Ovarian Ageing Evaluation

Frank J. Broekmans, MD, Phd

In the past decades, postponement of childbearing has led to increasing rates of age-related female infertility, which is almost exclusively owing to changes in the ovaries. The age-related decrease in follicle numbers dictates the onset of cycle irregularity and the final cessation of menses at menopause. The parallel decay in oocyte quality gives rise to the gradual decline in fertility and the final occurrence of natural sterility. These changes imply that if women postpone pregnancy until after the age of thirty, the chance of being faced with infertility may increase up to 30%. Unfortunately, medical treatment modalities such as IVF may not sufficiently solve the problems of couples suffering from age related fertility decline, necessitating the widespread use of egg donation.

The rate of ovarian ageing is highly variable among women. This is evident from the large variation in age at menopause, age at onset of cycle irregularity, and age at occurrence of natural sterility. Very early menopause, as in premature ovarian failure, may represent the extreme of this variation. In view of the large variation in the reproductive ageing process, the identification of women who have severely decreased ovarian reserve for their age is clinically relevant, as it may identify specifically those women who cannot afford to postpone their pregnancy.

Pregnancy at higher female age may also present increased rates of problems, which may affect the overall reproductive outcome. In pregnant women over 35 years of age, a substantial increase in the risks of developing gestational diabetes, pregnancy induced hypertension, premature birth is observed. Moreover, increased rates of artificial delivery and neonatal problems due to congenital anomalies or premature birth may lead to life time lasting sequelae.

In view of all these issues, there may exist a need to have advance notice on the stretch of the reproductive lifespan for an individual woman. Since menopause relates strongly to the occurrence of natural infertility some 10 years earlier, long term prediction of menopause may help women to timely start attempts to have children. Markers that could inform in advance on the individual timing of natural infertility and menopause, may be family history and quantitative ovarian reserve markers like AMH and the AFC. Results of longitudinal studies may provide predictive models for individual application. Moreover, application of genetic profiles may add to the predictive accuracy of the currently known endocrine and ultrasound markers. As studies sofar have failed to provide a set of genetic markers that explain the individual variation in the timing of this ageing process, to date information on the mother's age at menopause, combined with a quantitative test such as AMH for confirmation, may provide valuable information.

Ovarian stimulation in the poor responder

Assisted reproductive technology treatment is the most powerful step in the management of the infertile couple. Still, well timed transfer of morphologically normal embryos in the uterus only will allow one in three embryo's to implant and lead to a live birth. The patient factors that relate to the implantation chances for the embryo in its host are several. Female age, ovarian reserve and also lifestyle factors all will contribute to the outcome of the ART cycle.

The rate of ovarian ageing is highly variable among women. Identification of subfertile women who have severely decreased ovarian reserve for their age is therefore clinically relevant. Tests for ovarian reserve (ORT) relate mainly to the quantitative aspect of ovarian reserve. Basal endocrine, ultrasound morphological and challenge tests all have been proposed as possible outcome predictors enabling patient tailored treatment. Tailored treatment may imply refusing IVF treatment, applying adjusted dosages of gonadotropins or treatment schedules or just counselling on reduced prospects.

From recent systematic reviews and meta-analyses the accuracy and true clinical value of ORTs to predict poor ovarian response and the occurrence of pregnancy after IVF have become more apparent. It was shown that the best performing tests to date (AFC, AMH, basal FSH) have a rather good accuracy in predicting poor ovarian response. However, the value of the prior identification of a poor responder remains to be established for two reasons. First, poor response is not unequivocally related to a poor prospect for pregnancy. Second, measures like FSH dose increase, co medication or agonist/antagonist schedule adaptations in predicted poor responders may neither increase response nor the chances for pregnancy. Moreover, current comparative trials suggest that FSH doses of 200 and over will not further improve ovarian response. The only possible benefit may stem from the use of adjunct therapies like growth hormone or several forms of androgen medication, although studies supporting such use are mostly small and urgently need further confirmation.

Accuracy of ORTs in the prediction of the occurrence of pregnancy appeared almost absent. Only if an extreme cutoff is used, in order to prevent couples from wrongly being refused IVF, a very small minority of IVF indicated cases (~3%) is identified as having extremely unfavourable prospects in a first IVF treatment cycle. Based on these analyses the use of any ovarian reserve test for outcome prediction prior to starting IVF, although mostly cheap and not very demanding, can not be supported. Recent studies do have indicated that ovarian reserve tests such as AMH or the AFC could help fine tuning prognosis for pregnancy based on female age alone. Still, the designation of a very poor prognosis remains difficult, so that other than for counseling purposes routine testing may be only helpful in specific patient groups, such as older patients.

As the actual ovarian response to hyperstimulation will provide important information on ovarian reserve status, entering the first cycle of IVF without any prior testing seems to be the preferable strategy. In case a poor response is observed, the question then can be answered whether this response is caused by severely decreased ovarian reserve or by conditions leading to underdosing, like FSH receptor polymorphisms or obesity. This distinction seems possible by using ORTs as a posteriori tests and will assign those poor prognosis couples (expected poor responders) that are to be refused further treatment.

Ovarian stimulation in the high responder

Ovarian hyperstimulation for IVF aims at producing multiple embryos of high quality in order to make the chances of an ongoing pregnancy occurring as high as possible. Two distinct problems may arise when performing hyperstimulation: too low response with inherent reduction in pregnancy rates and too high ovarian response with the threats of the ovarian hyperstimulation syndrome developing. Both outcomes of the stimulation also bear the risk of cycle cancellation. It is therefore that prediction of the outcome response in terms of number of oocytes is of great importance.

In prediction of the outcome ovarian response two issues are keynote. One is that the relation between FSH dose level and the response of the ovaries in terms of number of dominant follicles growing, has not been clearly established. Sofar, evidence has shown that the dose response curve is very steep, indicating that with only small increases in FSH level single follicle growth is turned into maximal ovarian response. This implies that in the vast majority of patients the dosage administered (150 IU and over) will provide maximal stimulation of the ovaries. Second, the use of maximal stimulation dosages as a rule implies that the ovarian response is not principally dependent upon the dose of FSH applied, but on the size of the cohort of the FSH sensitive antral follicles present in the ovaries at the time of stimulation. The antral follicle cohort size is fully determined by the ovarian reserve status of the individual woman and expressed by female age and possibly by ovarian reserve tests. These two factors are therefore the most important tools for response prediction.

Prevention of the excessive ovarian response and its inherent risk of OHSS follows a two-step regime: primary and secondary. Secondary prevention comprises measures that can be applied once an excessive response is being observed. Cycle cancellation and thereby eliminating hCG exposure is the very safe but disappointing tool, while agonist triggering in antagonist cycles and coasting in agonist co-medicated stimulation regimes allow at least carrying out the oocyte pick up, with the option left of freezing all embryo's in case the oocyte yield will surpass a certain number. Once embryos have been replaced, tertiary prevention measures are mandatory in cases still at risk, and comprises ultrasound and haematocrit surveillance, early decision on the necessity of hospitalisation and intravenous fluid therapy.

The primary prevention based on identifying cases at high risk of developing hyperresponse has been mainly based on patient profiles, like very young age and the presence of the PCO Syndrome, as well as the general use of modest dosing schemes not exceeding 200 IU in first cycles. Recent review studies have shown that the correct prediction of hyperresponse is possible by using tests like the AFC or AMH. Still, whether effective strategies to manage predicted hyperresponders can be developed is currently not known. Specifically dose reduction may eliminate excessive response but also create socalled poor responders. It remains to be demonstrated that progressing to oocyte pick up and not cancellation in these cases will provide a sufficient level of chances for implantation of the embryo. Of importance here is the notion that a moderated response in predicted high responders will at least bring out the best quality oocytes, while leaving the poorer ones in the ovaries.

Reversal of sterilization. Laparoscopic tubal anastomosis

Charles H Koh, MD

Reversal of sterilization experiences pregnancy rates higher than IVF at the end of one year, especially when number of embryos transferred is reduced. The laparoscopic approach encourages women to try this operation whereas they may not want it if performed by laparotomy. We discuss the instruments, technique and results of our experience.

Laparoscopic myomectomy

Good RCT's have shown laparoscopic myomectomy to be equal or better than laparotomic myomectomy. We discuss the essential instruments, ports, operative and morcellation technique as well as indications between laparotomy and laparoscopy.

Deep infiltrative endometriosis. Surgery or IVF?

DEEP INFILTRATIVE ENDOMETRIOSIS – SURGERY OR IVF?
Deep endometriosis often causes severe symptoms and organ dysfunction, and hyperstimulation for IVF exacerbates the symptoms, sometimes necessitating emergency surgery – with bad outcomes. However when it is asymptomatic – should excisional surgery be performed before IVF? We look at how to perform laparoscopic surgery in deep endometriosis involving ureters, bowel and bladder and relevant literature.

Omics in Embryo Evaluation

Catherine Racowsky, Phd

One of the great challenges in clinical IVF is to refine embryo evaluation techniques so that the single most developmentally competent embryo can be reliably identified in every cohort of available embryos. While morphological evaluation has been the primary method used for embryo assessment, this approach has recognized limitations and there remains no consensus regarding the optimum day(s) for evaluation or the scoring systems to use.

In this lecture, we will review the principles and broad approaches relevant to evaluating embryos. We will then discuss the status of proteomic and metabolomic approaches for embryo assessment and appraise developing genomic technologies. We will discuss the advantages and disadvantages of performing blastomere versus trophectoderm biopsy and will critically evaluate available data obtained with microarray technologies. The presentation will conclude by considering issues regarding the application of developing genomic methods for embryo assessment to all patients versus specific patient populations, as well as giving brief consideration to prevailing challenges regarding choosing between cleavage stage versus blastocyst transfer.

LEARNING OBJECTIVES

At the conclusion of this lecture, the participants should be able to:

1. State the principles and broad approaches relevant to evaluating embryos
2. Discuss the status of metabolomic and proteomic approaches for embryo assessment
3. Describe the pros and cons of blastomere versus trophectoderm biopsy

4. Appraise current data regarding the efficacy of genomic technologies for embryo evaluation
5. Evaluate the application of genomic embryo screening with respect to patient populations and the optimum day of embryo transfer

Unexpected events in the IVF Lab

The main objective of any in vitro fertilization (IVF) program is to provide the highest quality of care for every patient being treated. Although "quality" can be interpreted in several ways, it is generally perceived as achieving a healthy live birth. Critical to achieving this goal is a comprehensive, effective and active quality management program that monitors and assures standards and safety are maintained and improvements introduced in the performance of the IVF laboratory.
The IVF lab can be considered analogous to a highly sophisticated manufacturing process in which checks and balances must constantly be implemented, and actions taken when there are deviations from the norm. Protocols must be current, effective and standardized; personnel must be trained and certified; and there must be continuous surveillance in staff performance, and assessment of the "manufactured" product to ensure outcome measures are not deviating from set targets. However, even with the most effective and diligent quality control and quality assurance programs in place, unexpected errors and events do occur in the IVF lab.
This lecture will begin by providing an overview of the variables influencing safety and success before briefly considering the definitions of quality control and quality assurance. We will then proceed to discuss some unexpected errors and events, from both a patient and systems perspective, and will consider solutions and actions for future avoidance. The presentation will conclude by outlining a process for managing the unexpected.

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:
1. Define and distinguish between Quality Control and Quality Assurance
2. Describe implementation of standardizations across protocols and personnel in the IVF laboratory
3. Discuss some unexpected errors and events in the IVF lab, and consider actions for future avoidance
4. Outline a general process for managing unexpected occurrences in the IVF lab

Cryo of Oocytes and Embryos

The evolution of cryopreservation techniques for clinical ART has undergone a striking progression over the last 40 years with slow freeze protocols being established for embryos first and then oocytes, followed by the introduction of vitrification protocols primarily for oocytes and then for embryos. We have thus seen a gradual transition in clinical ART from the almost exclusive use of slow freezing of embryos only, now to wide utilization of vitrification for both oocytes and embryos.

Every IVF laboratory should have efficacious cryopreservation protocols in place: More and more cancer

patients are attempting to salvage their fertility by pre-treatment oocyte and/or embryo freezing; Current controlled ovarian stimulation protocols frequently result in retrieval of supernumerary oocytes retrieved and formation of many more embryos beyond the optimum number to be transferred. And now, with continuing recognition that success of an IVF cycle should be measured by cumulative live birth rates (i.e. births from fresh and frozen transfers from the same oocyte cohort), there is even greater pressure on the IVF laboratory to ensure utilization of the most efficacious cryopreservation protocols.

This lecture will begin by providing a brief historical overview of the evolution of cryopreservation relative to ART. We will then consider the principles underlying cryopreservation, the fundamental differences between slow freezing and vitrification, and the devices and cryoprotectants in use today. We will then proceed to discuss the clinical application of oocyte and blastocyst vitrification, consider current data regarding their overall success rates, and briefly discuss the importance of endometrial preparation for cryo embryo transfers.

LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

1. Describe the evolution of techniques to cryopreserve oocytes and embryos for clinical ART
2. Discuss the underlying principles for successful cryopreservation of cells.
3. Compare slow freezing and vitrification protocols, and their devices
4. Appraise the clinical application and expected success rates with efficacious oocyte and blastocyst vitrification protocols.
5. Consider the importance of endometrial preparation in the success of cryo embryo transfers.

Time Lapse Embryo Monitoring

Renee A Reijo Pera, Phd

Human embryo development occurs via regulation and coordination of diverse cellular processes. We recently documented the development of normally-fertilized human embryos from the zygote to blastocyst stage using both time-lapse microscopy and gene expression profiling at the single embryo or single blastomere level. We observed that human embryo development follows strict timing in cytokinesis and mitosis and exhibits unique gene expression patterns that are diagnostic of embryo fate prior to embryonic gene activation (EGA) by the 4-cell stage on Day 2. Furthermore, we observed that human embryo development is cell autonomous; within each blastomere, RNA degradation is an active process that must precede EGA. Together, results of single cell imaging and molecular data suggest that human embryo fate is pre-determined cell-autonomously by maternally- and/or paternally-inherited programs and that computer algorithms are useful to precisely measure embryo cell cycle behaviors that predict success and failure.

Gametes from Stem Cells: is it Possible?

Human embryo development begins with the fusion of egg and sperm, a remodeling of the maternal and paternal pronuclei and a series of cleavage divisions. Subsequently, on Day 3, the embryonic genome is activated and the stage is set for a series of cell fate decisions that lead to formation of the distinct tissues of the blastocyst, the primary germ layers and the germ cell lineage. Our recent findings indicate that human embryo development is characterized by a complex pattern of gene expression with the vast majority of genes that are modulated being down-regulated. Moreover, we observed that the majority of genes that are expressed in early human preimplantation development are of unknown function/ identity. Thus, to probe gene function, and develop a potential platform for clinical intervention, we developed the tools necessary to examine one of the earliest decisions in human embryo development, namely the setting aside of cells in the early embryo to form the germ cells (egg and sperm) of the next generation. We have found that both human embryonic stem cells and human adult- and fetal-derived induced pluripotent stem cells can form the earliest germ cells and even meiotic male and female germ cells. Moreover, we have found that a family of translational factors regulates germ cell formation, maintenance and differentiation and can induce progression of germ cell development. We suspect that we can derive gametes from stem cells in whole or in part with transplantation required for full maturation and development.

Genetics and Epigenetics in the Human Oocyte to Embryo Transition

DNA methylation and the regulation of histone modifications are intricately associated, working together to epigenetically influence gene expression and chromatin structure. However, the precise relationship between DNA Methyltransferases (DNMTs) and histone modifications during human pre-implantation development remains largely unknown. Here, we investigated DNMT and histone modification expression patterns in early human embryos with comparison to the mouse to determine the relevance between DNA methylation, the regulation of histone modifications and mammalian development. While no common DNMT mRNA expression pattern could be detected between the different stages of mouse and human development, mouse and human embryos exhibited similar levels and timing of particular histone modification enzymes. In contrast to mouse embryos, which exhibited sub-compartmentalization of DNMTs and histone modifications between the morula and blastocyst stages, differential epigenetic expression patterns were detected in the embryonic blastomeres of human embryos beginning at the 4-8 cell stage. Differences in epigenetic gene expression patterns were also observed between embryos from fertile and non-fertile couples and supplementation with a growth factor cocktail restored epigenetic factor expression levels. Using morpholino technologies, we also demonstrate an essential role for the histone-modifying enzyme, Msk2, in mitosis during pre-implantation development. Our findings suggest that human embryonic blastomeres differ in their developmental potential earlier than the mouse and that the coordinated expression and function of specific epigenetic regulators is important for early mammalian development. This work contributes to our understanding of the epigenetic requirements for normal embryogenesis and in cases of human reproductive failure, a common cause of birth defects.

Freezing and ovarian transplant in oncology patients

Sherman J. Silber, MD

The aim of this review is to summarize the state-of-the-art of ovarian transplantation and cryopreservation. This field has progressed over the last half century from simple animal experiments to sophisticated application in humans. The initial poor results in humans began to improve when a series of nine monozygotic (MZ) twin pairs discordant for POF underwent ovary transplantation at one center. All of these fresh ovary transplants were successful, resulting in eleven healthy babies in seven of the nine recipients. The same surgical techniques were then applied to 3 frozen ovary tissue transplants, up to 14 years after the ovary had been frozen, resulting in 3 more healthy babies. Around the world, the number of healthy babies has now risen to 28. Even ovary allotransplantation is being attempted in the not so uncommon situation where a previous bone marrow donor is now willing to donate ovarian tissue to the same recipient.
Recipients routinely reinitiated ovulatory menstrual cycles and normal Day 3 serum FSH levels by 4-1/2 months. Most conceived naturally (three of them twice or three times from the same graft). Duration of function of fresh ovarian grafts, contrary to initial expectations, indicated minimal oocyte loss from ischemia time. Grafts of just modest portions of ovarian tissue have lasted more than 7 years. In vitro studies suggest vitrification of ovarian tissue may be an improvement over the 70% oocyte viability loss from slow freeze.

ICSI with MESA or TESE in azoospermic males: an 18 year study

Purpose:The purpose of this review is to summarize science-based new treatments for human reproductive failure and future developments.
Results: First will be discussed popular but erroneous myths of current non-science based treatments. Then will be discussed new treatments and their scientific base, including ovary and egg freezing, and transplantation to preserve fertility in young women undergoing gonadotoxic chemotherapy and radiation for cancer; new perspectives on human epididymal sperm maturation based on a comparison between ICSI (intracytoplasmic sperm injection) with testis sperm versus epididymal sperm; simplifying IVF and reducing cost by more intelligent and milder ovarian stimulation; and improving pregnancy rate in older women; sequencing of the X and Y chromosomes to find genes which control spermatogenesis and whose deletion or mutation causes spermatogenic failure; and human spermatogenic stem cell culture to treat azoospermia, and to preserve fertility in pre-pubertal boys undergoing cancer treatment.
Conclusion:Thus with new stem cell biology and molecular understanding of reproductive failure, new therapies for previously untreatable infertility are currently on the near horizon. Furthermore our clinical results with new therapeutic approaches are adding to our understanding of the basic science of reproduction.

Male infertility and the extinction of the dinosaurs

Study of the molecular genetics of human male infertility and the Y chromosome has helped to elucidate the evolution of our X and Y chromosomes. Particularly, the study of the Y chromosome in male infertility has also helped to clarify, in a surprising and unexpected way, a likely mechanism for dinosaur extinction, the biggest question all of us have entertained from our earliest childhood days.

There have been many claims in the popular press of "discoveries" on how the dinosaurs went extinct. These claims all relate to climate change events that occurred 65 million years ago that no one disputes occurred. But none have explored the biology of how so many animals escaped extinction while the dinosaurs and at least half of all other species did not. For example, why did large dinosaurs, as well as small dinosaurs the same size as chickens go extinct, but birds survived? Possibly the evolution of sex chromosomes holds the answer to this question.

Our studies of the Y chromosome and male infertility suggest that the default mechanism for determining the sex of offspring is the temperature of egg incubation, and that genetic sex determination (based on sex chromosomes like X and Y) has evolved many times over and over again in different ways, in different genera, as a more foolproof method than temperature variation of assuring a balanced sex ratio in offspring. The absence of such a genetic sex determining mechanism in dinosaurs may have led to a skewed sex ratio when global temperature dramatically changed 65,000,000 years ago, resulting in a preponderance of males, and consequentially a rapid decline in population.

Advanced female age and declining fertility

Carlos Sueldo, MD

From the early years of ART we learned that older reproductive age patients had a worse prognosis in ART compared to younger patients; they produced lower number of oocytes, and the embryos those oocytes generate were of lower quality, that implanted at a much lower rate than the IR seen in younger patients undergoing ET. The SART statistics published yearly by the CDC, make this fact more obvious, showing that older women have a much lower pregnancy rate and a much higher miscarriage rate than younger patients.

The uterus as a factor to explain this decline was rapidly ruled out by a number of studies utilizing egg donation as a model, Navot et al showed in a randomized study that younger patients (35.8 +-3.1 years) had a similar pregnancy rate compared to older women (44.0+-3.1 years), both groups receiving oocytes from young egg donors. So aging oocytes as women age advances seem to be the reason for this decline, why ? there is evidence (Plachot et al) that genetic abnormalities in oocytes from older women were far greater than in younger patients, that goes along the concept called "production-line hypothesis", namely oocytes that enter the first meiotic prophase early in ovarian differentiation are ovulated first after puberty and have fewer abnormalities that those oocytes that are ovulated late in life, these oocytes ovulated late in life have fewer chiasmata, which are formed prenatally when homologous chromosomes pair during

prophase of Meiosis I; there is a negative correlation between chiasma (points of crossing-over of chromosomal segments that result in recombination of genetic material)frequency and non-disjunction which results in trisomy.
In summary, fewer oocytes and of poor quality goes a long way to explain the decline in fertility with advancing female age, it does not explain every case but it is a concept that has supporting medical evidence ; that is why oocyte donation is so successful in this type of patients and is why a number of investigators are focusing their research in "rejuvenating aging oocytes" (Casper et al), in producing "artificial gametes from stem cells" (Reijo-Pera et al, Simon et al),in producing homologous mitochondria from ovarian stem cells (OvaScience) to improve oocyte quality.

Adjuncts to COH Protoco

ART has become one of the most effective infertility treatments available today; in the so-called good prognosis/good responders ART patients (both IVF and ICSI), the fresh transfer of two blastocysts in our Center generates a Clinical Pregnancy rate around 60 %, besides, as excess embryos are available for blastocyst freezing and future thawing and transfer, the overall pregnancy potential or cumulative pregnanle cycle/attempt in this patient population is quite impressive.

There is a large number of ART patients that fall outside the scope of this good prognosis/good responders ART group, as their ovarian response to COH is either excessive or very poor; they both create clinical problems, as they either do not have enough follicles/oocytes after ovarian stimulation to justify moving forward with the treatment cycle, or they hyper-respond to the stimulation protocol administered.
The hyper-responders are easier to deal by modifying the COH protocols in various ways; on the other hand poor responders are clinically a very difficult group to treat and is here where a number of adjuncts have been suggested in order to enhance the ovarian response. The use of aspirin, Growth hormone, testosterone and DHEA as adjuncts to COH protocols in poor responders (typically microdose flare or GnRh Antagonist, in tandem with high doses of gonadotropins) have been proposed by different investigators. Their possible mechanism of action and potential benefits is going to be discussed during this presentation.

Efecto de la edad en el potencial reproductivo masculino

Dr. Gastón Rey Valzacchi

En la actualidad es común el retraso en la búsqueda del embarazo en las parejas y también que hombres mayores conformen nueva pareja con mujeres en edad reproductiva. Así como está bien establecido el efecto negativo de la edad materna sobre la fertilidad, no es uniforme la información de la acción de la edad paterna sobre la misma.

El objetivo de esta presentación es referirse a los cambios asociados a la edad en el aparato reproductivo masculino, en el potencial de fertilidad y en los riesgos en la descendencia, para terminar con aspectos prácticos que deben ser considerados desde el punto de vista reproductivo en el hombre de edad avanzada.

La base fisiopatológica del impacto de la edad sobre la reproducción masculina puede ser dado por el efecto específico de la edad solamente, pero también pueden influir factores asociados a la edad como enfermedades vasculares, obesidad, infecciones de las glándulas accesorias del aparato reproductivo o por acumulación de sustancias tóxicas, todos estos, factores que suelen afectar de por si la fertilidad.

Efectos sobre el aparato reproductivo: A nivel testicular disminución del número de células de Leydig, de Sertoli y germinales, con engrosamiento de la membrana basal de los tubos seminíferos. Incremento en los niveles de FSH y disminución en la concentración de testosterona y testosterona biodisponible.

Efecto sobre el semen: disminución en el volumen eyaculatorio, la movilidad y la morfología, sin cambios claros en la concentración espermática. Es frecuente encontrar un incremento en la fragmentación del ADN espermático.

Efecto sobre la fertilidad: Los hombres de más de 40 años contribuyen a una reducción en la fertilidad, especialmente si la mujer tiene más de 35 años. El riesgo de aborto en mujeres de edad avanzada se incrementa con hombres mayores de 40 años.

Efecto sobre la descendencia: Se suele referir que la edad paterna se asocia con ciertas enfermedades autosómicas dominantes raras como la acondroplasia y el síndrome de Apert y con algunas enfermedades de etiología compleja como la esquizofenia. Debido al bajo porcentaje de niños nacidos de hombres mayores y a la baja frecuencia de estas enfermedades hay poco poder estadístico para demostrar esta asociación. La causa de esto podría estar relacionado al incremento en divisiones mitóticas que se producen en las espermatogonias a medida que pasan los años. Se calcula que una espermatogonia a los 20 años se replicó 150 veces y a los 50 ese número es de 840, por lo que a medida que aumentan las replicaciones aumente el riesgo de errores en el ADN. No se ha visto un incremento en la descendencia de alteraciones cromosómicas numéricas o estructurales, salvo en la trisomía 21.

Aspectos prácticos en estos pacientes: Debe realizarse una profunda evaluación de la ingesta o aplicación de medicamentos, ya que es frecuente en este grupo etario el uso de medicaciones con efecto negativo sobre la fertilidad (testosterona para reemplazo hormonal, bloqueantes cálcicos para la hipertensión, inhibidores de la 5alfa reductasa y bloqueantes adrenérgicos para la hiperplasia prostática, etc). Asimismo en el semen debe estudiarse el factor infeccioso y el daño del ADN por la mayor frecuencia. Otro aspecto a considerar es la mayor dificultad de estos pacientes en obtener la muestra espermática, especialmente ante una técnica de reproducción asistida, pudiendo prevenirse esa situación.

Conclusión: Existe una clara alteración de la función reproductiva y de los riesgos genéticos en el hombre mayor. Si bien en la actualidad la edad paterna avanzada no es una indicación para realizar un diagnóstico prenatal, posiblemente el avance en el desarrollo de de la tecnología molecular facilite el desarrollo de esta evaluación. Es importante la evaluación clínica del hombre de edad avanzada (independientemente de sus antecedentes de fertilidad) para detectar posibles factores que impactan negativamente la fertilidad.