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The influence of female sex hormones on skin thickness: evaluation using 20 MHz sonography

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Summary Changes in skin thickness and echodensity during the spontaneous menstrual cycle, in women taking hormonal contraceptives and pregnant women were investigated by high-frequency (20 MHz) ultrasound. Women with a spontaneous ovulatory menstrual cycle (group I), women taking one-phase contraceptives (group II), women taking three-phase contraceptives (group III) and pregnant women (group IV) were measured at the following locations: proximal and distal forearm and lower leg on both sides. The skin was investigated during three phases of the menstrual cycle: days 2–4 (phase A), days 12–14 (phase B) and days 20–22 (phase C). Oestradiol and progesterone levels were determined at each phase. The pregnant women were investigated 2 weeks prepartal and 6 weeks after delivery. Group I showed a statistically significant increase in the skin thickness from phase A to phase B, but not from phase B to phase C. Group II showed no significant changes in skin thickness, whereas the skin thickness increased from phase A to phase B in group III. In group IV, the skin was significantly thicker prepartal than after delivery. The measured echodensity showed a negative correlation with skin thickness in group III and in pregnant women. We were able to demonstrate that the status of female sex hormones influences the thickness of the skin. These results can be explained by hormone-induced water retention in the skin. Sonography at 20 MHz is able to quantify these effects, which should be considered when performing ultrasound measurement in women.

Skin thickness can be determined by biopsy, Harpenden skinfold caliper and xeroradiography.[1] Recent studies have shown that high-frequency ultrasound permits *in vivo* investigation of the human skin. Sonography at 20 MHz allows accurate non-invasive determination of skin thickness and echodensity.[2]

Up until now, the factors sex, age, location, body posture and menopause were described as influencing the thickness and echodensity of the skin. The skin of females is thinner than the skin of males.[3] Skin thickness decreases with increasing age.[4] The skin of the extensor side is thicker than the skin of the flexure side, and the skin of the trunk is thicker than the skin of the extremities. Thicker skin is less echolucent than thinner skin. Additionally, some locations, such as the extensor side of the forearm, show a subepidermal echopoor band with increasing age.[3] Stretched skin is thinner than relaxed skin. Advanced daytime and upright position lead to fluid retention in the lower limbs of older subjects and a decrease in the echodensity of the dermis. Furthermore, echodensity shows distinct inter- and intraindividual differences during daytime.[5,6] After the menopause, when female sex hormones decrease, the skin thickness decreases as well.[7] This effect is interpreted as the influence of oestradiol on the content of collagen in skin.

Although it is well known that sex hormones influence the female organism, especially the genitals, circulatory system and water balance, little is understood about how skin thickness changes during the menstrual cycle and during pregnancy. The aim of this study was to investigate whether there are changes in skin thickness in female subjects that could be correlated with different levels of female sex hormones.

Subjects and methods

Subjects

We compared four groups of women with different hormone levels. Group I: 22 healthy women aged from 20 to 30 years with a normal spontaneous menstrual cycle. Group II: 12 women aged from 20 to 30 years taking one-phase contraceptives, with a constant dose of oestrogen and gestagen; these contraceptives were taken over 21 days, followed by 7 days

without intake. Group III: nine women aged from 21 to 29 years taking three-phase contraceptives; these contained a low dose of oestrogen and gestagen for 7 days, followed by a higher dose for 7 days. In the last 7 days, the dose of oestrogen decreased again, and the dose of gestagen increased to simulate the hormone levels of a spontaneous cycle. Then, there was a pause for at least 7 days. Group IV: 15 pregnant women aged from 20 to 38 years with extremely high hormone levels. They were measured 2 weeks before delivery and 6 weeks after delivery when hormone levels had returned to normal values again. Written consent was given by all subjects.

Measurements

Echographic evaluations were performed using a 20-MHz ultrasound system (Dermascan C; Cortex Technology, Hadsund, Denmark), which supplies false-colour images representing a cross-section of the skin (b-mode). Owing to the frequency, the images have a high definition suitable for studying tissues close to the body surface (maximum depth 10 mm). The probe was coupled on the skin over a water path, a membrane and a jelly layer. Care was taken in placing the axis of the probe strictly perpendicular to the skin surface. We did only one measurement on each side and each visit, because the variations between repeated measurements were very low. The thickness of the gel layer was adjusted to about 1 mm, so that it was not necessary to use an additional ring to standardize these values. The gain/compensation curve was adjusted in the horizontal position at 25 dB. The velocity of ultrasound in the skin was 1580 m/s.[2] We determined this value to get standardized conditions, although changes in water content may influence the sound velocity. Thickness of the skin was calculated in b-mode outlining the image of a whole skin block with a cursor by hand on the screen, excluding the hyperechogenic entrance echo and the hypoechogenic subcutis. Echodensity, the average amplitude of the echoes in a defined area of the image, was determined in a region of interest (ROI). In a chosen area including the whole dermis, the amplitudes of the echoes of the single-image elements (pixels) are ascribed to a numerical scale (0–255). Values are given without dimension.

All ultrasound measurements were performed in the afternoon to exclude daytime-dependent influences. The subjects rested for 20 min in a supine position before measurement. Images were taken at 12 points from the following regions: (i) the upper extremities: on the forearm volar proximal and distal and on the hand dorsal, and (ii) the lower extremities: on the lower leg medial proximal, and medial and lateral distal. Measurements were taken on both the right and the left side.

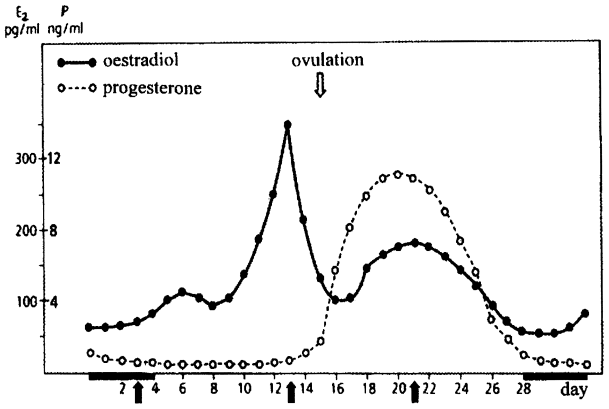

Figure 1 Measuring time points (arrows) during the menstrual cycle related to the serum hormone levels of oestradiol and progesterone (modified from Taubert HD, Kuhl H. *Kontrazeption mit Hormonen.* Stuttgart: Georg ThiemeVerlag, 1995; 142).

The measurements of skin thickness and echodensity were performed on days 2–4 (phase A), days 12–14 (phase B) and days 20–22 (phase C) of the menstrual cycle. These data were chosen to investigate the skin at times of maximal difference in hormone levels. At the beginning of the spontaneous cycle in group I (phase A), both oestrogen and gestagen were low. At the middle of the cycle (phase B), oestrogen increased to maximum and, at the third week (phase C), both hormones were relatively high (Fig. 1). At all phases, the serum levels of sex hormones were assessed by venepuncture.

Statistical analysis

The results are shown as mean ± SD for all measuring points and for the upper and lower extremities at the three phases. Data from phase A were compared with those from phases B and C by Wilcoxon signed-rank test for matched pairs. The chosen level of significance was $P < 0{\cdot}05$.

Results

Skin thickness

Group I. The thickness of the skin was lowest at the beginning of the menstrual cycle (phase A); it increased at the middle (phase B; $P < 0{\cdot}01$) and stayed elevated during the second half of the cycle (phase C; $P < 0{\cdot}01$).

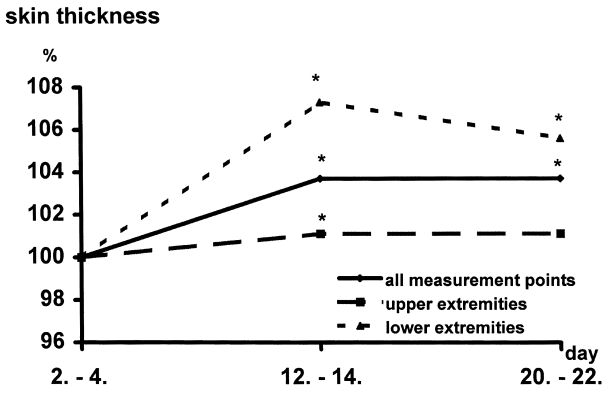

Figure 2 Changes in skin thickness (%, mean values) during the menstrual cycle of group I. Significant differences in relation to the values of the first measurements are marked by asterisks.

These changes could be observed on the arms as well as on the legs, where the effect was more pronounced (Figs 2 and 5a,b and Table 1).

Group II. The thickness of the dermis showed no significant changes at all three phases at both the upper and the lower extremities.

Group III. The thickness of the dermis showed an increase from phase A to phase B ($P < 0{\cdot}05$) and a slight decrease in phase C (not significant). These changes could be observed on the arms as well as on the legs. In Fig. 3 and Table 2, changes in skin thickness for groups I–III during the whole menstrual cycle are shown.

Group IV. The skin of pregnant women was significantly thicker 2 weeks prepartal than 6 weeks postpartal ($P < 0{\cdot}01$) (Fig. 6a,b and Table 4).

Skin echodensity

Group I. The echodensity showed a slight increase from phase A to phase B but subsequently decreased in phase C. However, these changes were not significant.

Table 1. Skin thickness (mm, mean values and SD) of group I, women with a spontaneous cycle

	Days 2–4	Days 12–14	Days 20–22
All measurement points	1·08 ± 0·23	1·12 ± 0·26	1·12 ± 0·26
Upper extremities	0·91 ± 0·09	0·92 ± 0·12	0·92 ± 0·12
Lower extremities	1·24 ± 0·19	1·33 ± 0·26	1·31 ± 0·21

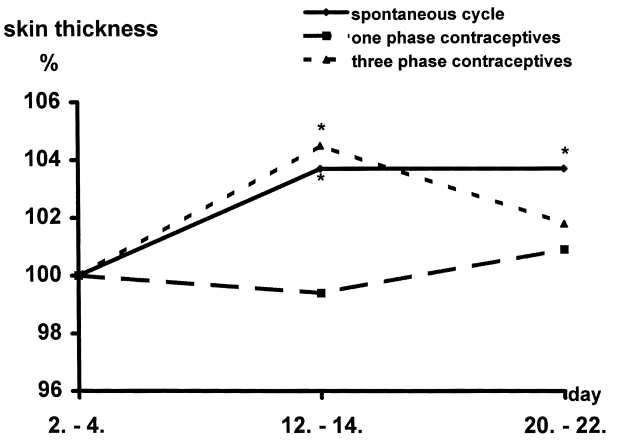

Figure 3 Changes in the skin thickness (%, mean values) of groups I, II and III during the menstrual cycle. The mean values for all measuring points are shown. Significant differences in relation to the values of the first measurements are marked by asterisks.

Group II. The echodensity showed an increase from phase A to phase B and then a decrease from phase B to phase C, while echodensity was higher in phase C than in phase A. The results were significant for all measuring points from phase A to phase B ($P < 0{\cdot}05$), but not from phase B to phase C.

Group III. Echodensity decreased from phase A to phase B and from phase B to phase C for all measuring points and at the lower extremities. Only the upper extremities showed an increase in echodensity from phase B to phase C, although these changes were not significant. Changes in echodensity for groups I–III during the whole menstrual cycle are shown in Figures 4 and 5(a,b) and Table 3.

Group IV. Echodensity increased significantly from prepartal to postpartal ($P < 0{\cdot}01$) (Fig. 6a,b and Table 4).

Discussion

Long-term influences of female sex hormones on the

Table 2. Skin thickness (mm, mean values and SD) of group I (spontaneous cycle), group II (one-phase contraceptives) and group III (three-phase contraceptives) for all measuring points

	Days 2–4	Days 12–14	Days 20–22
Group I	1·08 ± 0·23	1·12 ± 0·26	1·12 ± 0·26
Group II	1·08 ± 1·08	1·07 ± 0·26	1·09 ± 1·09
Group III	1·11 ± 0·28	1·16 ± 0·27	1·13 ± 0·25

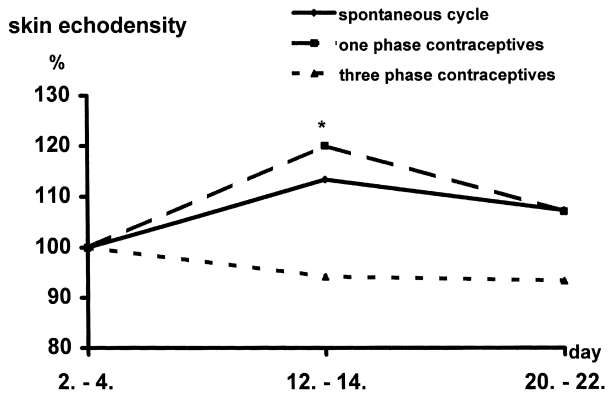

Figure 4 Changes in echodensity (%, mean values) of groups I–III during the menstrual cycle. The mean values for all measuring points are shown. Significant differences are marked by asterisks.

Table 3. Skin echodensity (mean values and SD) of group I (spontaneous cycle), group II (one-phase contraceptives) and group III (three-phase contraceptives) for all measuring points

	Days 2–4	Days 12–14	Days 20–22
Group I	21·8 ± 6·33	24·7 ± 8·55	23·4 ± 8·8
Group II	22·5 ± 5·96	27·0 ± 8·35	24·1 ± 9·38
Group III	25·9 ± 11·2	24·4 ± 10·96	24·2 ± 11·07

skin are well known. Decreasing levels after menopause,[7] castration or anorexia nervosa lead to a decrease in skin thickness. Prophylactic treatment with oestradiol reduces or inhibits this effect. The thickness of the dermis correlates with the content of collagen, which is assumed by some authors to be influenced by oestradiol.[7] Sonographic measurements have shown a significant increase in skin thickness after

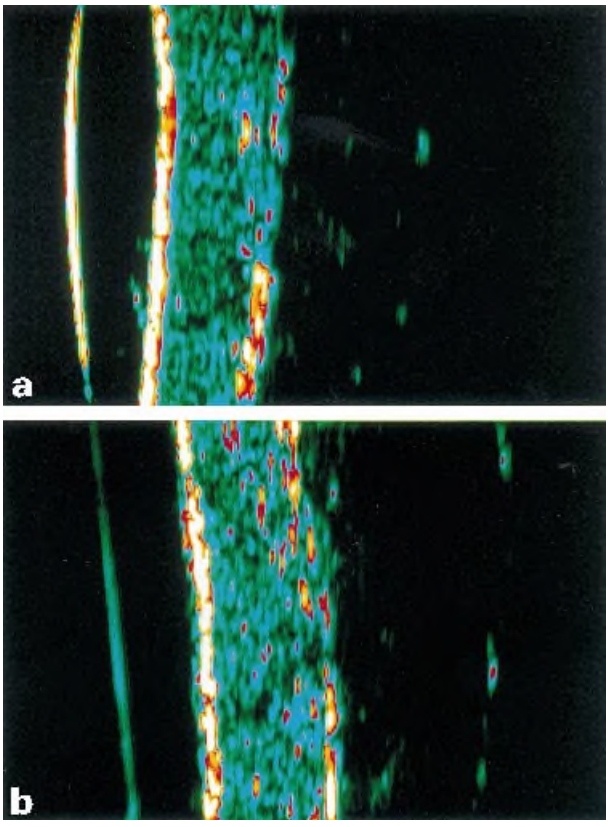

Figure 5 (a) Ultrasound (20 MHz) of the skin on days 2–4 in a woman with a spontaneous cycle (group I). In this case, the skin thickness was 1·49 mm and the echodensity 19·7 at the lower leg lateral distal. (b) Ultrasound (20 MHz) of the skin on days 12–14 in a woman with a spontaneous cycle (group I). In comparison with (a) at the same measuring point, the skin thickness was increased (1·66 mm) and the echodensity showed a slight increase (24·5).

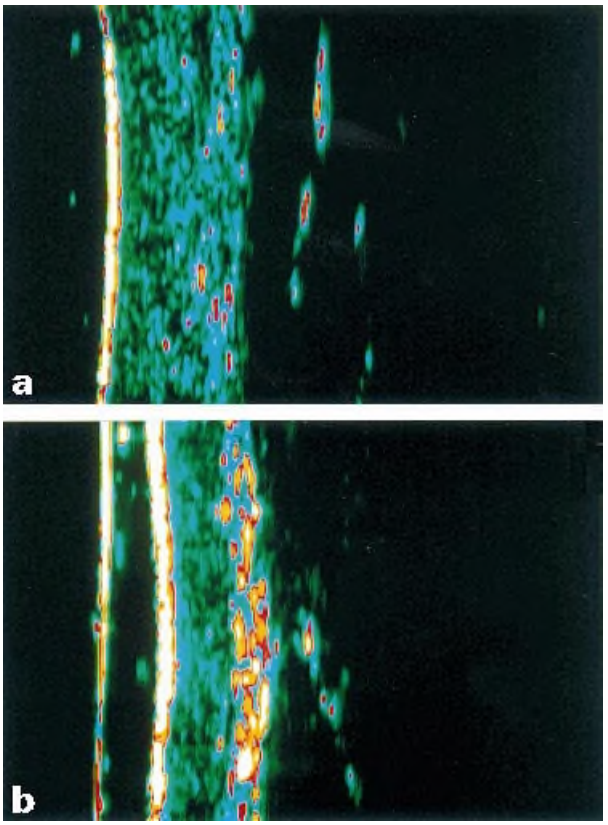

Figure 6 (a) Ultrasound (20 MHz) of the skin of a pregnant woman (group IV) 2 weeks before delivery. At the lower leg lateral distal, the skin thickness was 1·75 mm and the echodensity was 15. (b) Ultrasound (20 MHz) of the skin of the same subject 6 weeks after delivery. In comparison with (a) at the same measuring point, the skin thickness decreased (1·35 mm) and the echodensity increased (26).

Table 4. Skin thickness (mm) and echodensity of group IV (prepartal and postpartal)—mean values for all measuring points with SD

	Prepartal	Postpartal
Skin thickness	1·16 ± 0·26	1·05 ± 0·21
Skin echodensity	29·9 ± 12·2	41·6 ± 15·1

treatment with oestradiol over a period of 6 months.[8] The influence of female sex hormones on the skin over a short period of time, especially during the menstrual cycle, has rarely been described. Skin reactivity after irritation with sodium lauryl sulphate is enhanced at the end of the cycle. The corresponding increased skin thickness could also be measured by 20-MHz sonography.[9] It was observed that the skin was thinner during the first days of the cycle than in the middle. Furthermore, cyclic changes of transepidermal water loss and microcirculation could be observed.[10] Our results show a distinct influence of sex hormones on the skin thickness of women with a spontaneous cycle. At the beginning of the cycle, when sex hormones are lowest, the skin is thinner than at the middle of the cycle when oestradiol levels are highest, and a significant increase in skin thickness was observed. At the end of the cycle, with both high oestradiol and high progesterone levels, the skin was also significantly thicker than at the beginning.

The changes in skin thickness could be explained by the influence of oestradiol on fluid retention. This effect is caused by several mechanisms:

1 Oestradiol upregulates the renin–angiotensin system followed by electrolyte and water retention. The increase in sex hormones is correlated with aldosterone.[11] An increasing level of oestradiol activates vasopressin, which reduces fluid secretion. A simultaneous increase in adrenocorticotrophic hormone, cortisol and somatotrophic hormone, hormones with mineralocorticoid effects, has also been described.[12]

2 In addition, sex hormones influence haemodynamics. Oestradiol leads to systemic arterial vasodilatation with reduced peripheric resistance[13] and raises capillary permeability. Progesterone induces venous dilatation and reduces blood flow velocity.[14,15] High oestradiol levels in the mid-cycle and the luteal phase, which accompany high progesterone levels, are able to induce a watershift from the intravasal to the extravasal compartment. Under the effects of oestradiol, fluid transport from capillaries into the interstitial tissue has been described, and an increased volume of the feet has been measured.[16] Furthermore, bioelectric impedance measurements showed an increase in total body water during the ovulatory and luteal phases.[17,18]

3 Some authors have described tissue water retention as the retention of extracellular water bound to hyaluronic acid, which could also be stimulated by oestradiol.[19] Women taking one-phase contraceptives did not show significant changes in skin thickness during the cycle. This may be explained by constantly low sex hormone levels. In those taking three-phase contraceptives, skin thickness increased at the middle of the cycle, which corresponded to the high dose of synthetic oestradiol given at this time. With regard to pregnant women, the skin was significantly thicker prepartal than postpartal. During pregnancy with extremely high sex hormone levels, capillary changes such as proliferation, congestion and vasomotor instability have been described.[20] During the last trimenon, electrolyte and water retention are strikingly increased.[21] Changes in vessels and fluid retention also lead to a higher water content in the dermis. The increase in skin thickness during pregnancy was paralleled by generalized and localized oedema. The higher thickness values on the lower extremities could be explained by hydrostatic pressure.

Echodensity of the skin was reduced at the middle of the cycle in women taking three-phase contraceptives and in pregnant women. This correlated with the increasing skin thickness caused by oedema. Echodensity was significantly higher in pregnant women than 6 weeks after the birth. In the other groups, measurements of echodensity gave inconsistent results. We expected that echodensity and thickness were negatively correlated.[22] If the thickness changes were caused by water retention, echodensity is subsequently expected to decrease because of the oedema between the collagen bundles. Gniadecka *et al.*[6] demonstrated reduced echodensity in the skin of the lower leg in older subjects, which was induced by water retention. We observed these effects only if the increase in thickness was very marked. We used the standardized inbuilt ROI function for the evaluation of density and did not calculate the low echogenic pixels, which are especially influenced by water accumulation and are more sensitive to slight changes in echodensity. This may be why we did not find the expected changes in echodensity. Further studies of the water content of the dermis should consider the low echogenic pixels. Our results demonstrated that skin thickness is influenced by sex hormone levels during the menstrual cycle and during pregnancy.

These findings should be considered when performing ultrasound measurements in women.

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