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## Adult Height, Insulin Levels and 17 $\beta$ -Estradiol in Young Women

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*(Article begins on next page)*

## Adult height, insulin levels and 17 $\beta$ -estradiol in young women

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Key words: Adult height, insulin levels, 17  $\beta$ -estradiol, Norway

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**Background:** Adult height and insulin levels have independently been associated with breast cancer risk. However, little is known about whether these factors influence estradiol levels. Thus, we hypothesize that adult height in combination with insulin levels may influence premenopausal  $17\beta$ -estradiol throughout the entire menstrual cycle of possible importance of breast cancer risk.

**Methods:** Among 204 healthy women, aged 25-35 years who participated in the Norwegian EBBA I study, birth weight and age at menarche were assessed by questionnaire, personal health record and interview.  $17\beta$ -estradiol concentrations were estimated by daily saliva samples throughout one entire menstrual cycle using radioimmunoassay (RIA). Measures of height (cm) were taken as well as waist circumference (cm), body mass index (BMI  $\text{kg}/\text{m}^2$ ) and total fat percentage (DEXA % fat). Fasting blood samples were drawn, and serum concentrations of insulin were determined.

**Results:** The women reported a mean height of 166.5 cm, birth weight of 3389 g and age at menarche 13.1 years. Mean BMI was  $24.4 \text{ kg}/\text{m}^2$ , mean waist circumference 79.5 cm and mean total fat percentage 34.1%. Women with an adult height of more than 170 cm and insulin levels higher than 90 pmol/L experienced on average an 37.2 % increase in  $17\beta$ -estradiol during an entire menstrual cycle compared to those with the same height, and insulin levels below 90 pmol/L. Moreover, this was also observed throughout the entire menstrual cycle.

**Conclusion:** Our findings support that premenopausal levels of  $17\beta$ -estradiol vary in response to adult height and insulin levels, suggesting that women who become taller are put at risk for higher estradiol levels when their insulin levels rise of possible importance for breast cancer risk.

## Introduction

Attained adult height has consistently been positively associated with the risk of breast cancer [Palmer et al., 1995]. Genetic and early environmental factors are linked to attained height and therefore height may be a good marker not only on birth weight but also on susceptible periods of rapid growth and age at menarche. Additionally insulin and insulin resistance have been linked to birth size and sexual maturation as well as breast cell proliferation, suggested to influence breast cancer risk {2007 161 /id, Eliassen, 2007 2 /id}.

Obesity has been linked to mortality from the majority of cancers. The insulin/insulin-like growth factor (IGF) system may partly explain this effect. The metabolic syndrome, associated with hyperinsulinemia, may modulate this effect. Recent evidence supports the role of insulin and IGF-1 as important growth factors, acting through the tyrosine kinase growth factor cascade in enhancing tumor cell proliferation. The role of insulin is of concern because of the increasing levels of obesity and the associated metabolic syndrome {Boyd, 2003 9 /id}, and may be of importance in relation to the carcinogenesis of the breast.

To our knowledge, little is known about the association between adult height, insulin levels and premenopausal estradiol level throughout an entire menstrual cycle. However, the etiologic role of endogenous hormones as 17  $\beta$ -estradiol in relation to breast cancer risk is strongly supported [Pike et al., 1993], [Bernstein, 2002]. Additionally, the large variation in breast cancer incidence and in levels of sex hormones has been discussed to reflect both genetic variation [Bernstein, 2002], {King, 1996 1 /id} as well as variation in availability of energetic factors [Jasienska and Thune, 2001]. Therefore, we hypothesize that a combination of adult height and insulin levels may interact, and influence levels of 17  $\beta$ - estradiol throughout the entire menstrual cycle.

Because steroid levels in saliva represent free, rather than free plus bound circulating steroid levels, they allow for much finer discrimination of functional differences in steroid signalling. Because saliva can be readily collected from subjects on multiple occasions, it is possible to compare steroid levels across entire menstrual cycles among different women rather than relying on one or a few timed blood samples {Lipson, 1996 112 /id, Jasienska, 2006 4 /id}.

The aim of the present study was to assess if levels of 17 $\beta$ -estradiol throughout an entire menstrual cycle are influenced by variation in adult height together with variation in insulin levels. Such interactive effect may be of possible importance for susceptibility of breast cancer.

## **Material and Methods**

### *Subjects and study design*

Women aged 25-35 years, living in Tromsø and surroundings during 2000-2002, were invited to participate in the Norwegian EBBA study by announcements in newspapers and locally. Study subjects had to meet the following criteria; self reported regular menstruation (normal cycle length; 22-38 days within the previous three months), not taking hormonal contraceptives, no pregnancy or lactation over the previous six months, no history of endocrinological, gynecological disorder or chronic disorders (e.g. diabetes, hypo-/hyperthyroidism). A total of 206 women who met the inclusion criteria, were subsequently enrolled into the study and came to the Department of Clinical Research, University Hospital North Norway (UNN), at a scheduled time [Furberg et al., 2004]. Two women were excluded: one because of a measured cycle length of 47 days and the other because of abnormally high E<sup>2</sup> levels.

### *Questionnaires*

We used a general questionnaire (self-administered and by interview) to collect information on ethnicity, education, birth size, menstruation and reproductive history, previous use of hormones, family history of cancer and lifestyle habits (lifetime total physical activity, smoking, alcohol). Recall and memory- probing aid and interview by trained personal were used, including a lifetime calendar. A pre-coded food diary with photographic booklet on portion size was developed and used in order to collect dietary data on seven different days (follicular phase; day 3-6 and luteal phase; day 21-23) during the menstrual cycle.

### *Body composition measurements*

We measured attained height to the nearest half-centimeter with the women in standing position and with no footwear.

Body mass index (BMI, kg/m<sup>2</sup>) was used to estimate relative weight. Waist circumference (cm) was measured in a horizontal line 2.5 cm above the umbilicus.

Age at menarche was assessed by questionnaire and interview by the same trained nurse.

Study subjects made three subsequent visits to the laboratory over the course of one menstrual period: visit 1 (days 1-4), visit 2 (midcycle) and visit 3 (days 22-25). They came in on the first possible day after onset of the menstrual bleeding for clinical examinations, anthropometric measurements and for a fasting blood sample. All clinical procedures were

conducted by trained nurses at the Department of Clinical Research, UNN, Tromsø. Anthropometrical measures were taken twice (visit 1, visit 3) with subjects wearing light clothing and no footwear: waist circumference were measured to the nearest half- centimeter and weight was measured to the nearest 0.1 kilogram on an electronic scale who were standardized on a regular basis.

On the second visit (mid-cycle day 7-12) the participants met for whole body scan. Whole body scan was obtained by DEXA (DPX-L 2288, Lunar Radiation Corporation, Madison, WI, USA) operated by the trained nurse and percentage of fat tissue was estimated by Lunar software.

### *Serum samples*

Fasting serum blood samples were drawn from an ante-cubital vein three times during the menstrual cycle (visit I, visit II and visit III). The blood was centrifuged and the serum was separated. Serum concentrations of estradiol were measured in fresh sera at the Department of Clinical Chemistry, UNN, Tromsø. Serum concentrations of insulin and leptin were measured at the Hormone Laboratory, Aker University Hospital, Oslo in serum that were stored at -70°C for up to 3 years until analysis. Serum insulin and leptin were measured by RIA using kits from Linco Research Inc, St. Charles, MO, USA [Furberg et al., 2004].

### *Estradiol indices and assay procedure*

From the first day of bleeding and each day during the menstrual cycle the participants collected morning saliva samples at home according to previously established collection protocols at the Reproductive Ecology Laboratory at Harvard University, U.S.A, [Lipson and Ellison, 1996]. Concentrations of 17  $\beta$ -estradiol were measured in daily saliva samples from 20 days (reverse cycle day -5 to -24) of the cycle using an  $^{125}$  I based radioimmunoassay (RIA) kit (#39100, Diagnostic Systems Laboratory, Webster, TX, USA), along with published modifications of the manufacturer's protocol [Furberg et al., 2005]. All samples were run in duplicate. All of a woman's samples were run in the same batch, with women randomly assigned to batches. CV's were calculated from high to low value pools (appropriate to the range of 17  $\beta$ -estradiol) that were run with each batch [Furberg et al., 2005].

Before statistical analysis, all cycles were aligned to the day of ovulation following published methods [Furberg et al., 2005], based on the identification of the E<sub>2</sub> drop at the mid-cycle (day 0), which provides a reasonable estimate of the day of ovulation. The E<sub>2</sub> values for 20 consecutive days from each cycle, aligned on day 0, were used in data analyses

(day -10 to + 9). Satisfactory identification of the mid-cycle E<sub>2</sub> drop could not be made for 14 women and their cycles were not aligned.

### *Statistical analysis*

We studied the association between adult height, insulin and 17 β- estradiol levels throughout a menstrual cycle using linear regression analysis and linear mixed models for repeated measures (SAS statistical package version 9.1).

In order in detail to study the influence of variation in attained adult height on estradiol levels, the study population was divided into tertiles of adult height; 1) < 164cm, 2) ≥164cm and <170cm and 3) ≥170cm. These three groups of adult height were then compared with regard to selected characteristics of the study population. We used one-way analyses of variance for continuous variables and  $\chi^2$  tests for categorical variables.

Age and multivariate adjusted linear regression analyses were used to study the associations of average salivary 17β-estradiol concentration (overall, follicular and luteal phases of menstrual cycle), adult height and measures of body composition, serum insulin, leptin and cholesterol.

To study whether variation in insulin levels modified the association between adult height and salivary concentrations of 17β-estradiol, insulin levels were dichotomized at the 75th percentile (75th percentile insulin: ≥ 90). We used a linear mixed model for repeated measures to study salivary 17β-estradiol concentrations over the entire menstrual cycle in relation to adult height and levels of insulin.

In order to adjust for potential confounding factors multivariate analyses were performed. Based on biological plausibility possible covariates such as age, smoking, physical activity, age at menarche, energy intake, alcohol, previous use of hormonal contraceptives, age at first birth and number of children were tested in the model. The following variables fitted the model and were therefore included in the final model; age, smoking, physical activity and age at menarche. We have presented both age adjusted and multivariate adjusted estimates.

Measurements of 17β-estradiol at the start and finish of the cycles had higher coefficients of variation and higher rates of missing data as a result of variation in cycle length; therefore we included 17β-estradiol measurements from cycle day -10 to +9 in the linear mixed models. Results were considered statistically significant when the two-sided *p* value was < 0.05.

### *Ethical Consideration*

All the participating women signed an informed consent form. The study protocol was reviewed and approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

### **Results**

When dividing the women into tertiles of adult height (<164 cm, 164-170 cm, >170 cm), they did not vary much by their characteristics. However, women within the highest tertile of adult height ( $\geq 170$ cm) had a larger waist circumference ( $p= 0.008$ ) compared to those with a shorter adult height, but they did not seem to have a greater BMI or total fat % than those who become smaller. Of interest, the tallest women tend to have higher insulin levels, and they had later age at menarche ( $p=0.02$ ).

We studied the changes in overall average salivary 17 $\beta$ -estradiol concentration by 1 standard deviation (SD) change in explanatory variables for each tertile of adult height; birth weight (DS= x), BMI (SD= 3.8 ), waist (SD= 9.8 ) and by 1 SD change in serum leptin (SD= 562.9 ) or insulin (SD= 59.2 ) and cholesterol (SD= 0.78). We observed that an increase in any of these measures except for birth weight resulted in a multi-adjusted increase in 17 $\beta$ -estradiol concentration in the highest tertile of adult height ( $\geq 170$ cm), (Table 2). For each SD change in insulin levels in the highest tertile of adult height, the overall multi-adjusted level of 17 beta-estradiol increased by 3.1 pmol/L (95 % CI, 1.1, 5.2), equivalent to a 17.3 % change in mean average concentration of 17  $\beta$ -estradiol in the highest tertile of adult height. For each SD change in BMI in the highest tertile of adult height, the overall multi-adjusted level of 17 beta-estradiol increased by 3.0 pmol/L (95 % CI, 0.8, 5.3), equivalent to a 16.8 % change in mean average concentration of 17  $\beta$ -estradiol in the highest tertile of adult height.

For each SD increase in explanatory variables, except for insulin, 17  $\beta$ -estradiol seem to increase also among women in the lowest tertile of adult height (<164), - although not to the same degree as among the tallest women.

In order to study the association between adult height, insulin levels and 17  $\beta$ -estradiol we used a linear mixed model for repeated measures to study salivary estradiol concentrations throughout an entire menstrual cycle in relation to adult height and insulin levels (proc mixed), (Figure 1, 2). We observed no clear pattern between daily 17  $\beta$ -estradiol and variation in attained adult height or between daily 17  $\beta$ -estradiol and variation in levels of insulin



(figures not shown). In contrast, when analyzing the association between adult height in combination with insulin levels and 17  $\beta$ -estradiol, we observed that height in combination with insulin were associated with levels of premenopausal 17  $\beta$ -estradiol throughout the menstrual cycle. Women in the highest tertile of attained height ( $>170\text{cm}$ ) in combination with the highest tertile of insulin ( $\geq 90$ ) experienced on average 37.2 % increase in 17 $\beta$ -estradiol during an entire menstrual cycle compared to those with the same height, and insulin levels below 90 pmol/L, (Figure 1). The results became even more pronounced when we looked into those with adult attained height in the upper quartile  $\geq 172\text{ cm}$  and insulin  $\geq 90$  ( $p=0.006$ ), (Figure 2).

## Discussion

In our study among young healthy and regular menstrual cycling women, we found that tall women with an adult height  $\geq 170\text{cm}$  in combination with increased insulin levels (insulin levels  $\geq 90$ ), experienced 37.2 % increase in free 17  $\beta$ -estradiol levels during each menstrual cycle compared to women with an adult height  $\geq 170\text{ cm}$  and serum insulin  $< 90\text{ pmol/L}$ . To our knowledge no other studies have looked into the interrelationship of attained adult height, serum insulin levels and 17 $\beta$ -estradiol levels over an entire menstrual cycle.

Height is a result of both genetics and nutrition. Nutrition during periods of growth (childhood and puberty) seems to be an especially important factor for final height [Cold et al., 1998] [Tretli and Gaard, 1996]. Thus, height may be a proxy-variable of nutritional status during the years of growth. Consequently, attained height has been proposed as an indicator of childhood energy intake and it has been suggested that early exposures that possibly affect mammary mass [Albanes and Winick, 1988] may also be critical in breast carcinogenesis [Hunter and Willett, 1993].

Changes in life style that occurred during World War II in Norway affected children's height as well as their weight (Brundtland et al 1980). The most obvious reason for the reduction in growth-rate during this period was a change in nutrition [Vatten and Kvinnsland, 1990]. The incidence of breast cancer was lower than expected among women who experienced puberty during the war. The estimated configuration of the exposure variable showed an increase in exposure up to the start of WWII to twice the level in 1916, dropped by 13 percent during the war, and increased again after the war.[Tretli and Gaard, 1996]. This may support height as an important factor in relation to breast cancer risk.

Li et al found that age when maximum height was attained was related to breast cancer risk rather than attained height [Li et al., 1997]. The physiologic basis for this

observation may be that if women reach their maximum height later, their breasts mature later and, consequently, they have less time between their pubertal breast development and the protective breast proliferation that occurs at the time of the first live birth [Li et al., 1997]. However, height may also reflect the number of ductal stem cells that develop in the breast *in utero*, which implicates prenatal exposures in breast cancer aetiology [Trichopoulos and Lipman, 1992]. Attained height is also probably influenced by inherited patterns in endogenous hormones and growth factors that influence risk at puberty when breast tissue is rapidly developing in addition to promoting effects later in life. Dietary exposures other than energy deprivation may influence height, including an overabundance of energy and fat and variation in macronutrient intake in the years before puberty [Ziegler et al., 1996]. It has been suggested that better nutrition accelerates growth hormone release, which then increases insulin-like growth factor (IGF) levels [Stoll and Secreto, 1992]. The adolescent growth spurt involves stimulation by growth hormone, insulin, IGF and sex steroids, and one hypothesis is that the combination of IGF and sex steroids results in mitogenic effects on developing mammary tissue in adolescence and, therefore, an increased risk of epithelial atypia and carcinogenesis [Stoll, 1998]

Furthermore, abdominal-type obesity and higher circulating levels of insulin, testosterone and insulin-like growth factor 1 are further risk markers for breast cancer. [Stoll, 1994 1 /id}. Recent theories propose that a Western lifestyle may increase cancer risk through alterations in the metabolism of insulin and insulin-like growth factors (IGF), [Keown-Eyssen, 1994]; [Giovannucci, 1995]; [Kaaks, 1996]; [Werner and LeRoith, 1996]. Insulin regulates energy metabolism, and increases the bioactivity of IGF-I by enhancing its synthesis, and by decreasing several of its binding proteins (IGFBP; IGFBP-1 and -2). Insulin and IGF-I both stimulate anabolic processes as a function of available energy and elementary substrates (e.g. amino acids). The anabolic signals by insulin or IGF-I can promote tumour development by inhibiting apoptosis, and by stimulating cell proliferation. Furthermore, both insulin and IGF-I stimulate the synthesis of sex steroids, and inhibit the synthesis of sex hormone-binding globulin (SHBG), a binding protein that regulates the bioavailability of circulating sex steroids to tissues [Kaaks and Lukanova, 2001]. Epidemiological evidence is accumulating and suggests that the risk of cancers of the colon, pancreas, endometrium, breast and prostate are related to circulating levels of insulin, IGF-1, or both [Kaaks, 2004].

Weight gain, through typical Western diet; limited levels of activity; and, more recently, stress-related changes in neuroendocrine function may lead to insulin resistance and hyperinsulinemia. The opportunity for a multidisciplinary approach involving nutrition,

exercise, and stress reduction in an integrative setting may be crucial to limiting the insulin-resistant state and improving cancer outcomes {Boyd, 2003 9 /id}.

Despite the inverse relation on an ecologic (population) trend level, the analyses show that earlier age at menarche in individuals is related to shorter adult height. The latter may appear contradictory to the known effects of age at menarche and height on breast cancer risk. It is likely, however, that these risk factors affect breast cancer risk through different pathways. Early menarche may lead to an increased lifetime exposure to endogenous sex hormones, which may cause an increased risk of breast cancer (36+–38+). Taller adult height, on the other hand, is positively associated with high levels of growth hormone and insulin-like growth factor I and might be a reflection of increased growth hormone/insulin-like growth factor I activity during childhood, which is also hypothesized to increase breast cancer risk [Kaaks and Lukanova, 2001]

To our knowledge little is known about the relationship between adult height, adult body composition, serum insulin levels and 17 $\beta$ -estradiol throughout an entire menstrual cycle. However, epidemiological evidence implicating anthropometric risk factors in breast cancer aetiology is accumulating. Most previous studies have found a positive association between breast cancer and height [Cold et al., 1998]. The evidence is somewhat stronger from the cohort than the case–control studies, possibly because most cohort studies use direct measures of height while the majority of case–control studies use self-reported height. Among studies that could examine the risks by menopausal status, weaker associations are found for premenopausal women [Friedenreich, 2001]. Overall, the range of risks estimated from studies for taller, as compared to shorter, women is 0.8–2.0 for premenopausal women and 1.3–1.9 for postmenopausal women [Ballard-Barbash, 1994]. Women with a family history of breast cancer experience a greater risk with increased height (RR~2.0) than do women without such a family history (RR~1.2) [Ballard-Barbash, 1994].

The daily saliva sampling allowed for estimation of daily 17  $\beta$ -estradiol concentrations throughout one entire menstrual cycle which strengthen our study. We used well-developed and validated methods and assays to characterize the women's exposure to free, biologically active ovarian steroids and the comparisons of levels by aligned cycle days {Lipson, 1996 136 /id}. This study has the benefit of having collected samples every day over an entire menstrual cycle, as opposed to a random or selected day within a cycle. Furthermore, salivary levels of 17 $\beta$ -estradiol are quite stable within participants over time [Ellison and Lipson, 1999].

The use of one clinical research department at a university hospital with one specially trained nurse enhanced the quality of our data. It also allowed us to sample all clinical variables within the same narrow frame of the cycle for each participant, using uniform procedures. To limit any potential influence of season, women did not participate during months with no daylight (December and January). Height was measured according to standardized methods. Insulin was estimated in fasting serum samples after being stored not more than 3 years and then analyzed at The Aker University Hospital using well documented methods. We adjusted for potential confounders.

**Conclusion:** Our main findings suggest that taller women are put at risk for higher  $17\beta$ -estradiol levels when their insulin levels rise. This may influence levels of  $17\beta$ -estradiol during each menstrual cycle of possible importance for breast cancer risk.

Our findings support the hypothesis that tallness in combination with adult obesity and thereby elevated levels of insulin may influence biomarkers of importance for breast cancer risk.

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**Table 1** Characteristics of the study population by height (cm), means, (SD)\* (tertiles). The Norwegian EBBA-Study (N=204\*\*)

Study Characteristics	Height			p-value ‡ (trend)
	<164 n=68	≥164-- 170 n=68	≥170 n=68	
Age, Years	31.1 (1.3)	30.3 (3.3)	30.7 (3.0)	
Years of schooling				
Ethnic minority, sami %				
Anthropometric measurements				
BMI, kg/m <sup>2</sup>	23.9 (3.2)	25.2 (4.0)	24.1 (4.0)	0.9
Waist circumference, cm	76.5 (7.9)	80.9 (10.2)	81.1 (10.5)	0.008
Total fat, %	33.2 (7.7)	35.2 (7.7)	34.0 (7.4)	0.55
Saliva hormone concentrations, pmol/l				
Overall 17 beta-estradiol	16.8 (8.1)	19.7 (8.5)	17.2 (9.6)	0.83
Serum hormone concentration ≡ (mmol/l)				
s-Estradiol	0.14 (0.05)	0.15 (0.1)	0.15 (0.1)	
s-leptin	716.5 (4.2.2)	941.9 (606.9)	901.2 (625.7)	
s-glucose	5.0 (0.6)	5.0 (0.5)	5.1 (0.6)	
s-insulin	79.6 (65.1)	85.4 (43.0)	91.8 (67.0)	0.23
Menstrual and reproductive characteristics				
Menarche	12.9 (1.3)	13.0 (1.3)	13.4 (1.5)	0.02
Age at 1. birth, years	24.5 (4.4)	24.1 (4.1)	24.9 (3.2)	
Number of children	0.9 (1.0)	0.9 (1.2)	1.0 (1.2)	
Cycle length, days	28.0 (2.8)	28.3 (3.0)	28.4 (3.7)	

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Figure 1

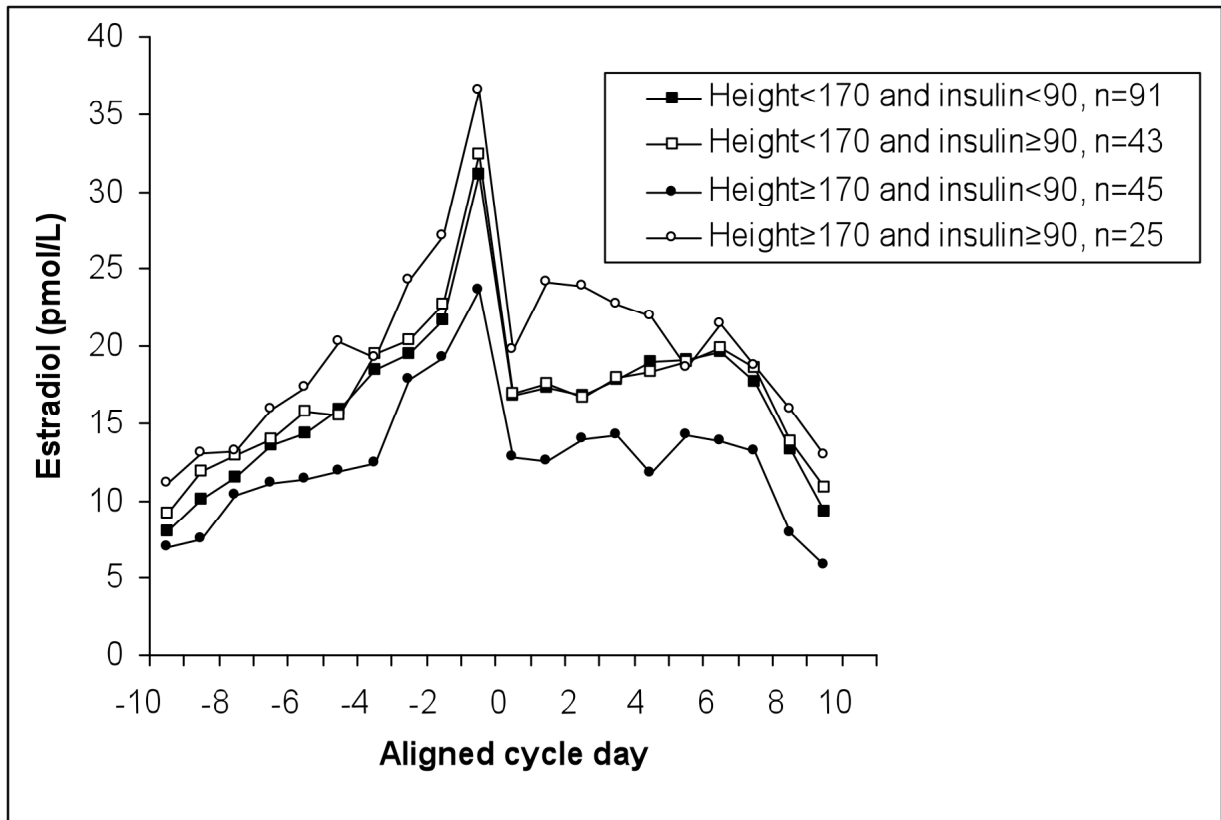




Figure 2

