DEBATE 1A

Female Age 42 Years Should Be the Upper Limit for Conventional IVF/ICSI Treatment

For

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The premise of this argument is that there is an appropriate age limit for conventional in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) treatment. Why should there be a limit at all? It may be argued that as long as we can squeeze an egg out of an ovary and a woman wishes to proceed, that should be enough for us to proceed.

Good medical practice dictates that doctors advise patients with honesty and integrity and that might include advising no treatment – there is no compulsion to provide a patient with treatment on request or payment. For fertility specialists to fulfil every patient request, whatever the 'cost', would class us alongside commercial surgery. If we are to argue that infertility is a medical diagnosis then we must not accept the definition of 'industry'.

There are a number of reasons why we might not accede to a request for IVF/ICSI in women past their 43rd birthday.

Uncertain Diagnosis

Any woman who continues to ovulate (pre-menopausal) has the potential for natural conception; however, fecundity declines significantly during the fifth decade such that it is rare for a natural conception to occur in a woman over 45.

In practical terms the diagnosis of infertility is based on knowledge of ovulatory function, tubal patency and semen analysis. Whilst more subtle features may be sought, IVF and ICSI are technologies that work around a problem rather than treating an underlying issue. This has become an acceptable way to increase the chance of pregnancy when there is a relative reduction in potential. Very few couples, however, are absolutely infertile and may be better described as subfertile. In women who are older, the margins of benefit of treatment may be very limited, as the effect of age increasingly becomes a major contributory factor to their problem – particularly where it is otherwise unexplained – thus affecting treatment success.

Success Rates

A woman trying to become pregnant in her 40s has a significant risk of failure and a further significant risk of not achieving a live birth even if she does become pregnant. Her chance of success declines year on year and is substantially less at 43 than at 40. She does, however, have an ongoing cumulative pregnancy chance which cannot be matched by a single cycle of treatment. Egg age is the key, and treatment success rates also decline significantly in women in their 40s. This is the result of declining ovarian reserve limiting the number of eggs available, but primarily of egg quality decline. In the United Kingdom the average live birth rate per embryo transferred for women at 40–42 is 11%, whilst at >43 it is 4.5%, demonstrating clearly the effects of these factors [1].

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Cost-Effectiveness

Artificial or arbitrary age limits are sometimes applied by commissioners in jurisdictions where state-funded treatment is provided. This is to limit the financial commitment, ensuring that funding helps those most likely to succeed and reducing the number of wasteful cycles. NICE guidance in the United Kingdom recommends a single cycle of treatment for women between 40 and 43 years of age if she has a reasonable ovarian reserve [2]. This was considered a fair approach to address what variability in prognosis may occur at that age point and maintain reasonable cost-effectiveness for state-funded treatment. That same premise may be applied to guide patients who are funding their own treatment where a realistic end point is desired.

Health of Mother and Child

There are a number of challenges in undertaking pregnancy and childbirth in older age:

Pregnancy/fetal health: the risk of miscarriage is significantly raised in older women – over 50% of clinical pregnancies will miscarry in women in their 40s, and the risk increases exponentially each year [3]. The risk of a baby with significant chromosomal abnormality increases with age. Intervention may be required to confirm a diagnosis, which adds risk to the pregnancy and mother even if unaffected, and managing a pregnancy problem incurs physical and mental health risks.

Maternal risk: there is an increased risk of pre-eclampsia and other medical complications with age, which lead to increased intervention and subsequent complications. Whilst only 4% of births in the United Kingdom are to women in their 40s, 11% of maternal deaths are in this age group (24/100,000 maternities; RR 4.34) [4].

Neonatal risk: prematurity risk increases with a woman's age as does perinatal death [5].

Child health and well-being: a woman over 43 will be over 60 when her child reaches adulthood. She is less likely to contribute greatly to their adult years and much less likely to be involved with her grandchildren.

Treatment Burden

IVF/ICSI techniques have become widely accepted as the mainstay treatment of infertility and yet remain a significant challenge to patients. Treatment programmes, although considered relatively safe, may not be without complication. Often described as an emotional rollercoaster, treatment is both physically and mentally demanding, sometimes at significant financial cost.

At what point on this rollercoaster does a woman get off? When she can't cope any more? When she runs out of money? When the medical team get fed up with her? The time to stop must be the concern of the specialist team. They should provide support, advice and counselling to allow patients to come to terms with ending the process before any of those 'breaking' points are reached. One factor for aiding that decision is the ongoing prognosis. If this is sufficiently low, the best advice may be a planned stop rather than to persist indefinitely. If poor prognosis is considered a legitimate guide to ending treatment, then it is a consideration for some as to whether to commence treatment in the first place. It is not uncommon for couples to state that they would 'do anything' or that they need to have 'tried everything' so as to have no later regrets. Specialists providing fertility treatment are not obliged to treat everyone who is prepared to put themselves forward and must manage

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those for whom treatment is not appropriate (for whatever reason) with both integrity and sensitivity.

Conclusion

IVF/ICSI (assisted reproductive treatment) is a technology that allows us to bypass specific (though sometimes unspecified) fertility problems in order to assist a woman to become pregnant when natural conception may not happen readily. It does not, however, overcome the natural process of fertility decline; success rates decline in parallel with natural conception and with age.

A woman who has a genuine fertility issue necessitating treatment may indeed have a higher pregnancy chance through treatment, but the overall success in a single cycle is limited. So-called unexplained subfertility in an older woman will almost certainly have age as a significant influence, and the cycle of treatment she may contemplate may not better her cumulative chance. To avoid reaching breaking point, appropriate intervention by the specialist may simply be to advise acceptance of continuing to try naturally.

I would advocate this approach for many women for whom age is the most significant factor in their failure to achieve pregnancy. For those women, their cumulative pregnancy rate, through the remainder of their reproductive lives, whilst limited, may yet be better than can be offered through treatment, and if a threshold is to be made, the age of 42 (up to the 43rd birthday) is an appropriate limit.

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