Reproductive Medicine for Clinicians

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Andrea R. Genazzani
John J. Sciarra · Liselotte Mettler
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Clinical Management of Infertility

Problems and Solutions

The International Academy of Human Reproduction

Springer

Reproductive Medicine for Clinicians

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This series will focuses on and presents developments in knowledge and practice within all aspects of reproductive medicine.
It will help to cover the important gap between the new possibilities offered by the most recent investigations and technical developments and the application in clinical practice.
The series will be a useful tool for professionals and practitioners in the fields of Gynecology, Obstetrics, and Human Reproduction. Trainees interested in the most complete information on the developments of reproductive medicine will benefit as well.

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Foreword

The International Academy of Human Reproduction is delighted to announce the publication of the second volume of the series titled: *Reproductive Medicine for Clinicians*, which is published by our loyal partner: Springer.

This series focuses on and presents developments in knowledge and practice within all aspects of reproductive medicine. The contents include original articles, reviews, and views arranged in five sections:

1. Ethical issues in Human Reproduction
2. Clinical Challenges: Patients and Therapies
3. Fertility Preservation and Cryopreservation
4. Prenatal Testing
5. Recurrent Implantation Failure and Pregnancy Loss

The chapters are written by established pioneers and experts in human reproduction and it is with great appreciation and gratitude that we thank them for their enormous contribution to this volume.

The main objectives of the Academy are to extend the knowledge in all aspects of human reproduction, to encourage clinical experience and promote scientific thoughts and investigation, and to consider the ethical and social implications of the current practice of human reproduction.

The fellows of the academy are elected based on their significant contribution to the field and must be acknowledged as world leaders in the discipline. The members of the academy are selected from among applicants from the fields of clinical medicine, medical education, medical and biological sciences, and other fields related to reproductive health and medicine. They are elected based on their singular and significant contributions to the field.

Starting in 1974 in Rio de Janeiro, the Academy has held successful congresses every 3 years in Europe, Asia, Africa, the Americas, and Australia. Our congresses promote excellence in reproduction and aims to bridge the gap between the expansion of information and its implementation in clinical practice.

During the COVID-19 pandemic, we have continued to exchange knowledge and research among members and the greater human reproduction community. Webinar sessions and our planned congresses in Jerusalem and Columbia, planned for 2021, will contribute to similar publications to this one.

The series *Reproductive Medicine for Clinicians* is a useful tool for professionals and practitioners in the fields of gynecology, obstetrics, and human reproduction. Trainees interested in the most complete information on the developments of reproductive medicine will benefit as well.

On behalf of the International Academy of Human Reproduction (IAHR), I trust you will support the sustainability of this high-quality book series devoted to human reproduction.

Jerusalem, Israel Joseph G. Schenker

Preface

This volume of *Reproductive Medicine for Clinicians* focuses on and presents developments in knowledge and practice within aspects of reproductive medicine. The contents include original articles, reviews, and views that will cover the clinical science and medical aspects of reproductive physiology, pathology, and endocrinology. Clinical aspects of infertility treatment, genetic diagnosis, fertility preservation, reproductive surgery, ethics, and social issues are discussed.

Religious groups are active in influencing the public regarding bioethical positions, and this is particularly evident with issues concerning procreation, abortion, and infertility therapy. Therefore, it is important to those who practice reproductive techniques to learn about different religious perspectives related to reproductive-health problems.

The attitude toward reproductive practice varies among the main monotheistic religions.

An important concern in clinical practice today is the dilemma faced in the use of imaging especially in the field of infertility. As assisted reproductive technologies become more common, more complex, and more expensive, the concerns to the appropriate use of imaging become more timely and important every day.

A social trend toward delaying childbearing has been observed in women of reproductive age. As a consequence, these women may be affected by age-related infertility when they decide to conceive, and fertility preservation techniques can be obtained through the so-called social egg freezing. There is a debate about whether it is morally permissible at all, the extent to which it should be permitted legally or even supported, and whether it is ethically desirable.

Cross-border reproductive care (oocyte, sperm, and embryo donation as well as surrogacy) with patients traveling even to other continents to get treatment involves medical, social, ethical, and legal aspects. The legal restrictions vary widely in different regions and countries due to cultural differences, religious beliefs as well as variation in access to advanced reproductive technologies.

Successful live births following uterine transplantation were achieved. It appears to be a viable option for women with uterine cause of infertility. The process is associated with significant risk, with the potential for complications in both donors and recipients, and a considerable risk of graft failure. Uterine transplantation remains an experimental procedure that requires the study and resolution of ethical, technical, financial, and social issues.

Adolescent gynecology is dealing with gynecological issues in girls from neonatal period till the completion of adolescence. Characterized by dynamic changes in anatomy and physiology of the reproductive system. Understanding the hormonal and metabolic homeostasis peculiar to this period enables correct approach to many disorders which may be an important hallmark for later reproductive health.

Ovulation induction by pulsatile administration of GnRH is a relatively cheap method with a high success rate and a very low risk for multiples and hyperstimulation. It represents the only physiological substitution of the missing hypothalamic hormone and re-establishes successfully follicular maturation and ovulation. A chapter consecrated to the circadian rhythm analyses all the aspects of the biological clock in relation to human reproduction.

Polycystic ovary syndrome (PCOS) sounds like it is exclusively a disease of the ovaries, but it is not. While PCOS does *affect* the ovaries and ovulation, it is actually a full-body endocrine and metabolic disorder. Recent studies demonstrated in PCOS patients that insulin resistance and compensatory hyperinsulinemia might have a certain grade of epigenetic origins that might be implemented by familial predisposition to specific dismetabolic diseases such as diabetes.

The direct hysteroscopic vision of the uterine cavity gives today optimal diagnostic and therapeutic possibilities of treatment.

Management of patients with endometriosis should always be individualized based on patient's age, main complaints, clinical presentation, and desire for future pregnancy. Treatment of endometriosis includes different medical and surgical approaches. Since in most cases endometriosis begins at an early reproductive age, preservation of fertility should be the top priority of treatment.

Whereas the therapeutic possibilities in female infertility have advanced in big steps, male infertility stayed behind. Only in the 1990s, significant developments in diagnostic techniques and assisted reproductive technologies (ART), the introduction of intracytoplasmic (ICSI) has made it possible for couples with severe male factor infertility to have their own genetic children.

A considerable number of young women are diagnosed with breast cancer during their reproductive life. Within this group, most cancer cases require cytotoxic chemotherapy and/or hormone therapy, which are responsible for a decrease in the patients' reproductive function, along with their age.

At present, the most widespread techniques to preserve fertility in women diagnosed with breast cancer are oocyte and embryo cryopreservation, immature oocyte retrieval and *in vitro* maturation, and ovarian tissue cryopreservation depending on the presence of a partner or according to legislative issues.

Ovarian tissue cryopreservation (OTCP) aims to provide a chance for future fertility for young women and pre-pubertal girls who are at major risk for significant ovarian injury and sterility, most commonly as a result of radiation/chemotherapy-induced loss of ovarian follicular reservoir.

A social trend toward delaying childbearing has been observed in women of reproductive age. As a consequence, these women may be affected by age-related infertility when they decide to conceive, and fertility preservation techniques can be obtained through the so-called social egg freezing. There is a debate about whether

it is morally permissible at all, the extent to which it should be permitted legally or even supported, and whether it is ethically desirable.

Modern methods such as noninvasive testing of cell-free DNA in the maternal plasma (NIPT), targeted cell-free DNA testing, or other noninvasive genetic techniques such as TRIC (trophoblast retrieval and isolation from the cervix) are discussed in an extensive review and compared with the benefits and risks of classical invasive methods.

One of the interesting developments in perinatal medicine is the Kurjak Antenatal Neurodevelopmental Test (KANET). KANET gives the clinician a new imaging tool to evaluate fetal behavior and to identify those fetuses at high risk for neurodevelopmental abnormalities.

Recurrent implantation failure (RIF) is deduced when good quality embryos fail to implant after a number of in vitro fertilization (IVF) treatment cycles. Several etiologies related to either maternal, embryonal, or paternal factors have been attributed to RIF. A couple presenting with RIF should have a systematic and through investigation. Treatment should be personalized accordingly, with novel methods and tools for better selection of embryos.

Recurrent pregnancy loss (RPL) affects approximately 2–5% of couples, depending on the definition of recurrent pregnancy loss. Etiology can be varied and in many cases the cause remains unexplained. The therapeutic approach should be a personalized depending on an accurate diagnosis, specific therapy, rather than treating RPL as homogeneous condition.

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Ethical Issues in Human Reproduction

Human Reproduction: Religious Perspectives

Joseph G. Schenker

Introduction

It is important to those who practice reproductive techniques to learn about different religious perspectives related to reproductive-health problems. Religious groups are active in influencing the public with bioethical positions, and this is particularly evident with issues concerning procreation, abortion, and infertility therapy.

The developments in reproductive medicine raise new ethical questions for different religions that do not always have clear answers. Religious leaders in some countries still exert a powerful influence on the development and practice of reproductive technology. In some countries, religious groups' main influence will stem from their direct influence on medical protocols.

Therefore, it is important for practitioners in the field of reproductive medicine to understand attitudes toward reproduction that derive from different religions.

According to the Web site Adherents.com, the numbers of adherents in the "Big Five" world religions are as follows: Judaism (14 million, 0.22%), Christianity (2.1 billion, 34%), Islam (1.5 billion, 24%), Hinduism (900 million, 14%), and Buddhism (376 million, 6%) [1].

The Jewish Law: Halakha

The world is derived from the Hebrew root that means "to go or to walk" [2]—is the collective body of Jewish religious law, including the biblical law (the 613 "mitzvoth," or commandments) and the later Talmudic and rabbinic law as customs and traditions.

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In principle, the halakhic literature is composed of two divisions:

1. The Written Law—the Torah—the first five books of the Scripture, which are the origin of authority.
2. The dominant parts of the Oral Law are the Mishnah, the Talmud, the post-Talmudic codes, and the responsa.

Torah The foundation of the Written Law and the origin of authority is the Torah, the first five books of the Scripture.

As stated above, the Written Law is defined as the origin of authority. This definition is derived from the ancient tradition and the belief concerning the original revelation on Mount Sinai, when God ascribed the Torah to Moses and to the Jewish people, the recipients.

The Torah is not an ordinary text of law. It is an expression of God's revelation, teaching, and guidance for man. The attitude to the Torah is therefore as to a unique and holy divine text, which includes moral values as well as practical laws. The Oral Law interprets, expands, and elucidates the written Torah and regulates new rules and customs.

Its authority is derived from the written Torah.

The Mishnah This early textbook was compiled systematically by numerous scholars over a few centuries.

Its final form was established early in the third century. The Mishnah includes early traditional and original interpretations of the written Torah, ancient regulations that are not written in the Torah, and postbiblical regulations. The Mishnah consists of six major section orders that cover all aspects of human life: Zeraim (laws regarding agriculture), Moed (laws regarding holidays), Nashim (laws regarding women and family life), Nezikin (civil law), Kodashim (laws regarding the Temple), and Toharot (laws regarding ritual purity). Two of the orders, Nashim and Toharot, are relevant to Judaic family practices.

The Talmud For approximately three centuries after the final compilation of the Mishnah, the great interpreters studied the six orders to the Mishnah and wrote a monumental composition, the Talmud.

The great interpreters (Amoraim) included within the Talmud commentaries and interpretative studies of the Mishnah and the Midrashim, or investigations, and established regulations and new customs.

The Amoraim in Babylon composed the Babylonian Talmud, while the Amoraim in the Holy Land composed the Jerusalem Talmud.

During the period of Jewish sovereignty in Judea, laws were made by the Sanhedrin, a body of 71 leaders gathered for this purpose, and by local courts with 23 judges.

After the fall of the Second Temple, halakha became primarily the creation of rabbinic Judaism.

Post-Talmudic codes An enormous amount of Talmudic knowledge was essential for accurate ruling. These post-Talmudic codes were compiled with the intention of assisting access to the laws, regulations, and customs of the Talmudic halakha.

Up to the sixteenth century, different scholars summarized and reviewed the halakhic conclusions of the Talmud in the post-Talmudic codes.

Among the scholars were Rashi (1040–1105), Rabbi Moshe Ben Nachman (1195–1270), and Rabbi Menachem Ben Shlomo Hameiri (1249–1316).

The most prominent post-Talmudic codes are the Sheilot, Halakhot, Maimonides, the Piskey Harosh, and the Shulchan Aruch.

Responsa The various attitudes of rabbinic scholars about the way halakha should be applied in a changing world are analyzed and discussed with regard to the legal codes.

Throughout the ages, written opinion has been given by qualified authorities to questions about aspects of Jewish law.

Responsa is a term usually confined to written replies given to questions on all aspects of Jewish law by qualified authorities from the time of the later Geonim to the present day.

About 1000 volumes, containing more than half a million separate responsa, have appeared in print.

Contemporary rabbinic scholars deal with new problems that arise with the investigation and treatment of infertility.

The responsa of later rabbinic authorities are often short monographs in which every text remotely relevant to the point at issue is quoted or discussed.

Different groups have developed among Jews from ancient times and especially in the modern era.

The Orthodox, Reform, and Conservative movements are the three major ones today.

Orthodoxy is the only movement formally and legally recognized by Israel; non-Orthodox movements have remained largely a feature of Judaism in the Diaspora.

Jews Law and Infertility

Jewish attitudes toward infertility can be discerned from the fact that the first command from God to Adam was “Be fruitful and multiply” after he was created (Gen. 1:28).

This commandment has been interpreted as an obligation on the part of the man to reproduce.

Marriage is a legal contract between a man and a woman. The couple commit themselves to their mutual duties and create between them a binding religious relationship that also affects others. From a practical perspective, marriage is a mitzvah, or religious duty. It is also the proper framework in which to fulfill God’s command to be fruitful and multiply. Sex is part of human life. The Jewish approach to sex has

always been free, healthy, and lacking frustration, and Jewish law recognizes sexual desire. Each partner has conjugal duties toward the other.

According to Jewish law, the infertile couple should be diagnosed and treated as a single unit [3]. The medical treatment is different for men and women.

When evaluating an infertile couple, one should first evaluate the female partner. If pathology is not found, one may proceed to investigate the male. The male factors that should be evaluated are inadequate or abnormal sperm production, ejaculation, or deposition of spermatozoa.

The chief halakhic impediment to the standard method of extracting semen (masturbation) is that doing so anywhere but inside one's wife is prohibited, because it is considered "wasting seed." Examination of the semen for infertility workup is not included in the prohibition against "spilling one's seed." According to Jewish law, the preferred method of seminal fluid analysis should be the postcoital test.

There are three basic principles, which, with certain restrictions, favor the permissibility of fertility treatment:

1. The commandment to "Be fruitful and multiply"
2. The mitzvah gemilut hasadim (loving-kindness)
3. Family integrity

In order to implement in vitro fertilization (IVF) and embryonic transfer in Israel, support of halakhic authorities is required.

In Israel, special legal problems arise due to the exclusive jurisdiction in matters of personal status that is vested in the rabbinical courts [4].

Although Israeli law is secular, legislated by the Knesset, Israel's parliament, matters of personal status are governed by halakhic law and enforced by special rabbinical courts.

Matters concerning marriage, divorce, paternity, legitimacy, and bastardy and cases of Jewish identity are therefore adjudicated according to Judaic law by these rabbinical courts.

The development of ARTs has made it necessary to consider the question of the beginning of life and the moral status of the embryo from different perspectives [5].

Procreation is acknowledged in the Bible to be the gift of God. The halakhic interpretation of when human life begins is extracted predominantly from the halakhic sources.

The conclusion as to when human life begins can be obtained from the Torah's stated position on the issue of abortion: The only indication considered for abortion is a hazard to the mother's life. Otherwise, the destruction of an unborn child is a grave offence, although not murder. It can be viewed that the fetus is granted some recognition of human life, but it does not equal that of the mother's and can be sacrificed if her life is in danger [5].

Artificial insemination by donor is unacceptable to most rabbinical authorities. Rabbis have been discussing the principles involving AID for many centuries. Their discussions are based on ancient sources in the Talmud and codes of Jewish law dating back to the fifth century. AID, according to the Jewish law, is prohibited for

a variety of reasons (e.g., the possibility of incest, a lack of genealogical identity [6], and the problem of inheritance). The child conceived through AID is considered by many rabbinical scholars as having the status of mamzer, or bastard.

Oocyte donation In order to start the clinical trial of an oocyte-donation program in the Hadassah Medical Center at the Hebrew University of Jerusalem, the authorization of a chief rabbi was required. The trial resulted in the world's first birth using oocyte donation [7].

In egg donation or embryo donation, the problem that arises is that of who should be considered the mother—the donor of the oocyte or the one in whose uterus the embryo develops, the one who gives birth. If one of the women is Jewish and the other is not, problems will arise, since according to Jewish law, the religious status of the child is determined by his mother—the one who gives birth. This interesting subject has an apparent precedent in the Rabbinical literature. According to ancient tradition found in the Talmud and the Midrashim, regarding the birth of Joseph by Rachel. The general opinion is that the gestational mother is regarded as a mother. The religious law decrees that only the offspring of a Jewish mother is regarded as a Jew. According to halakha, the donor should be a single woman.

Surrogacy is a source of great controversy in society and in the medical profession.

1. Partial natural surrogacy—has been known for thousands of years: The husband of the infertile woman has intercourse with another woman (the surrogate mother), who donates her genetic material and the use of her womb. The child is then given to the man who donated the sperm and to his legal wife, without adoption procedures.

   The first mother to become a partial natural surrogate was Hagar: "Now Sarai, Abram's wife, bore him no children. Sarai said unto Abram, go into my maid: it may be that I may obtain children by her. And Abram harkened to the voice of Sarai. And he went into Hagar, and she conceived" (Gen. 16:1–6).
2. Complete surrogacy—the sperm and the oocyte (genetic material) are of commissioner couple. The surrogate contributes the uterus and gives birth.

   There are three basic halakhic principles that, with certain restrictions, favor the acceptability of the practice of surrogacy: First, there is the commandment "Be fruitful and multiply."

   Second, there is the gemilut hasadim, the mitzvah of benevolence, which originates in the verse "Love thy neighbor as thyself" (Lev. 19:8). In cases of personal distress (material, mental, or both), a Jew is duty bound to practice the mitzvah and help one's neighbor. A childless couple falls within this category, in which a clear obligation exists to assist in every permissible way as long as no one else is thereby harmed.

   Third, domestic harmony and the integrity of the family are extremely important in Jewish law.

   Israeli legislation on surrogacy is partly based on halakha [8, 9].

Fetal reduction The advances of infertility treatment in recent years, throughout use of ovulation-inducing drugs and of multiple embryo transfer in IVF, contributed to multiple birth.

According to Jewish law, the fetus is regarded as a part of the mother's body and not as a separate being until it begins to egress from the womb during parturition and attains the status of nephesh. Prior to this time, the fetus is not considered a person. In fact, until 40 days after conception, the fertilized egg is considered to be mere fluid [10].

The question of multiple fetal pregnancy reduction (MFPR) was debated in the responsa literature by rabbinical authorities. If the mother's life is in danger, each fetus is a "rodef" and can be killed to save the mother. But if the danger is to the fetuses and not to the mother, each fetus is, with equal status for each role, both an aggressor and a victim. In this case, it might not be permissible to put aside one soul for the sake of another. Searching for a legal analogy for this situation, some rabbis focused on the case of a group of people who are in mortal danger and who can be saved by sacrificing one innocent member of the group. Most halakhic authorities agree that in case of multiple pregnancy, fetal reduction may be performed.

The multiple pregnancy had a high risk of ending in miscarriage of all the fetuses, ruling that each fetus had the status of a "rodef" [11].

Gender preselection Recent scientific advances have made highly reliable preconceptual sex selection possible by using preimplantation genetic diagnosis (PGD) or sperm separation by flow cytometry combined with AIH or IVF [12].

The requirement for a Jewish man to procreate by having a minimum of two children, a boy and a girl, is obligatory according to Jewish law. According to both schools, Shammai and Hillel, in order to fulfill the obligation of procreation, at least one son is required. Therefore, the application of sex preselection for nonmedical indications may be of practical importance.

Cryopreservation To date, successful results based on pregnancy rates and preservation of fertility for medical conditions have been obtained with cryopreserved spermatozoa, embryos, oocytes, and ovarian tissue [13].

Freezing of sperm and pre-embryos is permitted in Judaism only when all measures are taken to ensure that the father's identity will not be lost.

There are no restrictions of cryopreservation of oocytes and ovarian tissue.

Posthumous reproduction was debated in the halakhic literature. Jewish law permits posthumous reproduction by using cryopreserved sperm and by sperm retrieval after death, to the extent that they are used within the context of a traditional marriage and the husband's consents. Without the man's consent, the procedure is forbidden. But if it is clearly known that he would have wanted the procedure done, there is no prohibition against performing postmortem sperm retrieval.

There is a clear halakhic difference between unknown and uncertain paternity. With postmortem insemination using frozen sperm or with postmortem sperm retrieval, the biological father is known, and the controversy over paternity is strictly

legal. Therefore, if a widow who was not pregnant at the time of her husband's death was later inseminated with sperm he donated while still alive and becomes pregnant and gives birth, her deceased husband should be considered as having fulfilled the mitzvah of "pru urvu."

Pre-embryo research According to the Talmud, during the first 40 days from fertilization until the completion of organogenesis, the embryo is defined, for the purpose of certain laws, as plain water. An embryo under the age of 40 days is not considered to be a person in any legal sense.

According to this, pre-embryo research may be permissible if it is carried out in order to enable the sperm owner to have his own child. It is prohibited to use a preimplantation pre-embryo for research unless the research is essential for saving the pre-embryo's life potential.

The destruction or use of a preimplantation pre-embryo for research is forbidden as long as it has the potential to implant.

The in vitro creation of preimplantation pre-embryos for research is allowed if there are real chances that the person providing the spermatozoa may benefit and have his own child as a result of this research. When this does not apply, the creation of a pre-embryo for research purposes is strictly forbidden.

There is obviously a clear distinction between the preimplantation pre-embryo and the post-implantation embryo.

However, the arbitrary 14-day limit is not recognized by Jewish law.

Orthodox Jewish law does not forbid pre-embryo research, although some rabbinic authorities would permit it in spare embryos only, those left over in IVF treatment, and not in embryos created for the sole purpose of research.

The view held by law in Israel is that pre-embryo research is forbidden [10, 14].

Christianity

The Old and New Testaments comprise the scriptures that are sacred to Christians. The Old Testament emphasizes the agreement between God and his people and records Jewish history to illustrate how faithfully this agreement was observed.

The New Testament contains promises made by God to humanity, as depicted in the teaching and experiences of Christ and his followers.

Jesus Christ is viewed by Christians as the supreme revelation of God and as Lord of his followers.

Three principal divisions comprise Christianity: the Roman Catholic Church, Protestant Churches, and Orthodox Catholic Churches.

Christianity is particularly characterized by its universality and missionary activity. The most striking development in the evolution of Christianity from its Jewish origin was in its transition from a national religion (of the Jewish nation) to a universal religion. The church assumes a role inspired by a love for humankind in matters concerning reproduction and helps to define the rights and duties of members.

Roman Catholic Church

Roman Catholics base their beliefs on the Bible and the traditions of the church. Traditions are derived from declarations of church councils and popes in the form of dogmas.

The Roman Catholic Church is a Christian church characterized by an episcopal hierarchy, with the pope as its head and belief in seven sacraments and the authority of tradition.

The Catholic dogma contains three leading principles related to the status of the family, the child, and reproduction.

The first principle commands the protection of the human being from the moment of its conception.

The second principle is that procreation is inseparable from the physical union of the parents, and therefore, from the moral point of view, a child must be the fruit of marriage. Fidelity involves acknowledgment by spouses that they become parents only through one another and that their child is a living symbol of their love and a permanent sign of their conjugal union.

The third principle is related to the personal norm of human integrity and dignity and should be taken into consideration in all medical decisions and especially in the field of infertility.

The Vatican has had a clear position against assisted reproduction ever since 1956, when Pope Pius XII defined artificial fecundation as immoral and illegal because it affects human lives by separating procreation and sexual normal function.

The Vatican's instruction on respect for human life made an important contribution to discussions on the practice of new reproductive technologies.

It was issued by the Congregation for the Doctrine of the Faith in February 1987 [15], signed by Cardinal Joseph Ratzinger, and approved by Pope John Paul II.

Therefore, medical techniques used in assisted reproduction, such as embryo cryopreservation, embryo transfer (ET), application of embryonic stem cells, gamete manipulation, IVF, preimplantation genetic diagnosis, embryo editing, sex preselection, and surrogate motherhood, are not accepted by the Catholic Church.

The Catholic Church has been opposed to contraception since at least the second century. All sex acts must be both unitive and procreative.

In Pope Paul VI's *Humanae vitae* in 1968, artificial contraception is considered intrinsically evil, but methods of natural family planning may be used, as they do not interrupt the natural way of conception.

The official position of the Roman Catholic Church is that abortion under any circumstances, including abortion to save the life of the mother, should be prohibited.

Eastern Orthodox Church

The Eastern Orthodox Church, formally established in 1054 when it split from the Roman Catholic Church, consists mostly of several independent and self-governing churches. The most ancient self-governing churches are in Istanbul and Antakya in

Turkey, as well as Alexandria, Damascus, and Jerusalem. The largest national churches are in Armenia, Bulgaria, Cyprus, Georgia, Greece, Romania, Russia, and Serbia.

Orthodox Christianity claims to have fully preserved the traditions and doctrines of the original Christian church established by the apostles.

The Eastern Orthodox Church's stand on assisted reproductive practice is not as strict as the Roman Catholic Church's, allowing the medical or surgical treatment of infertility, but it is against IVF and other ARTs, surrogate motherhood, donor sperm insemination (which it considers adultery), and embryo donation.

The Greek Orthodox position on the ethics of assisted reproduction is similar to the Vatican's. The Church cannot recommend it as the solution to infertility; instead, it proposes a non-secularized perception on life that guarantees simplicity, peace, abstinence, and mutual trust between spouses.

It does not oppose resorting to medical help, but, at the same time, it suggests that men and women render their life into the hands of God [16].

The Russian Orthodox Church has condemned the practice of IVF methods. The Church's position is based on the belief that "an embryo is a future human being and not just an accumulation of cells or a part of a mother's body," and it "defends the dignity of human life from the moment of its conception until the natural demise of a human" [17].

The Coptic Church accepts IVF only under the circumstances where the oocyte and sperm are taken from the husband and wife and fertilization occurred in vitro, with no doubt about gamete mixing. ET must be performed on the mother who is the source of the oocytes. All the steps of IVF should occur with the approval of the husband and wife, and the treating physician should be alert to the fact that no mixing of gametes should occur [18].

The Protestant Church

The Protestant Church is one of the three major branches of Christianity, originating during the sixteenth-century Reformation.

The term Protestant applies to the beliefs of Christians who do not adhere to Roman Catholicism or Eastern Orthodoxy.

Protestantism resulted chiefly from the Reformation, a religious and political movement that began in Europe in 1517.

At its foundation was protest against the bureaucracies and policies of the Roman Catholic Church.

Protestantism is widespread mainly in Germany, the Netherlands, Switzerland, the United Kingdom and its former dominions (Australia, Canada, New Zealand), and the United States, as well as in the Scandinavian countries. It includes a number of autonomous churches and sects that differ somewhat in worship and organization but are linked by common origin and dogma.

The three fundamental principles of Protestantism are:

1. The supremacy of the Bible
2. Justification by faith alone
3. The universal priesthood of believers

Some Protestant denominations can be considered pro-life, while others may be considered pro-choice.

Protestant churches have not only refrained from established doctrine about IVF but have shied away from public discussions of the topic.

Moderate and liberal Protestant denominations mainly in the United States tend to affirm the right of individuals to discern for themselves how to make use of reproductive technologies. Conservative Protestantism positions on reproductive matters tend to include an active opposition to abortion, but assisted reproduction has not been much considered in formal church statements. In general, they "tend to approve of methods intended to correct physical problems that cause couples to be infertile, but they disapprove of methods that would violate the sanctity of the marriage bond by using donated sperm and eggs, as well as any method that would tamper with or discard a fertilized embryo."

Anglican Church

The Anglican Church is a body of churches in all parts of the world that are in communion with the Church of England. The establishment of an independent Church of England came during the reign of Henry VIII (1509–1547), when Pope Clement VII refused to approve the annulment of Henry's marriage to Catherine of Aragon.

There are 44 churches in the Anglican Communion, including the Anglican Church of Canada, the Scottish Episcopal Church, the Church in Wales, the Church of Ireland, and the Nippon Sei Ko Kwai Church in Japan.

There is no single Anglican Church with universal juridical authority, as each national or regional church has full autonomy, and Anglicans do not refer to one central authority to make decisions regarding moral issues. The titular head of the Anglican Communion is the Archbishop of Canterbury, and its leadership consists of bishops, who, since 1868, have met once a decade within the framework of the Lambeth Conference.

The Anglican Church allows assisted reproductive techniques, IVF, and ET and permits doctors to use sperm obtained after masturbation; however, it forbids gametal donation. The church, which believes moral status can be given only to an individual with a well-established personality, does not offer it to the embryo.

Some Anglican Churches have varying opinions about gametal donation: There are those who think that the genetic origins of a child are fundamentally important and those who think that what is more important is a loved child in a stable relationship. Some think that if donation takes place within a stable marital relationship, it is good, while others hold that it threatens marriage, as understood by Christians, and that it should be strongly discouraged.

There is unanimous agreement that surrogacy arrangements are unacceptable, and it is argued that while there is nothing wrong with adoption, it also states that the idea of surrogacy contracts entails legal complications and that it is an indignity for a woman to be paid for womb-letting services.

The Church of England generally opposes abortion. In 1980 it stated that "In the light of our conviction that the fetus has the right to live and develop as a member of the human family, we see abortion, the termination of that life by the act of man, as a great moral evil." But the Church also recognizes that in some instances abortion is "morally preferable to any available alternative."

The Anglicans were the first church to issue a statement in favor of contraception, which they did at the Lambeth Conference in 1930.

Islam

Instructions that regulate everyday activity of life an observant Muslim should adhere to are called sharia. There are two sources of sharia: primary and secondary.

The primary sources of sharia, in chronological order, are the Koran, the very words of God; the sunna and the hadith; the authentic traditions and sayings of Mohammed as collected by specialists in hadith; igmaa, the unanimous opinion of leading Islamic scholars; and qiyas (analogy), intelligent reasoning used to rule on events not mentioned by the Koran and the sunna by matching them against similar or equivalent events previously ruled on.

The secondary sources of sharia are istihsan, the choice of one of several lawful options; views of Mohammed's companions; current local customs, if lawful; public welfare; and rulings of previous divine religions if they do not contradict the primary sources of sharia.

The sharia is not rigid. It is flexible enough to adapt to emerging situations in different times and places. It can accommodate different honest opinions as long as they do not conflict with the spirit of its primary sources and are directed to the benefit of humanity [19].

In the Muslim world, religion still has a powerful meaning and greatly influences behavior, practices, and policymaking in the Muslim countries and among the Muslim communities in non-Muslim countries.

Reproduction in Islam

The primary sources of sharia have affirmed the importance of marriage, family formation, and procreation. A central feature of Muslim identity and family structure is authenticity of lineage. The Koran explicitly prohibits legal adoption. In Islam, treatment of infertility in married couples is encouraged, as it involves procreation and preservation of humankind childbirth. Child-rearing are regarded as family commitments of both partners, not just biological and social functions. ART

was widely accepted only after prestigious scientific and religious bodies discussed broadly the issue [19, 20].

If assisted reproduction is indicated in a married couple as a necessary line of treatment, it is permitted within the validity of marriage contract with no mixing of sperm and oocyte [21].

If the marriage contract has come to an end because of divorce or death of the husband, ART cannot be performed on the female partner, even when using sperm cells from former husband. These guidelines are followed by most Sunni Muslims.

The Shia guidelines, via fatwa from Ayatollah Ali Hosseini Khamenei in 1999, have opened the way to a third-party donation.

This fatwa allows third-party participation, including egg donation, sperm donation, embryo donation, and surrogacy.

Recently, there has been some concern about sperm donation among Shia, and most scholars today forbid sperm donation.

Surrogacy is practiced among the Shia, whereas most Sunni do not accept it.

The fatwa of the Islamic High Council of Mecca in 1984 allowed surrogacy by replacing the embryos inside the uterus of the second wife of the same husband who provided the spermatozoa.

In 1985, however, the council withdrew its approval of surrogacy [22].

Multifetal pregnancy reduction may be performed.

It is performed with the intention not to induce abortion but to preserve the life of remaining fetuses and minimize complications in the mother.

Pregnancy in postmenopause is now possible, with the development of cryopreservation, using one's own cryopreserved embryos.

Oocytes and autografted cryopreserved ovaries may be permissible in exceptional cases.

Sex preselection using preimplantation genetic technology (PGD) for nonmedical reasons such as sex selection or balancing sex ratio in the family may be applied in special cases [23].

Cryopreservation of oocytes, embryos, or ovarian tissue can be preserved by cryopreservation.

The frozen embryos are the property of the couple alone and may be transferred to the same wife in a successive cycle, but only during the validity of the marriage contract [21].

Marriage ends at death or divorce, and procuring pregnancy in an unmarried woman after divorce or after the death of her husband is forbidden by religious principles of the children's rights to be reared by two parents and by the child's right to inheritance. Neither gametes nor gonadal tissues can be donated to another person during the lifetime or after the death of their owner.

Embryo Research

According to Islamic teaching, organ differentiation occurs 42 days after fertilization.

Enrollment of the fetus occurs after 120 days following fertilization, although some authorities consider it to occur as early as 42 days postfertilization.

Embryo research, for advancement of scientific knowledge and benefit of humanity, is therefore allowed before 14 days after fertilization on surplus embryos donated for research with the free informed consent of the couple [24].

However these embryos should not be replaced in the uterus of the owner of the eggs or in the uterus of any other woman.

Hinduism

Hinduism is a diverse body of religion, philosophy, and cultural practice predominant in India, characterized by a belief in reincarnation and a supreme being of many forms and natures.

The religion is based in the teachings of the sacred Vedas. Hindu believers are governed by the three doctrines of dharma, or universal law; karma, or the cumulative effects of personal actions; and samsara, or the cycle of rebirth, liberation from which is the first goal of life.

Hinduism has no single book, such as the Bible, that serves as the source of its doctrine, but it has many writings, all of which have contributed to its fundamental beliefs.

A central belief of Hinduism is that an individual's soul or self is eternal. In Hinduism, the soul is believed to be passed from one living being to another in a process called reincarnation.

While views on the moral status of the human embryo differ, in traditional Hindu belief, conception is the beginning of a soul's rebirth from a previous life.

Some Hindu traditions place the beginning of personhood between 3 and 5 months of gestation, while a few believe that the soul's rebirth can occur as late as the seventh month.

Regarding fertility, the emphasis on reproduction is not just on having children but on having male offspring. There is a huge stigma attached to being infertile in Indian society, especially for the woman. In Indian society, men need children to have heirs and to prove their masculinity.

Society puts pressure on woman to become pregnant and give birth even though the male may be the one who is infertile. In Indian society, there is a strong desire for a son to continue the family line and perform religious rituals for the salvation of departed souls.

ARTs are acceptable in Hinduism because there is no single authority to accept or reject it on behalf of the faith.

The most important condition is that the egg and sperm are from a legally married couple.

In practice, artificial inseminations of donor and oocyte and embryo donation are performed with an anonymous donor.

It is preferable that the sperm donor be a close relative of the husband.

Modern Indians resort to ART, including oocyte and embryo donation, surrogacy, and sex preselection, enthusiastically.

India became a leading country for reproductive tourism, especially for surrogacy. The reasons for the surrogacy boom in India are the relative low cost and easy availability of women for surrogacy, especially those from socioeconomically disadvantaged backgrounds [25].

Buddhism

Buddhism, one of the major religions of the world, was founded in India about 500 BC by the Buddha.

At various times, Buddhism has been a dominant religious, cultural, and social force in most of Asia, especially in China, India, Japan, Korea, Tibet, and Vietnam. In each area, Buddhism has combined with elements of other religions such as Hinduism and Shinto.

All Buddhists have faith in the Buddha; his teaching, called the dharma; and the religious community he founded, called the sangha.

The basis of what Buddha preached in the dharma is that existence is a continuing cycle of death and rebirth.

Each person's position and well-being in life are determined by his or her behavior in previous lives.

Buddhists of all types in various countries are individualistic, and even their scriptures are not rigid. There is no central Buddhist authority to pronounce religious positions. They have no sacraments to administer or rites to perform for the people; every Buddhist is his or her own priest.

Marriage within Buddhism does not have the high priority that it has in monotheistic religions.

According to Buddhism, the three factors necessary for the rebirth of a human being are the female ovum, the male sperm, and the karma.

This karma energy is sent forth by the dying individual at the moment of his or her death.

Any technology that is used to achieve conception is morally acceptable, and treatment can be given to unmarried as well as to married women.

IVF has been practiced in Japan since 1982 and is also practiced in other countries with Buddhist populations.

In Buddhism, donation of sperm is not prohibited.

In Buddhism, reincarnation is described as the rebirth of the self. These beliefs that the soul or the self is reborn may lead to a greater acceptance of cloning technology.

To many Buddhists, cloning appears to be closely related to the transmigration of a person's soul from one body to another or to a rebirth of the self.

References

1. Adherents.com. The Adherents.com collection of religious adherent statistics. 9 Aug 2007. www.adherents.com/Religions_By Adherents.html.
2. Schenker JG, Halperin M. Jewish family practice and their evolution. Global Bioeth. 1995;1:35–47.
3. Schenker JG. Infertility evaluation and treatment according to Jewish law. Eur J Obstet Gynecol Reprod Biol. 1997;71:113–23.
4. Schenker JG, Frenkel DA. Medico-legal aspects of in vitro fertilization and embryo transfer practice. Obstet Gynecol Surv. 1987;42:405–10.
5. Schenker JG. The beginning of human life. J Assist Reprod Genet. 2008;25:271–6.
6. Schenker JG. Religious views regarding gamete donation. In: Seibel MM, Crockin SL, editors. Family building through egg and sperm donation. Boston: Jones and Bartlett; 1996. p. 238–50.
7. Navot D, Laufer N, Kopolovic J, et al. Artificially induced endometrial cycles and establishment of pregnancies in the absence of ovaries. N Engl J Med. 1986;314:806–11.
8. Knesset. Surrogacy Law, State of Israel. 1996.
9. Schenker JG. Women's reproductive health: monotheistic religions perspectives. Int J Gynaecol Obstet. 2000;70:77–86.
10. Eisenberg V, Schenker JG. The ethical, legal, and religious aspects of pre-embryo research. Eur J Obstet Gynecol Reprod Biol. 1997;75:11–24.
11. Schenker JG. Assisted reproductive practice: religious perspectives. Reprod Biomed Online. 2005;10:310–9.
12. Schenker JG. Gender selection. J Assist Reprod Genet. 2002;19:400–10.
13. Shufaro Y, Schenker JG. Cryopreservation of human genetic material. Ann N Y Acad Sci. 2010;1205:220–4.
14. Schenker JG. Jewish Law (Halakha) and Reproduction). In: Schenker JG, editor. Ethical dilemmas in assisted reproduction. Pub. DGRUYTER; 2011.
15. Congregation for the Doctrine of the Faith. Donum vitae: instruction on respect for human life in its origin and on the dignity of procreation: replies to certain questions of the day. Washington, DC: United States Catholic Conference; 1987.
16. Nikolaos M. The Greek Orthodox position on the ethics of assisted reproduction. Reprod Med Online. 2008;(Suppl 1):33.
17. Balashov N. Spokesman for the Russian Orthodox Church on IVF and Surrogacy Interfax-Religion. 6 Oct 2010.
18. Bishop Grigorios HG. The Christian opinion in in vitro fertilization coptic culture. Cairo, Egypt; 1988.
19. Gad El Hak AGE. In vitro fertilization and test tube baby in book of fatwa. Dar El Iftaa, Cairo. 1980;1225:1:115:3213–3228.
20. Serour GI. Islam and the four principles. In: Gillon R, editor. Principles of health care ethics. London: Wiley; 1994.
21. Serour GI, editor. Ethical implications of the use of ART in the Muslim World. Cairo: International Islamic Center for Population Studies and Research, Al-Azhar University; 1997.
22. Serour GI. In: Shenfield F, Sureau C, editors. Religious perspectives of ethical issues in ART: contemporary ethical dilemmas in assisted reproduction. London: Informa Healthcare; 2006. p. 99–114.
23. Dickens BM, Serour GI, Cook RJ, et al. Sex selection: treating different cases differently. Int J Gynaecol Obstet. 2005;90:171–7.
24. Serour GI, editor. Ethical implications of the use of ART in the Muslim World. Cairo: International Islamic Center for Population Studies and Research, Al-Azhar University; 2000.
25. Kumar A. Ethical aspects of assisted reproduction—an Indian viewpoint. Reprod Biomed Online. 2007;14(1):140–2.

Ethics in Clinical and Imaging Practice in Reproductive Medicine

Sanja Kupesic Plavsic and Sushila Arya

Introduction

The professional responsibility model of clinical ethics governs the referral by the primary obstetrician-gynecologist of infertile patients for assisted reproduction. The professional responsibility model is based on three commitments: becoming and remaining scientifically and clinically competent, protecting and promoting the health-related and other interests of the patient, and acting in the best patient's interest.

The first commitment creates an ethical obligation to refer patients to competent specialists in reproductive medicine, such that the diagnosis and treatment for infertility can occur in a time-sensitive manner. Preconceptional care also allows optimizing the overall health for improved infertility treatment success and neonatal-obstetrical outcome. The reproductive endocrinologist has a range of treatment options, from ovulation induction (OI), intrauterine insemination (IUI), and in vitro fertilization and embryo transfer (IVF-ET) to third-party reproduction (oocyte and sperm donation, gestational surrogacy). Ultrasound imaging is usually the first step in a comprehensive assessment of an infertile female patient, which enables identification of potential risks from treatment such as ovarian hyperstimulation syndrome and multiple pregnancies. The presence of hydrosalpinx and intracavitary abnormalities are associated with lower implantation potential, while structural uterine defects detected on a coronal plane by 3D ultrasound increase the risk of miscarriage and pregnancy complications.

The second commitment creates an ethical obligation to prepare the patient for the referral process with questions she should ask about the risks and benefits of

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infertility treatment, success rates, and cost involved with the investigation and treatment. The moral duty of a reproductive endocrinologist is to objectively inform and educate the patient about the artificial reproductive techniques (ART), estimated success rates, and associated risks, based on medical history and diagnosis of infertility for the patient or couple. Management of an infertile couple should always be conducted on the basis of evidence-based judgments. Unrealistic expectations for the predictive accuracy of new imaging and ART should be avoided, and the usefulness of sophisticated ultrasound and laboratory equipment and tools should be appropriately assessed.

The third commitment creates an ethical obligation to report inappropriate reproductive medicine services to professional associations and licensing authorities.

In this chapter, we will review the most common ethical problems and dilemmas facing practicing clinicians in the field of clinical and imaging practice in human reproduction.

Need for Timely Referral

Infertile patients typically present preconceptionally, enabling timely detection of the uterine, tubal, and ovarian conditions that may interfere with pregnancy, identification of risk factors related to pregnancy, and initiation of appropriate interventions (e.g., reinforcing folic acid supplementation). Ultrasound imaging is among the first tests performed in the initial work-up of an infertile couple, and the advanced high-resolution transvaginal ultrasound with 3D, color, and spectral Doppler modality has become a widely accepted "one-stop shop" fertility scan [1–3]. In case a physician is not able to provide optimal imaging service to subfertile and infertile patients, he/she should refer them to the centers where such services are available.

The gynecologist and reproductive endocrinologist (REI) have a range of treatment options, including IUI, IVF-ET, and third-party reproduction opportunities (e.g., oocyte donation, sperm donation, gestational surrogacy).

Conscientious objection in medicine is the notion that a healthcare provider can abstain from offering certain types of medical care with which he/she does not personally agree. This includes care that would otherwise be considered medically appropriate (e.g., a physician may not agree with oocyte donation treatment option or PGA). A potential solution for conscientious objection, in this case, is that the patient can be referred to the provider who is trained and willing to honor a patient's request for this type of service [4, 5].

Evidence-based medicine includes three components: research-based evidence, clinical expertise, and the patient's values and preferences [6]. An honest dialogue between the patients and the provider improves transparency and quality of care, leading to better outcomes.