Changes in egg number and quality with age:

It may be surprising to learn that all the eggs a woman ever produces are already present in the ovaries of a developing fetus as early as the 7th - 10th week of intrauterine life. From then on there is a reduction with time. There are 6 or 7 million eggs at 20 weeks of pregnancy and 1-2 million at birth with a residual store of approximately 300,000 when periods start.

At 38-40 years of age, the rate of loss is much more rapid and, in addition, the quality deteriorates.

When the egg changes from its resting phase to an active phase before fertilization is possible the chromosomes divide and separate on a spindle whose structure may become less regular with age so that the chromosomes may be displaced off the spindle. Consequently, the potential to make a normal embryo may be less good than in younger women. In addition, women over 40 produce fewer eggs following drug stimulation and a combination of these latter two factors means there may be fewer good quality embryos. This results in lower success per treatment cycle and an increased miscarriage rate and incidence of chromosome abnormalities, e.g. Downs syndrome, etc.

However, despite these natural changes, a successful outcome can be possible if fertility treatment is flexible and focused on a given couples problem.

Factors influencing fertility outcome with increasing age, these include the following:

• Whether there has been a previous pregnancy

• The duration of infertility

• The age of the woman producing eggs
• The number of quality eggs produced

• The quality of the partner's sperm

• The number of good/poor quality embryos generated

• The number of eggs/embryos transferred

• The availability of frozen embryos

• The number of previous assisted conception treatments

Other gynecological factors limiting fertility success, e.g. intrauterine fibroids, polyps adenomyosis, endometriosis and tubal damage with hydrosalpinges.

*This is relevant to natural conception, IUI, GIFT and conventional IVF (cIVF), but not to ICSI, since only 3% of patients fail to generate embryos in a treatment cycle.

**Proactive need for investigations and treatment**

The fact that natural fertility rates decline from 33 years of age, gradually until 38-39, and then more rapidly after the age of 40, indicates that those seeking help, and their medical advisors, should not be complacent about the situation.

There are also frequently other gynecological disorders which the woman may be quite unaware about and which need attention to maximize fertility, e.g. unsuspected fibroids or polyps, endometriosis or pelvic adhesions. It is simply unacceptable to advise a ‘hands off’ approach, or to be exhorted to try harder, or to fail to critically establish a causative factor. It is also quite inappropriate to omit performing the well proven clinical triad towards this end, i.e.

- Taking a detailed history
- Undertaking a physical examination
- Performing special investigations ideally of both partners. One needs in reality ‘to put the turbo on’ and to undertake a rapid ‘fertility MOT’ test.

At the age of 37 and over, investigations should include:

• Day 3 serum FSH, LH, prolactin and thyroid function tests

• Day 21 serum progesterone

• Pelvic ultrasound to exclude the polycystic ovary condition, endometriosis of the ovary, hydrosalpinges, intrauterine fibroids or polyps, and to assess ovulatory function.
Hysteroscopy and laparoscopy provide more critical information than hysterosalpingogram (HSG).

The latter does not provide as critical information about the free access of the ovaries to the ends of the fallopian tubes. Similarly the non-invasive HyCoSy ultrasound assessment does not give precise information about the relationship between the tube and ovary. This one requires at this particular age when a woman’s natural fertility is declining, since time is ‘of the essence’ for those to become pregnant using their own eggs.

Types of treatment available and the relevance of drug induction protocol. The range of treatments include:

- Timed sexual intercourse (TSI)
- Intrauterine insemination (IUI)
- Conventional IVF (cIVF)
- Intracytoplasmic sperm injection (ICSI)
- Gamete intrafallopian transfer (GIFT)
- Frozen embryo replacement (FER)
- Use of donated eggs or sperm with above
- Selective salpingography for adhesions blocking the entrance of the fallopian tubes into the uterus
- Laparoscopic laser surgery for endometriosis and tubal damage
- Resection of intrauterine fibroids and polyps

The drugs used to promote ovulation determine how many eggs, result which has particular relevance for women 40 years of age or over who have a significant lower risk of a multiple pregnancy than younger women. Therefore to prescribe clomiphene citrate tablets, which make on average 1.7 eggs per cycle, may only marginally improve fertility prospects, whereas adding gonadotropin injections (e.g. ESH) or even using an IVF drug protocol to maximize egg production, can have a positive effect on the success of IUI treatment since the risk of having triplets at this age is near to zero.

*Selection of treatment*

The treatment recommended will be influenced by the cause if one is identifiable. If none is apparent there is much to commend IVF to prove fertilization and to make embryos available for transfer. Proof of fertilization can alter suggested future management if pregnancy does not result
from IVF. This is particularly the case with those with open fallopian tubes where GIFT and/or IUI are at least logical alternatives, knowing that fertilization has resulted.

**Strategy of Management and Guidelines**

If by the age of 38 the patient has not become pregnant following three to six months use of noninvasive methods, e.g. TSI or IUI then the couples management needs to be more aggressive either by performing IVF, or alternatively, by using IUI with a drug protocol that is hopefully going to result in the stimulation of more oocytes, e.g. Clomid and gonadotropins, or even using a drug protocol normally reserved for IVF.

The guidelines restrict the number of embryos to a maximum of 3 which limits the possibility of success occurring in those already disadvantaged by reaching the age of 40 as referred to earlier.

Fertility Score Factors suggested for use for all patients with different potentials

1. The patient's age
2. The number of eggs produced
3. The quality of sperm
4. The fertilization index, i.e. how many embryos are generated
5. Whether any left over embryos have been able to be cryopreserved
6. Whether the patient has been previously pregnant and if so whether a child or miscarriage resulted
7. Whether there is evidence of endometriosis or hydrosalpinges
8. The amount of drug used to stimulate egg production
9. How many previous attempts at IVF, etc have been undertaken
10. How long the patient has been infertile

**Acceptance of the status quo**

For some women aged 40 and over fertility treatment can be predicted to fail especially for those who are peri-menopausal and who might have irregular cycles and for those who are found to have a raised FSH value on a day 2-3 blood sample. Others have recommended performing an ovarian challenge test to predict the ability of the ovary to respond to drugs and therefore to undergo treatment. In situations whereby natural conception or assisted conception is unlikely to
work, counseling services are necessary to allow those couples to adapt to their permanent childlessness.

**When and how to stop**

To date, there has not been a recorded IVF birth in the UK in women using their own eggs over the age of 46 and it is unlikely that success will occur if the patient has already reached the age of 44.

It is therefore inadvisable that more than 2 attempts of IVF or GIFT should be performed using ones own eggs. Counseling should be seriously considered if a decision is made to conclude active treatment since this represents a major watershed in a couple’s relationship.

**Outcome of pregnancy**

The incidence of miscarriage in women over 40 may be as high as 50%. Surprisingly the complications relating to older aged women are not significantly greater than those of younger years if a singleton pregnancy results unless there are other complicating factors such as diabetes and high blood pressure. Multiple pregnancy can compound a predicted problem and if triplets result from egg donation then selective reduction requires consideration.

In synopsis, women aged 37 or over need a totally different approach and understanding than those of younger years. Flexible strategies of management are required to maximize success in the limited time available.