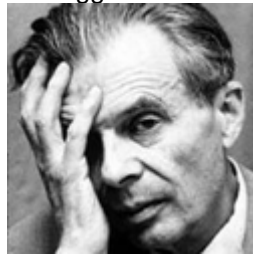


The History of IVF - Major Milestones of the Process

The History of IVF -The Milestones



The history of In Vitro Fertilization (IVF) and embryo transfer (ET) dates back as early as the 1890s when Walter Heape a professor and physician at the University of Cambridge, England, who had been conducting research on reproduction in a number of animal species, reported the first known case of embryo transplantation in rabbits, long before the applications to human fertility were even suggested.



Aldous Huxley

In 1932, 'Brave New World' was published by Aldous Huxley. In this science fiction novel, Huxley realistically described the technique of IVF as we know it. Five years later in 1937, an editorial appeared in the New England Journal of Medicine (NEJM 1937, 21 October) which is note worthy.

"Conception in a watch glass: The 'Brave New World' of Aldous Huxley may be nearer realization. Pincus and Enzmann have started one step earlier with the rabbit, isolating an ovum, fertilizing it in a watch glass and reimplanting it in a doe other than the one which furnished the oocyte and have thus successfully inaugurated pregnancy in the unmated animal. If such an accomplishment with rabbits were to be duplicated in the human being, we should in the words of 'flaming youth' be 'going places.'"



John Rock

In 1934 Pincus and Enzmann, from the Laboratory of General Physiology at Harvard University, published a paper in the Proceedings of the National Academy of Sciences of the USA, raising the possibility that mammalian eggs can undergo normal development in vitro. Fourteen years later, in 1948, Miriam Menken and John Rock retrieved more than 800 oocytes from women during operations for various conditions. One hundred and thirty-eight of these oocytes were exposed to spermatozoa in vitro. In 1948, they published their experiences in the American Journal of Obstetrics and Gynecology.



MC Chang

However, it was not until 1959 that indisputable evidence of IVF was obtained by Chang (Chang M. 1959, Nature 184:466) who was the first to achieve births in a mammal (a rabbit) by IVF. The newly-ovulated eggs were fertilized, in vitro by incubation with capacitated sperm in a small Carrel flask for 4 hours, thus opening the way to assisted procreation.

Professionals in the fields of microscopy, embryology, and anatomy laid the foundations for future achievements. The recent rapid growth of IVF-ET and related techniques worldwide are further supported by the social and scientific climate which favors their continuation.

Through the years numerous modifications have been made in the development of IVF-ET in humans: refinement of fertilization and embryo culture media; earlier transfer of the embryo; improvements in equipment; use of a reduced number of spermatozoa in the fertilization dish and embryo biopsy among others.

The purpose of this introduction is to acknowledge those who initiated new steps in the development of the treatment protocols and techniques that we now use facilitating such simple and promising IVF-ET procedures.

1961

Palmer from France described the first retrieval of oocytes by laparoscopy.



Laparoscopic retrieval



Georgeanna and Howard Jones



Robert Edwards

1965

In 1965, Robert Edwards together with Georgeanna and Howard Jones at Johns Hopkins Hospital in the USA attempted to fertilize human oocytes in vitro (Edwards et al 1966, Am J Obstet Gynecol 96, 192).



Fertilized human oocyte



Human oocyte



Carl Wood and John Leeton

1973

The first IVF pregnancy was reported by the Monash research team of Professors Carl Wood and John Leeton in Melbourne, Australia. Unfortunately, this resulted in early miscarriage (deKretzer et al, 1973, Lancet 2, 728).

1976

Y. Menezo developed the world's first B2 culture medium, known as 'the French medium'. This specific medium reflected the follicular, tubal and uterine environments of the sheep, rabbits and humans.



Yves Menezo

Stephoe and Edwards published a report on an ectopic pregnancy following transfer of a human embryo at the late morulae /early blastocyst stage. (Stephoe and Edwards 1976, Lancet ;1:880).

1978

The first ever IVF birth occurred in Oldham, England on July 25, 1978. This birth was the result of the collaborative

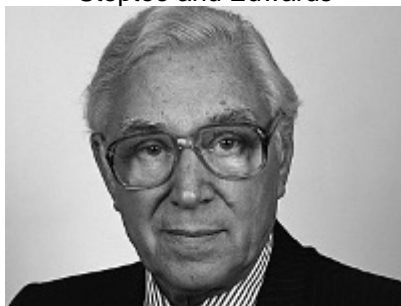
work of Patrick Steptoe and Robert Edwards (Steptoe and Edwards 1978, Lancet 312, 366).



Birth of Louise Brown



Steptoe and Edwards



Patrick Steptoe

1979

Pez et al, began tracking the growth of follicles by ultrasound. They showed an appreciable relationship between the echographic and laparoscopic observations (Pez et al., 1979, 17^e soirée gynéco-obstriciale de St Maurice le 9.10.79).



Alex Lopata

1980

The first IVF birth in Australia to the joint Victorian Monash-Melbourne team occurred at RWH. (Lopata et al. 1980 Fertil Steril 33,117)

1981

Howard and Georgianna Seegar Jones announced the delivery of the first IVF baby in the United States. This first IVF birth in the USA was achieved with the use of hMG .

Introduction of Clomiphene Citrate and hMG in the IVF treatment protocol (Trounson et al, 1981, Science 212, 681) .

The Clamart group in France developed an LH assay (LH-SIRO which could detect the initial LH rise in plasma allowing accurate prediction of the ideal time for the retrieval of oocytes (Testart et al., 1981, Fertil Steril 36, 50).



Jacques Testart



Rene Frydman



Lars Hamberger

1982

The first French IVF birth occurred in Clamart, France by the group of Frydman and Testart.

The first IVF birth in Sweden (Hamberger et al, 1982, Acta Med Rom 20, 370–378)

The first frozen embryo twins were born in Australia.

The introduction of culture medium (Mohr and Trounson, 1980, J Reprod Fertil 58,189)

The first report of the need for a delay between oocyte collection and insemination to allow oocytes collected to complete maturation (Trounson et al. 1982 J Reprod Fertil 64, 285)



Susan Lenz

Susan Lenz and Jörgen G Lauritsen demonstrated trans abdominal transvesical oocyte aspiration using an ultrasound-guided needle (Lenz and Lauritsen, 1982, Fertil Steril 38, 673).

Born Hall worlds first IVF Conference



1983

Donor egg: The Monash IVF team achieved the first birth by a woman without ovaries by using donor eggs creating of artificial menstrual cycles and a special hormonal formula for the first 10 weeks of pregnancy (Trounson et al. 1983, Br Med J 286, 835).

Monash IVF team reported on the birth of the first frozen embryo baby. (Embryo freezing developed in Cambridge, England on cattle – minor adaptations to adjust to humans). (Trounson and Mohr 1983, Nature 305, 707)



Frozen embryos



Alan Trounson



Robert Casper



Norbert Gleicher

Maturation and fertilization of morphologically immature human oocytes in a program of in vitro fertilization. (Veek et al, 1983, Fertil Steril 39:594)

First pregnancy after oocyte donation. (Trounson et al, 1983, Br Med J 286:835)

First successful delivery following egg donation. (Buster et al. 1983 Lancet 2:223).

Gleicher and his group reported the first vaginal egg retrieval using an abdominal ultrasound (Gleicher et al.1983, Lancet ;2:508)



Kretztechnik's mechanical rotary vaginal scanner in 1985 with puncture attachment

1984
The Government of Victoria established a review of IVF research and practice which led to the proclamation of the

research.

First surrogacy embryo transfer baby born in California

First report on pregnancy following translaparoscopic GIFT procedure (Asch et al, 1984, Lancet 2(8410):1034)

The first report on pregnancy following IVF and egg donation in a woman with primary ovarian failure. (Lutien et al, 1984 Nature 307(5947);174)

Introduction of GnRH agonists to the IVF treatment protocol (Porter et al, 1984, Lancet 2:1284)

A report of pregnancy following transfer of intact frozen-thawed embryos (Zeilmaker et al. 1984, Fertil Steril 42:293)

An unusual report of the possibility that abnormal spermatozoa could be enriched and give rise to healthy babies. (Cohen et al. 1984, Lancet 1(8388):1239-40)

Casper and his colleagues were the first to described the use of low dose hCG for support of the luteal phase in ART cycles. (Casper et al, 1983, lancet 2:1191)

1985

Human pregnancy by in vitro fertilization (IVF) using sperm aspirated from the epididymis. (Temple-Smith 1985 J In Vitro Fert Embryo Transf 2: 119)

Jacqueline Mandelbaum with Dan Szollosi described the microstructures of the human oocyte, which became known as 'oocyte dysmorphia' (Szollosi et al., 1986, J In Vitro Fertil Embryo Trans 3, 232).



Epididymis sperm aspiration



Vaginal oocyte aspiration



Ultrasound image of follicles



GIFT procedure

Matts Wikland in Gothenburg, Sweden, described the possibility of using a vaginal sector scanner (transvaginal technique) for oocyte aspiration (Wikland et al, 1985, Ann NY Acad Sci 442, 182).

First report of the use of abdominal ultrasound guidance for embryo transfer. (Strickler et al. 1985 Fertil Steril 43:54)

The first reported birth after replacement of hatching blastocyst cryopreserved at expanded blastocyst stage (Cohen et al, 1985, Lancet 1(8429):647)

First report about the Canadian IVF baby by the group of Victor Gomel at the University of British Columbia (Young S. Moon et al, 1985 Gamete Research 11:289).

In 1985 Quinn and Warnes published a formula entitled Human Tubal Fluid (HTF) which mimics the in vivo environment to which the embryo is exposed (Quinn P, Kerin JF, Warnes GM. 1985; Fertil Steril. 1985 :493).

1986

Monash IVF report on the world's first pregnancy and birth from the sperm retrieval operation performed on a patient who had a blocked sperm duct.



W Feichtinger



Paul Devroey



Zev Rosenwaks



Daniel Navot

First description of Transvaginal sector scan sonography for needle guided transvaginal follicle aspiration (Fiechtinger and Kemeter 1986, Fertil Steril 45:722)

First pregnancy, following IVF donated oocytes, in a non-ovarian failure patient. (Rosenwaks et al, 1986, Fertil Steril 45:417)

Navot et al. reported the possibility to artificially induced endometrial cycles and establishment of pregnancies in the absence of ovaries. (Navot et al, 1986 NEJM 314:806)

First report on pregnancy after translaparoscopic zygote intrafallopian transfer (Devroey et al. 1986, Lancet 1(8493):1329)

1987

Fertilization of human oocytes by microinjection of a single sperm under the zona pellucida (LawsKing et al, 1987 Fertil Steril 48, 637)

1988

Embryo biopsy technique was developed in mice by Professor Alan Trounson and Leeanda Wilton.



Leeanda Wilton



Alan Trounson

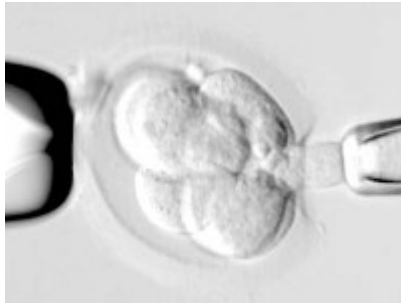
First two babies born after epididymal sperm aspiration for men with congenital absence of the vas deferens and naming of the technique MESA (Patrizio et al. Lancet 2, (8624): 1364)

Australia's first IVF surrogate birth.

The first baby birth using subzonal sperm injection at National University of Singapore (Ng et al, 1988, Lancet 2, 790)

Pregnancy was obtained from micromanipulation using zona drilling or mechanical partial zona dissection (Cohen et al. 1988 Lancet 2(8603):162)

The death of Dr. Patrick Steptoe -March 21 1988.



Biopsy of an embryo



Yona Tadir



Alan Handyside



Yael Gonen

1989

First report on biopsy of human preimplantation embryos and sexing by DNA amplification. (Handyside et al. 1989 Lancet 1:347)

First report of the use of laser techniques in the field of assisted reproduction for application in gametes or embryos (Tadir et al 1989, Fertil Steril 52: 870)

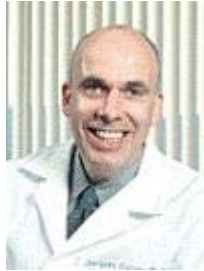
Gonen and her colleagues in Toronto pioneered the use of ultrasound for endometrial quality (thickness and pattern) related to IVF pregnancy. (Gonen et al. 1989 Fertil Steril 52:446)

1990

The first successful human cleavage-stage embryo vitrification followed by a successful delivery (Gordts et al., 1990, Fertil Steril 53, 469).



Hatching of a blastocyst



Jacques Cohen

Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification. (Handyside et al. 1990, Nature 344:768)

First report of assisted hatching in human embryos. (Cohen et al. 1990, Human Reprod 5:7)

The first report on polar body biopsy, transfer of the embryo and achieving pregnancy (Verlinsky et al, 1990 Hum Reprod. 1990, 7:826)

Gonen et al, proposed the use of GnRH agonist in place of hCG as a means to trigger the gonadotropic surge for IVF. (Gonen et al. 1990 J Clin Endocrinol Metab 71:918)

Gonen, Jacobson and Casper pioneered the use of combined oral contraceptives for follicle synchronization and cycle scheduling in IVF. (Gonen et al 1990, Fertil Steril 53:282)

1991

In Vitro Maturation (IVM) in unstimulated cycle resulted in pregnancy in a donor oocyte program (Cha et al 1991, Fertil Steril 55:109)



Daniel Palanker



Kwang Ryul Cha

The first report suggesting the use of GnRH antagonist, Nal-Glu, to prevent premature LH rise and progesterone in controlled ovarian hyperstimulation treatment. (Frydman et al. 1991, Fertil Steril 56:932)

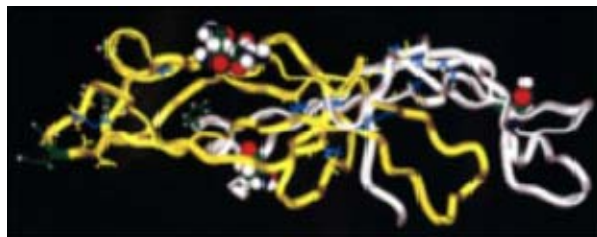
The first report on the use of a laser for Zona Pelucida drilling (Palanker et al. 1991, Laser Surg Med 11: 589)

Navot et al. confirmed that the age-related decline in female fertility is attributable to oocyte quality (Navot et al. 1991 Lancet 337(8754):137)

1992
Successful in-vitro fertilisation and embryo transfer after treatment with recombinant human FSH. (Germond et al. 1992, Lancet. 9;339(8802):1170)(Devroey et al. 1992, Lancet. 9;339(8802):1170)



Marc Germond

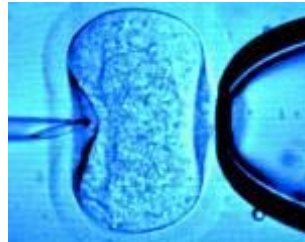


Three-dimensional model structure of FSH



Recombinant FSH

Assisted zona hatching was introduced in IVF programs to breach the zona pellucida and promote the natural process of hatching. (Cohen et al. 1992 Hum Reprod 7:685-691)



ICSI process



ICSI microscope



ICSI microscope

Discovery that men with congenital absence of the vas deferens have a mild form of cystic fibrosis: Two papers: (Anguiano et al. 1992, JAMA 267(13)1794)(Patrizio and Asch 1992, Annals Acad Med Singapore 21:533)



Andre Van-Steirteghem



Gianpiero Palermo

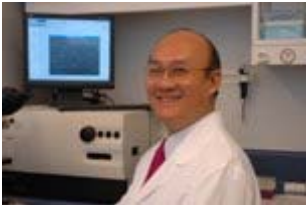


Pasquale Patrizio

Report of the first pregnancy after intracytoplasmic sperm injection (ICSI) by the group in Brussels (Palermo et al. 1992, Lancet, 2, 17)

Pregnancy after embryo biopsy and coamplification of DNA from X and Y chromosomes. (Gilbert et al, 1992 JAMA 268:727)

Ovulation induction by endogenous LH released by the administration of an LHRH agonist after follicular stimulation for in vitro fertilization (Empeaire et al. 1992 J Gynecol Obstet Biol Reprod (Paris) 21:489)



First report of cumulative conception and live birth rates after IVF in relation to patient age and cause of infertility (Tan et al. Lancet, 1992; 339:1390)

1993

The second term pregnancy after ICSI reported by a group in Sweden (Hamberger et al, 1993, In Gordts S (ed) Proceedings of European Symposium on Micromanipulation. Drukkerij Nauwelaerts, Leuven, Belgium, pp 85).

Confirmation that men with congenital absence of the vas deference, have cystic fibrosis mutations which can be transmitted to the offspring (Patrizio P et al. 1983, Hum Reprod 8:215)



Sherman Silber

First report on the use of TESE, testicular sperm extraction and ICSI (Silber et al. Hum Reprod 1994)

1994

The first live birth as a result of IVM following transvaginal ultrasound-guided oocyte collection. (Trounson et al 1994, Fertil Steril 62;353)

First two births from replacement of frozen embryos produced with epididymal sperm (Patrizio et al. 1992, Hum Reprod 7:652)

The first reported birth resulting a frozen-thawed oocyte and ICSI (Chen 1986, Lancet 1:884)

1995

Pregnancies after Testicular Sperm Extraction (TESE) and ICSI in non-obstructive azoospermia. (Devroey et al. 1995 Hum Reprod 10:1457)



Frank Barnes



Blastocyst

Birth after blastocyst development from IVM oocyte plus ICSI plus Assisted Hatching (Barnes et al 1995, Hum Reprod 10:3243)

The first report of aneuploidy testing (Munné et al. 1995 Am J Obstet Gynecol 172:1191)

Zenzes from the group of Casper in Toronto demonstrated adverse effects of cigarette smoking on nuclear spindle. (Zenzes et al. 1995 Hum Reprod 10:3213)

1996

The Valencia group reported on the first pregnancy employing cryopreserved testicular sperm following IVF-ICSI. (Gil-Salom et al 1996, Hum Reprod 11:1309)

Discovery that some men with severe oligoasthenospermia have deletions in the Y-chromosome (Rejio et al, 1996 Lancet 347(9011): 1290)

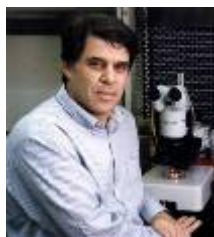
Juriscova from the group of Casper was the first to recognize that preimplantation human embryo fragmentation involved programmed cell death. (Juriscova et al 1996 Mol Hum Reprod 2:93)

Casper and his colleagues were the first to demonstrate and introduce the use of the hypo-osmotic swelling test for selection of immotile sperm for ICSI. (Casper et al. 1996 Fertil Steril 65:972)

First report on Cytoplasmic transfer (Cohen et al. 1996, Lancet; 350:186)

1997

Sun, Juriscova and Casper described the use of TUNEL for detection of DNA fragmentation in sperm and correlation with IVF outcome. They showed almost uniform presence of DNA fragmentation in round spermatids as explanation for failure to achieve pregnancy with these immature gametes. (Sun et al, 1997 Biol Reprod, 56:602)



Joseph Itskovitz-Eldor



David Gardner

1998

First establish pregnancy using recombinant FSH and GnRH antagonist (Itskovitz-Eldor et al 1998, Hum Reprod. 13:294)

Gardner introduced sequential media and blastocyst transfer which is now greatly assisting in the move to single embryo transfer.(Gardner et al., 1998 Human Reproduction, 13: 3434)

Births after intracytoplasmic injection of sperm obtained by testicular extraction from men with nonmosaic Klinefelter's syndrome (Palermo et al, 1998, N Engl J Med 338: 588)

First report on Cytoplasmic transfer (Cohen et al 1996 Lancet 350(9072):186)

1999

First unaffected pregnancy using preimplantation genetic diagnosis for sickle cell anemia. (Xu et al. 1999, JAMA 281: 1701)

Birth following vitrification of human oocyte (Kuleshova et al. 1999, Hum Reprod 14:3077)

Chian et al. demonstrated that hCG priming prior to immature oocyte retrieval in women with PCO increases the maturation rate and produces high pregnancy rates of 40% per IVM cycle started (Chian et al. 1999 N Eng J Med; 341:1624)

World's first IVF/ICSI pregnancy and live-birth after successful air transport of oocytes reported by the McGill Reproductive Centre, enabling the creation of an air-transport IVF program in large countries with scattered populations or in areas remote from infertility centers (Buckett WM et al. 1999, Fertil Steril; 71:753)



Kutluk Oktay

2000

Oktay and Karlikaya were the first to report on ovarian tissue transplant after frozen storage. (Oktay and Karlikaya 2000, NEJM 342:1919)

2001

First report using ultrasound for embryo transfer (Kojima et al. 2001, Hum Reprod 16:2578)



Embryo transfer Catheter



Ri-Cheng Chian

Embryo transfer Catheter is visualized by Vaginal Ultrasound

Birth of an infant from cryopreserved embryos (zygotes) produced by IVM oocytes derived from an unstimulated patient with PCOS (Chian et al., 2001 Hum. Reprod. 16, 1700).

Ongoing twin pregnancy after ICSI of PESA-retrieved spermatozoa into in-vitro matured oocytes reported by the McGill group. (Ahmad Kamal Abdul-Jalil et al, 2001, Hum Reprod, 16: 1424)

Live birth after sperm retrieval from a moribund man (Belker et al 2001, Fertil Steril 76:841)

2002

First live birth following blastocyst biopsy and PGD analysis. (De Boer et al. 2002, Reprod Biomed Online 4:35)

First clinical application of comparative genomic hybridization and polar body testing for preimplantation genetic diagnosis of aneuploidy. (Wells et al 2002 Fertil Steril, 78:543)

2003

Live births after vitrification of oocytes in a stimulated in vitro fertilization–embryo transfer program (Yoon et al, 2003 Fertil Steril 79:1323)



Ren-He Xu

First live birth after ovarian stimulation using a chimeric long-acting human recombinant follicle-stimulating hormone (FSH) agonist (recFSH-CTP) for in vitro fertilization (Beckers et al. 2003, Fertil Steril 79:621)

The first reported liveborn following preimplantation genetic diagnosis for Retinoblastoma (Xu et al, 2003, Am J Ophthalmol 18)

Implantation of the human embryo is the limiting factor in the success of IVF. Dr. Barash and Prof. Dekel showed an Increasing implantation rate following endometrial injury, performed by Pipelle curettage as a simple outpatient procedure. (Barash et al Fertil Steril. 2003: 79:1317).



Blastocyst biopsy



Yuri Verlinsky



Jacques Donez

2004

Successful pregnancy and delivery following combined treatment of In Vitro Maturation (IVM) and Testicular Sperm Extraction (TESE). (Fuchinoue et al. 2004, J of Assisted Reprod Genetics 21:371)

Jacques Donnez reporting about the first Livebirth after orthotopic transplantation of cryopreserved ovarian tissue (Donnez et al, 2004, Lancet 364(9443) :1405)

Gardner and colleagues performed the world's first prospective single blastocyst trial, which showed the feasibility of SBT and in keeping high pregnancy rates (Gardner et al., 2004 Fertil Steril 81: 551)

The first preimplantation HLA matching for stem-cell transplantation to affected sibling (Verlinsky et al 2004 JAMA, 291:2079)

First report of fertility preservation for cancer patients using IVM and oocyte vitrification (Rao et al. 2004, Lancet; 363:1829)

First report on natural cycle in IVF combined with IVM as a potential approach to infertility treatment (Chian et al. 2004, Fertil and Steril; 82:1675)

2005

Pregnancies and live births after trophectoderm biopsy and preimplantation genetic testing of human blastocysts. (McArthur et al Fertil Steril 84:1628)



Dror Meirou

First birth in Israel from thawed ovarian cortex re-transplants, (Meirou et al, 2005, N Engl J Med 535(3):318)

2006

First successful pregnancy after preimplantation genetic diagnosis for aneuploidy screening in embryos generated from natural-cycle IVF combined with IVM. (Ao et al. 2006, Fertil Steril 85;1510e)

Cryopreservation of intact human ovary with its vascular pedicle. (Bedaiwy et al. 2006, Hum Reprod 21:3258)

First successful pregnancy after preimplantation genetic diagnosis for aneuploidy screening in embryos generated from natural-cycle IVF combined with IVM achieved at the McGill Reproductive Centre (Ao et al. 2006, Fertil Steril; 85:1510)



Son Weon Young



Amir Arav and Pasquale Patrizio

2007

Report from McGill Reproductive Center, Canada and Maria Infertility Hospital Seoul, Korea on deliveries after transfer of human blastocysts derived from oocytes matured by In Vitro Maturation (IVM) (Weon-Young Son et al 2007, Fertil Steril 87:1491)

Introducing the concept of Mild Treatment Strategy for IVF (Heijnen et al, 2007 Lancet 369(9563):743)

A novel multi-gradient freezing technique for the cryopreservation of the whole ovary. Thawing the ovary resulted in normal ovarian architecture and no damage to the vascular wall or intima. (Arav and Pasquale 2007 Yale Practice 12:2)

A novel multi-gradient freezing technique for the cryopreservation of the whole ovary. Thawing the ovary resulted in normal ovarian architecture and no damage to the vascular wall or intima. (Arav and Pasquale 2007 Yale Practice 12:2)

First IVM egg donation pregnancy in North America achieved by McGill Reproductive Centre (Holzer et al. 2007, Fertil Steril; 88:62)

2008

Prof. Laufer at the Hadassah Medical Center in Jerusalem reported on a viable pregnancy achieved in a woman who carries the defective BRCA2 genes. After In-Vitro Fertilized Embryos were tested and implanted. (Sagi et al 2009 Prenatal Diagnosis, Published online DOI:10/1002/pd)

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