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ARTICLE

Childbirth close to natural menopause: does age at menopause matter?

BIOGRAPHY

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KEY MESSAGE

This study showed that more than 50% of the women who reached menopause before the age of 45 years had had a successful pregnancy within 10 years prior to natural menopause. Among women with menopause in their mid-fifties, less than 1% had had a successful pregnancy within the 10 years before natural menopause.

ABSTRACT

Research question: Does a successful spontaneous pregnancy in the years close to natural menopause depend on age at menopause?

Design: This was a retrospective population-based study of 4157 parous postmenopausal women in Norway, born during the years 1925–1940. Data were obtained by two self-administered questionnaires in the HUNT2 Survey (1995–1997). We calculated the proportions of women who gave birth within 5 years and within 10 years prior to menopause both among all women, and according to categories of age at menopause.

Results: Overall, 2.7% (114/4157) of all women gave birth within 5 years, and 11.7% (487/4157) gave birth within 10 years, prior to menopause. Among women with menopause before the age of 45 years, 23.5% (81/344) gave birth within 5 years, and 55.5% (191/344) gave birth within 10 years, before menopause. Among the women with menopause at the age of 55 years or older, no women (0/474) gave birth within 5 years, and 0.2% (1/474) gave birth within 10 years, prior to menopause.

Conclusions: More than half of the women with menopause before the age of 45 years gave birth within the 10 years before natural menopause, whereas virtually no women with menopause at the age of 55 years or older did. Thus, the length of the sterile interval before natural menopause may vary by age at menopause.

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KEY WORDS

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INTRODUCTION

Women's mean age at first childbirth has increased in many countries (*Mathews and Hamilton, 2016*). Mean age at menopause, however, has remained relatively stable over time (*Dratva et al, 2009; Schoenaker et al., 2014*). Thus, the number of years for reproduction has declined.

It is well known that women's fecundity decreases in the years close to menopause (*Broekmans et al., 2007*), and that women's age at menopause varies widely (*Schoenaker et al., 2014*). It is assumed that a successful spontaneous pregnancy is rarely achieved within a 10-year interval before menopause (*te Velde and Pearson, 2002; Towner et al., 2016*), and that such an interval is independent of age at menopause (*Faddy and Gosden, 1996; Nikolaou and Templeton, 2003*). Postponing pregnancy until the age of 35–40 years may therefore reduce a woman's chance of giving birth, particularly if she will go on to experience early menopause.

The assumption of a fixed sterile interval prior to natural menopause independent of age at menopause is poorly documented. This assumption is mainly based on retrospective data with a comparison of the age distribution at last childbirth in one population with the age distribution of menopause in another (*Desjardins et al., 1994; te Velde and Pearson, 2002; Tietze, 1957*). In these studies, the difference between mean age at menopause and mean age at last childbirth was 10 years. In addition, the poor success rate of assisted reproduction treatment in women older than 40 years (*Bopp et al., 1995; United States, National Summary Report, 2014*) supports the assumption that women cannot give birth within 10 years before menopause, as women's mean age at menopause is approximately 50 years (*Schoenaker et al., 2014*). However, none of these studies accounts for the large individual variation in age at menopause. We are not aware of any studies of childbirth in the years close to natural menopause using individual data of age at last childbirth and also of age at menopause.

Using a study population of 4157 postmenopausal women in Norway, born during the years 1925–1940, we calculated the proportions of women who had had a successful pregnancy within 5 years and within 10 years prior to natural menopause, and studied whether the proportions with a successful pregnancy differed by age at menopause.

MATERIALS AND METHODS

Study design and recruitment

We performed a retrospective study using data from a population-based survey in Norway (the HUNT2 Survey). This survey aimed to include all inhabitants aged 20 years or older in the Nord-Trøndelag county of Norway during the years 1995–1997. Details of the HUNT2 Survey are described elsewhere (*Holmen et al., 2003; Krokstad et al., 2013*).

Data were collected using two self-administered questionnaires, and only postmenopausal women who had given birth and had answered both questionnaires were eligible for our study. Of all women aged 20 years or older in the county of Nord-Trøndelag, 71% participated in the HUNT2 Survey and answered the first questionnaire. Of these, 87% also completed the second questionnaire that was answered by women aged 20–69 years. Thus, approximately 60% of women in this age group in the North-Trøndelag county answered both questionnaires (24,865 women). Women aged 60–69 years had the highest response rate.

We excluded women who had not given birth (n = 3554), women for whom information about the number of childbirths was lacking (n = 740) and women who had not reached menopause (n = 12,722) (Supplemental Figure). We also excluded women with missing or implausible values for age at last childbirth or age at menopause (n = 460). Additionally, we excluded women who had had both ovaries and/or the uterus surgically removed before natural menopause, or had missing information about age at such surgery (n = 1110). To avoid an overrepresentation of women with early menopause, we excluded menopausal women born after 1940 (n = 2122). Thus, 4157 women born during the years 1925–1940 were eligible to be included in our data analyses.

Study factors

The first questionnaire included questions about socio-demographic factors and health. The second questionnaire included questions about menstruation, childbirth and surgery on the ovaries or uterus. Information about the number of childbirths and age at last childbirth was based on the following questions: 'How many times have you given birth?', 'List the year of each childbirth' and 'How old were you at your last childbirth?'

Information about age at natural menopause was obtained using the following questions: 'Do you still have menstrual periods?' (yes/no) and 'If no, at what age did you have your last menstrual period?' In the analyses, age at menopause was categorized as: under 45 (early menopause), 45–49, 50–54 and 55 or more years old.

The time interval between last childbirth and menopause was calculated by subtracting age at last childbirth from age at menopause and categorized as childbirth within 5 years (yes/no) and childbirth within 10 years (yes/no) before menopause. The number of previous childbirths was categorized as 0–1, 2–3 and more than - 3.

Statistical methods

We used kernel density estimation to illustrate the age distributions at last childbirth and at menopause. Within the above-defined categories of age at menopause, we calculated the mean number of childbirths, mean age at last childbirth, mean age at menopause and mean time interval between last childbirth and menopause, as well as the standard deviations (SD) of these values. Differences in means between categories were assessed by analysis of variance (ANOVA). A 5% level of statistical significance was chosen for all analyses.

We then calculated the proportions of women who gave birth within 5 years and within 10 years before menopause among all the women, and within the categories of age at menopause. We repeated these data analyses after excluding women who had used oral contraceptives or had undergone sterilization. We also performed separate analyses among women born in 1930 or earlier, as these women had particularly limited access to oral contraceptives or intrauterine devices during their reproductive period.

In supplemental analyses, we calculated the proportions of women with childbirth

TABLE 1 DESCRIPTIVE CHARACTERISTICS OF THE STUDY SAMPLE; PAROUS WOMEN WHO HAD UNDERGONE NATURAL MENOPAUSE (*n* = 4157)

	Mean	SD	Median	IQR
Age (years)	62.5	4.2	62.3	58.8–66.1
Year of birth	1933	4.2	1934	1930–1937
Number of childbirths	3.2	1.3	3	2–4
Age at menopause (years)	50.0	4.1	50	48–53
Age at last childbirth (years)	31.7	5.0	32	28–35
Interval (years)[a]	18.3	6.3	19	14–23

[a] Interval between last childbirth and menopause.
IQR, interquartile range.

within 5 years and within 10 years prior to menopause according to the number of previous childbirths, and we repeated these analyses within the categories of age at menopause. All the data analyses were performed using Stata/SE version 14.2 (StataCorp, USA).

Details of ethics approval

The HUNT2 Survey was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian Data Protection Authority. All participants signed an informed consent form. The present study was approved by the Regional Committee for Medical and Health Research Ethics on 13 March 2017 (reference number 2017/105 REK South-East D) and by the HUNT Research Centre Review Board on 28 November 2017 (reference number 2017/11178/TRS).

RESULTS

The mean age of the women at data collection was 62.5 years (SD 4.2 years) (TABLE 1), and the mean number of childbirths was 3.2 (SD 1.3 childbirths). In total, 93.0% of the women had given birth to two or more children. Mean age at last childbirth was 31.7 years (SD 5.0 years), and mean age at menopause was 50.0 years (SD 4.1 years) (TABLE 1). Of all women, 12.7% had used oral contraceptives and 10.0% had undergone sterilization (in total 20.7%).

FIGURE 1A illustrates the distributions of age at last childbirth and age at menopause. In total, 6.3% (262/4157) of the women gave birth at the age of 40 years or older, and very few women gave birth at the age of 45 years or older (0.3%, 12/4157). Most childbirths at the age of 40 years or older were among women who reached menopause at the age of 50 years or older (66.8%, 175/262). Nonetheless, the distribution of age at last childbirth was similar across categories of age at menopause (FIGURE 1B, Supplemental Table A1). Thus, the proportion of women who had had their last childbirth at the age of 40 years or older was 4.1% (14/344) among women with menopause before the age of 45 years, and 6.6% (175/2670) among women with menopause at the age of 50 years or older. The mean time interval between last childbirth and menopause was 18.3 years (SD 6.3 years), and this time interval increased with increasing age at menopause (ANOVA, $P < 0.001$) (Supplemental Table A1).

Among all women, 2.7% (114/4157) gave birth within 5 years prior to menopause, and 11.7% (487/4157) gave birth within 10 years prior to menopause. These proportions increased with decreasing age at menopause (TABLE 2). Among the 8.3% (344/4157) who reached menopause before the age of 45 years, 23.5% gave birth within 5 years, and 55.5% gave birth within 10 years, prior to menopause. Among the women who reached menopause at the age of 55 years or older, no women gave birth within 5 years, and only one woman gave birth within 10 years, prior to menopause. We found a similar pattern among the women who had not used oral contraceptives or undergone sterilization (TABLE 2). Among the women who were born in 1930 or earlier and had reached menopause at the age of 55 years or older (114/1199), no women gave birth within the 5 years, and only one woman gave birth within the 10 years, before menopause (TABLE 2).

The proportion of women who had undergone childbirth within 10 years prior to menopause decreased with each remaining year to menopause (FIGURE 2), and only 1.0% (42/4157) of all women gave birth within the 2 years before menopause. However, among the women with menopause before the age of 45 years, 10% (34/344) gave birth within 2 years prior to menopause.

Additionally, the number of previous childbirths was related to childbirth in the years close to menopause. The higher the number of previous childbirths, the higher the proportion of women reporting childbirth within 5 years and within 10 years prior to menopause (Supplemental Table A2). This pattern was most prominent among women with menopause before the age of 45 years. In fact, 82.1% of the women with menopause before the age of 45 years and with more than three previous childbirths gave birth within 10 years prior to menopause.

DISCUSSION

In this retrospective population-based study of 4157 parous women, born during the years 1925–1940, more than half of the women with menopause before the age of 45 years gave birth within 10 years prior to menopause, whereas this was true for less than 1% of the women with menopause at the age of 55 years or older.

We performed a study of women in a population with many children and with limited access to modern contraceptive methods during most of their reproductive period. Age at last childbirth and age at menopause may have been erroneously reported by some women in our study. However, studies report that recall for pregnancies and childbirths, and also for age at menopause, is fairly accurate (*Catov et al., 2006; Rodstrom et al., 2005; Tomeo et al., 1999*). Women with early menopause in particular seem to report age at menopause accurately (*den Tonkelaar, 1997*). We have little reason to believe that possible erroneous reporting of age at menopause is related to age at last childbirth, and unsystematic errors in reporting may underestimate rather than overestimate associations (*Althubaiti, 2016*).

The prevalence of early natural menopause in our study was similar to that in reports from other studies (*Cooper and Sandler, 1998*; *Luoto et al., 1994*). Nevertheless, some women may have been misclassified. We excluded women who stopped having menstrual bleeding because of surgical removal

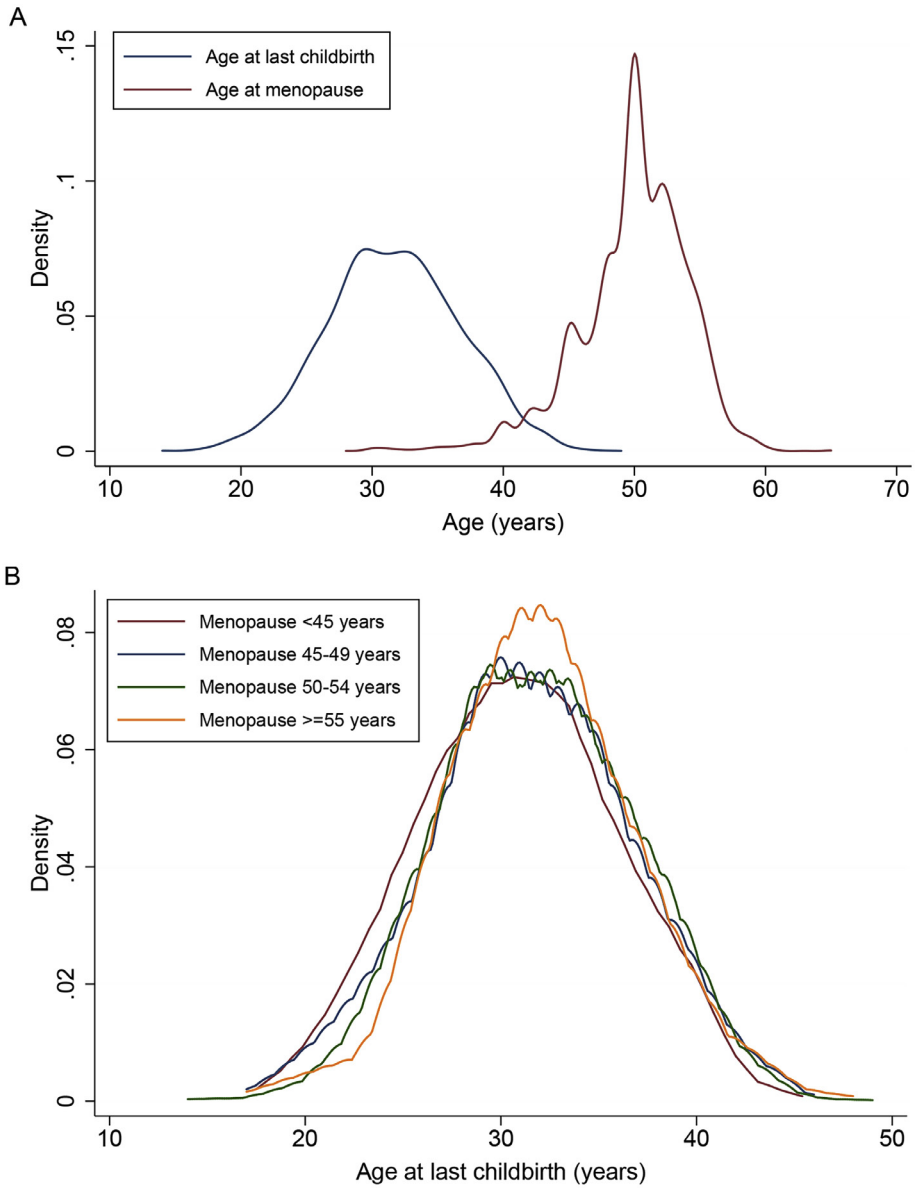

FIGURE 1 Distribution of age at last childbirth and age at menopause presented using kernel density estimation (n = 4157). (A) Age at last childbirth and age at menopause. (B) Age at last childbirth according to categories of age at menopause.

TABLE 2 PROPORTIONS OF WOMEN WITH CHILDBIRTH WITHIN 5 YEARS AND WITHIN 10 YEARS PRIOR TO MENOPAUSE AMONG ALL WOMEN, AND ACCORDING TO CATEGORIES OF AGE AT MENOPAUSE

	Model 1 All women in the study sample, born 1925–1940 (n = 4157)			**Model 2 Women with oral contraceptive use or sterilization excluded (n = 3298)**			**Model 3 Women born after 1930 excluded (n = 1199)**		
		5 years	**10 years**		**5 years**	**10 years**		**5 years**	**10 years**
	Total	***n* (%)**	***n* (%)**	**Total**	***n* (%)**	***n* (%)**	**Total**	***n* (%)**	***n* (%)**
All women	4157	114 (2.7)	487 (11.7)	3298	93 (2.8)	388 (11.8)	1199	49 (4.1)	220 (18.3)
Age at menopause (years)									
<45	344	81 (23.5)	191 (55.5)	261	64 (24.5)	142 (54.4)	112	33 (29.5)	68 (60.7)
45–49	1143	31 (2.7)	206 (18.0)	898	28 (3.1)	170 (18.9)	343	16 (4.7)	99 (28.9)
50–54	2196	2 (0.1)	89 (4.1)	1763	1 (0.1)	76 (4.3)	630	0 (0.0)	52 (8.3)
≥55	474	0 (0.0)	1 (0.2)	376	0 (0.0)	0 (0.0)	114	0 (0.0)	1 (0.9)

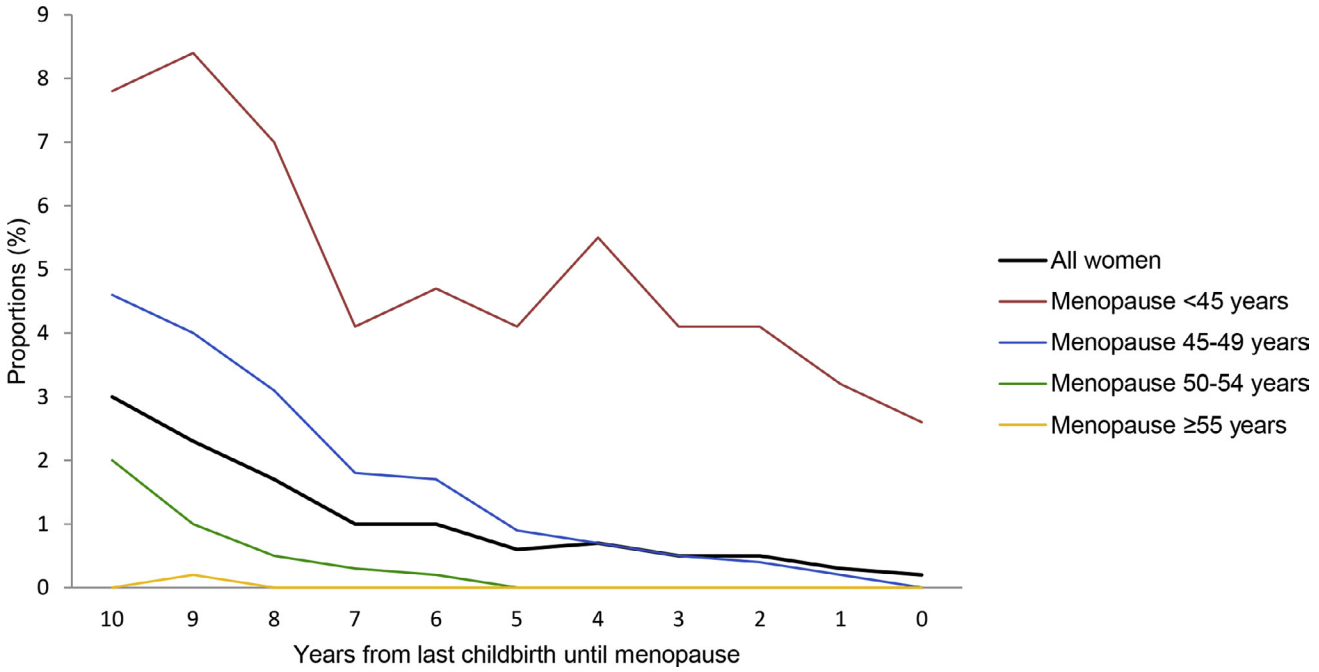

FIGURE 2 Proportions of women who gave birth within each year during the 10 years prior to menopause among all women, and according to categories of age at menopause (n = 4157).

of both ovaries and/or the uterus. In addition, some women may have had medical conditions or treatments that could have caused early menopause (*Byrne et al., 1992; Sklar, 2005; Talsania and Scofield, 2017*). In additional analyses, we identified 55 women who had been diagnosed with cancer prior to menopause, and 844 women with an autoimmune disease (rheumatoid arthritis, ankylosing spondylitis, hypothyroidism and/or asthma). After excluding these women, we found virtually no changes in our results (data not shown).

We are aware of no previous population-based studies of childbirth in the years close to menopause, using individual data. Previous studies have compared the distribution of age at last childbirth in one population with the distribution of age at menopause in another population (*Desjardins et al., 1994; Eijkemans et al., 2014; te Velde and Pearson, 2002*). One of these studies compared the distribution of age at last childbirth in a 19th-century Canadian natural fertility population with the distribution of age at menopause in a Dutch population of women born during the years 1911–1925 (*te Velde and Pearson, 2002*). The shapes of the distribution of age at last childbirth and age at menopause were almost identical, and the mean difference between the age distributions was approximately 10 years. A study from recent times of women who had undergone ovarian stimulation treatment found that women who responded poorly had a higher risk of reaching menopause within 10 years after treatment compared with women who responded well, independent of age at treatment (*Lawson et al., 2003*). Based on these studies, it has been suggested that there is a fixed interval between the onset of subfertility and menopause, independent of age at menopause (*Faddy and Gosden, 1996; Nikolaou and Templeton, 2003*). Few women reach menopause before the age of 45 years. Thus, a possible shorter subfertile interval prior to menopause among women with early menopause than among women with late menopause will not easily be detected unless these groups of women are studied separately.

The number of oocytes that a woman is born with makes up her stock throughout life. Atresia of the ovarian follicles has already started before birth and continues throughout the reproductive lifespan. Menopause is assumed to occur when fewer than 1000 follicles remain (*Faddy et al., 1992*). Early menopause may therefore be a result of a low initial number of ovarian follicles and a high rate of ovarian follicle atresia (*Depmann et al., 2015*). The rate of follicle atresia may vary between women (*Coxworth and Hawkes, 2010*), as well as throughout the reproductive lifespan, and may in particular accelerate after the age of 37 years (*Faddy and Gosden, 1996*). However, a later model suggests that there is a gradual increase in follicle atresia with increasing age (*Hansen et al., 2008; Knowlton et al., 2014*). We found that many women who reached menopause before the age of 45 years gave birth close to menopause. Hence, they were fecund and had functional oocytes close to menopause. This observation could suggest that they had a high rate of follicle atresia from the time of last pregnancy until menopause. In fact, among women with menopause before the age of 45 years, the proportion of women with childbirth close to menopause was highest among the women with many previous childbirths. This observation suggests a high rate of ovarian follicle atresia prior to early menopause. Rapid ovarian follicle atresia prior to early menopause is also supported by a recent Dutch study of 111 women diagnosed with premature ovarian insufficiency (*Daan et al., 2016*). In that study, the median time interval from the last conception to the final menstrual period was 4 years.

Among women with menopause in their fifties, very few gave birth within the 10

years before menopause. This finding could be explained by an inability to give birth, lack of or infrequent sexual intercourse, or use of methods to prevent pregnancy and childbirth. We studied separately women who had not used oral contraceptives or undergone sterilization. In these analyses as well, very few women with menopause in their fifties gave birth within 10 years prior to menopause. Unfortunately, we had no information about the use of other birth control methods. Some women may have had an induced abortion at an advanced reproductive age, despite restricted legal access to pregnancy termination in Norway before 1979. However, the pregnancy termination rates (*Vlietman et al., 2010*) and the birth rates (*Martin et al., 2017; Statistics Norway, 2017*) in women older than 45 years have been very low. These observations suggest that women with menopause in their mid-fifties may have a long sterile interval prior to menopause.

In addition to decreased number of ovarian follicles, oocyte quality also decreases with age (*Broekmans et al., 2007; Pellestor et al., 2006*). The understanding of ovarian ageing is still insufficient (*Cimadomo et al., 2018*). It is possible that the recruitment of ovarian follicles and the selection of a high-quality oocyte for ovulation is better in younger than in older women. Additionally, the meiotic divisions of the oocyte during ovulation or during the completion of the meiosis during the fertilization may fail more often in older than in younger women. Mitochondrial dysfunctions are assumed to play an important role (*Bentov et al., 2011*; *Jones, 2007*). Aneuploidy of the embryo is one of the most common causes of miscarriage (*Tsutsumi et al., 2014*). The low birth rates after the age of 45 years in women who still have menstrual periods may therefore suggest that the remaining oocytes are of insufficient quality for successful fertilization or for normal embryonic development.

In addition, impaired fallopian tube motility and lower receptivity of the endometrium could reduce the chances of successful pregnancy at a high age (*Klein and Sauer, 2001*). Furthermore, successful conception is not determined by only the fecundity of the woman. A high age of the woman's male partner may reduce semen quality and thereby the couple's chance of a successful spontaneous pregnancy (*Hassan and Killick, 2003; Kidd et al., 2001; Sharma et al., 2015*).

CONCLUSIONS

Among women with menopause before the age of 45 years, more than 50% had their last childbirth within the 10 years before menopause. This was true for less than 1% of the women with menopause at the age of 55 years or older. Thus, the length of the sterile interval prior to natural menopause may vary by age at menopause.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rbmo.2019.03.209.

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