Ovaries – The true beginning of a woman's reproductive lifespan and healthspan

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The ovaries play a significant role in a female's overall reproductive health, which can affect susceptibility to age-related conditions. Dr. Paula Benny and Adjunct Assistant Professor Zhongwei Huang from the NUS Bia-Echo Asia Centre for Reproductive Longevity and Equality discuss the factors influencing reproductive lifespan and healthspan

Each baby girl is born with her lifetime supply of eggs, which are surrounded by a layer of follicular cells nurturing the eggs' growth and development. (1) The flattened layer of follicular cells surrounding the egg is known as the primordial follicle. This pool of primordial follicles will form the true ovarian reserve a girl will ever possess in her lifetime. In women, all primordial follicles are formed in the fetus between six and nine months of gestation. During this period, a marked loss of oocytes occurs due to apoptosis, until approximately 1-2 million ovarian follicles are left at birth. The number of primordial follicles decreases progressively because of their recruitment during ovarian folliculogenesis, where they grow and develop, but only one will be selected for ovulation each month for reproductive purposes. This happens until there are 1000 primordial follicles or less, and culminates as the clinical menopause. The decline in the number of ovarian follicles is not linear throughout a girl's lifetime, with optimal fertility occurring during 18 to 31 years of age. This is then followed by a steep decline in the quantity and quality of ovarian follicles from 37 years of age and beyond, leading to fertility loss. Eventually, with the complete spontaneous cessation of menstrual cycles occurring at approximately 50 years of age, due to the clinical menopause, this marks the end of a woman's reproductive lifespan and the deterioration of healthspan.

Ovarian health and age-related disease

Menopause is a driver of age-related diseases in women, with an increased incidence of neurocognitive, cardio-metabolic, musculoskeletal, and urogenital health decline and deterioration. (2) One could ponder whether there is a way that we can predict the true ovarian lifespan and hence, be able to determine a girl's true reproductive lifespan, which is directly related to ovarian health and her healthspan.

The ovary is one of the first organs to functionally deteriorate with age, which results in a rapid decline of a woman's general health involving the neurocognitive, cardio-metabolic, musculoskeletal, and reproductive systems. (3) This is evidenced in the increased morbidity and all-cause mortality in women who suffer from early menopause, occurring at less than 40 years of age. Where the timing of menopause is critically implicated, later

menopause is associated with greater life expectancy and reduced all-cause mortality. [4] Interestingly, it was observed in pregnant mothers with female fetuses that in utero events such as low birth weight and diethylstilbestrol exposure could result in the female fetus being at risk of early natural menopause in the future. [5] Hence, any unnecessary exposure or risks that may adversely affect a girl's ovarian health will affect her future reproductive lifespan and health span. Careful considerations of her diet and environment from in utero life to birth, throughout her childhood and adolescence, will stand her in good stead, at least, to protect her ovarian health for future health.

Early-life and childhood nutrition

Early-life and childhood nutrition appeared to exert a significant impact on the onset of puberty. [6] Nutritional status is considered one of the most important factors involved in pubertal development, as much as 25% of the variation in the timing of puberty may be attributable to nutritional causes. [7] Importantly, the history of either early or late menarche, defined as a girl's first menstrual period, a significant milestone in a girl's transition from childhood to adolescence, was associated with a higher risk for adverse cardiovascular outcomes (e.g., coronary arterial disease later in life). [8] It is demonstrated in a multiethnic longitudinal follow-up cohort of over 1000 women, that women with early age of menarche (AAM) (<12 years) had significantly greater values in adiposity assessments, including increments in baseline of fat mass index (FMI), visceral adiposity tissue (VAT) and Homeostasis Model Assessment for Insulin Resistance (HOMA-IR). Early AAM (<12 versus 14-15 years) was associated with a 60% increased risk of developing type 2 diabetes [RR 1.60 (95%CI:1.04,2.45)].

Serial mediation analysis suggested a significant pathway underlying early AAM and type 2 diabetes, which was first mediated by FMI, followed by VAT, and lastly by HOMA-IR ($p<0.05$). [9]

Henceforth, utmost attention should be focused on mitigating modifiable risk factors from birth to childhood (e.g., diet, obesity, environmental exposure) that influence the age of menarche. Other than potential genetic influence on the timing of puberty onset, targeting the age of menarche is a potential way to mitigate lifetime risks of chronic diseases that reduce lifespan and healthspan. This will indirectly impact her ovarian health and lifespan.

It is vital that environmental and lifestyle factors are identified and any unnecessary exposures reduced, which could negatively affect ovarian health, leading to premature destruction of the ovarian follicles and ovarian ageing. The impact of endocrine-disrupting chemicals, such as bisphenol A and phthalates, can disrupt hormone signalling pathways, leading to alterations in ovarian reserve, oocyte quality, and ovarian folliculogenesis. [10] Moreover, lifestyle factors such as obesity, stress, and smoking can adversely affect ovarian health, accelerating ovarian ageing and drastically reducing reproductive lifespan. [10]

Understanding these risk factors is pivotal, from healthcare providers to parents, to develop targeted prevention strategies and interventions to protect ovarian health from a girl's birth and beyond, to promote and optimize reproductive lifespan and healthspan via

the preservation of ovarian health.

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