

INVESTIGATIVE REPORT

Effect of Pregnancy and Menopause on Facial Wrinkling in Women

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Women appear to be at greater risk of developing wrinkles with age than men. To evaluate the effect of pregnancy and menopause on facial wrinkling, a total of 186 Korean women volunteers aged between 20 and 89 years were interviewed for information on menstrual and reproductive factors. An 8-point photographic scale developed for assessing the severity of wrinkles in Asian skin was used. Cumulative sun exposure, both occupational and recreational, was estimated. In Korean women, the risk of facial wrinkling increases significantly with increasing number of full-term pregnancies (OR = 1.835, 95% confidence interval (CI) 1.017–3.314) and menopausal age (number of years since menopause) (OR = 3.909, 95% CI 1.071–14.275), while hormone replacement therapy is associated with a significantly lower risk for the development of facial wrinkling in postmenopausal women (OR = 0.221, 95% CI 0.047–0.949). Hypo-oestrogenism may play a part in the decrease of skin collagen leading to skin wrinkling in postmenopausal women. Key words: ageing skin; facial wrinkling; hormone replacement therapy; menopause; pregnancy.

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The ageing process of the skin can be divided into intrinsic ageing and photo-ageing. Damage to human skin as a result of repeated exposure to ultraviolet (UV) radiation from the sun (photo-ageing) and damage occurring because of the passage of time (chronologic ageing) are considered distinct entities rather than similar skin ageing processes. Clinically, naturally aged skin is smooth, pale and finely wrinkled. In contrast, photo-aged skin is coarsely wrinkled and associated with dyspigmentation and telangiectasia (1–3).

Alterations in collagen, the major structural component of the skin, have been suggested as a cause of the wrinkling observed in photo-aged and naturally aged skin (4, 5). The dermis contains predominantly type I collagen (85–90%) with lesser amounts of type

III collagen (10–15%). Dermal fibroblasts synthesize the individual polypeptide chains of types I and III collagen as precursor molecules called procollagen (6).

Markedly reduced collagen content due to chronic sun exposure has been believed to be responsible for severe wrinkle formation in photo-aged skin relative to the intrinsically aged skin of the elderly (7–9). Furthermore, reductions in collagen content correlate well with the clinical severity of photodamage (10). The clinical improvement in facial wrinkles by topical tretinoin treatment appears to be caused by the formation of new collagen (8).

The fine wrinkling in intrinsically aged skin is also thought to result from collagen deficiency. Recently, it has been suggested that collagen deficiency due to natural skin ageing may arise, as it does in photo-ageing, from elevated matrix metalloproteinase (MMP) expression with a concomitant reduction in collagen synthesis (5).

Recently, we reported an increased risk for development of facial wrinkles in Korean women, relative to Korean men, after controlling for age, sun exposure and smoking (11). Ernster et al. (12) also reported that women showed a 28-fold increased risk for developing wrinkles with age in their 60s than in their 40s in white Caucasian skin, as compared to an 11.4-fold risk for men. The reason why women show more wrinkles remains to be elucidated. Several studies have demonstrated that skin collagen content declines because of hypo-oestrogenism after menopause (13–17). We therefore hypothesized that the significant decrease of skin collagen content in postmenopausal women because of oestrogen deficiency may accelerate or aggravate skin wrinkling due to natural ageing and photo-ageing. Various endocrinological changes, such as menarche, menstruation, pregnancy, lactation, menopause, history of hormone replacement therapy (HRT), etc., may affect the collagen metabolism in the dermis, resulting in the development of facial wrinkles in women. However, until now, there has been no clinical study evaluating the relationships between these endocrinological changes and wrinkle formation in women.

In this study we confirm that the risk of facial wrinkling in women increases with increasing number of full-term pregnancies and menopausal age (number of years since menopause), while HRT is found to have protective effects on wrinkle formation.

MATERIAL AND METHODS

Subjects

A total of 186 women volunteers ranging in age from 20 and 89 years were involved in this study. To avoid selection bias, all subjects who volunteered during the period of study were accepted, irrespective of attempts to keep stratification of the groups exactly equal size by choosing individuals with certain characteristics. The volunteers were recruited from public health centres (non-dermatologic patients) and senior citizen centres in order to ensure the involvement of older persons over 60 years, located in both urban and rural areas. Although not obligatory, many subjects of 60 years and older spend their time in senior citizen centres during the day. Table I gives the age distribution of study subjects by variables such as menstrual, lactational and reproductive factors, etc. None of the subjects had ever had facial surgery or used any drug, including tretinoin, to treat wrinkles. All patients signed a consent form approved by the Institutional

Table I. Age distributions by menstrual, lactational and reproductive factors (the data are given as number with percentage in parentheses)

Characteristics	Age			Total ^a
	-49	50-69	70-	
Age at menarche				
-14	29 (72.5)	8 (20)	3 (7.5)	40 (100)
15-18	26 (21.6)	62 (51.6)	32 (26.6)	120 (100)
19+	3 (11.5)	17 (65.3)	6 (23.0)	26 (100)
Age at menopause				
-44	5 (14.7)	19 (55.9)	10 (29.4)	34 (100)
45-49	1 (3.4)	15 (51.7)	13 (44.8)	29 (100)
50+	0 (0.0)	51 (73.9)	18 (26.1)	69 (100)
Age at first full-term pregnancy				
-21	1 (2.9)	17 (50.0)	16 (47.1)	34 (100)
22-26	9 (11.0)	55 (67.1)	18 (22.0)	82 (100)
27+	24 (54.5)	15 (34.1)	5 (11.4)	44 (100)
Hormone replacement therapy ^b				
No	59 (35.1)	71 (42.3)	38 (22.6)	168 (100)
Yes	1 (5.6)	15 (83.3)	2 (11.1)	18 (100)
Menstrual regularity				
Irregular	20 (32.8)	26 (42.6)	15 (24.6)	61 (100)
Regular	38 (30.4)	61 (48.8)	26 (20.8)	125 (100)
Menopausal status				
Premenopausal	52 (96.3)	2 (3.7)	0 (0.0)	54 (100)
Postmenopausal	6 (4.5)	85 (64.3)	41 (31.0)	132 (100)
Full-term pregnancy ^c				
No	15 (93.7)	0 (0.0)	1 (6.2)	16 (100)
Yes	33 (20.6)	87 (54.3)	40 (25)	160 (100)
No. of full-term pregnancies				
1	4 (66.7)	1 (16.7)	1 (16.7)	6 (100)
2	23 (52.3)	14 (31.8)	7 (15.9)	44 (100)
3	6 (11.5)	36 (69.2)	10 (19.2)	52 (100)
4	0 (0.0)	23 (79.3)	6 (20.7)	29 (100)
over 5	0 (0.0)	13 (44.8)	16 (55.2)	29 (100)
Breast-feeding				
No	10 (76.9)	2 (15.4)	1 (7.7)	13 (100)
Yes	24 (16.4)	83 (56.8)	39 (26.7)	146 (100)

^aPercentages have been rounded and may not sum to 100. Owing to missing data for some women, values do not always up to 186.

^bNo information about the duration of HRT administration or the history of any contraceptive pills was obtained.

^cInformation about the abortion was not obtained.

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Photography

Facial photographs (*en face* and 45° oblique) of all volunteers were taken (11). To ensure a consistent standardized photograph, a specially designed stereotactic device was used in concert with a camera and a constant light source (Canfield Scientific, Inc, Fairfield, NJ). After removing all cosmetics and jewellery, the volunteers were instructed to keep their eyes closed while relaxing their face as much as possible.

Evaluation of wrinkling

In order to quantify the severity of wrinkles in the Korean women, an 8-point photographic scale developed for Asian skin was used for assessing wrinkles (11), i.e. grades 0 to 7, with 0 representing no wrinkling and 7 indicating severely wrinkled. The photographs of each subject were evaluated independently by two investigators (YCS and HEJ) who did not have knowledge of the subjects' interview responses, or menstrual, lactational and reproductive histories. After independent evaluation of each subject's wrinkle grade by the two evaluators, any differences were settled by compromise.

Collecting data about menstruation, lactation and reproduction factors

Information on menstrual, lactational and reproductive factors was collected by direct interview conducted by two interviewers (MRK and AKY) trained through repeated interviews under supervision. The interviewers filled in a detailed questionnaire about complete reproductive and lactational history with menstrual profile; age at menarche, age at menopause, age at first full-term pregnancy, menopausal age (number of years since menopause), menstrual regularity, menopausal status, number of full-term pregnancies, and history of HRT, full-term pregnancy and breast-feeding, etc.

Collecting data about sun exposure and use of sunscreen and smoking history

Further data were collected in order to estimate cumulative sun exposure, both occupational and recreational, and use of sunscreen. Exposure to sunlight was measured as average hours per day spent in the sun during one's whole lifetime. Subjects were questioned about time spent in the sun in spring, summer and fall during each decade of their lives. The average daily sun exposure time was then calculated. The volunteers in our study did not use sunscreen at all.

Cigarette smoking was quantified in pack-years (average number of packs per day multiplied by years of smoking), where 1 pack-year equals smoking 1 pack (20 cigarettes) per day for 1 year.

Statistics

The following categorical variables were included in the model: facial wrinkling, the outcome of interest (wrinkle grade: not severe grade ≤ 3 , severe grade ≥ 4); age (≤ 49 , 50-69, ≥ 70 years); sun-exposure time (≤ 1 h/day, 2-3 h/day, ≥ 4 h/day); cigarette smoking (0-0.9, 1-29.9, or ≥ 30 pack-years); age at menopause (≤ 44 , 45-49, ≥ 50 years); age at menarche (≤ 14 , 15-18, ≥ 19 years); age at first full-term pregnancy (≤ 21 , 22-26, ≥ 27 years); menopausal age (number of years since menopause ≤ 5 , 6-10, ≥ 11 years);

history of HRT (no, yes); menstrual regularity (regular, irregular); menopausal status (premenopausal, postmenopausal); history of breast-feeding (no, yes); history of full-term pregnancy (no, yes). Also included in the model as a continuous variable was the number of full-term pregnancies. The odds ratio by the number of full-term pregnancies indicated the relative risks of developing severe wrinkling with one more full-term pregnancy.

Analyses on menopausal age were confined to the postmenopausal women aged between 50 and 69 in this study ($n=87$), while analyses on the reproductive variables such as age at menarche, age at menopause, age at first full-term pregnancy, HRT, number of full-term pregnancy, and breast-feeding were restricted to the parous women ($n=160$). Age at first full-term pregnancy was defined as the age of the woman at the end date of her first pregnancy which extended into the third trimester, regardless of the outcome. Menopausal age is the number of years between menopause and interview.

All the above categorical and continuous variables were included simultaneously in each logistic regression model, with the presence of not severe (wrinkle grade ≤ 3) or severe wrinkling (wrinkle grade ≥ 4) as the outcome, in order to calculate the prevalence odds ratios (POR) at the 95% confidence interval (CI). All analyses were performed using the Statistical Analysis System (SAS Inc, Cary, NC, USA).

RESULTS

General characteristics of study subjects

Participating volunteers ranged in age from 20 to 89 years. The age distributions by menstrual, lactational and reproductive factors are given in Table I. Age at menarche ranged from 11 to 22 years ($n=186$, 16.3 ± 1.9 years (mean \pm SD)), age at menopause from 31 to 60 years ($n=132$, 47.5 ± 5.8 years), and age at first full-term pregnancy from 17 to 39 years ($n=160$, 23.9 ± 3.8 years).

Severity of wrinkles was increased with number of pregnancies

In pregnancy, plasma levels of oestrogens are known to be increased (18), and this may positively influence wrinkle formation. However, we found that wrinkle severity significantly increased with increasing number of full-term pregnancies. The relative risk of severe wrinkling is increased approximately 1.8-fold per extra experience of full-term pregnancy (OR = 1.835, 95% CI 1.017–3.314) (Table II).

Hormone replacement therapy reduces the severity of facial wrinkling in postmenopausal women

Many investigators have shown that HRT increases collagen content and dermal skin thickness (13, 19). In this study, we demonstrated that women who have a history of HRT have a significantly lower risk of facial wrinkling relative to those who have no history of HRT (OR = 0.211, 95% CI 0.047–0.949) (Table II).

Facial wrinkling is increased with menopausal age

Menopause involves an absolute decrease in the production of oestrogen. It can be hypothesized that the influences of menopause on wrinkle formation appear to be more directly related to the number of years since menopause (menopausal age) rather than age at menopause, since wrinkle formation may be a time-dependent consequence of collagen deficiency due to decreased oestrogen. It is known that with increasing years after the menopause, the skin tends to become thinner and this phenomenon is reversed with adequate oestrogen replacement therapy (13, 19–22).

We established that wrinkling in women who were 10 years postmenopause was more severe than that in women less than 5 years postmenopause ($n=87$, OR = 3.909, 95% CI 1.071–14.275) (Table III).

Effects of other endocrinological factors on facial wrinkles

The adjusted odds ratios of menstrual, lactational and reproductive risk factors related to wrinkling in Korean women are summarized in Table II. The tendency to develop more severe facial wrinkles increased with age at menarche and older age at menopause, but not to a statistically significant degree. Parous women demonstrated a tendency to develop more severe wrinkles (2.3-fold) than nulliparous women – again not significantly. The history of breast-feeding, menstrual regularity and age at first full-term pregnancy did not seem to affect the severity of facial wrinkles.

DISCUSSION

Wrinkling is a major feature of ageing skin. During the ageing process of the skin, reduced collagen content is considered the main cause in the pathogenesis of skin wrinkling. Recently, many investigators have suggested that MMP-mediated collagen destruction leading to collagen deficiency in the dermis accounts, in large part, for the wrinkle formation that occurs in photo-ageing and chronological ageing (4, 9). Climacteric skin ageing is an entity that is distinct from intrinsic ageing and photo-ageing. It is well known that the amount of skin collagen declines in the years following menopause (13, 17). Menopause-related reduction of skin collagen shows a faster rate of loss in the initial postmenopausal years than in later years, with approximately 30% being lost in the first 5 years (20). The average rate of loss of skin collagen is 2.1% per postmenopausal year (23). This postmenopausal decrease in skin collagen content due to oestrogen deficiency may aggravate the facial wrinkle formation in postmenopausal women (23).

We have demonstrated that postmenopausal women >10 years beyond the onset of menopause, showed

Table II. Prevalence odds ratio^a of menstrual, lactational and reproductive factors related to wrinkle risk in Korean women (the data are given as number with percentage in parentheses)

Characteristics	Severely wrinkled subjects ^b No. (%)	Prevalence odds ratio ^c	95% CI ^c
Age at menarche ^e			
-14	7 (35.0)	1.00	
15-18	74 (64.9)	3.39	0.593-19.365
19+	19 (78.0)	4.73	0.547-40.882
Age at menopause ^e			
-44	24 (38.1)	1.00	
45-49	24 (85.7)	3.56	0.565-22.398
50+	52 (75.3)	1.16	0.324-4.170
Age at first full-term pregnancy ^e			
-21	26 (77.5)	1.00	
22-26	57 (76.5)	3.44	0.823-14.391
27+	13 (29.5)	0.58	0.090-3.712
Hormone replacement therapy ^e			
No	92 (65.7)	1.00	
Yes	8 (44.4)	0.21	0.047-0.949
Menstrual regularity			
Irregular	34 (55.7)	1.00	
Regular	67 (53.6)	0.72	0.224-2.288
Menopausal status			
Premenopausal	1 (1.8)	1.00	
Postmenopausal	100 (75.7)	5.00	0.370-67.662
Full-term pregnancy			
No	1 (6.2)	1.00	
Yes	100 (62.5)	2.36	0.018-310.874
No. of full-term pregnancies ^{d,e} /unit		1.84	1.017-3.314
Breast-feeding ^e			
No	3 (23.0)	1.00	
Yes	96 (66.2)	0.09 ^f	0.003-2.649

^aAll of the variables with age and sun exposure were included simultaneously in the model.

^bDefined as a wrinkle grade ≥ 4 .

^cOR=odds ratios adjusted for all other covariates; CI=95%, derived from regression coefficients and standard errors in the multiple linear logistic regression model.

^dVariable included in the model as a continuous variable. The OR indicates the relative risks of severe wrinkling by one more full-term pregnancy (change in exposure of the magnitude of the units).

^eAmong parous women.

^fConsidering the confidence interval, the prevalence odds ratio has no statistically significant meaning.

Table III. Prevalence odds ratio^a of menopausal age (number of years since menopause) related to wrinkle risk in Korean women

Characteristics	Severely wrinkled subjects ^b No. (%)	Prevalence odds ratio ^c	95% CI ^c
Menopausal age			
-5	10 (40.0)	1.00	
6-10	13 (76.4)	5.07	0.985-26.064
11+	36 (80.0)	3.91	1.071-14.275

^aAge, sun exposure, age at menarche, menopausal age, age at first full-term pregnancy, hormone replacement therapy, number of full-term pregnancies and breast-feeding were included simultaneously in the model among the 50-69 year age group.

^bDefined as a wrinkle grade ≥ 4 .

^cOR=odds ratios adjusted for all other covariates; CI=95%, derived from regression coefficients and standard errors in the multiple linear logistic regression model.

significantly more severe facial wrinkling than postmenopausal women <5 years beyond menopause onset, after controlling for age, sun-exposure and other confounding variables. In our study, we analysed the effects of menopausal age on facial wrinkling among subjects of the 50-69 year age group, because wrinkles usually reach a maximal plateau at age over 70 years,

indicating that the hormonal effect cannot be discriminated beyond this age. In a previous study, we showed that Korean women tend to have a 3.7-fold increased risk of severe wrinkling than Korean men (11). Based on our data, under the age of 50, the risk of wrinkling is significantly greater in men than in women ($p < 0.05$, by Wilcoxon's rank sum test), while over 50

facial wrinkling starts to increase more rapidly with advancing years in women than in men. Korean women finally exhibit significantly more severe facial wrinkling after 70 than Korean men (unpublished data). These results suggest that in postmenopausal women hypo-oestrogenism may contribute more to the decrease in skin collagen than chronological ageing.

In this study, HRT displayed preventive effects on facial wrinkling in postmenopausal Korean women. Among postmenopausal women, those who received HRT had an approximately 1/5-fold decreased risk of developing severe facial wrinkling than the postmenopausal women who did not receive HRT. An overall beneficial effect on the skin has also been reported for HRT (15). Holland et al. demonstrated the formation of more mature collagen fibre in postmenopausal women on HRT (24). In a double-blind, randomized, placebo-controlled study (21) of 60 postmenopausal nuns receiving conjugated oestrogens for 12 months, an increase in skin thickness was found, as assessed by ultrasonographic and histological examination. It has been reported that oestrogen cream was significantly more effective than placebo cream in alleviating fine wrinkles and in increasing skin thickness (25). Oestrogens can also increase the expression of glycosaminoglycans and hyaluronic acid, and thereby increase the hydration of collagenous tissue of the dermis (26–28). The stimulatory effects of oestrogen on collagen and glycosaminoglycan production are probably responsible for the protective mechanisms in facial wrinkle formation.

Although there was a large scale of cross-sectional analysis of the relation between skin wrinkling and oestrogen, the severity of wrinkles was not quantified (29). Indeed, most of the participants were white and African American (29). Our study strongly suggests that HRT can prevent or improve the facial wrinkling in postmenopausal women.

We have also demonstrated the increased risk of facial wrinkling with increasing number of full-term pregnancies among parous women. Although the reasons for this are not known, the following hormonal changes may offer a partial explanation. During pregnancy, the plasma levels of oestrogens are known to be greatly increased (18). However, in the long run, parous women develop higher levels of sex hormone-binding globulin (which cause decreased free oestradiol level) and lower levels of free (non-protein-bound) oestradiol than their nulliparous counterparts (30). Thus, an increased number of full-term pregnancies may result in lowered oestrogen levels in multiparous women, with consequent negative effects on facial wrinkling.

This study confirms that menopausal age, HRT and number of total pregnancies are independently associated with the risk of facial wrinkling in Korean women. We suggest that hypo-oestrogenism may play an important role in the decrease of skin collagen leading to skin

wrinkling in postmenopausal women. In addition to oestrogen levels, very complicated endocrinological changes usually occur during menstruation, pregnancy and menopause. However, few studies have investigated the effects of hormones such as progesterone on the pathogenesis of wrinkle formation. More studies are needed to elucidate the hormonal effects on skin wrinkles.

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