

# Increased concentration of circulating calcitonin gene related peptide during normal human pregnancy

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## Abstract

**Calcitonin gene related peptide is an extremely potent vasoactive peptide that causes profound vasodilatation in man. Its distribution in perivascular nerves suggests that one of its functions may be the regulation of peripheral vascular tone. Pregnancy is a physiological condition in which there are major haemodynamic changes. An increase in plasma volume of about 40% necessitates changes in peripheral vascular tone. In a cross sectional study plasma concentrations of immunoreactive calcitonin gene related peptide were measured throughout normal pregnancy and at five to seven days post partum. Calcitonin gene related peptide concentrations were significantly increased throughout pregnancy but fell after delivery.**

**Calcitonin gene related peptide may participate in the physiological regulation of vasomotor tone in man.**

## Introduction

Pregnancy is accompanied by profound changes in maternal haemodynamics. Plasma volume expands considerably, but changes in the peripheral vascular tone usually prevent an increase in blood pressure. The precise regulation of such changes has not been documented.

Calcitonin gene related peptide is a potent vasoactive peptide<sup>1,3</sup> that normally circulates in man,<sup>4</sup> but its physiological role is not fully understood. To determine the gestational changes in its secretion we measured plasma concentrations of immunoreactive calcitonin gene related peptide on four occasions during entirely normal pregnancies and at five to seven days post partum in a cross sectional study. Such studies have not to our knowledge been undertaken.

## Patients and methods

**Patients**—Five groups of apparently healthy white volunteers, mean age 28.1 (range 16-39) years, were studied. Twelve were between 10 and 12 weeks pregnant, 10 were between 20 and 22 weeks, 11 were between 30 and 32 weeks, 13 were between 36 weeks and term, and nine were between five and seven days post partum. Each woman had had a normal antenatal and postnatal course up to the time of venepuncture, and the gestational age had been determined accurately by early ultrasound examination. No patient

had taken any drugs, apart from iron and folic acid supplements, for at least three months. All pregnancies were singleton and resulted in a full term delivery of a live, healthy baby of appropriate weight. Fasting venous blood samples were taken at about 9.00 am into cooled, heparinised tubes, and the plasma was separated immediately. The samples were stored at  $-20^{\circ}\text{C}$  until assayed.

**Controls**—Twelve normal, female volunteers who were not pregnant, mean age 32.3 (range 23-39) years, were used as controls. None of these women was taking any medication.

**Methods**—Plasma calcitonin gene related peptide was measured directly by radioimmunoassay<sup>4</sup> with rabbit antiserum CC2/1 raised against synthetic human calcitonin gene related peptide conjugated to bovine albumin. The sensitivity was 0.5 fmol/tube. Intra-assay and interassay variations were 6% and 9%, respectively.

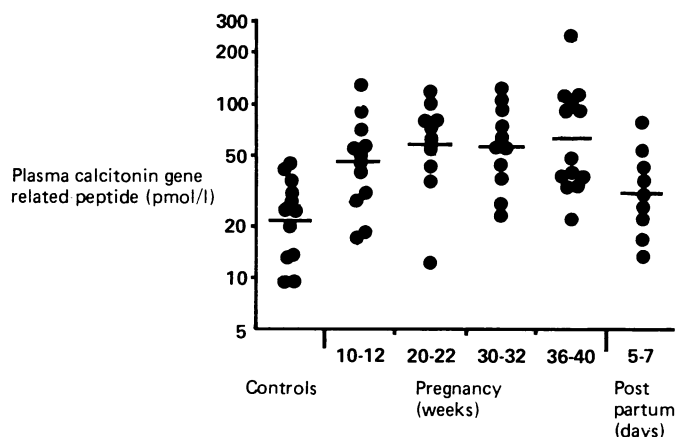
**Statistical analyses**—Analysis of variance and two tailed Student's *t* test were used after log transformation to make the data distribution normal.

## Results

Calcitonin gene related peptide concentrations were increased throughout pregnancy, with the highest concentrations being found towards term (table and figure). There was no significant difference, however, between the concentrations in the groups at the various stages of pregnancy. The concentrations decreased significantly ( $p < 0.02$ ) by five to seven days post partum, when they were not different from those in controls.

Mean (SEM) concentrations of calcitonin gene related peptide in control, pregnant, and postpartum women

	Calcitonin gene related peptide concentration (log <sub>10</sub> pmol/l)	<i>t</i>	Significance
Controls	1.32 (0.06)		
Pregnant women (weeks):			
10-12	1.66 (0.08)	3.33	$p=0.005$
20-22	1.76 (0.09)	3.99	$p=0.001$
30-32	1.75 (0.07)	4.50	$p=0.0001$
36-40	1.79 (0.08)	4.38	$p=0.0005$
Postpartum women	1.48 (0.08)	1.56	NS



Plasma calcitonin gene related peptide concentrations in normal, pregnant, and postpartum women. Horizontal bars represent group means.

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## Discussion

The calcitonin gene encodes several different peptides. With messenger RNA extracted from human medullary thyroid carcinoma, cloning and analysis of recombinant DNA first showed that human calcitonin is synthesised as part of a large molecular weight precursor peptide.<sup>5</sup> It is flanked by a large N-terminal cryptic peptide and by a 21 amino acid C-terminal peptide, katalcalcin.<sup>6</sup> During studies of a serially transplanted rat medullary thyroid carcinoma cell line,<sup>7</sup> however, a different messenger RNA was discovered, representing an alternative processing of the primary RNA transcript. This new messenger RNA coded for a precursor polypeptide that contained a similar large N-terminal flanking peptide but that had a 37 amino acid peptide replacing calcitonin. This predicted peptide was named calcitonin gene related peptide. Its existence in man was confirmed after it was isolated from a human medullary thyroid carcinoma.<sup>8</sup>

Calcitonin gene related peptide is distributed widely in the nervous system,<sup>9-14</sup> suggesting a role as a neurotransmitter or neuromodulator. It has profound effects on the cardiovascular system in both animals<sup>15, 16</sup> and humans.<sup>2, 3</sup> Indeed, it has been shown in human volunteers to be one of the most potent vasoactive peptides discovered.<sup>3</sup> Calcitonin gene related peptide is distributed in the perivascular nerves,<sup>9, 17</sup> which seem to be a major source of circulating peptide.<sup>18</sup> This suggests that calcitonin gene related peptide may be important in the physiological control of blood flow and peripheral vascular tone.

Plasma volume is significantly increased at 10 to 12 weeks' gestation and eventually increases by about 40%. Red cell mass also increases by a quarter. In view of its profound vasodilatory effects calcitonin gene related peptide is possibly responsible for changes in the peripheral vasculature in response to this expansion of plasma volume and such physiological changes are reflected by the increased circulating calcitonin gene related peptide concentration. Of course, a failure of the peripheral vasculature to expand in order to accommodate the increased plasma volume might result in an increase in blood pressure. It would thus be of interest to study calcitonin gene related peptide concentrations in patients with pregnancy induced hypertension and eclampsia.

We do not know, however, if the increased plasma concentration of calcitonin gene related peptide during pregnancy is derived from the perivascular nerves. As calcitonin gene related peptide is normally found in the thyroïdal C cells in humans<sup>11</sup> the increased circulating concentrations might derive from hyperplasia or increased activity of the C cells during pregnancy. Good evidence for this comes from the observation that plasma calcitonin concentrations are also increased throughout pregnancy<sup>19, 20</sup> and, to a lesser degree, in the early postpartum period.<sup>19</sup>

Finally, calcitonin gene related peptide is also found throughout the urogenital tract.<sup>21</sup> The uterus or placenta might thus possibly be the main tissue source of the observed increase in circulating concentrations. Indeed, calcitonin gene related peptide might even conceivably have a specific physiological role in the urogenital tract during pregnancy. A recent study showed that calcitonin gene related peptide inhibited spontaneous contraction of the human uterus.<sup>22</sup> Whether our findings reflect a physiological role for calcitonin gene related peptide during pregnancy remains unclear. Future studies in animals may help to clarify this issue.

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## 100 YEARS AGO

In addition to the force at present in the country (about 20,000 men), another force is under way from India consisting of 10,000 men, of artillery, cavalry, and infantry, with their followers. They commenced to leave India the second week in September, and will all be landed in Rangoon before the end of that month. It is hoped that this force, combining with the force now in Upper Burmah, will be able to quiet the country, and do away with the dacoiting. Most of these troops are coming over with the view of eventually relieving the troops which have become sickly from the severe service they have had in Burmah since the commencement of the operations in November last, and some troops who will have completed their tour of three years' service in Lower Burmah.

During the hot weather and rains, the troops in Upper Burmah have suffered severely from malarious fever and dysentery, but this has been much more marked in some stations than others, and particularly so amongst those troops who have had to go out into the jungles. Very little enteric fever has been seen during this campaign up to the present, and cholera has not prevailed to any extent since the early part of the campaign. Venereal diseases are still very rife amongst the British troops, but the native

troops and followers, whether from their chastity or from their being more cautious in their amours, have not suffered to nearly the same extent. (*British Medical Journal* 1886;ii:783.)

The *Pall Mall Gazette* is exercising itself as to the best colour of the eye for rifle-shooting. Arguing from a general impression that the best rifle shots have blue eyes, it concludes that eyes with bluish or greyish irides are less subject to the effects of mirage than those of darker colour. It is scarcely necessary to say that such a conclusion has not, so far, been verified by scientific observation. Assuming it to be the fact that light-eyed people are better shots, this cannot reside in their greater immunity from refractive errors, since we may say certainly that no such immunity exists, for the blue-eyed Germans are, as is well known, the most subject to myopia of all nations. The matter then rests for the present in doubt, unless we may assume that people of Saxon and Scandinavian blood excel in rifle-shooting in the same way, and for the same reasons, as in all other out-door exercises involving skill and nerve. (*British Medical Journal* 1886;ii:221.)