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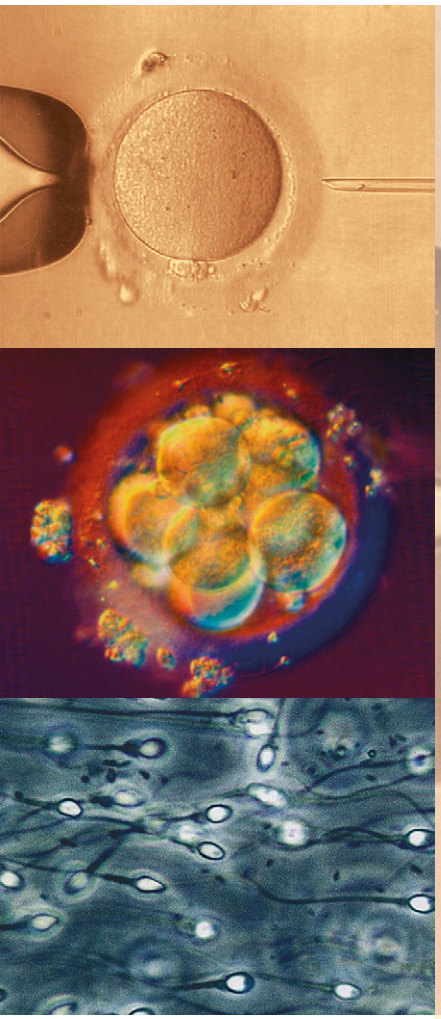

In-vitro Fertilization in Women of Advanced Reproductive Age

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*In-vitro Fertilization in Women of Advanced Reproductive Age**

M. Margreiter, A. Weghofer, W. Feichtinger

Postponement of family planning can be seen as a consequence of increased life expectancy and extended education in industrialized countries. The increasing number of prospective parents undergoing in-vitro *fertilization (IVF) due to advanced reproductive age, however, reflects the discrepancy between socio-cultural development and physical limits. Assisted reproduction is, therefore, challenged to create and adapt treatment regimens for women of advanced reproductive age to bridge between this wish for late parenthood and the age-related decline in fecundity. Consequently, the knowledge concerning age-related changes of reproductive functions gains in importance. While follicular depletion and impaired oocyte quality, frequently also called 'diminished ovarian reserve', are generally acknowledged as the underlying mechanisms for the decline in maternal fecundity, the way to correctly assess the status of ovarian reserve has remained controversial. Besides increasing attempts to achieve conception, deferring pregnancy and delivery into older age also implies medical risks and ethical considerations. The use of IVF in older women, therefore, raises the issue of the utilization of preimplantation genetic diagnosis (PGD) in the assessment of embryonic aneuploidies, as well as in attempts to optimize pregnancy rates with IVF. Moreover, expected future concepts in assisted reproduction are warranted to allow for the establishment of viable singleton pregnancies in women of advanced reproductive age.*

Key words: in-vitro *fertilization (IVF), age, ovarian reserve, preimplantation genetic diagnosis (PGD)*

In-vitro-*Fertilisation bei älteren Frauen.* *Postponierter Kinderwunsch ist als Konsequenz aus höherer Lebenserwartung und gesellschaftspolitischen Veränderungen in westlichen Industrienationen zu sehen. Der zunehmende Anteil an älteren Paaren mit unerfülltem Kinderwunsch spiegelt diese Diskrepanz zwischen soziokultureller Entwicklung und physiologischen Grenzen wider. Die moderne Reproduktionsmedizin steht daher vor der Aufgabe, alternative Therapiekonzepte für den altersassoziierten Fertilitätsrückgang zu entwickeln und so dem späten Kinderwunsch Rechnung zu tragen. Dem Wissen um altersabhängige Veränderungen reproduktiver Interaktionsmechanismen kommt in dieser Beziehung entscheidende Bedeutung zu. Qualitativen und quantitativen Alterationen des Follikelpools, die als kausaler Faktor des altersassoziierten Fertilitätsrückganges gelten, steht eine kontroversielle Diskussion über geeignete Evaluationsverfahren ovarieller Reserve gegenüber. Weiters erfordern medizinische Risiken durch IVF und Schwangerschaft bei Frauen vorgeschrittenen Alters Berücksichtigung. Der Einsatz assistierter Reproduktion in jener Patientengruppe impliziert zudem eine kritische Auseinandersetzung mit der Präimplantationsdiagnostik in der Evaluation altersassoziierter Aneuploidien sowie alternativer Behandlungsansätze hinsichtlich potentieller Erfolgsoptimierung.* ***J Reproduktionsmed Endokrinol 2005; 2 (1): 5–12.***

Schlüsselwörter: In-vitro *Fertilisation (IVF), Alter, Ovarielle Reserve, Präimplantationsdiagnostik*

Postponement of family planning is a common phenomenon in industrialized countries. Increased life expectancy and prolonged period of education are major contributing factors for this continuing trend. Contraception and liberalization of abortion facilitate women to exercise control over their fertility. Consequently, young women nowadays not only decide on whether to bear children or not, but they as well make demands on their right to determine the time of their prospective motherhood.

Advanced understanding of female reproductive endocrinology has revealed significant alterations of ovarian responsiveness with age (Figs. 1, 2). Experiments in animal models suggest an age-related decline in endometrial sensitivity to progesterone, caused by a reduction in estrogen receptors. Endometrial biopsies in women aged 35 and above revealed a decline or even the absence of secretory maturation during the menstrual cycle [1].

However, since oocyte donation to women of advanced age results in high pregnancy rates, uterine factors may be of minor importance for embryonic implantation and development [2, 3]. The aging process in human oocytes, in contrast, is attached great importance to. There are several hypotheses for this decline in oocyte quality with age: One theory assumes that high-quality oocytes are ovulated first, leaving poor-quality oocytes to be ovulated later in life. Another concept claims an age-dependent increase in intracellular oxidative stress, resulting in higher incidences of follicular depletion and chromosomal abnormalities with age [4, 5].

In-vitro fertilization needs to stay abreast of these changes. Intensive research is required to optimize fecundity in women of advanced age; concerns about increased risks of fetal malformations and potential neoplasm have to be met. Furthermore, ethical aspects of late parenthood require consideration.

Ovarian Reserve

The diversity of patients currently frequenting IVF clinics reflects a trend towards increasing utilization of ART as a principal infertility treatment. As a consequence, physicians face considerable new challenges as they find a need to adjust, previously rather standard ovarian stimulation protocols, to the individual patient's very specific needs.

The term 'ovarian reserve' is commonly utilized to describe the quality and quantity of a woman's remaining ovarian follicular pool. In that context, a 'decreased' ovarian reserve assumes relative follicular depletion and/or impaired oocyte quality [6]. When Garcia et al first characterized the phenomenon of 'diminishing ovarian reserve' in 1983, they defined the condition by peak estradiol levels < 300 pg/ml and a decreased number of oocytes at retrieval. However, even today, so many years later, the ART field still lacks standardized definitions for what really constitutes a decreased or diminished ovarian reserve [7].

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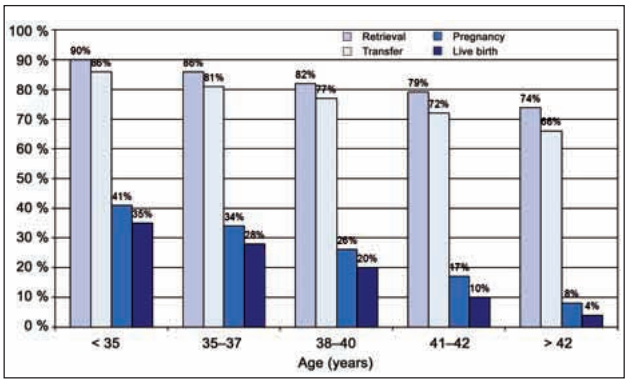

Figure 1: Outcomes of ART cycles by stage and age groups in the United States, 2001 (adapted from U.S. ART-Report, 2001)

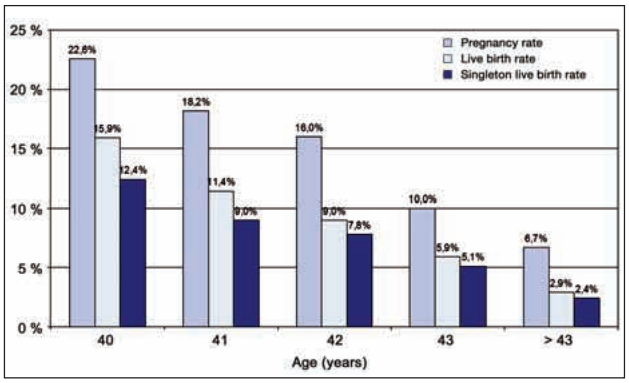

Figure 2: Pregnancy rates, live birth rates and singleton live birth rates for ART cycles among women aged 40 and older in the United States, 2001 (adapted from U.S. ART-Report, 2001)

Surrey et al suggested that a reduced number of follicles and/or number of oocytes retrieved after age-specific standard-dose gonadotrophin stimulation, ranging from less than three to five oocytes, is to be seen as a major criterion for impaired ovarian reserve [8]. In the presence of such defined impaired ovarian reserve, repeated IVF failures and prolonged stimulation periods to achieve proper treatment response may have to be anticipated [9].

While our knowledge about the causes of decreasing ovarian reserve is still limited, it is primarily believed to be age-related [4, 10]. The decline in fecundity with advancing female age is assumed to mirror a process of ovarian aging that precedes, parallels or follows women's chronological aging [6, 11–14]. While it is believed to be associated with female aging, it is so not exclusively [15, 16]. Ovarian reserve can also be adversely affected by such conditions as endometriosis, ovarian surgery, chemo- or radiation therapy, following treatment for cancer [17, 18], genetic predispositions, such as, for example fragile-X carrier status [19], environmental pollution and noxious lifestyle. Joesbury et al, for instance, implicated smoking to be responsible for follicular loss and premature ovarian failure [4, 20].

Beside age-related alterations of the ovary, there is also a considerable body of evidence that immune processes, especially abnormal autoimmune processes, can lead to a premature loss of ovarian function and, at its final stages, to complete premature ovarian failure (POF), also called 'premature menopause' [21]. Pellicer et al hold immunological mechanisms, such as auto-antibodies against granulosa cells, and ovarian vascular impairment responsible for ovarian resistance to age-specific standard-dose gonadotrophin stimulation [22, 23]. Gleicher et al suggested a similar concept when they referred to immunologically induced reproductive failure which can take the format of various clinical presentations and which they termed 'The Reproductive Autoimmune Failure Syndrome' (RAFS) [21, 24]. These and many other authors also suggested that, mostly experimental data in animals, suggest that normal pregnancy requires a switch from T helper-1 (Th-1) preponderance to T helper-2 (Th-2) predominance in immune responses. Immunological implantation failure might, therefore, be caused by continuance of Th-1 preponderance [25, 26].

Lee et al, in contrast, propose the concept of a FSH-receptor binding inhibitor, located in follicular fluid [27]. De Castro et al, in accordance with Perez et al, hypothesized that a FSH receptor genotype variant accounts for poor ovarian response [28, 29]. All of these published hypotheses, therefore, suggest the need to distinguish between diminished ovarian reserve and outright ovarian resistance.

Markers of Ovarian Reserve

Keay et al reported a prevalence of diminished ovarian reserve in 9–24 % of infertile women [30]. Neither any form of basal ovarian function testing (i.e. cycle day 2 or 3 FSH and estradiol testing, for example), nor any form of dynamic testing (i.e., for example the so-called 'clomiphene challenge test') have proven absolutely reliable in predicting premature ovarian aging. Errors in ovarian assessment can lead to unnecessary cycle cancellations, will, therefore, increase treatment costs and compound an already stressful situation [31]. The need for appropriate markers of ovarian function is, therefore, quite obvious. Such markers of ovarian aging would not only benefit fertility treatments but they could also help families to time their pregnancy schedules.

Inhibin B is currently under detailed investigation, although recent studies have revealed discordant results. Seifer et al, among others, associate decreased inhibin B (< 45 pg/ml) with diminishing ovarian reserve [32], whereas Creus et al postulate inhibin B to lack additional predictive power beyond the combined value of age and basal FSH [33]. Yong et al found inhibin B to be closely related to oocyte numbers and, furthermore, concluded that inhibin B concentrations, after FSH administration, correlate best with ovarian reserve [34]. Fried et al reported a significant correlation between inhibin B levels and the number of oocytes retrieved, though they were unable to show any correlation with the occurrence of pregnancy. The ratio IGF-1:IGFBP-1, in contrast, proved to be significantly increased in women who became pregnant and, thus, may reflect upon oocyte quality [35].

Compared to age, FSH, LH and E_2, inhibin B does currently not represent an inherent part of a routine diagnostic work-up for sub-fertility. Its predictive value needs to prove superior to currently used markers to warrant additional expenditure. The same applies to serum anti-Müllerian factor, to gonadotrophin surge-attenuating factor and to insulin-like growth factor-I. Martinez et al suggested that a low circulating gonadotrophin surge-attenuating factor may serve as a marker of impaired ovarian responsiveness [36], whereas van Rooij et al indicated

that a reduced baseline serum anti-Müllerian concentration reflects follicular loss [37].

Age-Related Maternal Risk Factors

Advanced female age generally implies adverse physical conditions for successful conception and is usually associated with increased body weight and a higher incidence of hypertension, diabetes and hyperlipidemia, summarized as the so-called 'metabolic syndrome' [38, 39]. The increased incidence of IVF pregnancies, affected by gestational diabetes and described by Koivurova et al, might be, at least in part, due to the classical metabolic conditions observed in PCO patients [40]. Tallo et al reported an increased incidence of pregnancy-induced hypertension in a case-control study of infertility patients, matched for maternal age, race, order of gestation and delivery, insurance type and neonatal gender [41].

Brizzi et al demonstrated significantly increased plasma lipid and apolipoprotein concentrations during ovarian stimulation [42]. Higher initial values of blood pressure and serum lipid concentrations, being partly lifestyle- and age-related, could imply elevated risks for atherosclerotic events in women of advanced age in the course of fertility treatment.

Beside possible cardiovascular side-effects of hormone therapy, one also has to consider other possibilities by which endocrine alterations may adversely affect female physiology. For example, Richardson et al suggested that excessive ovarian hyperstimulation in women with diminished follicular reserve might prematurely initiate menopause [43, 44]. Isikoglu et al recently published a case report on premature menopause of a 22 year old woman after repeated IVF cycles [45]. Whether ovarian hyperstimulation and the onset of menopause can, indeed, be related requires, however, further study. The fact that ovarian stimulation primarily matures an already in the prior month recruited cohort of follicles raises significant doubt about such a concept.

Climacteric-like symptoms, due to estrogen deprivation during pituitary suppression, and the ovarian hyperstimulation syndrome (OHSS) are the most likely complications to emerge in the course of *in-vitro* fertilization. Both, low ovarian responders and women of advanced reproductive age demonstrate, however, a reduced risk for OHSS.

The relationship between ovarian hyperstimulation and benign gynecological diseases was recently assessed by Klip et al. Their nationwide historical cohort study implicated elevated risks for uterine leiomyoma, ovarian cysts requiring surgical removal and thyroid disorders in low responders after *in-vitro* fertilization [46, 47]. Yet, whether these associations are the consequence or the cause of infertility treatment remains to be established. For example, there can be no doubt that thyroid disease, by itself, is associated with premature ovarian failure [48, 49].

Since fertility medications have been in use, the most feared potential complication has been the induction of malignancies by fertility drugs. Case reports, suggesting the occurrence of either breast, ovarian or uterine carcinomas, have emerged [44, 50–53], but the initial lack of nationwide registries, at least initially, did not permit a final resolution of this issue.

Recently, the incidence of malignant tumors linked to assisted reproduction has been evaluated in large-scale population based cohort studies. Whether, in principle, the underlying cause for fertility treatment (i.e. the cause of infertility itself) or exposure to fertility drugs was associated with an increased risk for invasive cancer of the breast, the ovaries or the uterus, has now been the subject of many large-scale epidemiological studies [54, 55].

In such studies Venn et al were not able to demonstrate any associations between ovarian superovulation with drugs and cancer induction, whereas they did show a higher than expected incidence of ovarian and uterine carcinoma in women with unexplained infertility. Number of treatment cycles and type of fertility drugs used were not significantly related to the risk for malignant tumors of the female genital organs, nor was there a dose-response [55, 56].

Though the overall incidence of cancer development was not greater than expected, the increased number of women being diagnosed with cancer within one year of ART does require some further attention [55, 57]. These findings have at least two possible explanations: Either women reach earlier diagnosis due to either their fertility work-up or growth enhancing effects of hormones on already existing, occult tumors. The lack of long-term tumor increase in patients following IVF, however, supports this hypothesis, suggesting no new induction of malignancies.

Another theory assumes tumor-promoting effects of hyperphysiological estrogen concentrations in the course of extensive gonadotrophin usage. The increased incidence of breast cancer observed during and shortly after pregnancy, which has been attributed to the high estrogen levels during pregnancy, offers a similar situation [54]. Recognizing a first peak incidence of breast cancer in women at approximate age of 35 and above assuming an increased risk for the occurrence of some carcinomas, like breast and ovarian cancers, in women with infertility, responsible fertility treatment means accurate tumor screening in the run-up and in the after-treatment periods to assisted reproduction cycles.

A continuous problem of ART is the much higher incidence of multiple pregnancies [58] (Fig. 3). Its essential causative factor is ascribed to multiple embryo transfers which in many countries lack legal or other regulatory supervision [59]. Multiple gestations are linked to an increased incidence of pre-eclampsia, cardiac strain, pre-

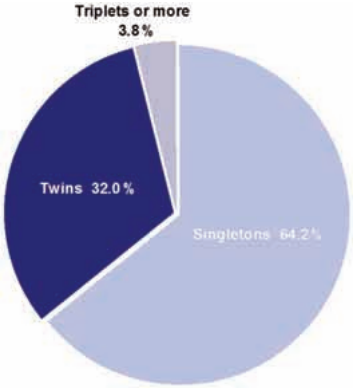

Figure 3:
Risk of having multiple-infant live birth from ART cycles in the United States, 2001 (adapted from U.S. ART-Report, 2001)

mature labor and delivery, pregnancy-induced hypertension, gestational diabetes and hemorrhage [60–62]. According to Tough et al, women aged 35 and above are at particular risk for low birth weight and preterm delivery of their offspring [63–65].

One of the most common complications after IVF represents first trimester vaginal bleeding. Its increased prevalence with IVF is believed to be, at least in part, the consequence of more 'vanishing twins'. IVF pregnancies have also been reported to demonstrate a higher incidence of placenta praevia and preterm uterine contractions [40].

Prospective mothers in their late thirties and forties demonstrate an increased risk for miscarriages [66]. Chromosomal abnormalities are believed to play a major role as a causal factor [67, 68]. According to Froster et al, most unbalanced chromosomal translocations result in spontaneous abortion [69]. Other causes of pregnancy loss can be hyperploidies (i.e. trisomy 18 or 16) and triploidies (69 instead of 46 chromosomes). Leridon et al report an age-dependent incidence of spontaneous abortion, resulting in miscarriage increase above 50 % in women aged 40 and above [70].

Though an essential part of chromosomal abnormalities is believed to originate from meiosis I errors, probably due to impaired meiotic recombination, paternal infertility may also account for up to a ten-fold risk of chromosomal aberrations in the offspring [71]. Verlinsky and collaborators have reported meiosis I errors to be responsible for two-thirds of aneuploidies in women aged 35 and above [67], while Munne et al reported an increased rate of mosaicism in embryos that failed to implant after ovulation induction [72].

The maternal age-specific risk for fetal trisomies 21, 18 and 13 is well documented in epidemiological studies conducted by Snijders et al [73]. In women aged 35 to 45, the age-related increase of hyperploidy is following an exponential curve, with a peak at 9–14 weeks of gestation [73].

The relative frequency of Down syndrome (trisomy 21) amongst chromosomal anomalies is only 33 % at birth, while as high as 54 % at 15–20 weeks gestation and weeks 9–14. Trisomies 18 and 13 account for 30 % of chromosomal abnormalities at 9–14 weeks' gestation with a decrease to 22 % at 15–20 weeks and 14 % at birth [73, 74].
ART research has, therefore, attempted to develop appropriate tools which would allow for the cytogenetic diagnosis of embryonic chromosomal abnormalities, especially, though not exclusively, in women of advanced reproductive age.

Preimplantation Genetic Diagnosis (PGD)

Beside gene defects which put couples at risk for the transmission of specific genetic disorders into their offspring, advanced female reproductive age has proven to be a main contributor to the occurrence of embryonic aneuploidy [75, 76]. As an underlying mechanism, Henderson and Edwards, among others, demonstrated a relation between the age-related reduction of meiotic crossing-over and the occurrence of aneuploidy. According to their 'production-line hypothesis', higher meiotic recombination frequency is observed in oocytes that differentiate early during fetal development and are, consequently, destined to ovulate first [77].

Gianaroli et al have reported aneuploidy rates of 60 % in embryos of women with repeated IVF failure, aged 36 and above. Chromosomal anomalies in first trimester pregnancies have been found to increase continuously from 0.6 % in patients aged 35 to 2.2 % in women above age 40 [75, 78]. These data strongly suggest that the majority of affected embryos is, indeed, subject to early cleavage arrest or implantation failure. After analysis of 2058 embryos, Munne et al concluded that there had to be a 90 % aneuploidy-related cleavage-arrest prior to or shortly after implantation [76, 79, 80].

The chromosomes most frequently involved in aneuploidy are reported to be chromosomes 22, 16, 21 and 15 [81]. The loss of embryos, affected by these aneuploidies, in the course of implantation, therefore, may explain both the age-related decline in fertility and the increasing implantation failure rate in women of advanced reproductive age [82].

According to Kuliev and Verlinsky, preimplantation genetic diagnosis in 6733 oocytes in women aged 35 and above revealed an overall aneuploidy of 52 %. Meiosis I errors accounted for 41.8 % of chromosomal anomalies, meiosis II errors were observed in 30.7 % and both, meiosis I and II errors, were seen in 27.6 % of the affected oocytes [67, 83].

Studies on the morphology of the meiotic spindles, performed by Volarcik et al, strongly support the hypothesis that the mechanisms of control over the process of physiological chromosome division and segregation in human oocytes is subject to age-related deterioration. While oocytes from young women showed regular bipolar spindle formation with tightly arranged chromosomes on the spindle equator, oocytes in older women depicted abnormally attached chromosomes and diffuse spindle formation during meiosis II [84].

Though the above noted aneuploidy rate in oocytes corresponded to that observed in preimplantation embryos, the types of chromosomal anomalies differed, however [67, 83]. These findings might be attributable to a high frequency of mosaicism in cleavage stage embryos and as a possible consequence of paternally derived genetic defects [81, 85, 86]. Some mosaicisms are associated with maternal age, whereas others are attributable to immaturity of centromeric sperm structures, as one encounters in testicular sperm extraction patients [75, 80]. 90 % of aneuploidy is, however, estimated to be related to meiosis. In such cases, polar body analysis for preimplantation aneuploidy screening, therefore, makes sense.

Comparative studies on FISH for chromosomes X, Y, 13, 15, 16, 18, 21, 22 plus a ninth probe (either 1, 7, 14 or 17) in a single cell in women aged 40 (PGD vs. non-PGD cycles in matched cohorts) demonstrated significantly higher implantation rates after PGD, particularly in first IVF cycles. Repeated IVF failure or substantially reduced numbers of zygotes, however, were identified as negative prognostic factors, resulting in impaired implantation [87, 88]. Pehlivan et al, in contrast, report pregnancy rates of 34 % (controls: 33 %) and implantation rates of 20 % (controls: 24 %) in PGD cycles of women with re-

current implantation failure, despite oocyte aneuploidy of 67 % (controls: 36 %). Pregnancies resulted when at least one unaffected blastocyst was available for transfer [89–91]. These findings agree with those of Gianaroli et al who describe pregnancy chances below 10 % in cycles lacking unaffected embryos, whereas they estimate a 30 % pregnancy rate for couples with at least two euploid embryos in their first cycle [75, 79].

As women currently seeking fertility treatment are, for an essential part, in their thirties and forties, aneuploidy screening could be a rather crucial additional benefit for their cycles [92–94]. Screening for chromosomal anomalies in patients who have been demonstrated as at risk for genetic defects that might further impair their already reduced chances for pregnancy and increase their risk of a genetically affected child, therefore, appears like a reasonable approach if such additional services can be integrated into IVF cycle costs at a reasonable additional cost [78, 95].

Future Aspects in Reproductive Medicine

One of the major challenges of current ART lies undoubtedly in its transition from being a treatment concept for a small group of patients to serving a much broader clientele, inclusive of a rapidly increasing number of couples of advanced reproductive age seeking for offspring [4].

Though *in-vitro* fertilization has proven extraordinarily successful through up to the birth of over one million children, stimulation regimens, currently still applied to patients with comparatively impaired chances for pregnancy, reveal weak spots in today's fertility treatments. Further research, therefore, appears mandatory to bridge this gap.

Improved knowledge on promoters and interactions, involved in follicular growth prior to gonadotrophin dependency, might disclose future treatment approaches in women with diminished ovarian reserve. Animal models in transgenic mice, for instance, have revealed various regulators of early follicular development, including growth differentiation factor 9, BAX1, BCL2 and Wilm's tumor gene. Though these factors are believed to either have stimulatory or inhibitory function in the initiation of oocyte development, little is known about their specific physiological role in the regulation of early follicular growth [96].

Henderson and Edwards, among others, demonstrated a relation between the age-related reduction of meiotic crossing-over and aneuploidy increase in women of advanced age. If oocytes with higher meiotic recombination frequency – which appears advantageous for appropriate chromosomal segregation – are destined to ovulate first, as they assume, the impact of external modulation of oocyte selection prior to gonadotrophin dependency would be well demonstrated. Beside follicular growth, oocyte maturation appears crucial in IVF. Better insight into the factors and modulators involved might, therefore, reduce the need to dispose of oocytes.

The process of fertilization plays an important role in the development of pre-implantation embryos. And it is important to note that not only female chromosomes are susceptible to damage. Indeed, the insertion of the paternal genome at time of fertilization may raise additional questions.

For example, etiologies for the so-called OAT-syndrome (oligo-astheno-teratozoospermia) deserve extensive study to generate a wider assortment of treatment options and to reliably assess paternally derived genetic risks in offspring. Whether children conceived by intracytoplasmatic sperm injection (ICSI) are, in fact, at higher risk for malformations awaits further study [97, 98]. Though ICSI enables a majority of infertile men to conceive genetically related offspring, it does not afford solution for all male disease patterns. Haploidization of male somatic cells might represent a future concept for severe forms of male sterility [99–101].

Implantation is the least currently understood process of human reproduction [102, 103]. At present, little is known about modulating factors that synchronize embryo and endometrium to allow for successful nidation [104]. Uterine vascularization and immuno-modulation appear to play a decisive but yet underestimated role in *in-vitro* fertilization. Though many underlying mechanisms of uterine receptivity so far have remained a mystery, an age-related decline appears likely. Luteal phase support in women of advanced reproductive age is, therefore, ascribed increasing importance.

Medication is another sector of interest in assisted reproduction that requires consideration [105]. Controlled ovarian hyperstimulation currently requires daily subcutaneous or intramuscular medications for weeks, a cause of considerable inconvenience for patients. Non peptide GnRH agonists and antagonists, that permit oral administration, are currently under evaluation to simplify fertility treatment [106].

Another difficulty with stimulation compounds, available at present, lies in their limited duration of effectiveness which, therefore, requires repeated daily administration. Long acting FSH, or sustained release FSH, with extended half-life compared to recombinant FSH (95 hours vs. 28 hours) would further contribute to a future of a more 'friendly' IVF cycle [106].

New treatment approaches may also become possible through the use of aromatase inhibitors which are assumed to activate positive feedback mechanisms at the pituitary level without negatively influencing estrogen receptors [106]. Serum estrogen concentrations could, thereby, be reduced to allow for physiologically adjusted stimulations.

Embryology plays a decisive, and still increasing, role in modern assisted reproduction. Microbiological advancement of culture conditions might facilitate enhanced cultivation to minimize cleavage arrest and to improve morphological embryo selection. Furthermore, a rational basis for complete karyotyping, using comparative genomic hybridization, could be provided.

Successful *in-vitro* fertilization is in an essential part subject to temporal constraints [106–108]. Cryopreservation sets the stages for wider scopes in fertility treatment that go beyond germ cell conservation. Single embryo transfer, genetic screening, stem cell storage and ovarian tissue banking are just some future areas in ART that require safe and efficient cryopreservation techniques.

Ovarian tissue banking is regarded as one of the most promising areas in to-be assisted conception. Initially intended for fertility preservation in cancer patients, scheduled for gonadotoxic radiation, autologous transplanted

ovarian tissue might, as well, yield hope for female fertility preservation in general. While other tissues of rapidly dividing cells, such as bone marrow and the gastrointestinal tract have the capability of restoration, ovarian tissue, where the number of germ cells is fixed since fetal life, lacks regenerative ability [109].

Total or partial oophorectomy in years of reproductive prime might, therefore, enable female procreation without the pressures of time. In contrast to cryopreservation of mature oocytes, that are susceptible to chilling injury, cryopreservation at prophase I, when chromosomes are not aligned along the spindle, is believed to result in minor risk for cytogenetic errors [110].

Recently, Bath et al reported on the first successful conception in a young woman who had ovarian cortical tissue cryopreserved before chemotherapy and radiotherapy for a Ewing's sarcoma of the pelvis. The patient had multiple biopsies of ovarian tissue cryopreserved for 5 years before re-implantation at the age of 19. A spontaneous conception occurred 1 year later and a healthy boy (birth weight 2.9 kg, 3rd–10th centile) was delivered at term by elective Caesarean section [111].

Data recently presented by Johnson et al could herald future fertility treatment. The scientists discovered challenging evidence for ovarian stem cells in mice, implicating oocyte renewal throughout the reproductive years. Though the occurrence of totipotent cells in human ovaries is just suggested so far, their existence could allow for diametrically opposed treatment options in infertile couples. Assuming continual genesis and decay of human oocytes, aneuploidy increase observed in women of advanced reproductive might be traced back to stem cell aging or even death. If stem cells, indeed, exist in human ovaries, knowledge on influencing factors of follicular reproduction and development could allow for either stem cell cryopreservation during prime or medical enhancement of flagging stem cell revival [112].

Extending fertility potential to older women appears one of the great challenges. Increasing aneuploidy in women of advancing reproductive age necessitates appropriate screening tools for the selection of genetically normal embryos – not only to improve pregnancy rates, but also to allow for healthy singletons [113, 114].

The strategy currently applied to achieve pregnancy in women aged 35 and above commonly utilized the transfer of multiple embryos in the hope for 'natural selection in utero' of genetically unimpaired embryos. Termination of pregnancy in couples, in whom IVF has either resulted in a fetal chromosomal abnormality or in pregnancy of higher rank, however, often causes significant psychological strains and feelings of guilt in would-be parents and surviving twins [114, 115].

Responsible fertility treatment, however, has the duty to minimize the risks associated with ART. To do this, the number of oocytes transferred has to be minimized, ideally to single embryo transfer in many, if not most, patients. Second, to ensure the implantation of only genetically normal embryos, PGD has to enter the routine IVF process in a more coherent way.

Gleicher et al recently presented data on blastomere transplantation between siblings to demonstrate integration and distribution of genetically normal blastomeres in chromosomally affected early human embryos [116]. Though long-term animal models are needed to gain further insight in the background mechanisms and implications of this discovery, it impressively depicts the chances of genetic medicine. Undoubtedly, there are risks involved, there are limits to be drawn. But for all that, regulations in this field should be principally based on expert opinion, serious discussion and reasonable skepticism rather than constraints of abstract fear from the unknown.

References:

1. Meldrum DR. Female reproductive aging – ovarian and uterine factors. Fertil Steril 1993; 59: 1–5.
2. Sauer MV, Paulson RJ, Lobo RA. Pregnancy after age 50: application of oocyte donation to women after natural menopause. Lancet 1993; 341: 321–3.
3. Sauer MV, Paulson RJ, Lobo RA. Reversing the natural decline in human fertility: an extended clinical trial of oocyte donation to women of advanced reproductive age. J Am Med Assoc 1992; 268: 1275–9.
4. Van Rooij IA, Bancsi LF, Broekmans FJ, Looman CW, Habbema JD, te Velde ER. Women older than 40 years of age and those with elevated follicle-stimulating hormone levels differ in poor response rate and embryo quality in in vitro fertilization. Fertil Steril 2003; 79: 482–8.
5. Huber J. Endokrine Gynäkologie. Wilhelm Maudrich, Wien, 1998.
6. Sharara FI, Scott RT Jr, Seifer DB. The detection of diminished ovarian reserve in infertile women. Am J Obstet Gynecol 1998; 179: 804–12.
7. Garcia JE, Jones GS, Acosta AA, Wright GJ. HMG/HCG follicular maturation of oocyte aspiration: phase II, 1981. Fertil Steril 1983; 39: 174–9.
8. Surrey ES, Bower JA, Hill DM, Ramsey J, Surrey MW. Clinical and endocrine effects of a microdose GnRH agonist flare regimen administered to poor responders who are undergoing in vitro fertilization. Fertil Steril 1998; 69: 419–24.
9. Schachter M, Friedler S, Raziel A, Strassburger D, Bern O, Ron-El R. Improvement of IVF outcome in poor responders by discontinuation of GnRH analogue during the gonadotropin stimulation phase – a function of improved embryo qualtity. J Assist Reprod Genet 2001; 18: 197–204.
10. Battaglia DE, Goodwin P, Klein NA, Soules MR. Influence of maternal age on meiotic spindle assembly in oocytes from naturally cycling women. Hum Reprod 1996; 11: 2217–22.
11. Kligman I, Rosenwaks Z. Differentiating clinical profiles: predicting good responders, poor responders, and hyperresponders. Fertil Steril 2001; 76: 1185–90.
12. Fasouliotis SJ, Simon A, Laufer N. Evaluation and treatment of low responders in assisted reproductive technology: a challenge to meet. J Assist Reprod Genet 2000; 17: 357–73.
13. Toner JP, Philput CB, Jones GS, Muasher SJ. Basal follicle-stimulating hormone level is a better predictor of in vitro fertilization performance than age. Fertil Steril 1991; 55: 784–91.
14. De Boer EJ, den Tonkelaar I, te Velde ER, Burger CW, Klip H, van Leeuwen FE. A low number of retrieved oocytes at in vitro fertilization treatment is predictive of early menopause. Fertil Steril 2002; 77: 978–85.
15. El-Toukhy T, Khalaf Y, Hart R, Taylor A, Braude P. Young age does not protect against the adverse effects of reduced ovarian reserve – an eight year study. Hum Reprod 2002; 17: 1519–24.
16. Derman SG, Seifer DB. In vitro ferilization in the older patient. Curr Womens Health Rep 2003; 3: 375–83.
17. Meirow D. Reproduction post-chemotherapy in young cancer patients. Mol Cell Endocrinol 2000; 169: 123–31.
18. Hock DL, Sharafi K, Dagostino L, Kemmann E, Seifer DB. Contribution of diminished ovarian reserve to hypofertility associated with endometriosis. J Reprod Med 2001; 46: 7–10.
19. Santoro N. Mechanisms of premature ovarian failure. Ann Endocrinol 2003; 64: 87–92.
20. Joesbury KA, Edirisinghe WR, Phillips MR, Yovich JL. Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score. Hum Reprod 1998; 13: 1506–13.
21. Gleicher N, Pratt D, Dudkiewicz A. What do we really know about autoantibody abnormalities and reproductive failure: a critical review. Autoimmunity 1993; 16: 115–40.

22. Pellicer A, Ardiles G, Neuspiller F, Remohi J, Simon C, Bonilla-Musoles F. Evaluation of the ovarian reserve in young low responders with normal basal levels of follicle-stimulating hormone using three-dimensional ultrasonography. Fertil Steril 1998; 70: 671–5.
23. Pellicer A, Ballester MJ, Serrano MD, Mir A, Serra-Serra V, Remohi J, Bonilla-Musoles FM. Aetiologic factors involved in the low response to gonadotropins in infertile women with normal basal FSH levels. Hum Reprod 1994; 9: 906–11.
24. Gleicher N, El-Roeiy A. The reproductive autoimmune failure syndrome. Am J Obstet Gynecol 1988; 159: 223–7.
25. Gleicher N. Some thoughts on the reproductive autoimmune failure syndrome (RAFS) and Th-1 versus Th-2 immune responses. Am J Reprod Immunol 2002; 48: 252–4.
26. Gleicher N, Vidali A, Karande V. The immunological „Wars of the Roses": disagreements amongst reproductive immunologists. Hum Reprod 2002; 17: 539–42.
27. Lee DW, Grasso P, Dattatreyamurty B, Deziel MR, Reichert LE. Purification of a high molecular weight FSH-receptor binding inhibitor from human follicular fluid. J Clin Endocrinol Metab 1993; 77: 160–8.
28. Perez MM, Gromoll J, Behre HM, Gassner C, Nieschlag E, Simoni M. Ovarian response to follicle-stimulating hormone (FSH) stimulation depends on the FSH receptor genotype. J Clin Endocrinol Metab 2000; 85: 3365–9.
29. De Castro F, Ruiz R, Montoro D, Perez-Hernandez D, Padilla ES, Real LM, Ruiz A. Role of follicle-stimulating hormone receptor Ser680Asn polymorphism in the efficacy of follicle-stimulating hormone. Fertil Steril 2003; 80: 571–6.
30. Keay SD, Liversedge NH, Mathur RS, Jenkins JM. Assisted conception following poor ovarian response to gonadotropin stimulation. Br J Obstet Gynaecol 1997; 104: 521–7.
31. Bancsi LF, Broekmans FJ, Eijkemans MJ, de Jong FH, Habbema JD, Te Velde ER. Predictors of poor ovarian response in in vitro fertilization: a prospective study comparing basal markers of ovarian reserve. Fertil Steril 2002; 77: 328–36.
32. Seifer DB, Lambert-Messerlian G, Hogan JW, Gardiner AC, Blazar AS, Berk CA. Day 3 serum inhibin-B is predictive of assisted reproductive technologies outcome. Fertil Steril 1997; 67: 110–4.
33. Creus M, Penarrubia J, Fabregues F, Vidal E, Carmona F, Casamitjana R, Vanrell JA, Balasch J. Day 3 serum inhibin B and FSH and age as predictors of assisted reproduction treatment outcome. Hum Reprod 2000; 15: 2341–6.
34. Yong PY, Baird DT, Thong KJ, Mc Neilly AS, Anderson RA. Prospective analysis of the relationship between the follicle cohort and basal FSH concentration, the inhibin response to exogenous FSH and ovarian follicle number at different stages of the normal menstrual cycle and after pituitary down-regulation. Hum Reprod 2003; 18: 35–44.
35. Fried G, Remaeus K, Harlin J, Krog E, Csemiczky G, Aanesen A, Tally M. Inhibin B predicts oocyte number and the ratio IGF-I/IGFBP-1 may indicate oocyte quality during ovarian hyperstimulation for in vitro fertilization. J Assist Reprod Genet 2003; 20: 167–76.
36. Martinez F, Barri PN, Coroleu B, Tur R, Sorsa-Leslie T, Harris WJ, Groome NP, Knight PG, Fowler PA. Women with poor response to IVF have lowered circulating gonadotrophin surge-attenuating factor (GnSAF) bioactivity during spontaneous and stimulated cycles. Hum Reprod 2002; 17: 634–40.
37. Van Rooij IA, Broekmans FJ, te Velde ER, Fauser BC, Bancsi LF, de Jong FH, Themmen AP. Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve. Hum Reprod 2002; 17: 3065–71.
38. Ochsenkuhn R, Strowitzki T, Gurtner M, Strauss A, Schulze A, Hepp H, Hillemanns P. Pregnancy complications, obstetric risks, and neonatal outcome in singleton and twin pregnancies after GIFT and IVF. Arch Gynecol Obstet 2003; 268: 256–61.
39. Nuojua-Huttunen S, Gissler M, Martikainen H, Tuomivaara L. Obstetric and perinatal outcome of pregnancies after intrauterine insemination. Hum Reprod 1999; 14: 2110–5.
40. Koivurova S, Hartikainen AL, Karinen L, Gissler M, Hemminki E, Martikainen H, Tuomivaara L, Jarvelin MR. The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in Northern Finland 1990–1995. Hum Reprod 2002; 17: 2897–903.
41. Tallo CP, Vohr B, Oh W, Rubin LP, Seifer DB, Haning RV Jr. Maternal and neonatal morbidity associated with in vitro fertilization. J Pediatr 1995; 127: 794–800.
42. Brizzi P, Dessole S, Tonolo G, Capobianco G, Milia L, Puddu L, Nardo LG. Effect of ovarian stimulation on plasma lipid and apolipoprotein concentrations in a population of infertile women undergoing IVF/embryo transfer. Reprod Biomed Online 2003; 7: 309–12.
43. Nikolaou D, Templeton A. Early ovarian ageing: a hypothesis. Detection and clinical relevance. Hum Reprod 2003; 18: 1137–9.
44. Mansour RT, Aboulghar MA, Serour GI, Al-Inany HG, Amin YM, Abou-Setta AM. The use of gonadotropin-releasing hormone antagonist in a flexible protocol: a pilot study. Am J Obstet Gynecol 2003; 189: 444–6.
45. Isikoglu M, Ozgur K. Rapid decline in ovarian reserve after repeated ART cycles in a 22-year-old IVF patient. Arch Gynecol Obstet 2003; 268: 206–8.
46. Klip H, van Leeuwen FE, Schats R, Burger CW; OMEGA Project Group. Risk of benign gynaecological diseases and hormonal disorders according to responsiveness to ovarian stimulation in IVF: a follow-up study of 8714 women. Hum Reprod 2003; 18: 1951–8.
47. Estienne V, Duthoit C, Costanzo VD, Lejeune PJ, Rotondi M, Kornfeld S, Finke R, Lazarus JH, Feldt-Rasmussen U, Franke WG, Smyth P, D'Herbomez M, Conte-Devolx B, Persani L, Carella C, Jourdain JR, Izembart M, Toubert ME, Pinchera A, Weetman A, Sapin R, Carayon P, Ruf J. Multicenter study on TGPO autoantibody prevalence in various thyroid and non-thyroid diseases; relationships with thyroglobulin and thyroperoxidase autoantibody parameters. Eur J Endocrinol 1999; 141: 563–9.
48. Weetman AP. Autoimmunity and endocrinology. Exp Clin Endocrinol Diabetes 1999; 107 (Suppl 3): S63–S66.
49. Valentino R, Savastano S, Tommaselli AP, Dorato M, Scarpitta MT, Gigante M, Lombardi G, Troncone R. Unusual association of thyroiditis, Addison's disease, ovarian failure and celiac disease in a young woman. J Endocrinol Invest 1999; 22: 390–4.
50. Pelinck MJ, Hoek A, Simons AH, Heineman MJ. Efficacy of natural cycle IVF: a review of the literature. Hum Reprod Update 2002; 8: 129–39.
51. Laing RW, Glaser MG, Barrett GS. A case of breast carcinoma in association with in vitro fertilization. J R Soc Med 1989; 82: 503.
52. Fernandez H, Frydman R. Cancer and in vitro fertilization. J In Vitro Fert Embryo Transf 1987; 4: 241–2.
53. Makrydimas G, Sotiriadis A, Paraskevaidis E, Pavlidis N, Agnantis N, Lolis D. Clear cell ovarian carcinoma in a pregnant woman with a history of infertility, endometriosis and unsuccessful IVF treatment. Eur J Gynaecol Oncol 2003; 24: 438–41.
54. Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet 1999; 354: 1586–90.
55. Venn A, Watson L, Lumley J, Giles G, King C, Healy D. Breast and ovarian cancer incidence after infertility and in vitro fertilisation. Lancet 1995; 346: 995–1000.
56. Dor J, Lerner-Geva L, Rabinovici J, Chetrit A, Levran D, Lunenfeld B, Mashiach S, Modan B. Cancer incidence in a cohort of infertile women who underwent in vitro fertilization. Fertil Steril 2002; 77: 324–7.
57. Lerner-Geva L, Geva E, Lessing JB, Chetrit A, Modan B, Amit A. The possible association between in vitro fertilization treatments and cancer development. Int J Gynecol Cancer 2003; 13: 23–7.
58. Hirtenlehner-Ferber K, Krampl E, Strohmer H, Husslein P. Multiple pregnancy. Ther Umsch 2002; 59: 683–8.
59. Schieve LA, Peterson HB, Meikle SF, Jeng G, Danel I, Burnett NM, Wilcox LS. Live-birth rates and multiple-birth risk using in vitro fertilization. J Am Med Assoc 1999; 282: 1832–8.
60. Adashi EY, Barri PN, Berkowitz R, Braude P, Bryan E, Carr J, Cohen J, Collins J, Devroey P, Frydman R, Gardner D, Germond M, Gerris J, Gianaroli L, Hamberger L, Howles C, Jones H Jr, Lunenfeld B, Pope A, Reynolds M, Rosenwaks Z, Shieve LA, Serour GI, Shenfield F, Templeton A, van Steirteghem A, Veeck L, Ulla-Britt W. Infertility therapy-associated multiple pregnancies (births): an ongoing epidemic. Reprod Biomed Online 2003; 7: 515–42.
61. Kametas NA, McAuliffe F, Krampl E, Chambers J, Nicolaides KH. Maternal cardiac function in twin pregnancy. Obstet Gynecol 2003; 102: 806–15.
62. Elster N. Less is more: the risks of multiple births. The Institute for Science, Law, and Technology Working Group on Reproductive Technology. Fertil Steril 2000; 74: 617–23.
63. Pinborg A, Loft A, Schmidt L, Langhoff-Roos J, Andersen AN. Maternal risks and perinatal outcome in a Danish national cohort of 1005 twin pregnancies: the role of in vitro fertilization. Acta Obstet Gynecol Scand 2004; 83: 75–84.
64. Bryan E. The impact of multiple preterm births on the family. BJOG 2003; 110 (Suppl 20): 24–8.
65. Tough SC, Newburn-Cook C, Johnston DW, Svenson LW, Rose S, Belik J. Delayed childbearing and its impact on population rate changes in lower birth weight, multiple birth, and preterm delivery. Pediatrics 2002; 109: 399–403.
66. Jansen RP. The effect of female age on the likelihood of a live birth from one in-vitro fertilization treatment. Med J Aust 2003; 178: 258–61.

67. Kuliev A, Verlinsky Y. The role of preimplantation genetic diagnosis in women of advanced reproductive age. Curr Opin Obstet Gynecol 2003; 15: 233–8.
68. Kuliev A, Cieslak J, Ilkevitch Y, Verlinsky Y. Chromosomal abnormalities in a series of 6,733 human oocytes in preimplantation diagnosis for age-related aneuploidies. Reprod Biomed Online 2003; 6: 54–9.
69. Froster UG. Genetic risks of in vitro fertilization. Geburtshilfe Frauenheilkd 1995; 55: 121–6.
70. Leridon H. Recent trends in late child-bearing. Contracept Fertil Sex 1987; 15: 271–4.
71. Sloter E, Nath J, Eskenazi B, Wyrobek AJ. Effects of male age on the frequencies of germinal and heritable chromosomal abnormalities in humans and rodents. Fertil Steril 2004; 81: 925–43.
72. Munne S, Magli C, Adler A, Wright G, de Boer K, Mortimer D, Tucker M, Cohen J, Gianaroli L. Treatment-related chromosome abnormalities in human embryos. Hum Reprod 1997; 12: 780–4.
73. Snijders RJ, Holzgreve W, Cuckle H, Nicolaides KH. Maternal age-specific risks for trisomies at 9–14 weeks' gestation. Prenat Diagn 1994; 14: 543–52.
74. Snijders RJ, Sundberg K, Holzgreve W, Henry G, Nicolaides KH. Maternal age- and gestation-specific risk for trisomy 21. Ultrasound Obstet Gynecol 1999; 13: 167–70.
75. Gianaroli L, Magli MC, Fiorentino F, Baldi M, Ferraretti AP. Clinical value of preimplantation genetic diagnosis. Placenta 2003; (Suppl B): S77–S83.
76. Gianaroli L, Magli MC, Ferraretti AP, Tabanelli C, Trombetta C, Boudjema E. The role of preimplantation diagnosis for aneuploidies. Reprod Biomed Online 2002; (Suppl 3): 31–6.
77. Henderson SA, Edwards RG. Chiasma frequency and maternal age in mammals. Nature 1968; 217: 22–8.
78. Munne S, Sandalinas M, Escudero T, Velilla E, Walmsley R, Sadowy S, Cohen J, Sable D. Improved implantation after preimplantation genetic diagnosis of aneuploidy. Reprod Biomed Online 2003; 7: 91–7.
79. Ethics Committee of the American Society for Reproductive Medicine. Sex selection and preimplantation genetic diagnosis. Fertil Steril 1999; 72: 595–8.
80. Wilton L. Preimplantation genetic diagnosis for aneuploidy screening in early human embryos: a review. Prenat Diagn 2002; 22: 512–8.
81. Pujol A, Durban M, Benet J, Boiso I, Calafell JM, Egozcue J, Navarro J. Multiple aneuploidies in the oocytes of balanced translocation carriers: a preimplantation genetic diagnosis study using first polar body. Reproduction 2003; 126: 701–11.
82. Shenfield F, Pennings G, Devroey P, Sureau C, Tarlatzis B, Cohen J. ESHRE Task Force on Ethics and Law. V. Preimplantation genetic diagnosis. Hum Reprod 2003; 18: 649–51.
83. Verlinsky Y, Cieslak J, Ivakhnenko V, Evsikov S, Wolf G, White M, Lifchez A, Kaplan B, Moise J, Valle J, Ginsberg N, Strom C, Kuliev A. Preimplantation diagnosis of common aneuploidies by the first- and second-polar body FISH analysis. J Assist Reprod Genet 1998; 15: 285–9.
84. Volarcik K, Sheean L, Goldfarb J, Woods L, Abdul-Karim FW, Hunt P. The meiotic competence of in-vitro matured human oocytes is influenced by donor age: evidence that folliculogenesis is compromised in the reproductively aged ovary. Hum Reprod 1998; 13: 154–60.
85. Munne S, Bahce M, Sandalinas M, Escudero T, Marquez C, Velilla E, Colls P, Oter M, Alikani M, Cohen J. Differences in chromosome susceptibility to aneuploidy and survival to first trimester. Reprod Biomed Online 2004; 8: 81–90.
86. Pal L, Santoro N. Age-related decline in fertility. Endocrinol Metab Clin North Am 2003; 32: 669–88.
87. Gianaroli L, Magli MC, Ferraretti AP, Munne S. Preimplantation diagnosis for aneuploidies in patients undergoing in vitro fertilization with a poor prognosis: identification of the categories for which it should be proposed. Fertil Steril 1999; 72: 837–44.
88. Pujol A, Boiso I, Benet J, Veiga A, Durban M, Campillo M, Egozcue J, Navarro J. Analysis of nine chromosome probes in first polar bodies and metaphase II oocytes for the detection of aneuploidies. Eur J Hum Genet 2003; 11: 325–36.
89. Gianaroli L, Magli MC, Ferraretti AP, Fiorentino A, Garrisi J, Munne S. Preimplantation genetic diagnosis increases the implantation rate in human in vitro fertilization by avoiding the transfer of chromosomally abnormal embryos. Fertil Steril 1997; 68: 1128–31.
90. Pehlivan T, Rubio C, Rodrigo L, Romero J, Remohi J, Simon C, Pellicer A. Impact of preimplantation genetic diagnosis on IVF outcome in implantation failure patients. Reprod Biomed Online 2003; 6: 232–7.
91. Ludwig M, Geipel A, Berg C, Gembruch U, Schwinger E, Diedrich K. Is intracytoplasmic sperm injection itself an indication to perform preimplantation genetic diagnosis (PGD)? About PGD, invasive prenatal diagnosis and genetic sonography. Fetal Diagn Ther 2001; 16: 68–82.
92. Obasaju M, Kadam A, Biancardi T, Sultan K, Fateh M, Munne S. Pregnancies from single normal embryo transfer in women older than 40 years. Reprod Biomed Online 2001; 2: 98–101.
93. Simpson JL. Changing indications for preimplantation genetic diagnosis (PGD). Mol Cell Endocrinol 2001; 183 (Suppl 1): S69–S75.
94. Verlinsky Y, Ginsberg N, Lifchez A, Valle J, Moise J, Strom CM. Analysis of the first polar body: preconception genetic diagnosis. Hum Reprod 1990; 5: 826–9.
95. De Neubourg D, Gerris J. Single embryo transfer – state of the art. Reprod Biomed Online 2003; 7: 615–22.
96. Te Velde ER, Pearson PL. The variability of female reproductive ageing. Hum Reprod Update 2002; 8: 141–54.
97. Koivurova S, Hartikainen AL, Sovio U, Gissler M, Hemminki E, Jarvelin MR. Growth, psychomotor development and morbidity up to 3 years of age in children born after IVF. Hum Reprod 2003; 18: 2328–36.
98. Koivurova S, Hartikainen AL, Gissler M, Hemminki E, Sovio U, Jarvelin MR. Neonatal outcome and congenital malformations in children born after in-vitro fertilization. Hum Reprod 2002; 17: 1391–8.
99. Tesarik J, Nagy ZP, Sousa M, Mendoza C, Abdelmassih R. Fertilizable oocytes reconstructed from patient's somatic cell nuclei and donor ooplasts. RBM Online, 2(3), 2001.
100. Kato O. A new approach for maturation arrest assisted induced activation using donor sperm. J Assist Rep Gen 2000; 17: 471.
101. Feichtinger W, Weghofer A. Somatic nucleus haploidization: The future from a clinician's point of view. J Assist Reprod Genet 2002; 19: 252.
102. Hohlagschwandtner M, Unfried G, Heinze G, Huber JC, Nagele F, Tempfer C. Combined thrombophilic polymorphisms in women with idiopathic recurrent miscarriage. Fertil Steril 2003; 79: 1141–8.
103. Unfried G, Bocskor S, Endler G, Nagele F, Huber JC, Tempfer CB. A polymorphism of the interleukin-6 gene promoter and idiopathic recurrent miscarriage. Hum Reprod 2003; 18: 267–70.
104. Lunenfeld B, Insler V. Future trends in infertility treatment: challenges ahead. Fertil Steril 1997; 68: 977–80.
105. Modan B, Ron E, Lerner-Geva L, Blumstein T, Menczer J, Rabinovici J, Oelsner G, Freedman L, Mashiach S, Lunenfeld B. Cancer incidence in a cohort of infertile women. Am J Epidemiol 1998; 147: 1038–42.
106. Griesinger G, Schultze-Mosgau A, Felberbaum R, Diedrich K. Zukünftige Wege der ovariellen Stimulation. Gynaekol Endokrinol 2003; 1: 150–8.
107. Hefler LA, Worda C, Huber JC, Tempfer CB. A polymorphism of the Nos3 gene and age at natural menopause. Fertil Steril 2002; 78: 1184–6.
108. Laml T, Schulz-Lobmeyr I, Obruca A, Huber JC, Hartmann BW. Premature ovarian failure: etiology and prospects. Gynecol Endocrinol 2000; 14: 292–302.
109. Almodin CG, Minguetti-Camara VC, Meister H, Ceschin AP, Kriger E, Ferreira JO. Recovery of natural fertility after grafting of cryopreserved germinative tissue in ewes subjected to radiotherapy. Fertil Steril 2004; 81: 160–4.
110. Revel A, Schenker J. Ovarian tissue banking for cancer patients: is ovarian cortex cryopreservation presently justified? Hum Reprod 2004; 19: 14–9.
111. Bath LE, Tydeman G, Critchley HO, Anderson RA, Baird DT, Wallace WH. Spontaneous conception in a young woman who had ovarian cortical tissue cryopreserved before chemotherapy and radiotherapy for a Ewing's sarcoma of the pelvis: Case report. Hum Reprod 2004; 19: 2569–72.
112. Johnson J, Canning J, Kaneko T, Pru JK, Tilly JL. Germline stem cells and follicular renewal in the postnatal mammalian ovary. Nature 2004; 428: 145–50.
113. Fasouliotis SJ, Schenker JG. Preimplantation genetic diagnosis principles and ethics. Hum Reprod 1998; 13: 2238–45.
114. Hengstschläger M. Kranke Gene. Das ungeborene Leben und die moderne Biomedizin. Maudrich, Wien, 2001.
115. Vergeer MM, van Balen F, Ketting E. Preimplantation genetic diagnosis as an alternative to amniocentesis and chorionic villus sampling: psychosocial and ethical aspects. Patient Educ Couns 1998; 35: 5–13.
116. Gleicher N, Tang Y. Blastomere transplantation in early human embryos. Fertil Steril 2003; 80 (Suppl 3): S77.

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