

**Fertility in midlife – a new challenge****Tissera WGM¹, Atapattu PM²**¹*Senior Registrar in Subfertility, De Soysa Maternity Hospital, Colombo, Sri Lanka*²*Professor in Physiology, Faculty of Medicine, University of Colombo, Sri Lanka***Corresponding Author:** Tissera WGM,
Email - g.m.tissera@gmail.com**Abstract**

Introduction: Midlife is the age between 40 to 65 years of age where complex transitions occur between younger and older adulthood. During which there will be physical and psychological challenges of ageing will occur. Natural fertility as well as success of fertility treatment both diminish during advancing age, but globally maternal age is rising. Hence it is important to discuss fertility and midlife.

Fertility potential and trend: The fertility potential of a woman is dependent on the ovarian reserve which gradually diminishes with ageing. However, the fertility requirement in middle age is rising due to women tend to postpone pregnancy for multiple reasons.

Discussion: While the ability to conceive is reduced in midlife to establish fertility in midlife demand for Assisted Reproductive Technology (ART) is rising. It can challenge the natural limitation of fertility where we need to have a focus discussion and consensus on the age limit for fertility treatment. The welfare of women and offspring is a core consideration for the decision of limitation.

Conclusion: The increasing trend of fertility needs in midlife urges to have an age definition in midlife fertility and an age limit for fertility treatment.

Key Words: Midlife, Fertility, Assisted Reproductive Technology

Introduction

Midlife is the period of younger and older adulthood age between 40 to 65 years¹². It is a complex period of balancing the life responsibilities of adulthood with the physical and psychological challenges of ageing³. Therefore, ‘midlife crisis’ is the popular conceptual description for this middle adulthood⁴.

Natural fertility as well as the success of fertility treatment diminishes with advancing age. Women younger than 35 years have a live birth rate of 40% whereas women over 42 years have a 4.5% live birth rate with assisted reproductive technology (ART)⁵. At the same time, the need for fertility in midlife is on the rise due to various factors. Around 10 % of all first-time births occur after 35 years of age⁶. There is almost a fold rise in women giving birth after 45 years of age by 2010. Interestingly women giving birth after 50 years have risen from zero to 0.5% around the same period⁷. Which lead to an entirely new category ‘very advanced maternal age’, defining pregnant women over 45 years of age⁸.

Due to the reduction in fertility potential in middle age, there is a growing demand for fertility services in the age group. Also, the advancement of ART and the worldwide availability of ART have given middle-aged women successful fertility outcomes. However, women getting pregnant even after menopause challenges the natural limit to



reproduction as well as the welfare of the offspring and the women.

This review highlights the timely appropriate discussion on fertility in midlife including fertility potential, and fertility trends in midlife.

Fertility potential in midlife

The natural human Reproductive lifespan of a woman starts with puberty and declines with menopause. Because fertility depends on productive ovarian reserve. Ovarian reserve is the quality and quantity of ovarian primordial follicular pool which is determined by multiple factors⁹. It is an indirect term for women's capability of producing a healthy egg that can fertilise and subsequently give rise to a healthy pregnancy. Gradually this ovarian reserve declines with age. This reduction of ovarian reserve is more marked after 37-38 years when it becomes less than 25000¹⁰. Forty-year-old women have around 10000 follicles. That means ovarian reserve is around 3% from the onset of puberty with 300000. Therefore It limits an individual's ability to conceive with her eggs. Natural, conception with any monthly cycle is 5% at 40 years of age and it is less than 1% after 45 years¹¹.

There isn't a defined period for midlife fertility. However, fertility potential is reduced significantly at the beginning of midlife and ceases with menopause due to a lack of ovarian reserve.

Fertility trend in midlife

Even though fertility potential declines with age, the fertility trend is directed other way. Maternal age of first pregnancy is rising

globally. In 2018 in the United States, 18 % of first-time mothers are above 35 years it was 8% in 1990¹². In England and Wales 4% of first-time mothers over 40 years which was only 1% in 1980¹³.

This trend is similar in the Asian region. South Korea has the highest mean maternal age 32.27 in 2020 and Japan owns the Mean maternal age of childbearing of 31.4 years in 2021. In India birth in women after 45 years increased by five times from 0.4 to 18% over 1990 to 2010. Also, women giving birth after 50 years was raised from zero to 0.3 per thousand deliveries over the same period⁸. Even though, enough published data is unavailable fertility trend has a similar pattern in Sri Lanka.

Role of ART in Midlife fertility

There are multiple background reasons like women entering into the workforce, availability of effective contraception and abortion services and most women being carrier-oriented and postponing marriage and pregnancy^{14,15}. Some are waiting for a stable relationship to obtain parenthood. Not only that job stability, university education and a higher income level have a link to delaying pregnancy¹⁶.

As a result of the increased fertility trend in middle age, the demand for assisted reproductive techniques (ART) has increased. There were less than 200 embryo transfers in 1988 in women with advanced age it was increased to more than 17000 by 2012⁸.

ART is the process of handling eggs, sperm, and embryos to make a pregnancy¹⁷. Because most middle-aged women need assisted



reproductive techniques to get conceived. In vitro-fertilisation (IVF), fertility preservation, IVF with ovum/embryo donation, Mitochondrial spindle transfer, Preimplantation Genetic testing and surrogacy are the main modes of ART used to manage fertility in midlife.

The cumulative birth rate of women aged 41 to 42 years by IVF with their own eggs is less than 10 %. It is even more than 5% after 42 years of age. Usually, women over 42 years do not recommend IVF with their eggs. There several adjuvants have been tried to improve the ovum quality before IVF like weak androgen before ovulation induction, growth hormone during ovarian stimulation and mitochondrial nutrients are some of it. However, nothing has shown acceptable results to date to improve the quality of ovum in old age¹⁸¹⁹.

Middle-aged women getting pregnant with donated ovum or embryo is an accepted successful modality. The cumulative success rate is around 56% with donor ovum for women at 40 years²⁰. With ovum donation can have offspring genetically related to the male partner. It's a good option for women with a poor ovarian resource or menopause having a normal uterus. The uterus responds to the hormone even after the menopause.

Surrogacy is also another option for women with the inability to conceive uterine or endometrial pathologies or hysterectomy.

Various methods of fertility preservation of ovarian tissue to ovum women can preserve their fertility and it can be artificially extended over the limit dictated by nature. Women with plans of postponing the pregnancy preserve their ova at a younger age

preferably before 35 years and use them for the IVF later to get conceived when she is ready to conceive.

Pre-implantation genetic testing is the genetic analysis of cells of the embryo before transfer for genetic anomalies which is practised worldwide now. It helps to increase the live birth rate, reduce miscarriages, and improve the success of ART. Not only that mitochondrial donation or mitochondrial spindle transfer is an available treatment modality to prevent identified mitochondrial inherited disease.

Discussion

The shifting of maternal age to midlife and the advancement of assisted reproductive techniques has made the possible for women to get pregnant at advanced age. However, there are important facts that need to be addressed and discussed among policymakers. Those are the well-being of the old age mother as well as well well-being of the offspring.

There are multiple social psychological and physical challenges that women have to face when they become pregnant after 40 years. Her pregnancy is a high-risk pregnancy with the possibility of complications like miscarriage, preterm delivery, gestational hypertension and preeclampsia, diabetes in pregnancy, risk of fetal growth restriction and ending up with caesarean delivery. Even with the donated ovum risks are all the same. This risk is even higher when maternal age is above 50²¹.

On the other hand, when a child is born to an old age woman, parental age can affect the long-term health of the child. When women



are aged more than 45 years there is a 15 % risk of losing parents before 15 years of age. The child might have to play the role of a caregiver to the parents and might have the risk of losing financial and social support for their education. Occasionally these children might have to face conflicts for their legal inheritance too²².

So, there can't be infinity of fertility potential. Age limit for fertility treatment is essential when careful consideration is to satisfy offspring's wellbeing as well as women's wellbeing. Most fertility clinics have an upper age limit of 42 to 45 years for IVF with their own ovum. National Health Services United Kingdom has an age limit of 42 years for IVF but some Clinical Commissioning groups (CCG) sticker criteria. American Society of Reproductive Medicine (ASRM) strongly denied or discouraged embryo transfer to any women over 50 years old with underlying issues and even healthy women over 55 years⁸.

All those issues highlight the fact that need for discussion and policymaking for these new challenges associated with fertility related to midlife, not among Gynaecologists or ART Practitioners but with society, judiciary, regulatory authorities, Governments and Research Organizations.

Conclusion

Infertility affects the physical, psychological, and quality of life of both partners. Now global trend is to delay pregnancy due to personal, financial, and social reasons which has led to an increase the maternal age. Advanced maternal age has medical and psychological complications, on the other hand, fertility potential is low in advanced

age. As a result, most of the middle-aged women need additional medical support to get conceived. It has led to increasing demand for ART and high development of the ART field. However, there should be a safe and appropriate age limit for fertility treatment and a definition of fertility age limit for mid-life fertility. It is high time for policymakers to have a global discussion on it.

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