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Current Perception Threshold Increases During Pregnancy but does not Change Across Menstrual Cycle

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Abstract

It is well known that pregnancy reduces anesthetic requirements in response to various noxious stimuli. However, there have been no detailed reports concerning functional changes in nerve fibers during pregnancy. Using a Neurometer®, a recently available commercial quantitative sensory monitor, we measured current perception threshold (CPT) values for three frequencies corresponding to the stimulation of A-beta, A-delta and C fibers on the median nerve in women at several stages: late pregnancy, the follicular phase and the luteal phase. A significant difference in CPT values on A fibers was noted between the gravid and the nongravid women, but, no significant difference in CPT values was noted in any of the nongravid women in the follicular or luteal phases. Our results support the current theory that pregnancy changes nerve fiber conduction, as indicated by an increase in CPT values especially on myelinated fibers, but does not cause changes in CPT values across the menstrual cycle.
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Key words: current perception threshold, pregnancy, progesterone, menstrual cycle

Introduction

There have been many studies demonstrating reduced anesthetic requirements in response to various noxious stimuli during pregnancy[1–8]. Furthermore, the highest pain threshold values are always observed during the luteal phase of the menstrual cycle, as determined by measuring pain thresholds for electrocutaneous pulses applied to the skin of the abdomen and limbs[9]. However, whether physiological changes accompanying pregnancy or menstrual cycles can change sensory perception thresholds is unclear, as is the exact mechanism of those changes.

Until recently, no devices allowing quantitative measurement of sensory perception threshold (SPT) values were commercially available. The measurement methods used in previous studies were varied, and problems were encountered in quantitative evaluation. The Neurometer CPT/C™ (Neurotron Inc., Baltimore) is a newly developed device capable of quantifying the amount of current that can be detected by a subject at several primary frequencies[10]. Using the current perception threshold (CPT) as an index of SPT abnormality, many studies have indicated the usefulness of this device in the quantification of nerve dysfunction in patients[11,12]. However, there have been no detailed studies on

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the evaluation of the function of nerve fibers in pregnancy using the Neurometer.

This study was conducted in order to investigate whether or not gravid women have higher CPT values than nongravid women during the follicular phase and whether or not CPT values during the luteal phase are higher than those during the follicular phase.

Materials and Methods

Study criteria: The protocol used was reviewed and approved in accordance with the guidelines of the ethics committee of Nippon Medical School. All subjects gave their informed consent in accordance with these guidelines.

Gravid and nongravid comparison: The criteria for a subject's inclusion in the study were as follows: the gravid women had to be scheduled for an elective Cesarean section or admitted for the control of threatened labor; the nongravid women had to be healthy and of childbearing age with normal neurological examination results.

The criteria for a subject's exclusion were the use of hormone-altering medications, age of less than 18 years, postmenopausal state or incidence of irregular menstruation, refusal to participate, or presence of neurological abnormalities.

CPT values were obtained for the gravid women as soon as possible after admission and for the nongravid women during the follicular phase (7 days after onset of menstruation).

Follicular and luteal phase comparison: The inclusion criteria required that each woman was healthy and of childbearing age with a normal menstrual cycle and normal neurological examination results.

CPT values for the follicular phase were determined at the same time on day 7 after the onset of menstruation, whereas CPT values for the luteal phase were obtained 14 days later, (21 days after the onset of menstruation).

CPT Protocol: The Neurometer is a device that emits sinusoidal alternating currents at 2,000, 250 and 5 Hertz at intensities from 0 to 10 mA. This constant current output automatically compensates for alterations in skin resistance and provides a standardized stimulus independent of different skin thickness, degree of skin dryness or perspiration, or drying of the electrode paste. Electrical stimulus was initially increased until a specific sensation was reported by the subject[13]. A double-blind (microprocessor-controlled) methodology was used in this study that the subject was stimulated with six to ten cycles of randomly selected real and false stimuli both above and below the perception threshold level, until the exact CPT value was determined within a ± 20 μA range[14]. This device can generate three kinds of constant current stimulus: 2,000 Hertz preferentially stimulates the A-beta fibers; 250 Hertz preferentially stimulates the A-delta fibers; and 5 Hertz preferentially stimulates the unmyelinated C fibers[15].

All CPT measurements were conducted in the median nerve in the index finger of the nondominant hand at the distal interphalangeal joint. All comparative measurements in the same individual were performed at 17: 00 hours in order to minimize the effect of diurnal variation. All measurements were carried out with the women lying supine in a quiet room[16]. The measurements were performed by the same examiner using the double-blind forced choice paradigm employed in CPT measurements described by Katims et al[17]. CPT values were obtained at three primary frequencies: 2,000 Hertz, 250 Hertz, and 5 Hertz.

The criterion of excluding subjects with neurological abnormalities was also applied to the CPT test; that is, any woman with a baseline abnormality in CPT values was also excluded from further tests.

Statistical analyses: *Student's* t-test for the comparison of demographics and the Mann-Whitney U-test for the comparison of CPT values between gravid and nongravid women were used for statistical analyses. The Wilcoxon rank test was used for the comparison of CPT values in the follicular and luteal phases. P values of less than 0.05 were considered to indicate statistical significance.

Results

Twenty-five gravid women and 25 nongravid women were enrolled in the first part of the study.

Table 1 Demographic data

	Gravid women (n=24)	Nongravid women (n=22)	
Age (years)	30.9±3.8	29.0±5.6	
Height (cm)	156.9±5.6	159.3±5.1	NS
Weight (kg)	60.8±10.0	52.9±8.9	NS
Gestational Weeks	33±8		p=0.01

(mean±SD)

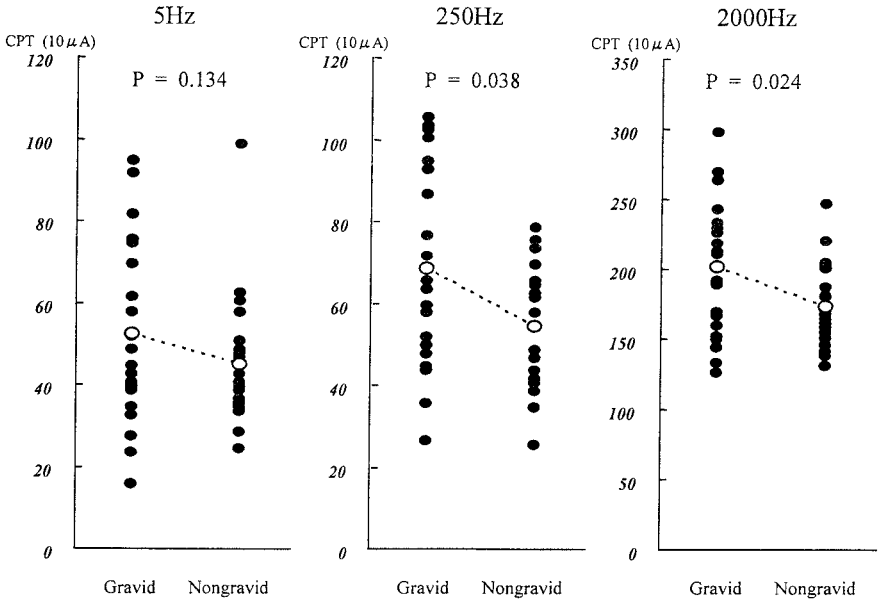


Fig. 1 Comparison of sensory CPT values between gravid and non-gravid women

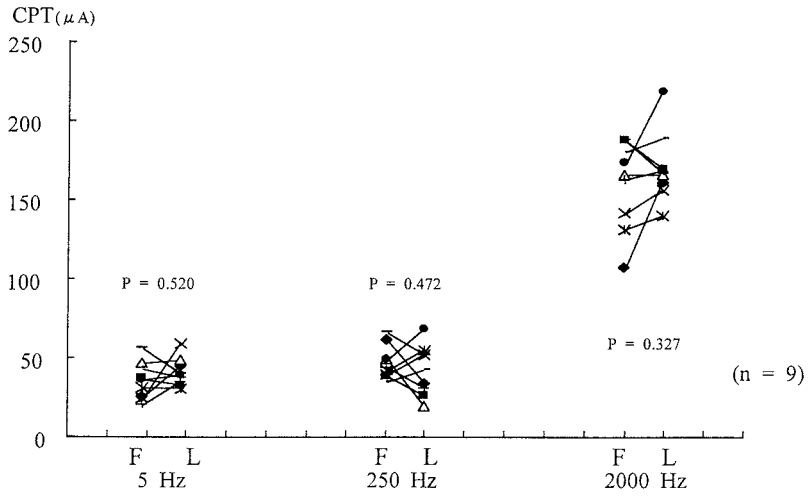
However, we excluded one gravid woman because of abnormally high CPT values and three nongravid women because of abnormally low CPT values. In total, 24 gravid women and 22 nongravid women participated in the first part of the study.

Table 1 summarizes the demographic features of the subjects enrolled in the first part of the study. There were no statistically significant differences in either age or height ($p>0.05$). However, the gravid women weighed considerably more than the nongravid women ($p=0.01$). CPT values are summarized in **Fig. 1**, showing statistically higher CPT values at 2,000 Hertz and 250 Hertz frequencies in the gravid women than in the nongravid women ($p< 0.05$).

Nine women were recruited for comparison of CPT values in the follicular and luteal phases of the menstrual cycle. **Fig. 2** shows the CPT values obtained from the same nongravid women in both phases at all three frequencies. There was no significant difference in CPT values in the follicular and luteal phases of the menstrual cycle ($p>0.05$).

Discussion

Previous studies of animals and humans have demonstrated decreased anesthetic requirements in response to various noxious stimuli during pregnancy. Some authors attribute this effect to increased blood progesterone levels[1,2], while others attribute it to endogenous opioids such as endorphins and encephalins[3]. This maternal analgesia appears to be centrally mediated via activation of the spinal cord dynorphin/kappa-opioid system[3-5]. Indirect



There were no significant differences in the CPT values at any frequency between the follicular and luteal phases of the menstrual cycle ($p>0.05$).

Fig. 2 Comparison of sensory CPT values within the same women between the follicular and luteal phases of the menstrual cycle

evidence suggests that increased levels of endogenous opiates in the central nervous system during pregnancy, along with the increased progesterone levels associated with pregnancy, may contribute to this effect[1,2,6,7,8]. Progesterone can also produce neural effects independent of its hormonal activity[18]. *In vitro* studies have shown that progesterone (and its metabolites) rapidly inhibits nerve cell excitability by potentiating γ-aminobutyric acid (GABA)-mediated increases in chloride ion conductance[19].

The mean progesterone production is 2 mg/day in the follicular phase, 25 mg/day in the luteal phase, and 250 mg/day in the late-pregnancy phase[20,21]. Therefore, we measured and compared CPT values at these phases. We found that the gravid women have higher CPT values in myelinated fibers than the nongravid women. These fibers represent A-beta (2,000 Hertz) and A-delta (250 Hertz) fibers; these are, respectively, heavily myelinated and thinly myelinated fibers. Our result was consistent with those of prior investigations. During pregnancy, the conduction velocity of A fibers in nerves obtained from pregnant animals is slower than that from nonpregnant animals. However, there is no statically significant difference in the conduction velocity of C fibers from pregnant and nonpregnant animals[1]. The A fiber conduction blockade induced by bupivacaine is consistently greater in nerves from pregnant animals[2]. These reports may indicate a basic change in the nerve membrane caused by elevated progesterone levels[1,2].

Irrespective of these data, no statistically significant differences were observed in CPT values obtained during the follicular and luteal phases of the menstrual cycle. From the viewpoint of blood progesterone level in the luteal phase, it is thought that the concentration does not increase enough to influence nerve conduction, and that there is not enough time to cause physiological changes. Our results are not consistent with those of prior investigations[9]. One of the reasons for these different results is probably differences in the methodology used. In clinical settings, a lot of biological factors, such as menstrual cycles, segmental sites, tissue depth and sex, affect pain thresholds[9]. A further study designed to produce standardized stimulation methods, stimulation sites and objects is necessary to resolve this issue.

Detection of subclinical carpal tunnel syndrome in gravid women remains an important concern. The gravid women had a significantly greater body mass than their nongravid counterparts. Pregnancy is usually considered a risk factor in carpal tunnel syndrome. Compression of the median nerve corresponds to the area of abnormality determined by electrodiagnostic testing in approximately 96% of cases[22]. Up to 50% of all pregnant women are said to

have nocturnal hand symptoms mostly in the third trimester[23], but fewer than 1% of pregnant women are newly diagnosed as having clinically significant carpal tunnel syndrome[24]. Although results of this study would suggest that the determination of CPT values is a very sensitive test for detecting subclinical median nerve compression[13], we consider that it is unlikely because none of gravid women in our study had symptoms of carpal tunnel syndrome and all CPT values were within the normal range.

In conclusion, pregnancy, but not menstrual cycle, has appreciable effects on sensory perception thresholds and increases CPT values in myelinated fibers.

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