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Infertility: definitions and strategies

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Anti-Müllerian hormone is a sensitive marker of ovarian reserve and is suitable for screening. This is important for all women whose age is not critical yet and who not started their "project of family planning". Looking up individual anti-Müllerian hormone levels in percentile normograms inform about the biological clock which might be put back or forward. By this anti-Müllerian hormone supports clinical decisions.

Key words: **Reproductive history - Biological clocks - Anti-Muellerian hormone - Infertility.**

In most western societies the reproductive situation has changed dramatically in the last decades. From the end of the 60th onwards the link between sexuality and reproduction was broken for the first time. Personal careers and development became possible more easily and participation in the world of work became easily possible as well by delaying family planning or even deciding not to have children. But later in life an increasing number of women change their mind. So, the reproductive situation of today may be summarized as follows:

— late first pregnancy;

— exact timing of pregnancies to a period compatible with personal lifestyle;

— pregnancies after long periods of contraception, mostly in the last quarter of the fertile years and;

— finally, a low number of children.

In the future the fear of childlessness might arise. Consequently, we will have an increasing demand for reproductive medicine. Therefore, reproductive medicine has to figure out treatment procedures balancing between possible under-treatment and possible over-treatment if couples come for a late first child. This includes the necessity of ovarian reserve assessment which is of great importance because of increasing costs by the increasing demand for medical assistance. Though, a new "medical subspeciality" was born: periconceptional medicine preparing women and men for optimal health conditions before conceiving.

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Heterogeneity of female fertility

Female fertility declines with age. This decline is due to a decreased probability of conception on the one hand and an increased risk of spontaneous abortions on the other hand. The decreasing probability of conception with age is the result of accumulated risks of events which might have

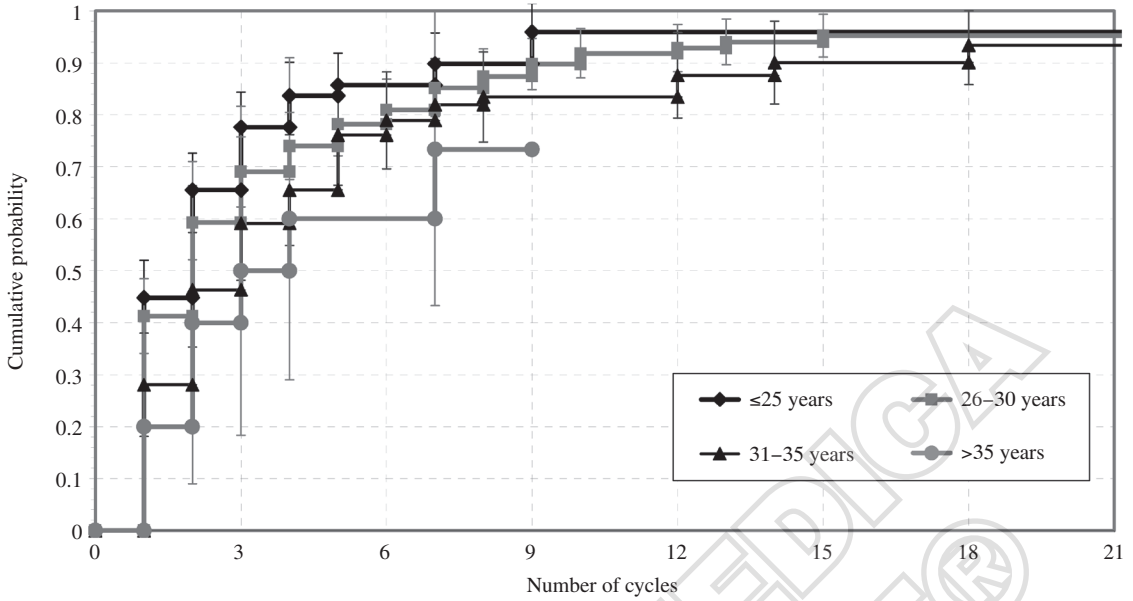

Figure 1.—Cumulative probability distribution of conception for all couples in different age categories over time calculated from the Kaplan-Meier survival functions for unselected couples, according to Gnoth *et al.*[3]

affected fertility (*e.g.*, tubal disorders after pelvic infections or ectopic pregnancies) and, mainly, ovarian aging. Chromosomal aneuploidy is the major course of "bad" oocytes with low fertilisation potential and the increasing risk of early pregnancy loss with advancing age.[1] Structural and biochemical abnormalities in oocytes with impaired mitochondrial function are involved as well.

The best outcome measures for human fertility are cumulative pregnancy and cumulative live birth rates.

Two important prospective studies report on cumulative probabilities of spontaneous conceptions. Wang *et al.* observed 518 newly married Chinese textile workers (20-35 years of age), trying to conceive.[2] They only recorded vaginal bleeding, episodes of sexual intercourse and took daily pregnancy-tests from the first morning urine specimens. About 15% of the women became clinical pregnant in the first two cycles and more than 50% in the first six cycles. In the same year Gnoth *et al.* published on 346 women using natural family planning methods to conceive from the first cycle onwards.[3] Only cycles with intercourse in the fertile phase were included. Pregnancy was assessed by either ultrasound, positive pregnancy test or a luteal phase over 18 days. In the latter cases only later confirmed clinical pregnancies were included.

Figure 1 shows the cumulative spontaneous probability of conception for all women stratified for different age groups. About 80 % of all women became pregnant in the first six cycles. The differences between the age groups are of course statistically significant. For those who finally conceived (Figure 2) they found an important difference in contrast: 88% of all women conceived in the first six cycles but there were no statistical significant differences between the different age groups. Obviously, there is a group of highly fertile women even with advancing age, conceiving as quickly as the younger ones. This accounts for the increasing heterogeneity of fertility with advancing age.

This heterogeneity in fertility with advancing age is because of the well-known variability of female reproductive, mainly ovarian, aging.[4] There is a wide range in age from the onset of subfertility, sterility, cycle irregularity or menopause. From the clinical point of few it is of great importance

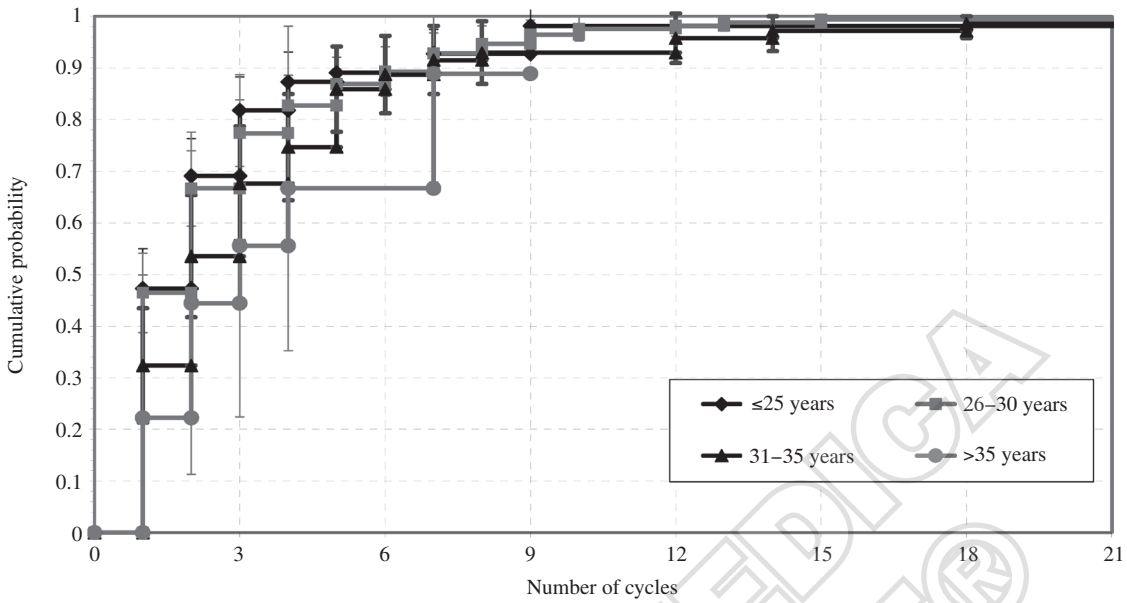

Figure 2.—Cumulative probability distribution of conception for truly fertile couples in different age categories over time calculated from the Kaplan-Meier survival functions, according to Gnoth *et al.*[3]

to detect the onset of subfertility which may range from the early 20th up the late 30th because there is still some time to act. But what really is the face of subfertility?

Subfertility generally describes any form of reduced fertility with prolonged time of unwanted non-conception. Nowadays infertility is used synonymously with sterility with only sporadically occurrence of spontaneous conceptions. Concluding from prospective conception studies we have a prevalence of about 20 % of at least slightly subfertile couples after six unsuccessful cycles but still having a 50% chance of conceiving spontaneously in the next six cycles. But half of them are already moderately or probably seriously subfertile. These are those couples who were finally unsuccessful in twelve cycles to achieve a pregnancy, which was the old definition of infertility. Again 50% of these couples will conceive in the next 36 months. After this time about 5 % of all couples are remaining being nearly completely infertile with only sporadic spontaneous conceptions in the future (Table I). Only they may be called sterile.[5]

Age independent, the onset of subfertility has to be diagnosed after six unsuccessful cycles with fertility focused intercourse.[6] After that a basic infertility work up will identify couples with severe infertility problems.

TABLE I.—*Definition and prevalence of subfertility and infertility, according to Gnoth* et al.[5]

Time	Prevalence/Grading	Chances to conceive spontaneously in the future
After six unsuccessful cycles	About 20% at least slightly subfertile couples	50% of these couples will conceive spontaneously in the next six cycles, the remaining are moderately subfertile
After 12 unsuccessful cycles (former clinical definition of infertility/sterility)	About 10% at least moderately or seriously subfertile couples	50% of these couples will conceive spontaneously in the next 36 months, the remaining are nearly complete infertile
After 48 months	About 5% nearly complete infertile couples (= sterile)	Couples with only sporadic spontaneous conceptions

Those may benefit from an early resort to assisted reproduction treatment. Others may be encouraged to wait.

Assessing ovarian reserve: the biological clock

Waiting or treating? Balancing infertility under- and over-treatment will be possible much easier by assessing the ovarian reserve. Age of the female partner, ovarian reserve and time of involuntary childlessness are the key variables determining the reproductive potential (Figure 3). Each of the factors opens up or closes down the reproductive window.

In the last few years the anti-Müllerian hormone (AMH) has become the most promising variable assessing ovarian reserve [7, 8] and is strongly correlated to the antral follicle count.[9] Newest studies show that it its performance is better than FSH or age alone.[10] A lot of important studies have been published on anti-Müllerian hormone. The facts could be summarized as follows:

1. the glycoprotein AMH belongs to the TCF-β-family, coded on chromosome 19. It is positive correlated with the histological pool primordial follicles.[11] AMH receptor-polymorphisms and AMH as well as AMH mutations has been described and associated with irregular cycles;[12; 13]

2. AMH is a product of primary and small antral follicles (around 4 mm up to 7 mm a state in which the follicles become relevantly receptive for FSH). It inhibits FSH secretion and within the ovary recruitment of primary follicles out of the primordial follicle pool;[14, 15]

3. AMH levels decline with age but show high standard deviations;[16-18]

4. AMH has no clinical relevant, intra- and inter-cycle variations;[14]

5. AMH levels are obviously not influenced by oral contraceptives.[19]

— Three to four years prior to menopause AMH will no longer be detectable.[20-22] Long-time predictions of menopausal transition still do not have enough and robust evidence yet to pinpoint the exact individual age of menopause because of the differences in individual rates of decline of anti-Müllerian hormone levels, especially in young patients. However, the current models are intriguing and with increasing data volume and two point measurements predictions will be more reliable soon. Most important however is the detection of a diminished ovarian reserve with an early loss of follicles especially in younger women and not the exact prediction of menopause. For this purpose anti-Müllerian hormone shows sufficient diagnostic performance for clinical decisions.

— Very recently new anti-Müllerian hormone reference values [23] and percentile normograms were published (Figure 4).[24] The percentiles are based on internationally collected, cross-sectional data of an infertile population. PCOS patients were excluded. For the first time they allow an individual positioning of patients and also show the probable future decline of anti-Müllerian hormone levels. A series of measurements in a young woman with falling levels may be an early warning signal suggesting rapidly declining fertility. Although the normograms were calculated from data of an infertile population this is not a relevant limitation for a general use.[25] Women with a

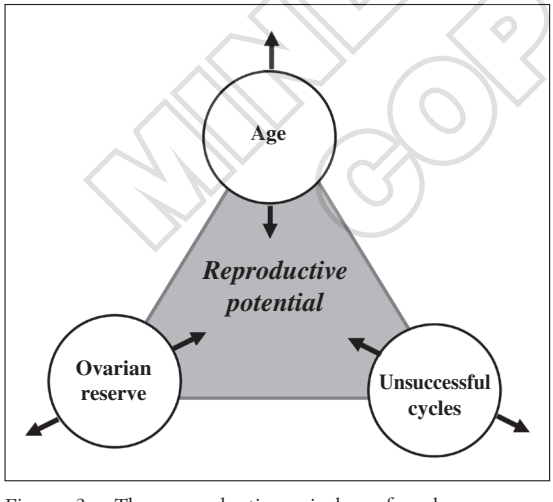

Figure 3.—The reproductive window: female age, ovarian reserve and time of involuntary childlessness (number of unsuccessful cycles) are the key variables determining its size.

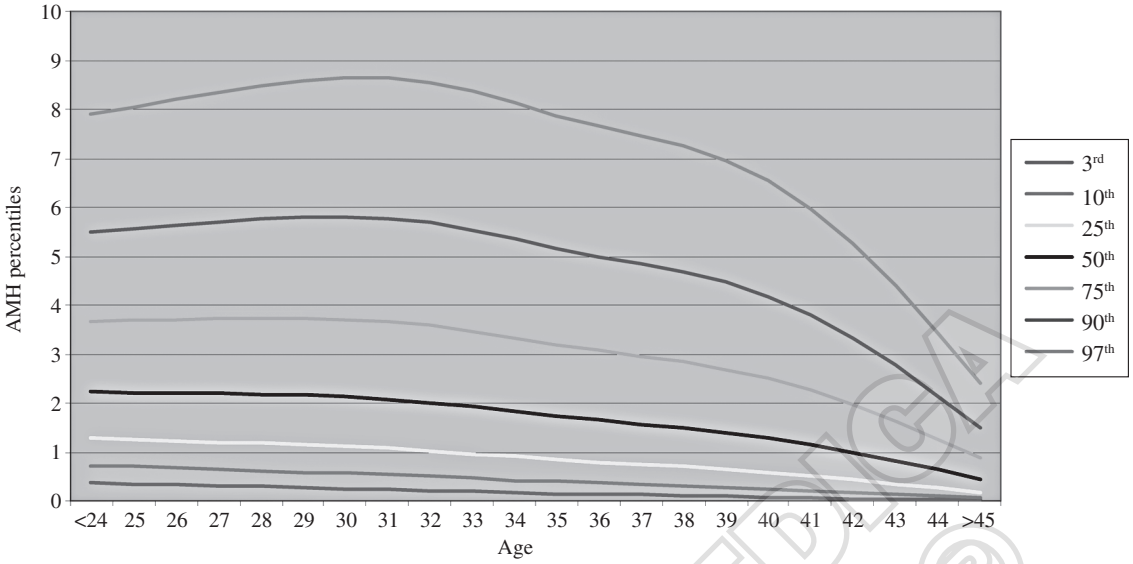

Figure 4.—Age-related normogram for anti-Müllerian hormone (AMH in ng/ml) with correlation between the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles, according to Almog *et al.*[24]

reduced ovarian reserve might be over represented in this cohort but then low levels of anti-Müllerian hormone in a presumably fertile woman are even worse.

— Also in this study anti-Müllerian hormone revealed its best correlation to the antral follicle count, less to FSH or age alone. This fact again accounts for the high heterogeneity in reproductive aging in which the year of age alone is not a suitable parameter assessing ovarian reserve and conception probabilities.

— Anti-Müllerian hormone levels ≤1.7 ng/mL (cut off, Beckman Coulter/DSL assay generation 2 [26]) detect 80 % of our patients with a reduced ovarian reserve assessed from the results of later ovarian stimulations.[27] Levels ≤0.7 ng/mL will be found in patients with a massive reduced ovarian reserve with less than 3 oocytes after high dose stimulation and oocyte retrieval afterwards. Undetectable levels will precede the final menopause three to five years.[22, 28] This is of importance because the spontaneous pregnancy rates seven years prior to menopause are less than 10 % per year.[29, 30]

— Anti-Müllerian hormone has also been suggested as a tool for screening and diagnose of polycystic ovary syndrome and as a essential parameter for classification of hyperandrogenism. Cut-off levels of 8 ng/mL for PCOS were published.[31, 32]

— Therefore measurement of anti-Müllerian hormone plays an important role in women over 30 and especially over 35 years of age. With the help of percentile normograms we may assess whether the biological clock has been put forward or back.

— The percentile normograms for anti-Müllerian hormone show a very low discriminatory capacity ≤1 ng/mL. Therefore, confirmation tests are required. Because of the strong correlation of anti-Müllerian hormone to the antral follicle count AFC-percentile normograms have also been published recently (Figure 5).[33]

— Both normograms complement each other beautifully because AFC-percentile normograms have a much better discriminatory capacity below the 50th percentile. The antral follicle count however depends on different, partly very variable factors (examination time, ultrasound machine, body weight of patients, investigator's experience). Therefore, the AFC is not a suitable screening method but a reliable confirmation test.

— It has been a controversial matter of

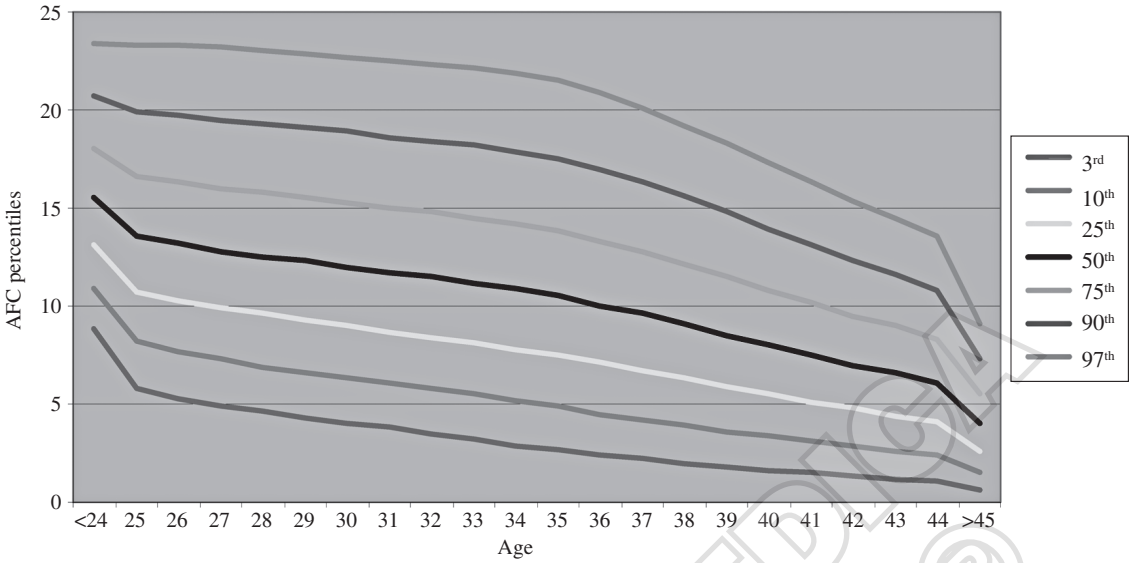

Figure 5.—Age-related normogram for antral follicle count (AFC, both ovaries) with correlation between 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles, according to Almog *et al.*[33]

discussion whether anti-Müllerian hormone may be also a marker of oocyte quality. According to the results up to now oocyte quality is much more dependent on the individual woman's age.[34-37]

Impending subfertility has a face - Anti-Müllerian hormone screening

Age, number of unsuccessful cycles with fertility focused intercourse and the woman's individual position in the anti-Müllerian hormone percentile normogram reflect the couple's reproductive potential.

Anti-Müllerian hormone is a very promising and predictive marker of the reproductive potential when age is not critical yet and "the project family planning" has not started yet.[16] Anti-Müllerian hormone could be used as a screening parameter for those who want to start their "project of family planning" in the future. If an individual anti-Müllerian hormone level is on a low percentile an infertility work up should be done early to exclude further factors which might close down the reproductive window.[28, 38-40] Figure 6 suggests clinical procedures based on the results of an anti-Müllerian hormone screening.

In case of resort to assisted reproductive techniques including ovarian stimulation only, intrauterine inseminations after controlled ovarian hyperstimulation and all extracorporal techniques) ovarian stimulations should be dose-adjusted based on anti-Müllerian hormone levels. If anti-Müllerian hormone is ≤0.7 ng/mL a high dosage of gonadotropins should be chosen right from the start of stimulation to avoid cycle cancellation because of unsatisfying ovarian response in an IVF setting.[27, 41]. In case of anti-Müllerian hormone levels ≥6 ng/mL a reduced dosage and an adapted protocol for controlled ovarian stimulation is important to minimize the danger of a hyperstimulation-syndrome later.[42] Both considerations are important and patient friendly because cycle cancellation due to suboptimally adjusted dosages of gonadotropins is very unsatisfying because of the enormous costs of these drugs. It is very important to notice that anti-Müllerian hormone (especially >0.7 ng/mL) does not correlate with the clinical pregnancy rates

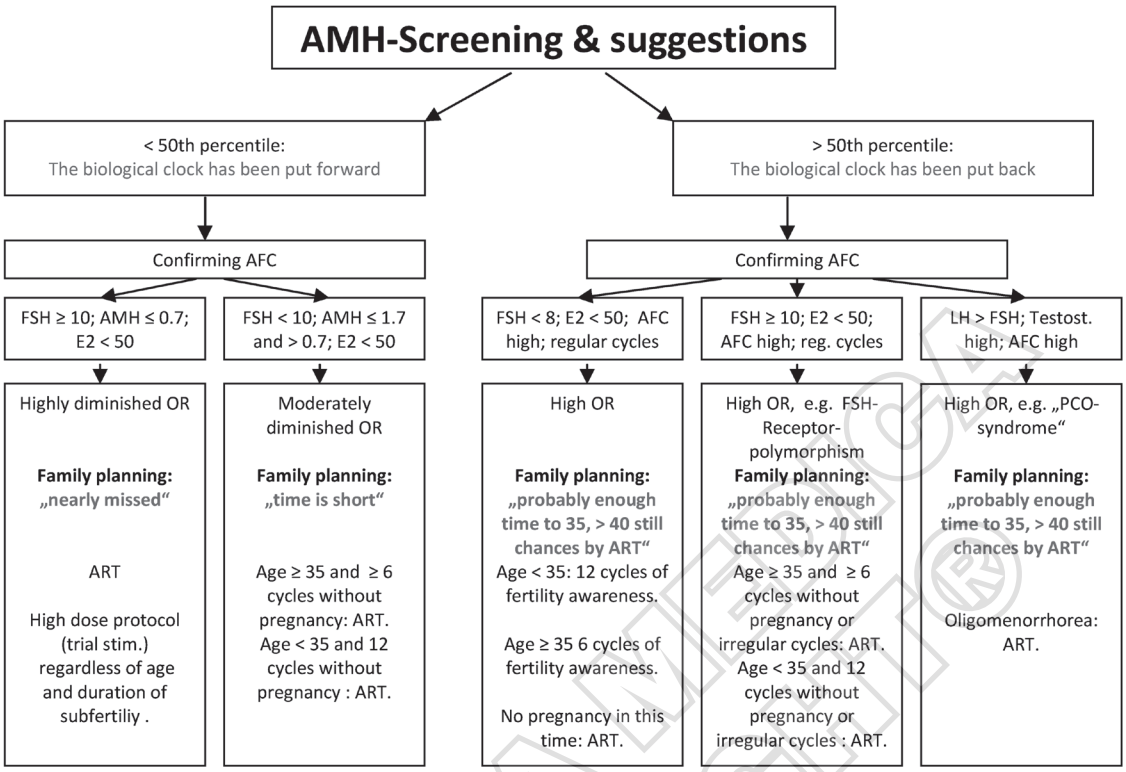

Figure 6.—Screening of anti-Müllerian hormone (AMH) with suggestions for clinical decisions. AFC: antral follicle count. OR: ovarian reserve. Fertility awareness: fertility focused intercourse (natural family planning, urinary LH detection, cycle monitors). ART: resort to assisted reproductive techniques including ovarian stimulation only, intrauterine inseminations after controlled ovarian hyperstimulation and all extracorporal techniques.

in IVF.[43-46] Especially in younger patients with only a small number of oocytes but with better quality oocytes certain compensations with high dose protocols are possible. So, even very low anti-Müllerian hormone levels should not be the sole basis of denying reproductive interventions. The quality of embryos for transfer is mainly a result of the patient's age and duration of infertility. The success of ART is finally a result of the number of transferred embryos over time.[47]

Nowadays contraception's most important side-effect is risk of subfertility by delaying pregnancy. A screening for anti-Müllerian hormone levels supports further decisions especially in women over 30 years of age, *e.g.*, a change to fertility awareness methods for further contraception or planning a pregnancy. After six unsuccessful cycles a basic fertility work-up should be considered before advising further waiting and trying.

Conclusions

Anti-Müllerian hormone is a sensitive marker of ovarian reserve and is suitable for screening. This is important for all women whose age is not critical yet and who not started their "project of family planning". Looking up individual anti-Müllerian hormone levels in percentile normograms inform about the biological clock which might be put back or forward. By this anti-Müllerian hormone supports clinical decisions.

Riassunto

Infertilità: definizioni e strategie

L'ormone antimulleriano è un marker sensibile della riserva ovarica ed è adatto per lo screening. Ciò è importante per tutte le donne in età non ancora critica che non abbiano ancora attuato il loro "progetto di pianificazione famigliare". L'identificazione dei livelli individuali di ormone antimulleriano su nomogrammi con distribuzione percentile fornisce informazioni sull'orologio biologico, che potrebbe essere regolato in anticipo o in ritardo. In questo modo, l'ormone antimulleriano può essere utilizzato a supporto delle decisioni cliniche.

Parole chiave: Riproduzione, storia - Orologi biologici - Ormone anti-Muelleriano - Infertilità.

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