icology books, visit our website www.jaypeebrothers.com, for detailed information on forensic medicine & toxicology books

Forensic Medicine & Toxicology

VOLUME 2

Recent Advances in Forensic Medicine & Toxicology

Good Practice Guidelines and Current Medicolegal Issues

Editor
Gautam Biswas

Forewords
Joseph A Prahlow
Uwom O Eze

JAYPEE

CONTENTS

SECTION 1: MEDICAL JURISPRUDENCE AND LEGAL ISSUES

1. Medical Negligence and Medical Law **3**
Gopinath Shenoy

- Service and Deficiency of Service *4* • Negligence and Rashness *5*
- Duty of Care and Standard of Care *8* • Accepted Practices and Procedures *10* • Deviation from Accepted Practices *11*
- Accidents or Misadventures or Mishaps *11* • Error of Judgment *12*
- Inherent Risks of Treatment *12* • Choice of Treatment—Discretion *13*
- Guarantee and Warranty *13* • Vicarious Liability *13*
- Deficiencies in Statutory Requirements *15*

2. Medical Evidence in Examination of Rape/Sexual Assault Survivor **18**
Jagadeesh Narayanareddy

- Definitions *21* • History *23* • Frequently Encountered Questions *24*
- Instructions for Doctors *31*
- Medicolegal Examination of the Accused *35*

3. Critical Appraisal of the Pre-conception and Pre-natal Diagnostic Techniques Act **41**
Prashant Onkar

- Definitions (as Per the PCPNDT Act) *44* • Regulation of Pre-natal Diagnostic Techniques *46* • Registration of Genetic Counseling Centers, Genetic Laboratories, and Genetic Clinics *48*
- Maintenance of Records (for 2 Years) *50* • Indications *52*
- Offenses and Penalties *54* • Action Taken *55*
- Who can Make a Complaint? *56* • Illegal Advertisement *56*
- Use of Portable Ultrasound Machine *56* • Six-Months Training *57*
- Important Time Limits *58*

4. Legal and Ethical Issues in Oocyte Cryopreservation **61**
Gautam Biswas, Priya Selvaraj

- Definitions *64* • History *64* • Indications *65*
- Female's Fertility Cycle *68* • Informed Consent *68*
- Ideal Age and Reported Age of EOC *69* • Procedure *70*
- Complications *73* • Cost *74* • Success Rate *74*
- Legal Issues *75* • Medicolegal Issues *76*
- Ethical and Social Issues *77*

5. Moment of Death **91**
Pradeep Kumar MV

- Definitions *92* • History *93* • Process of Death *93*
- Moment of Death *96* • Determination of Brain Death (Brainstem Death) *101* • Limitations of Brain Death Criteria *105*
- Controversies over Brain Death Diagnosis *106*
- Indian Context *107*
- Medicolegal and Ethical Issues of Determination of Death *109*

6. Concept of Dying Declaration in India **115**
Anil Kohli

- Recording of Dying Declaration *116*
- Conditions for Admissibility *121*
- Nonadmissibility of Dying Declaration *122*
- Evidential Value *123* • Multiple Dying Declarations *124*
- Fitness of Person to Give Dying Declaration *125*
- Principles Governing Dying Declarations *128* • Deposition *130*

7. Unclaimed Bodies—Legal, Ethical, and Humanitarian Issues **134**
Prateek Rastogi

- Few Words *136* • Epidemiology *136* • Legal Issues *137*
- Ethical and Humanitarian Issues *137*
- Dealing with an Unknown Dead Body *139*

SECTION 2: CLINICAL FORENSIC MEDICINE

8. Assessment and Documentation of Injuries **145**
Virendar Pal Singh, Vivekanshu Verma

- Definitions *147* • Assessment and Documentation *149*
- History *149* • General Physical Examination *151*
- Photographs *160* • Investigations *161*
- Clothing Examination *161*
- Collection of Evidence and Maintaining Chain of Custody *161*
- Duration, Nature and Circumstances of the Injuries *162*
- Abrasion *163* • Contusion *164* • Laceration *167*
- Incised Wounds *169* • Stab Wounds *171*
- Chop Wounds *174* • Checklist *174*

9. An Approach to Examination of a Case of Erectile Dysfunction **177**
Lavlesh Kumar

- History *179* • Definitions and their Explanations *180*
- Penile Anatomy *182* • Physiology of Sexual Intercourse *183*

- Pathophysiology of Erectile Dysfunction *184* • Epidemiology *184*
- Etiology *185* • Assessment of a Case of Erectile Dysfunction *187*
- Laboratory Investigations *192* • Neurological Assessment *192*
- Framing the Opinion *194*
- Medicolegal Issues in Relation to ED *194*

10. An Approach to a Case of Ocular Trauma **204**
Gurkirat Singh Bajwa

- Gross Anatomy *206* • Definitions *208* • Epidemiology *209*
- Types of Injuries *210* • Classification of Ocular Trauma *214*
- Ocular Trauma Score *215* • Evaluation of Traumatic Eye *217*
- Ocular Examination *219* • Examination of Eyeball *222*
- Ocular Imaging *224* • Photo-Documentation *225*
- Medicolegal Report *227* • The Doctor and the Law *229*
- Medicolegal Issues *230* • Malingering *232*

11. An Introduction to Bite Mark Documentation and Analysis **237**
Nitul Jain

- History *240* • Definition *240*
- Uniqueness of Bite Marks and Skin Dynamics *240*
- Skin Dynamics *241* • Classifications of Bite Marks *242*
- Composition of Bite Marks *243* • Animal Bite Marks *245*
- Sites of Human Bite Marks *246*
- Appearance of Human Bite Marks *247*
- Distortion in Human Bite Marks *249*
- Bite Mark Severity and Significance Scale *250*
- Investigations of Bite Marks *250*
- Bite Mark Analysis Guidelines *251*
- Evidence Collection from Victim *251*
- Evidence Collection from Bite Suspect *255*
- Bite Mark Analysis and Scoring *257*
- Recommended Terms for Indicating Degree of Confidence *262*
- Terminologies Used in Bite Mark Analysis *262*
- Advancements in Science of Bite Marks Analysis *264*
- Lacunae and Difficulties Encountered in Bite Mark Analysis *266*

12. Legal Aspects and Examination of a Torture Survivor **270**
Sherien Salah Ghaleb, Kholoud Samy Alsowayigh, Mostafa A Hamd, Magdy Kharoshah

- Definitions, Scope and Implications *272* • Incidence *274*
- Torture in Recent History *275* • Torture in International Law *277*
- The Istanbul Protocol *278* • Torture Techniques *281*
- Physical Torture *282* • Sexual Torture *292*
- Psychological Torture *292* • Pharmacological Torture *293*

- Examination of Torture Survivor *293*
- Torture as a Public Health Problem *300* • Doctor and Torture *302*

SECTION 3: FORENSIC PATHOLOGY

13. The Neuropathological and Clinical Features of Chronic Traumatic Encephalopathy **309**
Hanish Bansal, Michael L Alosco

- History and Origins of Chronic Traumatic Encephalopathy *310*
- Neuropathology of CTE *310* • RHI Exposure and CTE *311*
- Clinical Features of CTE *314* • Potential Biomarkers for CTE *316*
- Risk Factors for CTE *317*

14. An Introduction to Digital Autopsy **323**
Mohammed Nasimul Islam, Jesmine Khan, Kazuya Ikematsu, Pramod G Bagali, Mathavan A Chandran

- Modalities *324* • Medical Visualization Standard (DICOM Compatibility) *331* • Three-Dimensional Visualization *338*
- Digital Tools for Autopsy *342* • Exploration of Pathology by Digital Autopsy *345* • Measurement and Recording *348*
- Digital Autopsy as a Service *351*

15. Pathophysiology of Maternal Deaths **355**
Sudha R, Jagjiv Sharma, Rupesh Kumar

- Definitions *357* • Classification of Maternal Deaths *358*
- Epidemiology *359* • Direct Causes of Maternal Deaths *363*
- Indirect Causes of Maternal Deaths *380* • Late and Fortuitous Deaths *385* • Role of Maternal Autopsy *385*

16. Recent Advances in the Autopsy Diagnosis of Drowning **394**
Parthapratim Mukhopadhyay, Soumeek Chowdhuri

- History *397* • Definition of Drowning *398*
- Types of Drowning *398* • Pathophysiology of Drowning *400*
- Autopsy Diagnosis of Drowning *403* • Histopathology *413*
- Laboratory Tests *414* • Biochemical Examination *418*
- Other Methods and Recent Developments *420*

17. Autopsy in Perinatal Deaths and its Medicolegal Implications **431**
Gautam Biswas, Praveen C Sobti, Rajinder Gulati

- Definitions *432* • Epidemiology *433*
- Grounds for Feticide/Neonaticide *433*

- Role of Forensic Pathologist *434* • Postmortem Examination *437*
- Interpretation of Postmortem Findings *444*
- Liveborn or Stillborn *450* • Cause of Death *456*

18. Autopsy in Suspected Pediatric Non-Accidental Head Injuries **465**
Serenella Serinelli, Lorenzo Gitto, Ponni Arunkumar, Giorgio Bolino, Aniello Maiese

- Crime Scene Investigation *467*
- Medical History and Police Investigations *467*
- Radiological Surveys *468* • Dissecting Room Examination *471*
- Macroscopic and Microscopic Study of the Nervous Tissue *489*
- Macroscopic and Microscopic Study of Eye and Optic Nerve *493*
- Special Procedures *496*

19. Autopsy in Cases of Torture and Custodial Deaths **503**
Amar Jyoti Patowary

- Definitions *506* • Guidelines Issued by the National Human Rights Commission (NHRC) *507*
- Autopsy Procedure in Alleged Torture or Custodial Death *508*
- Autopsy Examination *510* • Video Filming and Photography *526*

20. Checklist in Medicolegal Practice **529**
Swapnil S Agarwal

- Definitions *530* • Current Scenario *531*
- Checklists in Medical Field *531* • Caution with Checklists *534*
- Use in Medicolegal Practice *534*

SECTION 4: FORENSIC ANTHROPOLOGY

21. Examination of Skeletal Remains **543**
Hareesh S Gouda, Shashidhar C Mestri

- Definitions *544* • Examination Procedure *545*
- Examination of Burnt Bones *577* • Dating of Bones *579*

22. The Practical Application of Forensic Anthropology **583**
Carolyn V Isaac, Jered B Cornelison

- Locating and Recovering Human Remains *583*
- Processing Remains *586* • Skeletal Inventory and Determination of Minimum Number of Individuals *587*
- Biological Profile Assessment *587* • Taphonomy *608*
- Positive Identification *610* • Trauma Analysis *611*

SECTION 5: FORENSIC SCIENCE

23. Controversies in Forensic Tests, Investigations and Expertise **623**
Jagadeesh Narayanareddy, George Paul

- Current Scenario *626* • Emerging Issues *634*
- Hard Facts *638* • Discussion *643*

Index *649*

4 Legal and Ethical Issues in Oocyte Cryopreservation

Gautam Biswas, Priya Selvaraj

"As long as we have memories, yesterday remains, and as long as we have hope, tomorrow awaits".
—Abhysheq Shukla (Speaker, author, political consultant)

Abstract

Since the first live birth from oocyte cryopreservation (OC) three decades ago, it has become an important component of assisted reproductive technology. Cryopreservation techniques have evolved, leading to higher success rates and the introduction of OC into IVF clinics worldwide. Females are accessing and receiving OC for a wide range of indications—both medical and elective, and there has been a marked increase in their numbers. Patients at risk of infertility due to disease, oocyte donation programs, couples who fail to produce semen when required for IVF and patients with legal or ethical reasons against embryo cryopreservation are potential candidates for OC. Moreover, many females who plan to delay childbearing are interested in OC in order to protect against age-related fertility decline. OC for circumventing age-related infertility is becoming more widely accepted. The success rate using OC has increased and the current use of vitrification has improved outcomes. IVF pregnancy rates with frozen oocytes are now similar to those achieved with fresh oocytes. Controversial ethical debates focus on the risks of the technique for mother and child, the scope of reproductive autonomy and the commercialization of reproduction. This chapter discusses the various developments in OC, as well as legal and ethical issues pertaining to this technique, and how this may affect reproductive practices and choices.

***Keywords*:** vitrification, reproductive autonomy, elective oocyte cryopreservation, donor oocyte, biological clock, age-related infertility

JAYPEE BROTHERS

CASE STUDY 1

Neha, a 29-year-old airline professional is too busy to consider getting married just yet. She is aware of age-related fertility problems later in life and decided to have her oocytes frozen. She came to know of alternatives to preserve fertility through internet. Her job requires her to travel frequently and she is ready to wait another five years before getting married. Oocyte cryopreservation (OC) would mean that in a few years when she is married and ready to have a child, she could use her frozen oocytes stored at the infertility center, get them thawed and after in-vitro fertilization (IVF) procedure, implant the embryo in her uterus (if she is unable to have a child naturally).[1]

CASE STUDY 2

Maya, 30, an unmarried female is currently pursuing further studies after doing her undergraduation. She is pressurized by her family to get married but is worried that her financial situation will stabilize until after a few years when she gets a good job. She considers OC will give her time to tide over her current situation while not having her pregnancy chances lowered with age.[2]

CASE STUDY 3

Jaya, 34, is a childless divorcee. She hopes it will not be too late for her to have children if she finds a husband of her choice. She believes OC would grant her the time she needs to find the right partner this time.[2]

INTRODUCTION

Reproductive medicine saw the introduction of a variety of new procedures, such as IVF-ET (in vitro fertilization-embryo transfer), oocyte cryopreservation, intracytoplasmic sperm injection (ICSI), assisted hatching, blastocyst culture, pre-implantation genetic diagnosis (PGD), cytoplasmic transfer and embryo co-culture so as to offer more men and women the chance to become parents. Oocyte cryopreservation (OC) empowers females by giving them a way to preserve oocytes against the threat of disease or age. A female could bear children even after chemotherapy or menopause, as well as store oocytes extracted for in vitro fertilization (IVF). In all the above-mentioned cases (with some modifications), this technique gives females an opportunity to slow down their biological clock by cryopreserving their oocytes and postponing motherhood for a few more years till they are ready for conception. Some of the critics disapprove the use of the technique in healthy females in general, while others support it.[3] While it empowers them in many respects, it creates unwanted social pressure to compete in the labor market and alienation in others.[4] According to data from the Society for Assisted Reproductive Technology (SART) in 2009, only about 500 females used OC, whereas in 2013 almost 5,000 used this technology. Thaws nearby quadrupled from 123 in 2009

JAYPEE BROTHERS

to 414 in 2013. By 2018, it is estimated that 76,000 females will electively freeze their oocytes—a 151% increase in less than 10 years.[5]

OC is no longer considered 'experimental' as a result of advances in techniques to cryopreserve oocytes that have resulted in significant improvements in successful pregnancy.[4-7] However, the American Society for Reproductive Medicine (ASRM), the SART, the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice, the Royal College of Obstetricians and Gynecologists, the British Fertility Society and the Canadian Fertility and Andrology Society does not endorse elective oocyte cryopreservation (EOC), i.e. this should not be used as a family planning technique.[4,8-11] Currently, mature OC following IVF is recommended for women facing infertility due to chemotherapy or other gonadotoxic therapies. In fact, the American Society of Clinical Oncology recommends that healthcare providers discuss OC as an option for preserving fertility in female's diagnosed with cancer.[12]

In spite of the lack of efficacy and safety data, vulnerable patients and healthy young fertile females are being offered EOC by practitioners of reproductive medicine.[3] It is important to remember that there is no guarantee with the process—success is dependent on the age and fertility health of the female, as well as the methods used.[8,12]

Many Hollywood celebrities like Sofia Vergara, Kim Kardashain, Bridget Marquardt and Maria Menounos have used this technology to cryopreserve their oocytes.[13,14] Former Miss World Diana Hayden recently gave birth to a healthy baby girl at the age of 42, having cryopreserved 16 oocytes eight years ago. It gave new hope to females who are in no rush to becoming mothers.[15] In a bid to attract and retain more female employees, Facebook (31% female staff) and Apple (30% female staff) announced health insurance coverage to female employees to cover the cost of OC and storing so as to enable them to postpone child-bearing and pursue their career.[1,16-18] Countries with low total fertility rate are also encouraging the use of this technology, because of its perceived potential for increasing birth rates.[2] Urayasu, a city in Japan announced that it will pay 80% of the cost of OC for any female aged 25 to 34 years as part of a program aimed at raising the country's low birth rate (currently at 1.4 births/female).[19,20]

Advocates of OC believe that it is a great stride forward and the benefits of the procedure are comparable to contraception.[1] Although, EOC is legitimate in some of the countries, it is still a debatable issue for many medical, ethical, religious and social reasons, such as long-term effects of cryopreservation, controversial offspring quality from cryopreserved gametes, ownership and disposition of stored oocytes, oocyte freezing market and the changing of family patterns.[6,21] The partial endorsement of OC by various medical societies unquestionably influences the ethical debate about this reproductive technology.[12] This chapter explores current techniques and success rates, clinical applications, the rise of EOC, and legal and ethical issues associated with the technique.

JAYPEE BROTHERS

DEFINITIONS

- **Oocyte:** The immature female reproductive cell–"egg"—prior to fertilization.[22]
- **Natural conception:** Indicate any conception without clinical intervention.[22]
- **Assisted reproductive technology (ART):** All techniques that attempt to obtain a pregnancy by manipulating the sperm or/and oocyte outside the body and transferring the gamete or embryo into the uterus.[22,23]
- **In vitro fertilization (IVF):** The procedure of obtaining gametes from intended fathers or donors and artificially fertilizing the egg in vitro, before placing the embryo into the womb where it develops in utero.[22]
- **Infertility:** The failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse, or failure to achieve a pregnancy after a series of inseminations of donor sperm in a same sex couple (WHO).[6,11,13,23]
- **Cryopreservation:** It is a process of cooling of cells and tissues (gametes, zygotes or embryos) to sub-zero temperatures (cryogenic temperatures, typically using –196°C liquid nitrogen) wherein all chemical reactions, biologic processes and physical interactions—intra- and extracellular are in a state of suspended animation and preserve them for future use.[23]
- **Oocyte cryopreservation (egg freezing or egg banking):** A process in which mature oocytes are extracted, frozen and stored for later use—a method used to preserve reproductive potential in females.[22]
- **Embryo cryopreservation:** The oocyte has already been fertilized through IVF with either partner or donor sperm and has been frozen until the female is ready to begin pregnancy.[23]
- **Medical egg freezing:** Females who choose the oocyte freezing technology because of a medical condition or disease that threatens to destroy their genetic reproductive capacities, for e.g., a woman diagnosed with cancer.[24]
- **Elective oocyte cryopreservation or social egg freezing:** The use of oocyte cryopreservation technology by all other females, i.e. OC to guard against future age-related infertility.[13,24]
- **Vitrification:** It is the process of cryopreservation using high initial concentrations of cryoprotectant and ultra-rapid cooling to solidify the cell into glass-like state without the formation of ice crystals.[23]

HISTORY

The science of cryobiology was mentioned way back in 2500 BC wherein early civilizations used cold for medicinal purposes.[7] The first reported effects of low temperature on spermatozoa was recorded by Lazaro Spallanzani

JAYPEE BROTHERS

in 1776.[25] The first efforts at freezing sperm began in the mid 1800s when Dr Paolo Mantegazza suggested that a man dying on the battlefield could still have a legal heir born to his widow, if he would leave behind frozen sperm before going to war.[25]

Cryopreservation of cells and tissues was started only in mid-twentieth century. Chronology of events is given in Table 4.1.

INDICATIONS

OC was first developed as a way to potentially preserve fertility in cancer patients and others who received treatment that could cause infertility.[13,34] Currently, it is increasingly being used by females in many countries to delay childbearing (Flowchart 4.1).[13,14]

Medical

Patients Receiving Gonadotoxic Therapies

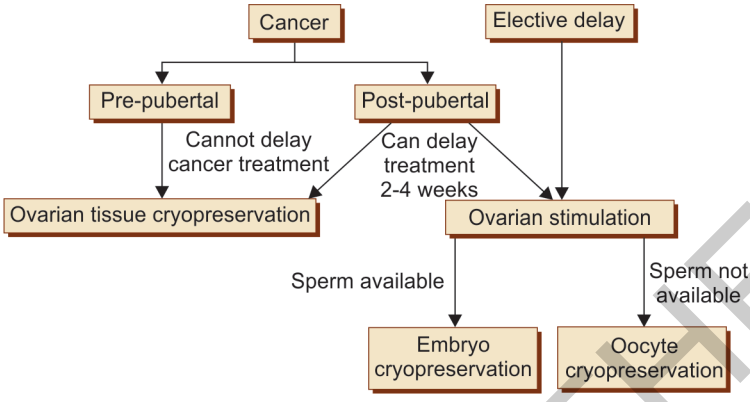
Cancer is the most common medical indication for seeking OC. Invasive cancer treatment with chemotherapeutic drugs and radiotherapy is gonadotoxic which may result in infertility. Bone marrow or stem cell transplantation, some autoimmune diseases and hematological diseases are treated with chemotherapy. These may also result in infertility in future.[11,12,14,24,29,35,36]

Table 4.1: Important events in the history of cryopreservation

Year	*Event*
1940s	Glycerol was found to protect sperm from damage during cryopreservation and thawing.[7]
1949	Improved methods of freezing and thawing sperm were developed.
1953	First human birth from frozen sperm was reported.[22]
1960s	Experiments in freezing mammal eggs first began using oocytes of rats.[26]
1970s	Cryoprotectants such as propanediol, ethylene glycol and dimethyl sulfoxide were found to minimize cell damage.[7]
1980s	Freezing embryos were routinely done.[22] Oocyte cryopreservation for humans was first used.[26]
1986	First successful pregnancy using slow freezing technique followed by the first live birth in 1987 was reported by Dr Christopher Chen in Australia.[7,14,22,27-29]
1997	Intracytoplasmic sperm injection (ICSI) was first used to fertilize frozen-thawed oocytes, circumventing zona hardening caused by the cryopreservation process.[30,31]
1999	First live birth with oocyte cryopreservation after vitrification.[30,31]
2008	First live birth after the transfer of embryos generated from frozen-thawed oocytes in India was reported by Dr Priya Selvaraj and her team.[28,32]
2009	First twin births after the transfer of embryos generated from vitrified and thawed oocytes in India was reported by Dr Priya Selvaraj and her team.[33]

JAYPEE BROTHERS

Flowchart 4.1: Fertility preservation options



Genetic and Other Medical Conditions

Certain genetic conditions such as Turner syndrome, fragile X premutation and deletions of the X chromosome predispose females to primary ovarian insufficiency. Patients with these risk factors may be candidates for fertility preservation before ovarian failure ensues. However, the risk associated due to chromosomal abnormalities in the offspring is of significant concern. A female with a family history of pre-mature menopause (pre-mature ovarian failure), polycystic ovary syndrome (PCOS) or undergoing surgery for endometriosis might be motivated to freeze her oocytes. Similarly, inheriting a mutation in the BRCA1 or BRCA2 genes [BRCA1 and BRCA2 (stands for Breast Cancer 1 and 2) are tumor suppressor genes] significantly increases the risk of breast and/or ovarian cancer. Even without a cancer diagnosis, a female who discovers she has a BRCA mutation might choose to undergo a prophylactic oophorectomy to decrease her risk of cancer. OC in advance of prophylactic oophorectomy can be a means of preserving potential future fertility, if childbearing and pregnancy is not a option at that time.[7,11,12,14,29,30]

Hollywood actress Angelina Jolie had undergone a preventative double mastectomy and bilateral salpingo-oophorectomy to reduce her chances of getting breast and ovarian cancer. She had a family history of cancer (her mother died of ovarian cancer) and has BRCA1 gene mutation. Doctors estimated that she had an 87% risk of breast cancer and a 50% risk of ovarian cancer.[37]

JAYPEE BROTHERS

Failure to Obtain Sperm for IVF

Occasionally, the male partner of a couple undergoing IVF is unable to provide a semen sample for oocyte insemination on the day of the oocyte retrieval. In addition, males with azoospermia may have insufficient sperm for fertilization of retrieved oocytes. In such instances, oocytes may be cryopreserved for insemination and embryo transfer at a later date. OC affords more time for the procurement of needed sperm.[7,11,12,16,30]

Unable to Cryopreserve Embryos

Cryopreserving oocytes, rather than embryos would be an option for patients unable or not wishing to cryopreserve embryos on religious, legal or ethical grounds. This procedure is being investigated as an alternative to embryo cryopreservation by countries that do not permit the freezing of embryos, such as in Italy and Germany.[38,39] Females who are divorced or may have lost a partner in death may consider banking mature oocytes as a reasonable fertility-preserving alternative.[4,11,14,22]

Some couples undergoing IVF cannot or wish not to cryopreserve supernumerary embryos that are not transferred in a fresh cycle. If the stored oocytes are no longer needed, they could be discarded without the ethical issue of discarding frozen embryos.[4] In these cases, the indication to cryopreserve unfertilized oocytes is not actually medical, but non-medical.[12]

Establishment of Donor Oocyte Banks

Oocyte cryopreservation can simplify oocyte donation. Commercial oocyte banks make cryopreserve donor oocytes widely available. Oocyte donation cycles require coordination of fresh cycles between the donor and recipient, which can be inconvenient and costly. This technique may provide females with more choices in selecting a donor, more flexibility in timing pregnancy and reduce the cost.[12,29-31]

Military Personnel

In the US, active duty military personnel are allowed to cryopreserve their oocytes prior to deployment with the Pentagon's pilot fertility preservation program.[26]

Elective or Social

Elective oocyte cryopreservation is most common indication, as well as most varied and controversial group. Females who freeze their oocytes for elective reasons want to defer child bearing for the future, for

JAYPEE BROTHERS

whatever reason. Since, there is a progressive loss of oocyte quantity and quality that occurs with aging, the prevalence of infertility and the incidence of pregnancy loss and chromosomal abnormalities increase steadily up to age 35, and more rapidly thereafter. Technologies, such as OC may allow females to have an opportunity to have biologic children later in life.[4,7,11,20,30]

FEMALE'S FERTILITY CYCLE

A female's reproductive life span is finite, and depends on the number of oocytes with which she is born. Over the time, they diminish in number and cellular integrity.[5,10,11,36] At birth, she normally has approximately 1-2 million oocytes, the immature follicles comprising the ovarian reserve. This drops to 200,000-500,000 at puberty and to a meager 1,000 by menopause. Her oocyte quality peaks between 16 and 28 years representing reproductive prime. Oocytes can still be acceptable from age 29 to 38 (the mid-reproductive years), but their quality diminishes greatly from age 39 to 44.[11,13] Beside age, other factors which may accelerate the decrease in the number of primordial follicles and earlier menopause are—genetic factors, family history of early menopause, ovarian surgery, smoking, pelvic irradiation and the use of chemotherapeutic agents or both.[11]

After the age 35, her chances of conceiving naturally are less than half what they were in her prime, since there is a sharp decline in the oocyte reserve.[27] A female's fertility drops from 86% at age 20 to 52% at age 35, 36% at age 40 and to only 5% at age 45.[7,13] There are also obstetric and neonatal risks, which increase as the woman's age increases. The risk of aneuploidy increases steadily with advancing age, especially after the age of 35 years. While the ovaries and eggs age faster as a woman gets older, the uterus is not as vulnerable to the aging process (although her endometrium is thinned out and becomes less receptive as she gets older especially in her forties, uterus reactivation can be done using hormone dosage), so it is possible for a female to carry a fetus even if her oocytes are less viable.[14,22,40]

INFORMED CONSENT

A female who requests for OC is legally entitled for balanced and comprehensive information about the procedure and risks associated with it—including what is not yet known about its safety and efficacy.[13]

It is suggested that doctors should use a heightened standard for informed consent for OC for elective reasons, similar to the informed consent taken for research, and not the typical informed consent for treatment.[13] The ASRM has outlined the essential elements of informed consent for EOC (Box 4.1).[22]

JAYPEE BROTHERS

Box 4.1: Informed consent for EOC

- Pre-treatment counseling to ensure that she understands the potential benefits
- Risks and limitations of the procedure, including the risks associated with oocyte retrieval
- Clinic specific data and outcomes, such as live birth rate per oocyte thawed and embryo transferred
- Relevant costs.

The female should be explained about the various health risks to her and the unborn child associated with the procedure. She should also be explained that there are risks that are currently unforeseeable and there is no guarantee on the success/failure of the procedure.[3,11,13]

The doctor would need to convey information regarding the success rates with OC broken down by age-groups, and alternatives to it. The doctor should also inform the female of that clinic's success rates and his/her own experience and successes (or failures) with such procedures.[6,7,13] If a patient is seeking an EOC for elective reasons, a reasonable doctor may not disclose that he/she has never performed such a procedure before, although a reasonable patient may consider such information important in choosing a doctor. This is important especially in this context, based on the expectation that their frozen oocytes are likely to make them biological mother, even though that may not be the case. It is also important to ensure that the female understands the disclosures before deciding for OC.[13]

The costs of cryopreservation and subsequent IVF will have to be borne by the female, so it should be disclosed to her within the informed consent procedure.[13] The consent process should specify how long the oocytes to be stored, and whether they should be used for her own treatment only or can be donated for someone else's treatment. She should also specify how the oocytes should be disposed off in the case of death, failure to pay storage fees or other contingencies—whether they are to be entrusted to members of her family, destroyed or donated to an egg bank, or used for research or training.[6,22]

All the above information should be explained in a simple language and the words that she can understand. After duly counseling the female, an informed written consent should be taken.

IDEAL AGE AND REPORTED AGE OF EOC

EOC is primarily utilized by older reproductive age females. The mean reported age for EOC is around 38 years. As already mentioned, by this age the quality of a female's oocytes is already in decline. Oocytes frozen at this stage will result in comparably lower success rates in pregnancy and childbirth.[3,22] To achieve higher success rates with IVF, EOC should be at an age younger than 35 years.[6,30,31] While EOC for females aged over 38 years need not be disallowed, they should be informed about the low probability of

JAYPEE BROTHERS

successful thawing, fertilization, implantation and live birth.[11,12] At the very least, fertility clinics should refrain from targeting females above 35 for EOC.[22]

The actual target group for EOC is younger females. The recommended age for EOC is 30-35 years, but females in this age group tend not to consider OC, because they believe they have plenty of time and/or they underestimate their natural fertility decline after age 35 years (Table 4.2).[12,15,20,22] A Swiss study cited by the National Center for Biotechnology Information noted that EOC should ideally be performed on females around 25 years of age in order to increase their chances of a future pregnancy.[4,41,42]

Indian females from the US usually visit India for EOC after they are 35 years. In the US, menopause sets in later among the natives, while in Indian women it sets in earlier. Hence, the limitations need to be informed.[1]

Table 4.2: Success of pregnancy in relation to the candidates

	Excellent chance of success	*Good chance of success*	*Guarded chance of success*	*Unlikely chance of success*
Age	≤ 30 years	31–34 years	38–39 years	≥ 40 years
Hormone levels	FSH < 7 mIU/mL Estradiol (E2) < 70 pg/mL	FSH < 8 mIU/mL E2 < 80 pg/mL	FSH < 10 mIU/mL E2 < 100 pg/mL	FSH > 10 mIU/mL E2 > 100 pg/mL
Follicles/ovary	≥ 10	≥ 10	≥ 5 but < 10	< 5

PROCEDURE

Beginning of Treatment

Under supervision of a doctor, the female self-administers daily gonadotropins injections for 10-14 days to stimulate production of oocytes, beginning on the third day of the menstrual cycle. Instead of the single oocyte normally produced through normal menstruation, multiple oocytes are stimulated into maturing. The oocyte formation is monitored with ultrasound scans.[11]

The pre-oocyte cryopreservation testing requires the usual initial fertility work-up: circulating anti-müllerian hormone (AMH) assay, antral follicle count (AFC) and basal follicle stimulating hormone (FSH) testing.[11]

Oocyte Retrieval

Ovulation is triggered by a single dose of human chorionic gonadotropin and the mature oocytes are retrieved transvaginally in an operation theater by the technique known as trans-vaginal oocyte retrieval (TVOR) in 34-36 hours later. The 10-20 minutes (5-10 minutes by an experienced reproductive medicine surgeon) procedure is performed under intravenous sedation, paracervical block, or general, spinal or epidural anesthesia.

JAYPEE BROTHERS

Local anesthesia is not typically used because local anesthetic agents interfere with follicular cleavage and the technique requires multiple needle punctures. With the female in dorsal lithotomy position, the surgeon guided by ultrasound, pushes a long needle (16 or 17 gauge) through the posterior vaginal wall and into the ovary. Once the needle punctures the ovary, it is maneuvered to pierce one follicle after another and suction is then applied to draw the follicular fluid into a test tube with culture medium (Fig. 4.1). The test tubes are handed over to the embryologist. The oocyte retrieval is continued on the contralateral ovary. Multiple egg retrieval cycles may have to be done for the optimal number of eggs. Most females of 30-38 years of age can expect to cryopreserve 10-20 oocytes/cycle. The greater the number of oocytes extracted, the higher the chances for success.[11,13,14,35,43-46]

Oocyte Freezing

The oocytes retrieved are then immediately frozen using a slow-freeze method or a flash-freeze process called vitrification.[13,26] Slow freezing method is a time consuming procedure. It is cooled to –7°C at –1 to –2°C/min, seeded at –7°C and further cooled to –30°C to –35°C at –0.3°C/min, then free falling to –50°C; it takes about 3 hours for the whole freezing procedure.[43] Slow-freezing has the advantages of using low concentrations of cryoprotectants, but carries the risk of intracellular ice formation.[4,11,21,29] Alternatively, vitrification is a method of flash freezing to –270°F and requires high concentrations of cryoprotectants (1.0–1.6 mol ethylene glycol and DMSO) that solidify the oocytes without crystallization (i.e. they are less likely to fracture upon

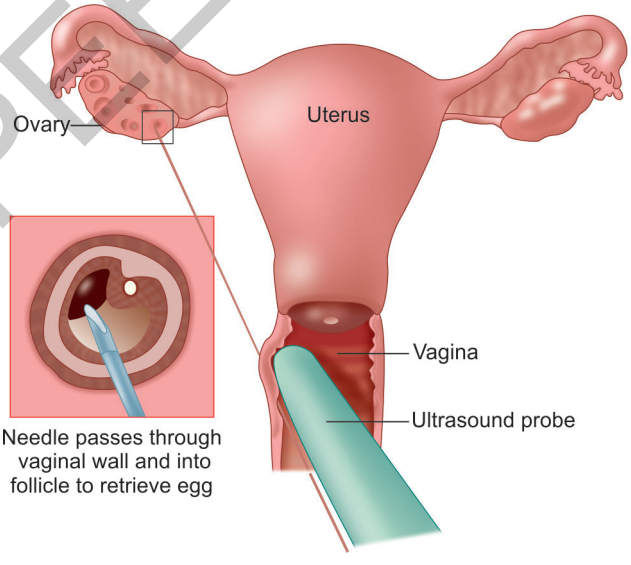


Fig. 4.1: Egg retrieval

JAYPEE BROTHERS

thawing) and meiotic disruption.[4,21,29,47] Studies have found vitrification is more effective than slow-freezing, offering higher survival rate (and hence higher pregnancy rate, both per started cycle and per transfer, and implantation), faster cellular volume recovery, faster spindle recovery and similar DNA fragmentation.[11,14,21,29,48]

Oocytes are then stored in liquid nitrogen (at –196°C) and cryoprotectants (for long-term storage); preserved until the female is ready to use them (Fig. 4.2). The complete cycle, which culminates with the oocytes being cryogenically preserved takes four to six weeks, although some centers are performing the technique in as little as two weeks.

Storage of Oocytes

Limited data exist regarding the effect of duration of storage on oocyte survival and pregnancy. No official cut-off is there as the technology of vitrification is relatively new. It has not been possible to demonstrate cell aging or damage caused by the length of storage in the case of vitrified embryos. It is recommended that the cryopreserved oocytes should be used within 10 years of freezing. In Denmark, the law stipulates a maximum storage period of five years for frozen oocytes.[3]

Thawing and Fertilization

When the female is ready to use her oocytes, it is thawed and then fertilized with a sperm.[13] The oocyte is thawed by quickly warming and removing the anti-freeze solution (Fig. 4.3). An embryologist injects a single sperm into each rehydrated oocyte, since there is zona hardening of the oocytes after thawing. This technique is called intracytoplasmic sperm injection (ICSI) (Fig. 4.4).[7,11,34] Before thawing, it should be decided as to how many oocytes are to be removed from cryostorage and the number of embryos to be



Fig. 4.2: Ooctye cryopreservation

JAYPEE BROTHERS



Fig. 4.3: Thawed oocytes



Fig. 4.4: Intracytoplasmic sperm injection

transferred after fertilization.[27] Not all the oocytes will survive the cryopreservation and/or the thawing process. It is better to inform the percentage of survival, fertilization and per-embryo transfer success rates to the female.

Implantation

These fertilized oocytes (embryos) are transferred to the uterus (Fig. 4.5). Before the transfer is attempted, the embryos are graded and determined whether the three day or five day transfer is better for the patient. The implantation procedure takes five minutes and is performed without anesthesia. The patient is monitored for several days afterwards.[4,13]

COMPLICATIONS

There is a rare chance (0.4-2%) of ovarian hyperstimulation syndrome (OHSS), and sometimes oocyte retrieval may endanger her life.

Related to the drugs: Abdominal pain, mood swings, bloating, thirst, nausea, vomiting and diarrhea may be seen in patients with mild to moderate OHSS, which will only require observation.[22] Severe form of OHSS needs hospitalization, which may present with variable degrees of severity. These include abdominal pain, uncontrollable vomiting, ascites, hypovolemia, hypotension, dyspnea, oliguria, electrolyte imbalance, hepatorenal failure, thrombosis and acute respiratory distress syndrome.[6,13,22,44]

Related to oocyte retrieval procedure: Rarely, use of an aspirating needle to retrieve eggs causes bleeding, pelvic infection or damage to the bowel, bladder or a blood vessel damage to the ovaries that are punctured during retrieval.[2,22] Risks associated with general anesthesia also might pose a concern.[13,44]

Psychological: The psychological risks are more difficult to quantify, but include stress and depression whilst undergoing the procedures. However, all of these risks are the same as for any IVF treatment in females of comparable age.[22]

JAYPEE BROTHERS



Fig. 4.5: Embryos

COST

There are three stages to finance—the retrieval of the oocytes, the cryopreservation and storage, and the thawing and IVF procedure.[22] Depending on the female's health, age, location and other factors, the cost of egg freezing can vary. An annual fee is charged for storage of the cryopreserved oocytes after the first year.

In India, it costs ₹ 100,000 to ₹ 175,000 (in the US, cost is about $10,000–15,000) to undergo an oocyte retrieval cycle. This estimate includes all testing, monitoring, medications and oocyte freezing.[1,15] Thereafter, annual storage charge is about ₹ 15,000–30,000/year (in the US $500–1000; Memorial Sloan Kettering Cancer Center quote a price of $900). The oocyte thaw, fertilization and embryo transfer procedure costs approximately ₹ 100,000 to ₹ 200,000 per cycle (in the US, it is between $5,000–10,000), and is payable at the time of thaw.[12,13,35]

SUCCESS RATE

Successful pregnancy is dependent upon many factors—factors related to female, stimulation protocols and IVF techniques, cryopreservation methods (slow-freezing or vitrification) and devices/system used for vitrification (cryotop, cryoleaf, cryotip), as well as indications for OC (medical, nonmedical or IVF-related reasons).[30,31] Out of these, the two most critical factors for successful live birth are the female's age at oocyte collection and the total number of oocytes available.[12] It took more than 20 years for OC

JAYPEE BROTHERS

for detailed information on forensic medicine & toxicology books, visit our website www.jaypeebrothers.com, for detailed inf

Recent Advances in
Forensic Medicine & Toxicology

This book has been written in clear language along with detailed discussions on current topics, which are suitable for a wide audience of readers. Similar to the previous edition, it is well illustrated with color photographs, diagrams, text boxes, tables and flow charts to emphasize salient points and clear communication of concepts. There are twenty-three chapters in this volume comprising of some common forensic topics likely to be encountered in daily routine. Specialized topics, which are not so frequently encountered, including both legal obligations and ethical responsibilities of those involved in forensic setting are also discussed. The chapters are written by authors who are authorities in their field of specialty. Each chapter is extensively researched and referenced. The book is divided into five sections:

- Section I of the book focuses on medical jurisprudence, covering legal and ethical issues and essential concepts in the interface between medicine and the law.
- Section II deals with clinical forensic medicine that will help in serving as a practical guide to daily medicolegal work.
- Section III covers forensic pathology and discusses the current issues and concepts and future directions.
- Section IV discusses forensic anthropology.
- Section V deals with forensic science.



Gautam Biswas was born in Kolkata and did his schooling from Delhi. He passed his MBBS and MD (Forensic Medicine) from University College of Medical Sciences and Guru Teg Bahadur Hospital, New Delhi. Now a leading author in Forensic Medicine and Toxicology, he began his career in 2001 at Dayanand Medical College and Hospital, Ludhiana, Punjab, India, where he is presently Professor and Head. In the year 2009, his book 'Review of Forensic Medicine and Toxicology' was published and now in its 3rd edition. Within a few years, it became the best seller in the category of forensic books, and it has been appreciated by undergraduate and postgraduate students alike. Recent Advances in Forensic Medicine and Toxicology, Volume 1 was conceived, since there was no textbook specifically for postgraduates, faculty, and medical practitioners working in the emergency set-up in India. It was the first such book in that direction and Volume 2 is subsequent addition to this.

Available at all medical bookstores
or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
FORENSIC MEDICINE
& TOXICOLOGY

ISBN 978-93-5270-124-7