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Sympathetic reactivity in late pregnancy is related to labour onset in women

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Abstract

Stress regulation during pregnancy is considered to be connected to the timing of labour initiation. Although increasing knowledge is emerging on the regulation of parturition, there is currently no way to predict the start of spontaneous labour in women. The main aim of this study was to assess pain threshold and the sympathetic nervous system response to cold pain in relation to the onset of labour in healthy pregnant women. Ninety-three pregnant women were recruited and assessed for skin conductance (SC) activity during a cold pressor test in gestational week 38. Pain threshold and cold endurance were also measured and the results were compared with data obtained from hospital records. Seventy-four women had a spontaneous labour onset and a valid SC measurement. SC activity during the cold pressor test decreased significantly with the number of days left to spontaneous parturition. This may indicate a gradual decrease in sympathetic autonomic nervous system reactivity even during the last weeks of pregnancy. Measuring SC activity during mild stress provocation is a rapid and non-invasive means to study variation in sympathetic reactivity during pregnancy, and may be useful in research on stress regulation in pregnancy and its relation to labour initiation.

Keywords: *Cold pressor test, initiation of labour, pain threshold, pregnancy, skin conductance, sympathetic activity*

Introduction

During pregnancy, physiological changes take place in the preparation of labour. One adaptation is that pain thresholds in humans and other mammals increase during late pregnancy (Gintzler 1980; Cogan and Spinnato 1986; Saisto et al. 2001; Carvalho et al. 2006). This phenomenon has been accounted for by changes in opioid signalling (predominantly via dynorphin and enkephalin) in the spinal cord, which are brought on by the increasing concentrations of female sex steroid hormones (Gintzler and Liu 2001). However, pregnancy-induced analgesia in the rat is also the result of synergistic effects between descending spinal α_2-noradrenergic activity and the opioid system (Gintzler and Liu 2001).

Together with the pain threshold changes, both autonomic nervous system reactivity (DiPietro et al. 2005) and hypothalamic–pituitary–adrenal (HPA) axis stress responsivity become blunted during late pregnancy, the latter evidenced by decreased adrenocorticotropic hormone and cortisol responses to HPA axis challenge (Schulte et al. 1990; Kammerer et al. 2002; Entringer et al. 2010). Meanwhile, the basal levels of HPA axis hormones and the basal activity of the autonomic nervous system are well above non-pregnant levels (DiPietro et al. 2005; Slattery and Neumann 2008). A down-regulation of the maternal stress response has been suggested to protect fetal development and increase maternal energy storage (Brunton and Russell 2008; Glynn et al. 2008; Weinstock 2008). Stress regulation may also be important for the timing of labour onset (Glynn et al. 2001; Petraglia et al. 2010; Zhu et al. 2010).

Although an increased tone and a decreased reactivity of the HPA axis activity in late pregnancy are well documented (Slattery and Neumann 2008), the adaptations of the sympathetic nervous system during normal human pregnancy are less studied.

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Increased sympathetic tone (Greenwood et al. 2001), decreased cardiovascular autonomic responses to exercise (Avery et al. 2001) and psychological stressors (Matthews and Rodin 1992; DiPietro et al. 2005; Entringer et al. 2010) during pregnancy have been reported. The increase in adrenaline release and the increase in forearm vascular resistance in response to a cold pressor test are also lower in healthy women during late pregnancy than 2–3 months after delivery (Nisell et al. 1985). However, muscle sympathetic nerve activity and cardiovascular autonomic responsivity to the cold pressor test have also been reported not to differ between pregnant and non-pregnant women (Schobel et al. 1996).

Although most cardiovascular parameters are influenced by both parasympathetic and sympathetic activity, the palmar and plantar sweat glands are mainly sympathetically innervated and skin conductance (SC) is therefore a direct function of sympathetic nervous system output (Dawson et al. 2000). Thus, change in SC is a good measure of sympathetic reactions to experimental stressors. Recently SC has also been used as an objective measure of pain, particularly in post-operative and neonatal clinical settings (Ledowski et al. 2006; Gjerstad et al. 2008).

Several studies have found that experimental heat, cold and pressure pain thresholds and/or pain endurance are increased in late human pregnancy compared to early pregnancy, non-pregnant controls or *post-partum* period (Cogan and Spinnato 1986; Saisto et al. 2001; Carvalho et al. 2006), although results are inconsistent (Goolkasian and Rimer 1984; Dunbar et al. 1988). Cogan and Spinnato (1986) found an increase in pressure pain thresholds in six women during the last 16 days before spontaneous parturition. Other studies have not assessed pain thresholds in relation to spontaneous onset of labour, but Carvalho et al. (2006) found increased heat pain tolerance in pregnant and *post-partum* women compared to non-pregnant controls. Similarly, Saisto et al. (2001) found significantly lower cold pain ratings during pregnancy but detected no difference in cold endurance. The cold pressor test is a simple and widely used model for the assessment of human pain and stress response (Wolf and Hardy 1941; Greenwood et al. 1998). In this test, the study subject is typically asked to submerge a hand or foot into cold water or crushed ice until the cold-induced pain becomes intolerable, while the physiological response of interest is concurrently measured. The HPA axis response to the cold pressor test has been shown to be blunted in late pregnancy (Kammerer et al. 2002).

Given the limited knowledge of pain threshold and sympathetic nervous system adaptations in late human pregnancy, the aim of the present study was to assess pain threshold and sympathetic nervous system response to cold pain in relation to the onset of labour in healthy pregnant women. Based on previous studies on pregnancy-induced analgesia in rats and in humans, our hypothesis was that pain sensitivity as measured by pain perception threshold, cold endurance and pain ratings would be decreased in women approaching spontaneous labour. In addition, we hypothesized that this decrease in experienced pain would also be reflected in decreased SC reactivity.

Materials and methods

Subjects

Ninety-three women in gestational weeks 37–40 were recruited through public maternity health care units in Uppsala County and through local newspaper advertisement. Healthy primiparous and multiparous women above 18 years of age with an uncomplicated singleton pregnancy were eligible for inclusion. The exclusion criteria were current treatment with psychoactive drugs (including benzodiazepines, selective serotonin reuptake inhibitors) during 3 months prior to inclusion, ongoing major depressive disorder, alcohol abuse or primary anxiety disorders detected by Mini International Neuropsychiatric Interview (Sheehan et al. 1998), use of analgesics within 24 h of the test session, severe pregnancy complications (pre-eclampsia, intrauterine growth retardation) and planned caesarean section. Relevant data concerning each delivery (predicted date of delivery, actual date of delivery, spontaneous or induced labour, obstetric complications) were extracted from hospital records. One assessor performed all tests and interviews.

The study procedures were in accordance with the ethical standards for human experimentation, and the study was approved by the Independent Research Ethics Committee, Uppsala University. Written informed consent was obtained from all subjects before inclusion.

SC response during the cold pressor test

SC was measured with the Med-Storm SC Algesimeter (Med-Storm Innovation AS, Oslo, Norway) via three self-adhesive single-use electrodes (Pain Monitor^{TM} electrodes, Med-Storm Innovation AS) placed in the palm of the subject's non-dominant hand according to the manufacturer's instructions. The woman was seated with the non-dominant hand resting on a pillow and was instructed to sit still and be silent during the experiment, with the exception of reporting when she could start sensing pain. The subject was also told to remove her hand from the water when the pain was "unbearable" and that the cold pressor test would otherwise be terminated after 1 min. The test started with the immersion of the subject's dominant hand into a 35 ± 1°C water bath during 1 min to obtain a baseline SC measurement. The subject was then asked to move her hand to a

0 ± 1°C water bath. The assessor recorded the time points for immersion into hot and cold water, as well as time points for the woman's report of first pain sensation (cold-induced pain threshold) and her hand withdrawal (cold endurance). Immediately after the experiment, the woman was asked to rate her pain during the cold pressor test on a 10 cm visual analogue scale ranging from "no pain" to "worst pain imaginable".

The SC data were collected with the SCMS software (Med-Storm Innovation AS). Time windows of 30 s were selected, starting from immersion into 35°C (baseline) and 0°C (cold pressor) water, respectively. Subjects with shorter cold endurance were consequently excluded from analyses including SC measurements. The measures obtained from the software included the rate of SC change (μsiemens per second), the area under the curve (μsiemens per second, with the baseline for the area under the curve established at the first minimum of the measurement window) and the number of SC fluctuations per second (peaks per second). The SC response, as a measure of autonomic arousal, is typically measured as peak amplitude or number of SC fluctuations (peak frequency) following a discrete stimulus (Dawson et al. 2000). In addition, peak frequency has been used as primary outcome in pain studies and is related to subjective pain ratings (Ledowski et al. 2006; Choo et al. 2010). For the purpose of our study, where a prolonged stimulus was given, the SC activity was measured during a specified time range by use of SC area under the curve, rate of change and number of SC fluctuations. The rate of SC change denotes the slope of a given portion of the SC curve while the area under the curve is a function of the peak frequency and amplitude over time, all dependent on changes in sweat gland activity (Dawson et al. 2000).

Data analysis

To obtain a contrast between the women close to spontaneous parturition and the women with more days left, the data were split at the median (14 days). Based on the literature in post-operative patients and panic disorder patients, and assuming a difference in rate of change of 0.015 with an SD of 0.2, the study had a power of 0.8 to detect a difference between groups based on the median split (Wise et al. 2011).

Because SC variables were not normally distributed, within-subject responses were evaluated by the Wilcoxon signed-rank tests, whereas between-group differences were assessed by the Mann–Whitney *U*-test. Linear regression was used to assess the correlations between self-rated pain intensity, cold pressor test measures and SC activity with days to spontaneous labour. All statistical analyses were performed with the SPSS statistics 17.0 software. Data are presented as mean ± SD unless otherwise stated.

Results

The mean age of the women was 30.6 ± 4.5 years and 55 (59.1%) were primiparous. The test session was performed in gestational weeks 38.1 ± 0.6, based on routine ultrasound dating in weeks 17 and 18. The total gestational length was 40.3 ± 1.1 weeks and the median number of days between the test session and parturition was 14 days (range 1–32 days). Seventy-nine women (84.9%) went into spontaneous labour and have been used in the analyses involving onset of labour. Five women with cold endurance below 30 s were excluded from analyses involving SC measurements (two women with less than 2 weeks left before spontaneous parturition and three women with more than 2 weeks left). Thus, the main results of SC reactivity in relation to spontaneous parturition are based on data from 74 subjects.

Cold pressor test outcome

Cold-induced pain perception threshold, cold endurance, self-reported pain intensity and SC measures from the cold pressor test are given in Table I. As expected, all SC measures were greater during the cold pressor test than during baseline (area under curve, $z = -6.87$, $p = 0.000$; rate of change, $z = -7.32$, $p = 0.000$; number of SC fluctuations per second, $z = -6.62$, $p = 0.000$ (Figure 1)).

Self-reported pain intensity was negatively correlated with cold-induced pain perception threshold ($r = -0.601$, $p = 0.000$). The self-reported pain intensity was also positively correlated with SC area under curve ($r = 0.241$, $p = 0.026$) and with rate of SC change (linear regression: $r = 0.354$, $p = 0.001$) while the positive correlation with the number of SC fluctuations per second (linear regression: $r = 0.209$, $p = 0.055$) only approached significance. The women who endured the cold pressor test for 60 s had lower SC rate of change than the women with shorter cold endurance (medians 0.18 and 0.34 μS/s, respectively, $p = 0.015$) but not significantly lower area under the curve values (medians 127.5 vs. 228.4 μSs, $p = 0.166$) or the number of fluctuations per second (medians 0.20 vs. 0.20 μSs, $p = 0.778$). No cold pressor test measure was correlated with age, parity or pre-pregnancy body mass index (all p-values > 0.28).

Cold pressor test outcome in relation to spontaneous onset of labour

Cold-induced pain perception threshold, cold endurance and self-reported pain intensity did not differ between women with less than 2 weeks to spontaneous parturition and women with more than 2 weeks left to spontaneous parturition, Table I.

However, the SC rate of change was decreased in women with less than 2 weeks to spontaneous

Table I. Results from the cold pressor test in all participating women, women with more than 2 weeks left to spontaneous parturition (≥14 days, median value) and in women with less than 2 weeks to spontaneous parturition (≤13 days).

	All women, spontaneous and induced labour ($n = 93$)	Women with more than 2 weeks to spontaneous parturition ($n = 40$)	Women with less than 2 weeks to spontaneous parturition ($n = 39$)
Cold-induced pain perception threshold (s)	21 (1–50)	22 (6–50)	21 (7–45)
Number of women who did not reach pain threshold within 60 s	8 (8.6%)	1 (2.5%)	4 (10.3%)
Number of women with cold endurance >60 s	64 (68.8%)	27 (67.5%)	29 (74.4%)
Self-rated pain intensity (mm VAS)	55.7 ± 20.3	59.6 ± 18.6	52.6 ± 19.4
Area under curve (μSs)⋆	205.1 (0–1375.4)	250.6 (0.49–1375.4)	133.5 (0.00–744.2)†
Rate of skin conductance change (μS/s)⋆	0.24 (−0.19–2.33)	0.35 (−0.10–2.33)	0.15 (−0.16–1.34)‡
Number of skin conductance fluctuations per second⋆	0.20 (0.00–0.43)	0.20 (0.03–0.43)	0.20 (0.00–0.37)

Note. Data are presented as mean ± SD or median [range] (depending on whether the variable is normally distributed or not), or count (%); ⋆ Since the SC measurements are retrieved from 30 s time windows, only 74 women are included in this analysis; † $p = 0.053$ compared to subjects with more than 2 weeks left to parturition (Mann–Whitney *U*-test); ‡ $p = 0.009$ compared to subjects with more than 2 weeks left to parturition (Mann–Whitney *U*-test).

parturition compared to women with more than 2 weeks left (mean difference: 0.32 μS/s, 95% CI: −0.53 to −0.11; $z = -2.60$, $p = 0.009$ (Table I)). The corresponding difference in SC area under the curve approached significance (mean difference: 179.2 μSs, 95% CI: −320.2 to −38.1; $z = -1.94$, $p = 0.053$, (Table I)). Furthermore, negative correlations were obtained between days left to parturition and SC area under the curve ($r = -0.313$, $p = 0.007$) as well as SC rate of change ($r = -0.319$, $p = 0.006$) (Figure 1b and d). The baseline SC was independent of time to parturition (SC rate of change: $r = 0.107$, $p = 0.364$; area under curve: $r = -0.049$, $p = 0.678$; number of fluctuations per second: $r = 0.116$, $p = 0.325$) (Figure 1a, c and e), as was the number of SC fluctuations during the cold pressor test ($r = -0.036$, $p = 0.760$; Figure 1f). Significant negative correlations between days left to parturition and SC area under the curve as well as SC rate of change remained when adjusted for gestational age ($\beta = -0.278$, $p < 0.05$ and $\beta = -0.289$, $p < 0.05$, respectively).

Examples of SC curves can be seen in Figure 2.

Discussion

In line with previous studies, the cold pressor test induced expected increases in the SC measures (Dawson et al. 2000; DiPietro et al. 2005). The main finding of the current study was that the SC response to the cold pressor test was lower in women with fewer days left to spontaneous parturition. When the group was split at the median of days left to parturition, women with less than 2 weeks left to parturition had a significantly lower SC response than women with 2–4 weeks left. In addition, the cold pressor-induced responses in SC area under the curve as well as SC rate of change were correlated with the number of days left to actual delivery, also after adjustment for gestational age.

Many physiological changes, including an increase in β-endorphin levels, take place during the final months of pregnancy (Cogan and Spinnato 1986; DiPietro et al. 2005; Dabo et al. 2010). Consequently, it is reasonable to assume that temporal changes in the SC response to cold pain would be most pronounced during the last weeks of gestation. Our results also agree with several studies showing reduced stress responses in women in late pregnancy and the *post-partum* period compared to early pregnancy, *post-partum* period or non-pregnant controls (Nisell et al. 1985; Matthews and Rodin 1992; Altemus et al. 1995; Kammerer et al. 2002; DiPietro et al. 2005; Nierop et al. 2006; Entringer et al. 2010). However, the study designs and outcome variables vary greatly, and no other study has previously shown a gradual decrease in sympathetic response during the very last weeks of pregnancy.

By use of microneurographic recordings, Greenwood and colleagues reported increased muscle sympathetic nerve activity during rest (sympathetic tone) in women in late pregnancy compared to non-pregnant controls (Greenwood et al. 2001). Similarly, in a longitudinal study, DiPietro and colleagues found that SC at rest increases from mid- to late pregnancy. In the same study, the SC response to a psychological stressor was lower in pregnant than in non-pregnant women (DiPietro et al. 2005). Although increased baseline sympathetic level throughout pregnancy could hypothetically result in the reduced responsivity seen in our study, we were unable to detect any difference in baseline SC measures with respect to time to parturition. Hence, it is unlikely that our findings are explained by the gradually increased sympathetic tone during pregnancy.

Self-reported pain threshold, pain intensity and pain endurance were not associated with remaining days to parturition. Longitudinal studies have indicated that pressure, heat and cold pain thresholds are increased in late pregnancy (Cogan and Spinnato 1986; Saisto et al. 2001; Carvalho et al. 2006). However, the pain threshold results are partly contradictory and increased willingness to report pain during

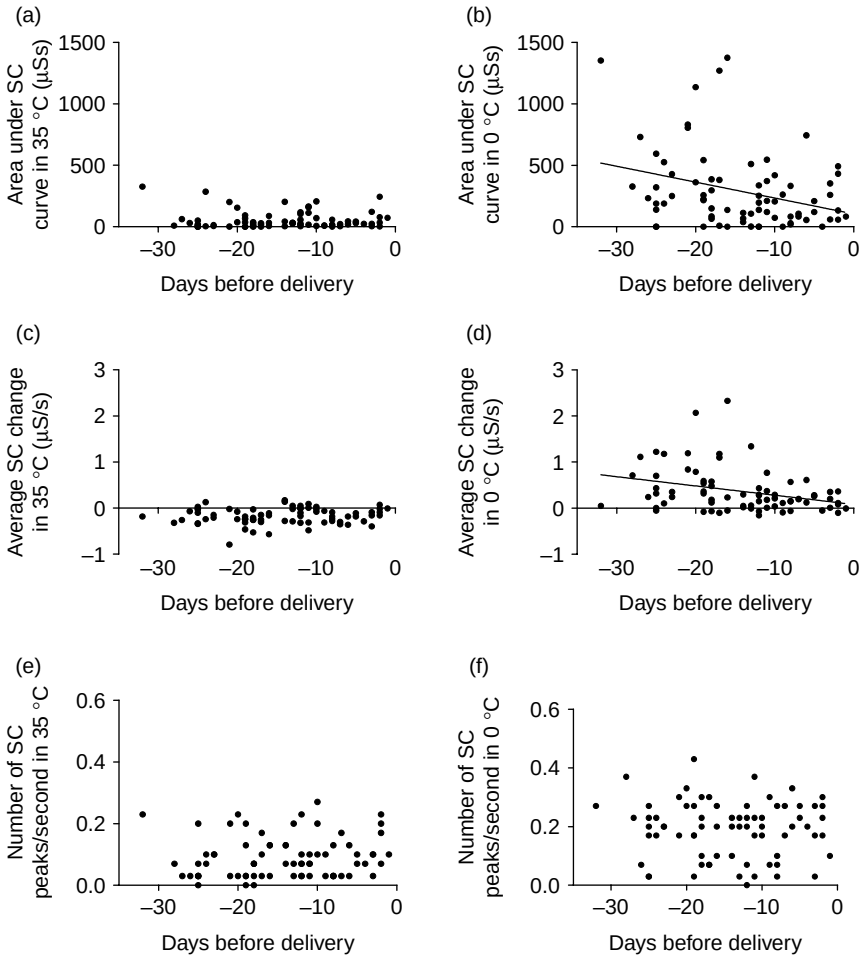

Figure 1. SC activity (area under the curve, a and b; rate of change, c and d; peaks per second, e and f) during baseline (left column) and during the cold pressor test (right column) and their relationship to the number of days between the test and spontaneous delivery. Linear regression lines denote correlations of days to delivery with the area under the curve and with the rate of change ($r = -0.313$, $p = 0.007$ and $r = -0.319$, $p = 0.006$, respectively).

late pregnancy has also been reported (Goolkasian and Rimer 1984). Although pain threshold and endurance are subjective measures of the complex experience of pain, our data support the idea that for research purposes, SC is a more objective measure by which at least one aspect of pain sensitivity and pregnancy-induced analgesia can be captured.

Several recent studies using SC as an algesimeter in post-operative patients have employed number of SC fluctuations as primary outcome (Ledowski et al. 2006; Choo et al. 2010). Indeed, the number of SC fluctuations per second was clearly increased in our subjects during the cold pressor test, but the increase was not associated with time to parturition. In our study, the area under the SC curve (Dubé et al. 2009) and the rate of SC change (Gjerstad et al. 2007) were the measures that correlated with the proximity to delivery. In addition, the SC rate of change was the measure most closely related to self-reported pain intensity and cold endurance as well as to days to spontaneous parturition. Furthermore, the SC rate of change is independent of the large inter-individual variations in actual starting value (Gjerstad et al. 2007).

The cross-sectional study design and the narrow range of gestational ages are important limitations for the interpretation of the study results. Because of this, the study is unable to fully disentangle whether our findings are due to advancing gestational age or proximity to parturition. Although a definitive answer is not possible, the analyses that take gestational age at assessment into account are consistent with the suggestion that proximity to parturition is more important than advancing gestational age. Furthermore, longitudinal studies could render more insight into the patterns of pregnancy-induced stress adaptation over the course of pregnancy and the puerperium. Given the limitations, the only possible interpretation of our results is that the sympathetic stress response is continuously decreasing even in the last weeks before giving birth, whereas the baseline sympathetic level remains stable. Exactly how the mechanisms of blunted stress and pain reactivity are related during human pregnancy remains to be demonstrated.

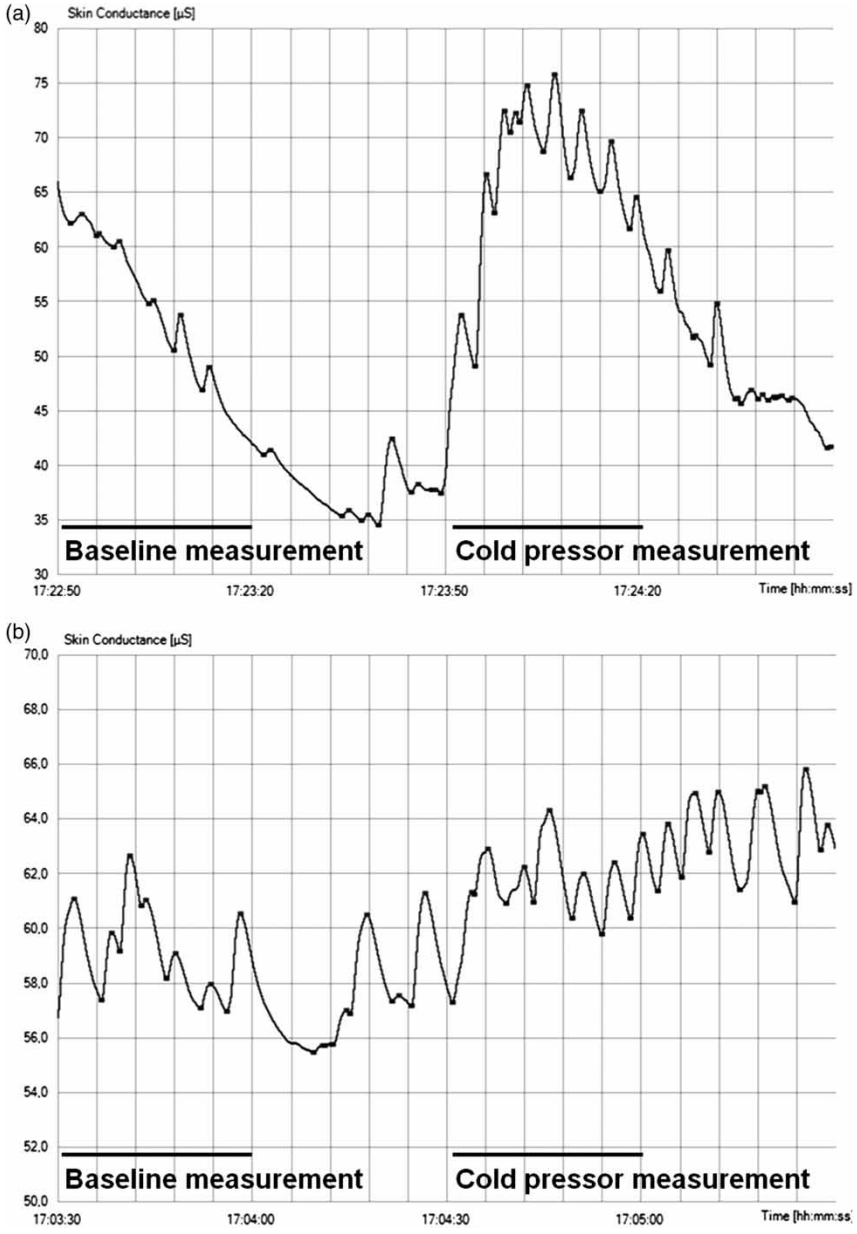

Figure 2. Examples of SC traces during baseline and during the cold pressor test from two women with 21 and 2 days left to spontaneous delivery, respectively. Note that *y*-axes differ. (a) Predicted delivery 14 days after test, parturition 21 days after test. Cold pressor measurement: area under curve: 831.4 µSs, rate of change: 0.84 µS/s. (b) Predicted delivery 14 days after test, parturition 2 days after test. Cold pressor measurement: Area under curve: 133.5 µSs, rate of change: 0.11 µS/s. Please note that the SC measurements do not discriminate between women with less than 2 weeks to delivery and those with more than 2 weeks left on an individual level.

The initiation of human labour is not fully understood. Stress regulation has been implicated in the onset of labour with fetal and maternal HPA axis function, alterations in bioavailable placental corticotropic hormone and/or functional progesterone withdrawal as possible determinants of gestational length (Zakar and Hertelendy 2007; Petraglia et al. 2010). Involvement of the sympathetic nervous system in the initiation of labour is supported by the marked reduction in adrenergic innervation of the uterus during pregnancy, a process that may have a role in the regulation of uterine contractions (Brauer 2008). Our finding indicates that the sympathetic stress response is continuously decreasing even in the last weeks before giving birth at term, whereas the baseline sympathetic level seems to be stable during the final month. Measurement of SC is an easy and non-invasive means to assess sympathetic stress response and may be used in basic research to increase knowledge about sympathetic reactions during pregnancy, with possible relevance for spontaneous labour.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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