IOSR Journal of Nursing and Health Science (IOSR-JNHS)
e-ISSN: 2320–1959.p- ISSN: 2320–1940 Volume 11, Issue 2 Ser. VII (Mar. – Apr. 2022), PP 28-34
www.iosrjournals.org

Measure of Reproductive Lifespan and Health: A Review from Menarche to Menopause

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Abstract
The present work is a review from menarche to menopause – a measure of reproductive lifespan. Menarche and menopause are the two milestones in a woman's life as it denotes the start and end of reproductive lifespan and reproductive health. By addressing both, age at menarche and age at menopause, reproductive lifespan of a female can be measured. The aim of this report is to review the recent developments and the current knowledge in the pubertal onset and the factors (genetic and environmental) which influence menarche and menopause. In this article, the relationship between age at menarche and menopause has also been reviewed along with the implications of early or late menarche and menopause on a woman's life. The reproductive health has been studied in terms of age at menarche and age at menopause. The fitness to produce variable number of offspring is termed as reproductive fitness. Thus, the mean age of menarche is about 13.5 years and the mean age of menopause is about 49.5 years and hence, the mean age of reproductive lifespan is about 36 years.

Keywords: *Menarche, Menopause, Reproductive health, Reproductive lifespan.*

Date of Submission: 14-04-2022 Date of Acceptance: 30-04-2022

I. Background

There are several stages in the life of a girl child as she grows to become a fully mature female able to reproduce. The major event of this sexual development is the first menstrual blood flow referred to as menarche [*Ameade et al., 2016; Ersoy et al., 2005*]. The age at menopause marks the final step in ovarian aging, while the age at menarche indicates the onset of the reproductive cycle in female; however the life course of the oocytes begins in the womb [*Forman et al., 2013; Skinner, 2005*]. Age at menarche and menopause marks important points of physical, biological and cultural maturation. These ages can be predictive of health and disease status [*Hazel et al., 2006; Kelsey et al., 1993*]. The interval between menarche and menopause defines a woman's reproductive lifespan. These important developmental stages in females have been found to vary greatly across countries [*Ameade et al., 2016; Thomas et al., 2001; Xiaoyan et al., 2014*]. By addressing the age at menarche and menopause, the study was able to define a measure of reproductive lifespan of women. Changes in both the average ages at menarche and menopause have implications for the total length of exposure to high levels of circulating oestrogens during reproductive lifespan [*Hazel et al., 2006*].

The landmarks of the pubertal events in girls are the onset of puberty, peak height velocity (PHV) and menarche. The onset of puberty is marked by the development of breast tissue and mammary gland, while PHV is the highest velocity that is observed during the pubertal growth and development. Menarche is a rather late event in puberty and usually occurs 6 months after PHV is achieved. The age that menarche occurs varies and is dependent on the interaction between genetic and environmental factors [*Ameade et al., 2016; Karapanou et al., 2010*]. Earlier menarche is associated with risk of depression, cardiovascular disease (CVD), insulin resistance, polycystic ovarian syndrome and metabolic syndrome like overweight or obesity [*Forman et al., 2013; Golub et al., 2008*]. Poorer school performance and health risk behaviours such as early age of smoking inhalation, early sexual activity and teenage pregnancy have been linked with earlier menarche [*Forman et al., 2013; Stice et al., 2001*]. Due to exposure of different hormonal and environmental determinants, early or late onset of these events may be associated with an increased risk of several chronic health issues [*Xiaoyan et al., 2014*]. Early menopause has been associated with increased risk of mortality from all causes, cardiovascular disease (CVD) and coronary heart disease (CHD), but may not be associated with mortality from ischemic heart disease (IHD) [*Ossewaarde et al., 2005; Xiaoyan et al., 2014*]. Other than CVD, few studies have examined the association of age at menarche and menopause with cause specific mortality and the results have been inconsistent [*Mondul et al., 2005; Xiaoyan et al., 2014*].

Delays in age at menarche may alternatively have detrimental effects on other health outcomes, such as bone fracture and mineral density [*Hazel et al., 2006, Kritz et al., 1999*]. In addition, age at menopause has been

associated with risk of heart disease and osteoporosis as well as with all-cause mortality [*Hazel et al., 2006, Sowers et al., 1995*]. Menopause is the permanent cessation of ovulation and menses. The final menstrual period confirmed by the subsequent 12 consecutive months without a menstrual period. Late age at natural menopause (that is, self reported absence of menses for 12 consecutive months not due to radiation, hysterectomy or drug use) is associated with risk of breast and endometrial cancers [*Forman et al., 2013*].

The interval between the age at menarche and menopause is the length of a female's reproductive lifespan and this is associated with risk for chronic disease and life expectancy as well as having implications for population structure and dynamics. Understanding whether there is a relationship between age at menarche and menopause, the magnitude and direction of this relationship, and the factors influencing the relationship might lead to preventive strategies for chronic disease and improvement in quality of life. Menarche is the event signalling the onset of the female reproductive cycle. Mounting evidence has established the significance of menarche as both a footprint for chronic disease risk and compass for healthy lifespan. Adverse effects from an early menarche include risk for premature death, breast and endometrial cancer [*Forman et al., 2013; Jacobsen et al., 2003; Xiaoyan et al., 2014*]. The risk for this cancer is partially a function of the number of ovulatory cycle, the length of each cycle and years of menstrual cycles that contribute to the cumulative exposure of breast cells to endogenous steroid hormones like oestrogen over the life course [*Forman et al., 2013, Parkin, 2011*].

The variation in menarcheal ages recorded across the world could be attributed to the study participants as well as the measurement instrument [*Ameade et al., 2016; Morabia et al., 1998*]. However, several factors have been found to significantly influence menarcheal age and they include genetics, environmental conditions, body stature, family size, body mass index, socioeconomic status, and the level of education. Secular trend shows that age at menarche is declining in most countries. However, in developed countries which have lower menarcheal ages, there have been little or no changes in these values for a long time. Improvement in sanitation, better nutrition as well as improved socio-economic status and better healthcare provisions in several countries are possible factors responsible for the decline or stabilization of the age at menarche. Late menarche on the other hand presents with its own health burden since it has also been associated with osteoporosis, depression and social anxiety problems [*Ameade et al., 2016; Zacharias et al., 1969*].

In the 19th century factors that were thought to exert an influence on the physical maturation of girls were climate (particularly the mean annual temperature), ethnic origin, social status, urban or rural residence, physical activity, education, sexual stimulation, housing, inheritance, and health status. Studies carried out in the 20th century documented other factors associated with the age at menarche, e.g. season and month at birth, physique, family income, occupation and education of parents and family size [*Heidi, 1986; Karapanou et al., 2010*].

Women's reproductive lifespan history

Women's reproductive lifespan history included age at menarche, parity, age at birth and breastfeeding duration for each live birth, menopause status and age at menopause for post-menopausal women, and history of oral contraceptive (OC) use, hysterectomy, ovarian or breast surgery [*Birla et al., 2018a*].

Neuro-endocrinology of puberty

Onset of puberty occurs after reactivation of the hypothalamic Gonadotropin Releasing Hormone (GnRH) secretory system. The GnRH secretory network initially develops and is temporarily active during fetal and neonatal life and early infancy, i.e. during the first 6 months of life, the so-called 'mini-puberty'. These early periods of GnRH activation may be important for masculinisation or feminisation of the brain [*Karapanou et al., 2010; Morris et al., 2004*].

At puberty, the rhythmical GnRH secretion and the subsequent occasional pituitary gonadotropin secretion, which is necessary for normal development and functioning of the gonads, is triggered by the activation of the GnRH pulse generator. GnRH pulse generator is comprised by scattered neurons that are distributed in the arcuate nucleus (also known as infundibular nucleus) of the mediobasal hypothalamus and the preoptic area in the anterior (front) region of the hypothalamus [*Karapanou et al., 2010; Krsmanovic et al., 2009*].

Genetic determinants of menarche

Menarcheal age is influenced by heredity but the specific genetic determinants are largely unknown. Evidence for hereditary influences on the age at menarche comes from studies that show a trend for maternal age at menarche to predict daughter's age at menarche [*Graber et al., 1995; Karapanou et al., 2010*].

Assessment of menarcheal age

There are three methods for assessing age at menarche: a) the status quo, b) the recall or retrospective, and c) the prospective methods [*Cameron, 2002*].

a) In the status quo method data regarding menarcheal age can be obtained by asking a girl (or her parent) of her "current status", i.e. whether she has had her first menses by the time of assessment, and her birth date. In the status quo method the sample must be large, representative of the population, and in the developed countries the age range should be from 8 to 16 years old.

b) In the recall method menarcheal data are obtained by asking post-menarcheal females (or their mothers) to recall their age at first menses. The recall method may be less valid and its accuracy is decreased with greater time elapsed between menarche and asking for the date, because it is fraud with poor memory. Furthermore, all girls included must be at an age that they normally should have already started menstruating.
c) The prospective method is more accurate, however such studies are not easy to perform as they should be longitudinal having pre-menarcheal girls followed regularly, ideally every 3 months, and asked at each visit whether they have begun to menstruate. Therefore, most studies on menarcheal age have employed the status quo or the recall methods [*Karapanou et al., 2010*].

Age at menarche

The age at which a girl menstruates for the first time and has a marked bearing on her reproductive potentiality, is the menarche. The onset of the first menstrual period in the female adolescent is the menarche. It has been a common observation that girls undergoing menarche at an early age have a better reproductive capacity than those menstruating at a higher age [*Birla et al., 2019b; Birla et al., 2018b*]. The age at menarche is itself determined by several factors, the most important being food and atmospheric temperature. Higher temperature range and rich food are said to be favouring early menarche [*Birla et al., 2018a; Ritu et al., 2015*]. Menarche is the time in female's life when menstruation begins for the first time. The mean age at menarche among Munda and Oraon populations of Madhepura district (Bihar) is 13.56 years and 13.19 years respectively [*Ritu et al., 2015*]. The mean age of menarche among Saundik of Munger district (Bihar) in India range from 13.48 years to 13.55 years [*Birla et al., 2019b*]. Age at menarche when compared with the upper castes, it reveals that the girls of higher castes menstruate earlier [*Sinha et al., 1980*]. This difference may be due to better living standard among the higher castes. There are numerous studies (Table 1- National Health and Nutrition Examination Survey) examining the secular trend of age at menarche in various populations. In general, there is a continuous trend for earlier ages at menarche for the most part of the 20th century, although this trend tends to slow down or stabilize [*Karapanou et al., 2010; Parent et al., 2003*].

Table 1: Age at menarche (in years) in various countries around the world.

Country/Population	Year	Mean or Median Age
Belgium	1985	13.1
Cameroon	1999	13.2
Denmark	1998	13
Finland	1993	13
France	2006	12.6
Germany	1996	13.5
Greece	1999	12.3
Hong Kong	1997	12.4
India	1998	12.1
Italy	1995	12
Japan	1992	12.6
Netherlands	2000	13.2
South Africa	1990	13.2
Spain	2002	12.6
Sweden	1996	13.2
Switzerland	1983	13.4
Thailand	1997	12.5
UK	1993	13
USA	2001	12.5
Venezuela	2000	12.6

Age at menopause

The termination or end of the menstrual cycle in the female is the menopause. Menopause, also known as the climacteric, is the time in most women's lives when menstrual periods stop permanently, and they are no

longer able to bear children. Age of menopause was defined as the age at last menstruation. It is the end of fertility. There are numerous studies (Table 2) examining the secular trend of age at menopause in various populations. The age at menopause ranges between the age of 46 and 53 years among Saundik of Munger district (Bihar) in India. The average age at menopause is about 49-50 years. It is 49.39 years among Biahut Kalwar, 49.45 years among Kalal, 49.46 years among Jaiswal and 49.51 among Dhaneshwar [*Birla et al., 2019b*]. The period in a woman's life, typically between the ages of 45 and 55, when menstruation ceases is the menopause. Menopause marks the end of the reproductive phase of a woman's life and usually occurs between the ages of 40 and 60 years [*Birla et al., 2019b; Birla et al., 2018b; Bromberger et al., 1997*], and in Western industrialized countries is between 48 and 52 years [*Birla et al., 2019b; Birla et al., 2018b; Hardy et al., 2000*].

Table 2: Age at menopause (in years) in various countries around the world.

Country/Population	Age Range	Mean or Median Age	Citation / Reference	Source
26 Countries Review	46-52	49.2	*Thomas et al., 2001*	Ref. 45
African-American, US	40-60	51.5	*Bromberger et al., 1997*	Ref. 7
America, US	40-59	49.5	*Forman et al., 2013*	Ref. 13
Boston, MA	40-55	47.5	*Ley et al., 2017*	Ref. 26
Britain, UK	48-52	50	*Hardy et al., 2000*	Ref. 16
China, Shanghai	45-52	48.5	*Xiaoyan et al., 2014*	Ref. 47
India, Bihar, Munger	46-53	49.5	*Birla et al., 2019b*	Ref. 4
Norway, Oslo	49-54	51	*Bjelland et al., 2018*	Ref. 6
Norway, Tromso	40-55	49	*Jacobsen et al., 2003*	Ref. 19
United States, Atlanta	40-54	49.5	*Mondul et al., 2005*	Ref. 28
United States, WHI	40-55	47.5	*Shadyab et al., 2017*	Ref. 39

Assessment of reproductive lifespan

The time from menarche to menopause in a female's life is the reproductive lifespan. Age at menarche was defined as age at the first menstrual period and age of menopause was defined as the age at last menstruation. By addressing both age at menarche and age at menopause, reproductive lifespan of a female can be measured. The duration of reproductive lifespan can be generated by subtracting the age at menarche from the age at natural menopause [*Hazel et al., 2006; Ley et al., 2017*]. Overall, the mean age of menarche is 13.5 years and the mean age of menopause is 49.5 years and hence, the mean age of reproductive lifespan is about 36 years.

Environmental influences on pubertal or menarcheal timing

Socioeconomic factors or life setting, such as urban or rural residence, family size, family income, level of parental education, may also influence pubertal development. Girls from families with a high socioeconomic status experience menarche at an earlier age than girls from families with lower socioeconomic status [*Karapanou et al., 2010; Sinha et al., 1980; Wronka et al., 2005*].

The mean recall age at menarche of female university students in northern Ghana was 13.66 ±1.87 years for a female population of mean age, 23.04±5.07 years. Compared to female students who lived in rural settings, urban and suburban areas dwellers significantly recorded earlier menarche ($p = 0.0006$). Again, females from high income earning families experienced menarche earlier than those who were born to or lived with lower income earners ($p = 0.003$). Lower menarcheal age increased risk of experiencing menstrual pain prior to menses rather than during menstrual flow for dysmenorrhic females [*Ameade et al., 2016*].

Health implications of early or late menarche

Early puberty is associated with increased body mass index, insulin resistance, total number of metabolic syndrome components and hence increased cardiovascular risk [*Feng et al., 2008; Karapanou et al., 2010*]. Moreover girls with early menarche exhibit elevated blood pressure and glucose intolerance compared with later maturing girls, independent of body composition [*Karapanou et al., 2010; Remsberg et al., 2005*].

Among 111,589 Korean women who took part in the Health Examinees (HEXA) study, a total of 2.2% (1342/60,114) women were diagnosed with depression after menopause, and 5.9% (500/8472) showed depressive symptoms. As the age of menopause and duration of reproductive years increased, the odds ratio of depression decreased (P-trend <0.001). As the age of menarche increased, the likelihood of physician-diagnosed

depression also increased (P-trend 0.048). As the number of both spontaneous and induced abortions increased, the odds ratio of depression increased [*Jung et al., 2015*].

Multiple studies confirm that early menarche is a risk marker for breast cancer [*De et al., 1988; Karapanou et al., 2010*]. This predisposition is enhanced by the observation that earlier onset of menarche is accompanied by abdominal- type obesity and thus higher circulating levels of insulin, testosterone and insulin-like growth factor 1 (EGF-1), which in turn act as growth factors for mammary tissue proliferation and are likely to promote mammary gland carcinogenesis [*Karapanou et al., 2010; Stoll et al., 1994*]. Early menarche leads to earlier sexual intercourses and is a risk factor for adolescent depression [*Kaltiala et al., 2003; Karapanou et al., 2010*].

Among Chinese women the associations between age at menarche and risk of CVD differed by birth cohort, suggesting other factors may also underpin the association. The mean (SD) age of menarche was 15.4 (1.9) years, decreasing from 16.2 (2.0) among women born before 1940 to 14.7 (1.6) for those born during the 1960s–1970s. The patterns of association between age at menarche and CVD risk appeared to differ between different birth cohorts, with null associations in older generations but U-shaped or weak positive associations in younger women, especially those born after the 1960s. After minimizing the potential confounding effects from major CVD risk factors, both early and late menarche, compared with menarche at age 13 years, were associated with increased risk of CVD morbidity and mortality, which was more pronounced in younger generations [*Yang et al., 2017*]. On the other hand, girls with constitutional delay in puberty and onset of menstruation feel that this delay has an impact on school, work or social status and would prefer to accelerate their growth spurt by treatment [*Crowne et al., 1991; Karapanou et al., 2010*].

Relationship between age at menarche & age at menopause

There is conflicting evidence concerning the relationship between ages at menarche and menopause. Some studies have found a relationship between earlier menarche and earlier natural menopause [*Birla et al., 2018b; Parazzini, 2007*]. Early menarche is responsible for early menopause and late menarche is responsible for late menopause [*Birla et al., 2019b*]. Some studies report that women with early menarche also have early menopause, other studies report that women with early menarche have late menopause, or they report no association [*Nagata et al., 2000; Nagel et al., 2005*]. If age at menarche is not related to age at menopause, women with early menarche may have a longer time interval between menarche and menopause than women with late menarche. This interval is often referred to as the woman's reproductive period [*Bjelland et al., 2018*]. Ages at menarche and menopause have been shown to be associated with adverse health outcomes in later life. For example, earlier menarche and later menopause have been independently linked to higher risk of breast cancer. Earlier menarche may also be associated with an increased risk of endometrial cancer, menstrual problems and adult obesity [*Birla et al., 2018a; Mishra, 2009*].

Reproductive health

Longer reproductive lifespan, defined as the time interval between menarche and menopause, has also been associated with decreased morbidity and mortality. Thus, later age at menopause and longer reproductive lifespan may increase the likelihood of long-term survival [*Shadyab et al., 2017*]. The reproductive health has been studied in terms of fertility, mortality, age at menarche, age at menopause, frequency of never-pregnant women and birth of twins etc. Menarche and menopause are the two landmarks that signal the beginning and the end of normal reproductive lifespan of women respectively. Reproduction is the prime characteristic of all living beings. The fitness to produce variable number of offspring is termed as reproductive fitness. Reproductive fitness of an organism is its capacity to leave behind its progeny [*Birla, 2019a*]. According to Darwinian view, the organism that leaves behind a larger progeny is fit than that leaves a lesser number of offspring. Every individual must reproduce to survive and also must survive to reproduce. An individual is said to be more fit than other, if he/she is be represented by more descendants in future generations.

II. Conclusions

In conclusion, the factors explaining differences of age variability in menarche and menopause in human females are poorly known. Results demonstrate that on a large spatial scale different factors may be responsible for the observed variation in age at menarche and menopause. In fact, age at menarche seems to be closely related to extrinsic factors such as living conditions and, especially, the energy balance allocated to individuals. Conversely, age at menopause appears to be more sensitive to intrinsic parameters, such as the reproductive history of individuals. Overall, the mean age of menarche is 13.5 years, the mean age of menopause is 49.5 years and the mean age of reproductive lifespan is 36 years.

Age at menarche was influenced by socio-economic status of the girl child and their families as females who lived in urban areas and from higher socio-economic environment, experienced early menarche than those from rural and lower income situations. Lower menarcheal age was associated with an earlier onset

of menstrual pains in dysmenorrhic females. The improvement of socioeconomic conditions that took place in the 20th century resulted in an earlier onset of puberty in children, indicated by the fall of the age at menarche.

Multiple factors, including hormonal and environmental exposures, socioeconomic status are hypothesized to influence the menarche, menopause, body development, health and hence the reproductive lifespan in women. Early menarche was associated with higher risk of mortality from all causes, stroke, and diabetes, but with lower risk of mortality from respiratory system cancers. Younger age at menopause was associated with higher total mortality. A longer reproductive span was associated with higher mortality from gynaecological cancers.

Shorter duration of reproductive lifespan is associated with a higher risk of CVD, which is likely driven by the timing of menopause induced either naturally or surgically. Extremely early age at menarche is also associated with a higher risk of CVD. The different associations between age at menarche and menopause with CVD risk among different populations have implications for future research. Findings from one population may not be applicable to another that has a different distribution of age at menarche, thus, systematic reviews or meta-analyses on this topic should take into account these varying distributions in populations from different studies. Further investigation from both observational and genetic studies is needed on the underlying reasons for differences in the patterns of association between age at menarche & menopause and disease risk, and interplay with related generational, life-style or other reproductive factors.

Menarcheal age has important health implications, as early menarche is associated with more cardiovascular incidents and higher all cause, including cancer, especially of the breast, mortality. Late menarche is associated with osteoporosis and increased fracture risk. Moreover, early menarche has been related to anxiety symptoms, depression, premature intercourse and violent behaviour. Both ages of menarche and menopause show increased likelihood of post-menopausal onset depression. However, the age of menopause seems to be more important in depression prevalence. Based on the results, it is suggested that women with earlier menopause and increased number of abortions should be checked for depression carefully.

More studies are needed in order to predict which girls may develop metabolic or psychological disturbances due to early or late menarche & menopause and whether they can be benefited by medical manipulation of the pubertal events. Further studies are also needed to elucidate lifestyle, genetic, and environmental factors associated with ages at menarche and menopause and reproductive lifespan to determine potential mechanisms explaining the link between characteristics of reproductive lifespan and longevity.

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Dr. Saurabh Birla Ph.D.. "Measure of Reproductive Lifespan and Health: A Review from Menarche to Menopause." *IOSR Journal of Nursing and Health Science (IOSR-JNHS)*, 11(02), 2022, pp. 28-34.