to aspirate oocytes from the follicles.

It was this need for gynaecologists and embryologists to work as a team that brought Patrick Steptoe and Robert Edwards together – a collaboration that, after ten years of research, culminated in the delivery of Louise Brown in July 1978, the first child to be born as a result of in vitro fertilisation.
In 1968, Patrick Steptoe, the gynaecologist, and Robert Edwards, the scientist, met at the Royal Society of Medicine and started their collaboration.

In 1973, a group from Australia, led by Professors Carl Wood and John Leeton reported the first human IVF pregnancy, but it turned out to be a “biochemical pregnancy”.

Steptoe and Edwards in 1976 then announced the first clinical IVF pregnancy – but it was found to be an ectopic pregnancy.

After 102 failed embryo transfers (ET), Steptoe and Edwards achieved the first ongoing human IVF pregnancy.
On 25 July 1978, Louise Brown was born by Caesarean section at Oldham General Hospital, England – the first baby to be born as a result of IVF in a human.
There were, of course, researchers in other countries, who were pursuing the “Holy Grail” of births from IVF in humans, and successes followed over the next few years from many groups. The most prominent of these were the Melbourne team of Wood and Lopata, and the American pioneers Howard and Georgeanna Jones.

Friendly exchanges of opinions and experiences took place between the many teams, and the treatment of infertile couples by IVF techniques spread worldwide.
4 Jan 1979: Alastair MacDonald is born, the second IVF baby and first boy child, as a result of the work of Steptoe and Edwards.
In 1980, Candice Reed, the World’s third IVF baby is born in Melbourne, Australia, as a result of the pioneering work of Professors Carl Wood and Alex Lopata.

Drs. Howard and Georgeanna Jones announce the delivery of the first IVF baby conceived in their pioneering program in the United States. Born 28th of December 1981. This was the first birth using hMG in a stimulated cycle.
The World’s leading pioneers in IVF meet at Bourn Hall in September 1981. Steptoe, Purdy and Edwards are seated on the right.
The basic technique of IVF soon led to the development of many new ideas. These included the cryopreservation of embryos, and later of oocytes; the development of simpler ultrasound guided techniques to collect oocytes via the vagina. Intrauterine insemination (IUI) and gamete intra-fallopian transfer (GIFT) developed as variants of standard IVF. Arguably the most important later development was of intracytoplasmic sperm injection (ICSI), which allowed men with the most intractable infertility problems to enable pregnancies, where previously their only option has been to resort to the use of donor sperm, if allowed. Oocyte donation program developed from about the mid-1980s, and, in a few countries, gestational surrogacy became available to treat women without an uterus.
In 1982, Lenz and Lauritsen developed the technique of abdominal ultrasound (US) guided transvesical needle oocyte recovery.

This US technique was further developed in 1983 by Gleicher.

Wikland in Sweden developed the transvaginal US needle guided approach.
So many developments have occurred in IVF and its related technologies that not all of them can be mentioned. This is a brief outline of some of the "pivotal" milestones in IVF:

1984. In Australia, the Government of Victoria passed the first legislation on IVF procedures by the 'Infertility (Medical procedures) Act of 1984. Asch et al. developed the technique known as GIFT (gamete intrafallopian transfer). Porter and Craft, from London, developed the use of GnRH-agonists in IVF stimulation protocols to prevent premature LH surges.

1985. In 1985, the first IVF baby born through gestational surrogacy was reported, born in California, as a result of the work of Utian et al.

1985. Prof. Wikland and his team developed the concept of vaginal ultrasound probe guided oocyte collection.

1986. Prof. Feichtinger and Kemeter published the first experience in vaginal ultrasound guided oocyte recovery. Navot et al. published the first report on preparing the endometrium of ovum recipients with estrogens and progesterone.
In 1987 the first reports on sub-zonal micro-injection of sperm to oocytes by Laws-King and Trounson in Australia were published.

Dr. Patrick Steptoe, pioneer of IVF and collaborator with Dr. Robert Edwards, died on 21 March 1988. Together they "created" Louise Brown, and founded Bourn Hall.

In 1989, Handyside and his colleagues showed that it was possible to take a blastomere from an embryo, perform pre-implantation genetic diagnosis (PGD) and sex the embryos. This advance led to a whole new sub-specialty of diagnostic techniques including the ability to detect the sex of an embryo, and a multitude of genetic abnormalities, including single gene defects as well as to perform screening for aneuploidy.

In the clinical practice, major changes have occurred within stimulation protocols, based on the introduction of GnRH-agonists in the mid-1980s and GnRH-antagonists in the 1990s. Furthermore, the development and usage of gonadotropins for ovarian stimulation has progressed from the impure urinary, to pure urinary and later to recombinant gonadotropins. Most recently, there has been a trend to advocate more "mild" stimulation protocols.
In the United Kingdom a regulatory system was proposed, and an Interim Licensing Authority put into place pending the passage of ‘The Human Fertilisation and Embryology Act’ in 1990.

Also in 1990 the first report by Verlinsky et al. of polar body biopsy, subsequent embryo transfer and pregnancy was published.

In 1991 Cha et al. developed in-vitro maturation (IVM) of oocytes and reported the first pregnancy. Furthermore, the first report on the use of GnRH-antagonist in ovarian stimulation protocols in IVF was published by Frydman et al.

1992: First pregnancies achieved using the newly developed recombinant-FSH (r-FSH), reported by Germond et al., and by Devroey et al. as well as reports on the first pregnancy achieved by intracytoplasmic sperm injection (ICSI) of oocytes by Palermo et al. of the VU Brussels group.

1994: First report by Silber et al. on testicular sperm extraction (TESE) combined with ICSI.
In 1996 Reijo et al. published the finding that some men with severe oligoasthenozoospermia have deletions on the Y-chromosome.

Iskovitz-Eldor et al. reported the first pregnancy using GnRH-antagonist and recombinant-FSH in 1998.

Oktay et al. reported in 2000 the first autologous transplantation of frozen/thawed ovarian tissue.

In 2002: Wells et al. reported the use of comparative genomic hybridization and polar body testing by PGD for aneuploidy.


Donnez et al. reported the first live birth after orthotopic transfer of frozen/thawed ovarian tissue in 2004.

2006-2007: The development of the concept of “IVF Lite” – a mild stimulation strategy for IVF, by Heijnen et al. and other groups.
In 2009, most countries now have some form of regulation, some strict, others not; while other countries have guidelines.

It is unlikely that any Universal, or even European Union, regulatory system will ever be enacted, due to widely differing cultural and ethnic differences.

The fascinating story of human IVF spans a period of about 40 years only, but the research leading up to the final success with the birth of the first baby in 1978 was preceded by several centuries of work on many different animal species.

The infertility treatment using IVF and related techniques is now well established and almost universally practised, with an estimated four million babies being born worldwide. The early pioneering days may be over, but there is a limitless amount of research still to be done in our field, particularly in genetics and stem cell research. The future of IVF and ART is built upon the past achievements of the early pioneers, and the story behind our specialty bears more in-depth study, for which a short reading list is provided to interested students.
The following slides provide a short list of key publications regarding the history and development of IVF. It is, as mentioned at the beginning, only a very abbreviated list. More can be found within these publications.
Recommended reading list

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