Family planning, desire to have children and fertility in older woman

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Summary

It is no longer the exception to find older couples that wish to have children visiting gynecological practices. It is crucial that these patients commence basic diagnostics as soon as possible and start the required treatment immediately. It is also of fundamental importance to realistically judge the slender prospects of success of conventional therapies such as clomiphene stimulation and intrauterine insemination. Care should be taken not to spend too much time on measures that have little prospect of success. Couples should be made aware of the limited perspective from the beginning, even if advanced techniques such as in vitro fertilisation (IVF) and controlled ovarian hyperstimulation are employed.

Beyond that, pregnancy loss and chromosomal anomalies represent a further psychological burden that increases with age. This article reviews demographic changes as well as individual patterns of reproduction and discusses the diagnostic parameters of the female ovarian reserve: FSH, AMH, Inhibin B and antral follicle counts.

Introduction

During the 20th century, reproductive behaviour in industrialized countries has radically altered the pattern of population growth, on a hitherto unknown scale. Apart from the availability of contraceptives and increased knowledge of reproductive processes, sociodemographic developments, such as a higher proportion of working women, altered role models, and an individualized life perspective, play a significant role. Reproductive behaviour is influenced by two determinants: women bear fewer children and they wait until they are older to have them.

Despite this decrease in desired parity, the increase in the number of older women wishing to have children leads to new problems and requirements for gynecological practices that will be dealt with in this article.

Terminology of reproductive medicine

Table 1 shows a short overview of some of the terminology used in reproductive medicine.

Tab. 1: Important terms used in reproductive medicine

Fertility	is the time-dependent distribution of conception, in a normal unselected population. Normal fertility is described as conception within a period of up to two years, if a couple has regular sexual intercourse during this period. Natural fertility depends on the ages of both partners, among other factors (The ESHRE Capri Workshop Group 2001).
Subfertility, infertility, and sterility	describes the cohort of women who do not conceive within the two-year period (WHO 2001). The term sterility applies either to the female or male individual, whereas the terms subfertility and infertility apply to the couple.
Fecundity	is defined as the probability of a woman conceiving during the menstrual cycle.

Historical background

During the first half of the 20th century, the decrease in fertility went hand in hand with a decrease in maternal age. This trend was largely due to a fall in the number of high-order pregnancies. In France, for example, the mean maternal age at childbirth fell from 29.5 years of age in 1901, to 26.5 years of age in 1977. However, since then the maternal age at childbirth has increased and in the year 2000 almost reached the level of 1900. A similar trend can be observed in Germany (see Fig. 1). This is mainly due to the fact that maternal age at first birth is rising (Daguet 2002).
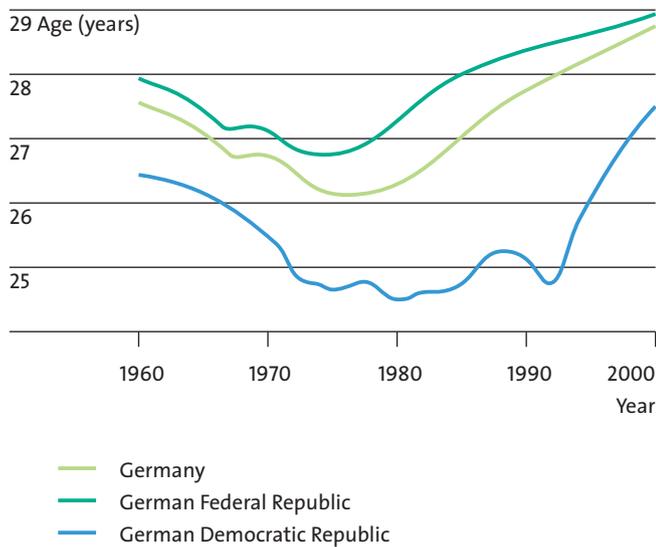
Figure 1: Average age of women at childbirth 1960-2001
(zdwa-Grafik/source: Europarat)

The average age of parents is steadily increasing: in 1980,
the average age of West German women at first birth was
27.1 years of age; in 1999, this had increased to 28.9 years
(Fig. 2). In East Germany, the average maternal age rose
from 24.5 to 27.5 years of age during the same period.

* In these countries only children born in existing marriages
  were included in the statistics.

Figure 2: Average age of women at first birth (Source: Europarat, OECD;
national statistics for Japan and the USA)

Furthermore, the total fertility rates in highly developed
countries are steadily decreasing and have reached extra-
ordinarily low figures. Under natural conditions, the fer-
tility rate is determined by three factors:
• the age at marriage or partnership,
• the length of the lactation period and
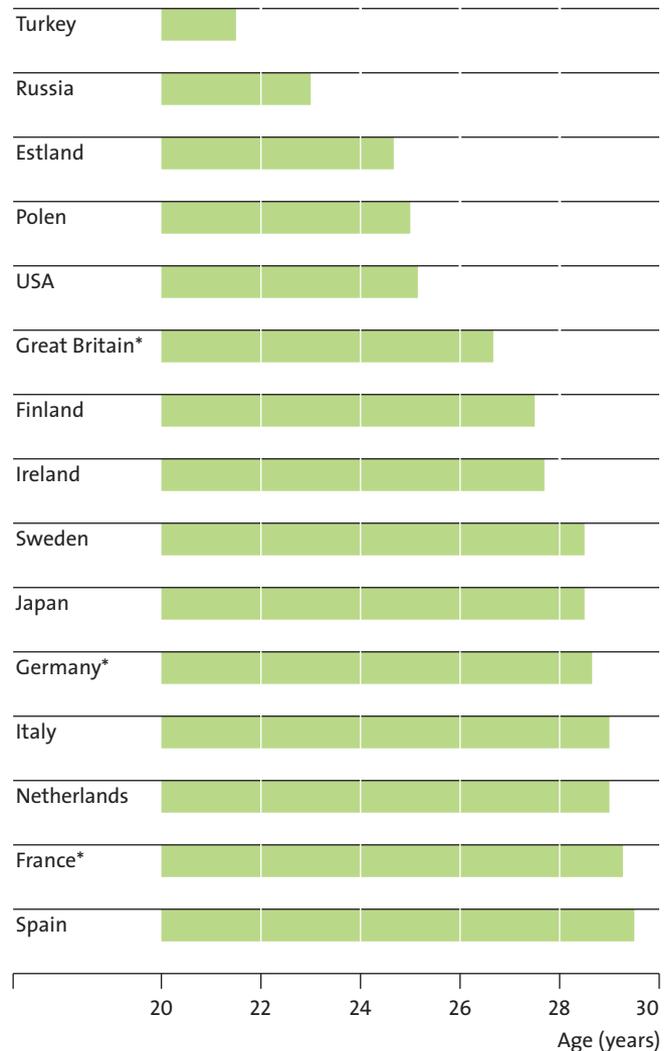• the maternal mortality rate.

Various studies have shown that in 17th century Europe the
average number of progeny per marriage was between five
and six children. This relatively low natural fertility rate was
due to late marriage (about 25 years of age or older), obli-
gatory breast feeding, and early death or widowhood.

In the past decades, the number of working women and
related length of professional training, availability of effec-
tive female contraceptive methods, and a decrease in stig-
matization of childless women have led to a strikingly low
rate of fertility. This can be described as the transition from
natural fertility to controlled fertility.

Present situation in Central Europe
Since 1972, there have been fewer births in Germany per
year than deaths in the same period. With an average birth
rate of 1.4 children per women, the generation of children
born does not replace the generation of their parents.
Hardly any European country has a birth rate sufficient to
maintain the size of its population without immigration.

Western Germany has one of the highest rates of nonchild-
bearing women (25 %) worldwide (Rostock Center for the
Study of Demographic Change 2008). The birth rate in the
Federal Republic of Germany is also low compared to birth
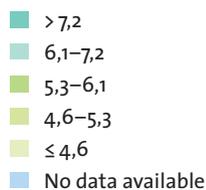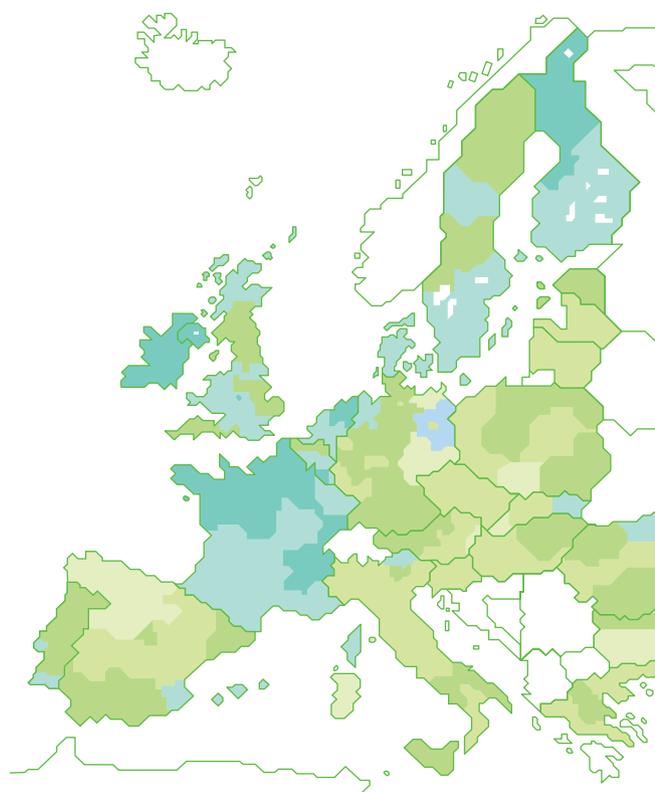rates of other European countries (see Fig. 3).

Societal consequences

The decrease in birth rate leads to demographic alterations, with serious consequences for the whole of the social system. These losses cannot be compensated by immigration. Social wealth is largely dependent on the size of the labor force. Because of the shift towards older age groups in the age pyramid, due to fewer births and the increase in life expectancy, the perceptible imbalance in favor of the older section of the population has grown. This leads to greater social and financial burdens on young wage earners and in particular, on families.

Giving support to couples who desire to have a child is therefore, not a correction of failed life and family planning but is urgently necessary in the interests of society. Unfortunately, during the past years, politics and the mutual social societies have increasingly revoked social necessities, so that despite the availability of more effective methods of treatment, the growing number couples desiring to have a child is being denied the required medical care for financial reasons. The statutory health insurance Modernization Act 2004 is especially to blame for placing therapies for childlessness in the domain of lifestyle medicine, which is bound to emerge as a grave mistake in coming years.

Physiological fundamentals of decreasing fertility

Under natural circumstances about 75 % of all women up to the age of 30 become pregnant within a year during unprotected sexual intercourse, which corresponds to a pregnancy rate of 6-7 % per menstrual cycle. The analogous data for 35 year-old women are 66 % per year and 5.5 % per cycle and for 40 year-olds 44 % per year and 3.7 % per cycle. The cumulative pregnancy rate in relationship to the number of cycles exhibits an exponential curve, as seen in Figure 4.

Delaying having children until a later age coincides with the decrease in physiological fertility. Studies carried out by Menken et al. (1986) show a significant decrease in natural fertility in various cohorts of married women (Fig. 5).
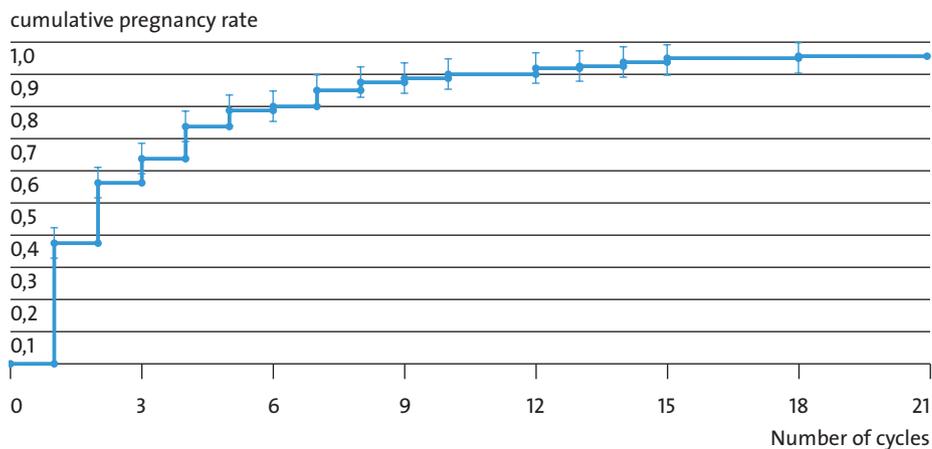

- > 7,2
- 6,1–7,2
- 5,3–6,1
- 4,6–5,3
- ≤ 4,6
- No data available

Figure 3: Average regional overall fertility rate, 2000–2002 – NUTS 2
(Source: Statistical Data: Eurostat Database: REGIO)

cumulative pregnancy rate

Figure 4: Cumulative pregnancy rates in relationship to the number of menstrual cycles (Gnoth et al. 2003)

- Hutterite, married from 1921 to 1930
- Citizens of Geneva, husbands born between 1600 and 1649
- Canada, married from 1700 to 1730
- Normandy, married from 1760 to 1790
- Hutterite, married before 1921
- Tunis, marriages of Europeans 1840 to 1859
- Normandy, married from 1760 to 1790
- Norway, married from 1874 to 1876
- Iran, village marriages 1940 to 1950
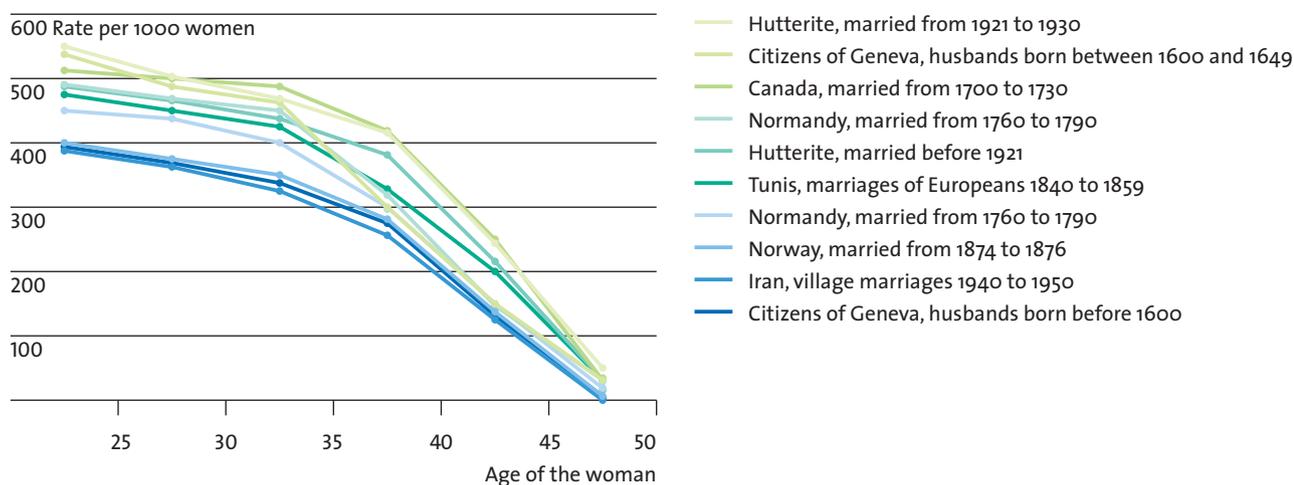- Citizens of Geneva, husbands born before 1600

Figure 5: Relationship between fertility and a woman's age (Menken et al. 1983)

Which factors explain the decrease in the age-dependent birthrate?

Worsening quality of sperm

During recent years, a number of studies have been published describing the worsening quality of sperm. In a study carried out between 1985 and 1986 by the Andrological Department of the University Clinic Leipzig on 1650 young men, a pronounced decreased in sperm concentrations, from 59.7 to 56.2 m/ml, was observed. In addition, the average sperm count in ejaculate fell from 195 to 138 million (Thierfelder et al. 1999). However, when evaluating this data one should take into account the fact that the men participating were from couples attending the university clinic for treatment for childlessness. The altered structure of the study cohort over the years may therefore have affected the data.

A study published in 1995 analyzing healthy sperm bank donors over a period of 20 years caused considerable interest. Within this period, there was a statistically significant decrease in mean sperm concentrations from 89 to 60 m/ml (Auger et al. 1995).

Furthermore, studies show that the quality of sperm depends on a man's age. The older a man is, the greater the impairments in the ejaculate volume, progressive motility, and sperm concentrations (Eskenazi et al. 2003).

Increase in male urogenital disease, particularly of infections

Infections that lead to obstruction of the ducutus deferenti or to testicular or epididymal damage also result in a decreased pregnancy rate. With increasing age, mumps infection in adults is a particular cause of male subfertility.

Decrease in coital frequency

Although it is often assumed that with increasing age the frequency of sexual intercourse decreases in both men and women, there are hardly any studies on this factor, which probably plays a role in sterility.

Increase in anatomic alterations to the female genital tract (e. g. fallopian tube obstruction, myoma, and endometriosis)

Postinflammatory alterations of the fallopian tubes, of the abdominal areas close to the ovaries, and of the endometrium are the main causes of decreased fertility in women. Although the incidence of acute urogenital infection is lower in older women, the proportion rises cumulatively in the total cohort of patients with postinflammatory impairments. Some studies point to a connection between socio-economic status, sexual behaviour, and sterility caused by inflammation.

Similarly, implantation failure is more frequently caused by myomas. Smaller structures may also affect the pregnancy rate, depending on the localization of the myoma (e. g. intracavital myomas).

Decrease in the number of potentially maturable follicles

Primordial follicles formed during the embryonic development of the female and oocytes capable of maturing decrease considerably during the female reproductive phase. The probability of multiple ovulations falls significantly, as reflected in the reduced incidence of twin births in older women. The proportion of anovulatory cycles also rises with increasing age, thus lowering the likelihood of conception.

Further age-dependent factors
• Impairment of oocyte quality
• Increased frequency of disrupted meiosis I and II
• Increase in mitotic disruption in early embryonic development

Influence of life style and environmental factors

For many years, it has been recognized that life style also influences a woman's chances of conception. Smoking, for instance, considerably impairs the rate of pregnancy. The 2006 German IVF Registry annual report showed a drop in the pregnancy rate from 28.9 % to 27 % per IVF or ICSI cycle. Adipositas reduces the pregnancy rate to almost the same extent as smoking. Both factors are determinants that can be influenced by the patient. The physician should therefore openly discuss this topic with patients and recommend adjustments in their life style. If necessary, patients should also receive dietary counseling. Patients who wish to have children are usually easily motivated to alter their life style, change their diet, take up some kind of sport, or to stop smoking.

A selection of methods of fertility diagnosis

Sonographic antral follicle count (AFC)

The antral follicle count is a simple and routine clinical method of evaluating expected fertility. During the early follicular phase, the number of follicles with a diameter of less than 10mm is counted in both ovaries. A meta-analysis of previous studies showed a good clinical correlation when predicting individual ovarian reserve (Broekmans et al. 2006).

FSH – follicle-stimulating hormone

This hormone has long been considered a parameter of ovarian function. FSH is a glycoprotein that consists of an α- and β-subunit, which is secreted by the anterior lobe of the pituitary gland. FSH stimulates the ovaries, especially influencing the further development of matured antral follicles. FSH levels are controlled by a feedback circuit via estradiol and activin. As estradiol is produced mainly by the granulosa cells of the maturing follicle, the rising level of estradiol (as a result of oogenesis) inhibits secretion of FSH. Therefore, FSH levels indirectly reflect the estradiol synthetic capacity.

FSH levels rise during the menstrual cycle, in the course of the preovulatory gonadotropin peak, and are then partially suppressed during the luteal phase. FSH levels should therefore be evaluated at a defined point in time (3rd day of the cycle). Although raised FSH levels usually indicate an unfavorable prognosis, the predictive significance of an FSH value within the reference interval for premenopausal women is only limited.

Inhibin

Inhibin is also a glycoprotein (proteohormone) with two subunits (dimers) of the α- and β-chain; it belongs to the TGF-β group of cytokines. There are two known types of β-chain: A and B.

Inhibin A is only produced in the granulosa cells of women, as well as in the feto-placental unit during pregnancy. Inhibin B is produced in the Sertoli cells in men and in the granulosa cells in women. It directly inhibits and regulates FSH secretion in the pituitary gland.

Early on in the transitional period of the perimenopause, the inhibin B levels circulating during the follicle phase fall considerably, without any significant alteration in estradiol or FSH levels. Serum levels of inhibin B should therefore be determined if there is any suspicion of ovarian exhaustion and should be taken into consideration when a couple plans to have a child. However, concentrations vary greatly during the menstrual cycle. Recent studies could only establish a moderate predictive value with regard to ART treatment results ("assisted reproductive technology"). Thus, determination of serum inhibin B levels is only of limited significance (Popovic-Todorovic et al. 2003).

Anti-Mullerian hormone

Like inhibin, the anti-Mullerian hormone (AMH) is a growth hormone. It is a dimerized glycoprotein, the synthesis of which is coded by the gene on chromosome 19. The hormonal function played by AMH in sexual development and embryonic differentiation has long been established. AMH is produced by the Sertoli cells in the fetal testicles and leads to involution of the Mullerian ducts, structures of the female genital tract after which it is named.

In recent years, other characteristics of AMH have been discovered that make it a valuable parameter when estimating ovarian reserve: AMH is produced by ovarian granulosa cells of the primary follicle. Preantral and antral follicles express the maximum secretion of AMH. The synthesis of AMH slowly decreases during follicular development and finally disappears during FSH-dependent maturation of the follicle. However, the remaining follicles in the pool continue to produce AMH, which makes cycle-independent determination possible. The concentration of AMH in serum most probably reflects the existing potential of female fecundity. Values below 1 ng/ml point to a decreased ovarian reserve. This reserve, an expression of actual fecundity, consists of the number of potentially maturable follicles as well as the quality of the oocytes. It would thus seem reasonable to search for reliable follicle pool markers. Over the past years, various hormonal and sonographic parameters have been studied. Apart from determination of the number of antral follicles (> 10 mm, AFC), determination of AMH concentrations would appear to be a similarly reliable method for estimating ovarian reserve.

The latest studies have established a connection between AMH concentrations and insemination rates in in-vitro fertilization. It therefore appears likely that AMH determination not only provides a method of estimating the number, but also of assessing the quality of oocytes (Lekamge et al. 2007).

Methods of fulfilling the desire to have a child

In general, diagnostics and treatment should be initiated without delay for older couples who desire to have a child. Present data show an alarming decline in pregnancy rates, even if methods of assisted reproduction are employed while time elapses. For this reason couples should undergo basic examinations during their first visit to the gynecologist to provide initial information on possible fertility impairments. These tests include an ultrasound examination that is more detailed than usual. The thickness of the endometrial layer should be measured in relationship to the phase of the menstrual cycle. Possible myoma or endometrial polyps, which appear as light patches in the endometrium, should be paid particular attention. If the view is altered from the sagittal to the transverse plane, uterine malformations such as a uterus bicornis are easily recognizable. A hysteroscopy should be carried out to examine what may appear to be minor abnormalities. The examination can be performed with miniaturized instruments, without anesthesia. The adnexal area should be examined for endometrioma or hydrosalpinges. Any findings in these areas should be followed by laparoscopic inspection and examination of the patency of the fallopian tubes.

Under the dictates of SHI medicine, it is generally not opportune to carry out extensive endocrinological diagnostics. An initial mid-luteal test should be performed for a first appraisal of a couple's situation; estradiol and progesterone levels should be determined, as well as TSH for orientation. During menstruation, FSH and AMH levels should also be tested. Dysfunctions in prolactins and androgens can be excluded with some certainty if the findings of these tests are negative. If No. 32013 is entered on the laboratory assignment, hormone analysis costs do not burden the practice budget.

The physician should request the man to undergo a spermiogram at the same time as initial diagnostics are carried out for the woman. This request is occasionally met with resistance, particularly from men with a migratory background. The author's own personal experience in reproductive medicine has shown that even if a man claims to have previously fathered children, the possibility of andrological sterility still cannot be discounted.

If the findings do not warrant a laparoscopy, the fallopian tubes should still be examined using a hydrosonographic contrast medium, even if the female anamnesis is normal.

Hamilton et al. (2003) has shown that hysterosalpingo contrast sonography is just as diagnostically significant as laparoscopic inspection of tubular patency when both examinations are compared in view of subsequent pregnancies. There is contention, however, as to whether inspection of the fallopian tubes using water-soluble contrast medium subsequently leads to an increase in the pregnancy rate (e. g. Echovist 200®) (Johnson et al. 2005).

Clomiphene treatment is recommended for many older patients who wish to have a child. As documented by a large study carried out by the Harvard Medical School (Dovey et al. 2008), this method is only of limited significance. The data from 4 199 insemination cycles stimulated by clomiphene, from 1730 patients, show a clear drop in pregnancy rate in the older patients (Fig. 6). The rate of pregnancy decreases from 11.5 % per insemination cycle in women under the age of 35, to 4.3 % for women from 41-42 years of age. Of the 55 patients under the age of 42, only one woman became pregnant. The largest number of pregnancies was conceived during the first two cycles. Clomiphene therapy is not recommended for women from age 40 onwards. Furthermore, clomiphene treatment should be limited to only a few cycles in the 35-40 year-old age group and as soon as treatment is changed to stimulation with HMG or FSH, or if participation in an IVF program at a specialist clinic is considered.

Even if effective stimulation and in vitro fertilization achieve significantly higher pregnancy rates, there are age limitations. The author's own studies attest not only to a decreased pregnancy rate, but also to an increasing frequency of aneuploidies and female genital tract disease, as an associated higher rate of spontaneous abortion. As shown in Figure 7, the rates per live birth have fallen to about 10 % per IVF or ICSI cycle in patients over the age of 40. The miscarriage rate in this age group has also risen to over 35 %. During counselling, couples should be informed of the high frequency of miscarriage and particularly of the possibility of aneuploidies such as trisomy 21.
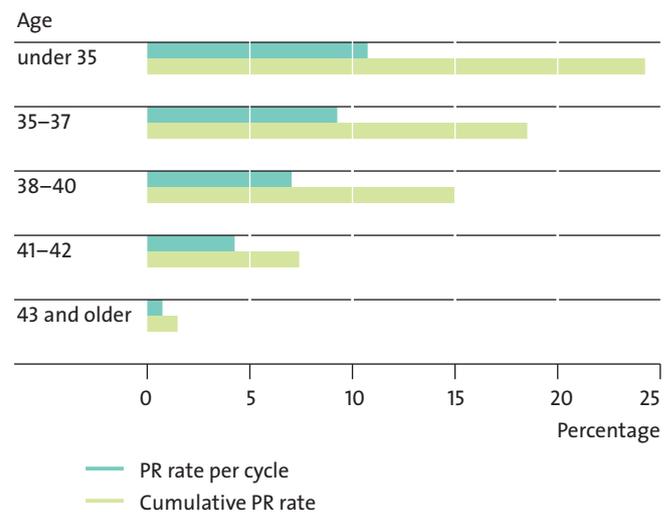

Figure 6: Age-dependent pregnancy rates in women after stimulation with clomiphene (according to Dovey et al. 2008)
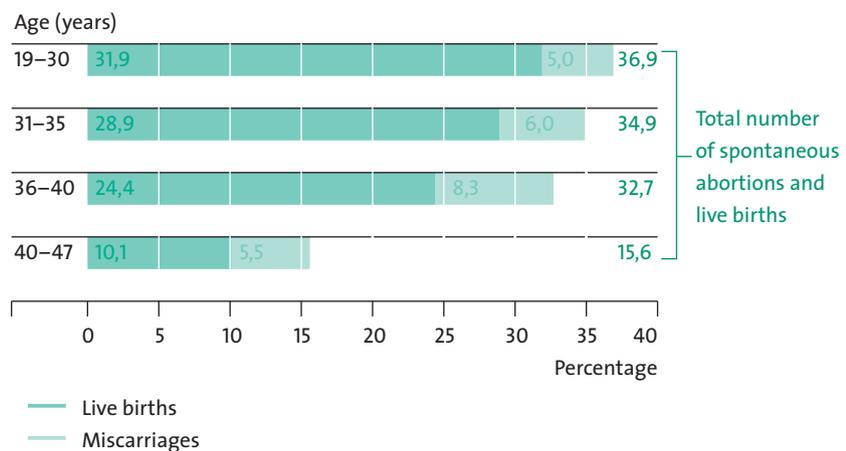PR rate: Pregnancy rate

Figure 7: Age-dependent pregnancy rate per IVF cycle; clinical pregnancy rates and miscarriages per embryo transfer; median age 35.5 years; n = 1512 per year.

In recent years, there had been hopes of achieving an increase in pregnancy rates and the number of life births by selecting chromosomally normal oocytes (so called polar body diagnostics). This assumption is only valid in certain cases: women who do not produce more oocytes than would be transferred any way, naturally cannot benefit from polar diagnostics. A meaningful selection of genetically normal oocytes and pronuclear cells presupposes that an adequate number of oocytes, a number not normally attained in older women, can be collected.

As shown in Figure 8, the rate of pregnancy that can be attained is dependent on the number of oocytes collected and the number of embryos transferred for each individual woman.
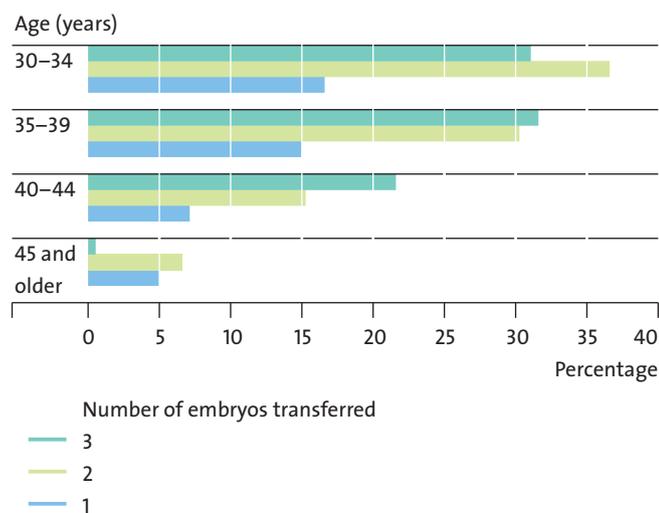

Figure 8: Pregnancy rate per embryo transfer, depending on the age of the woman and the number of embryos transferred; data from the German IVF Registry 2006

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CME-Continuing Medical Education

Family planning, desire to have children and fertility in older woman

Question 1
The decrease in fertility in the first half of the 20th century was due to
a. the loss of men during both world wars,
b. more widespread use of oral contraceptives,
c. a decrease in high-order motherhood,
d. increased tubular sterility resulting from genital infections,
e. prolongation of the lactation period.

Question 2
The number of twin births decreases with age. This is caused by
a. a decrease in the number of multiple ovulations,
b. a decrease in coital frequency,
c. an increase in the number of maturing follicles,
d. a rise in AMH levels,
e. contraceptive measures.

Question 3
Fertility is defined as
a. the probability of conceiving during a menstrual cycle,
b. the time-dependent distribution of conception in a nonselected normal population,
c. the number of children born to a woman,
d. the period from cessation of contraception to conception,
e. the figure by which the birth rate exceeds the mortality rate in a population.

Question 4
Inhibin B
a. is a growth hormone,
b. is produced in the oocytes,
c. consists of two subunits,
d. production increases with age in women,
e. is only found in women.

Question 5
The "antral follicle count" (AFC)
a. makes it possible to estimate the number of oocytes that can be collected before follicular puncture,
b. is a better predictive method of estimating ovarian reserve than determination of FSH,
c. is best carried out before ovulation,
d. only includes follicles with an average diameter of over 10 mm,
e. does not correlate with age.

Question 6
With older patients wishing to have children
a. the physician should proceed conservatively due to the lower pregnancy rate,
b. clomiphene is the medication of choice,
c. diagnostics and therapy should be commenced as soon as possible,
d. a better pregnancy rate is attained using clomiphene than by FSH and HMG preparations,
e. a spermiogram is unnecessary as female factors determine the pregnancy rate.

Question 7
In patient cohorts desiring to have a child
a. the pregnancy rate does not depend on the age of the man,
b. the likelihood of spontaneous pregnancy decreases, the longer the couple have to wait before conceiving,
c. most pregnancies are conceived after the 3rd insemination cycle,
d. the pregnancy rate does not depend on the number of oocytes collected during in vitro fertilization,
e. the pregnancy rate does not correlate with coital frequency.

Question 8
AMH
a. is not found in the male fetus,
b. does not play an important role in sexual differentiation,
c. consists of unsaturated fatty acids,
d. can be determined irrespective of the phase of the menstrual cycle,
e. is a decapeptide and inhibits the pituitary gland.

Question 9

Which of the following statements is correct?

a. About 75 % of all women under the age of 30 become pregnant within a year if contraceptives are not used.

b. 30 % of all sexually mature women fall in love at least once a year.

c. If contraceptives are not used, the average pregnancy rate per cycle increases with the number of cycles, within one year.

d. A male partner who smokes does not influence the pregnancy rate of a couple wishing to have a child.

e. There is no correlation between overweight and the decrease in the pregnancy rate.

Question 10

Which statement is *incorrect*?

a. In Germany, women bear an average of 1.4 children.

b. The number of mortalities is greater than the number of births.

c. The SHI Modernization Act has improved the situation of couples desiring a child, especially that of older couples.

d. At present, the birth rate in Eastern Germany is lower than that in the former West German states.

e. In 17th century Europe, the average number or progeny per marriage was between five and six children.