

Do Gonadotropins Influence Serum Lipoprotein(a) Concentrations? Observations on Children, Adolescents and Adults

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Summary: Data from 7045 subjects were examined. The main groups consisted of the following in- and outpatients: 1414 neonates, 2554 children and adolescents (1336 males, 1218 females), 1209 women directly postpartum, 786 non-pregnant women and 1090 men aged between 18 and 100 years of age. Unless otherwise stated, persons were under medical observation or therapy.

The results were obtained over a three-year period using an in-house immunoluminometric assay specific for apolipoprotein(a) using two polyclonal antibodies and a single lot of reagents to allow for comparability of results.

Girls aged between 10 and 12 years of age had significantly higher serum lipoprotein(a) (median 124 mg/l) levels than boys (median 88 mg/l) of the same age ($p < 0.05$ – *Mann-Whitney U-test*). Post-pubertal lipoprotein(a) concentrations were not significantly different from pre-pubertal levels. Between the ages of 0–9 and 13–17 years there were no statistically significant sex-linked differences in serum lipoprotein(a).

In adults, lipoprotein(a) serum levels were significantly higher in women (median 163 mg/l) aged between 50 and 59 years, when compared with men (median 128 mg/l) of the same age group ($p = 0.05$ – *Kruskal-Wallis one way ANOVA* followed by the *Nemenyi* test).

There was no significant difference in serum lipoprotein(a) concentrations between healthy women (median 91 mg/l), women direct postpartum (median 116 mg/l) and in-patient women (median 117 mg/l) aged between 18 and 41 years of age ($p = 0.11–0.96$). There was no correlation between maternal lipoprotein(a) and birth weight in mature newborns ($r = -0.028–0.085$).

The results may indicate a direct influence of gonadotropins at puberty and during the menopause which cause an increase in serum lipoprotein(a) concentrations.

Introduction

Although lipoprotein(a) is an accepted additional and independent risk factor for early onset atherosclerotic changes (1–4), relatively little is known about factors influencing its concentration in blood. Conflicting reports about changes in lipoprotein(a) concentrations in serum in response to hormonal activity may be due to several conditions, including the size of the group studied (5, 6), the time-period of observation (6, 7), the method used for quantitation (8), and the statistics used for comparison (9).

The non-Gaussian distribution of lipoprotein(a) concentrations, together with the wide range of concentrations found in serum, allow only non-parametric statistics to be used. In addition, the median value for lipoprotein(a) lies in a concentration range where relative few results are to be found, in contrast to the mean value in a normally distributed population. The consequence of this

fact is that large numbers of observations within a group are needed to obtain a stable median lipoprotein(a) concentration.

The results presented in this article have been derived from over three years of observations using a single lot of reagents, thus excluding variation due to methodology and changing reagents and calibration materials.

The hypothesis that lipoprotein(a) concentrations may be affected by gonadotropins has been examined using observations made in this hospital as well as from those published in the literature, where the effects of pregnancy (7, 10–14), pituitary hormones (15, 16) and different drugs (11, 17–19) are well documented.

Subjects and Methods

Data from a total of 7045 subjects (3159 males, 3886 females) were processed in this study and included 2554 children and adolescents (1336 males, 1218 females), 1209 mothers directly post-

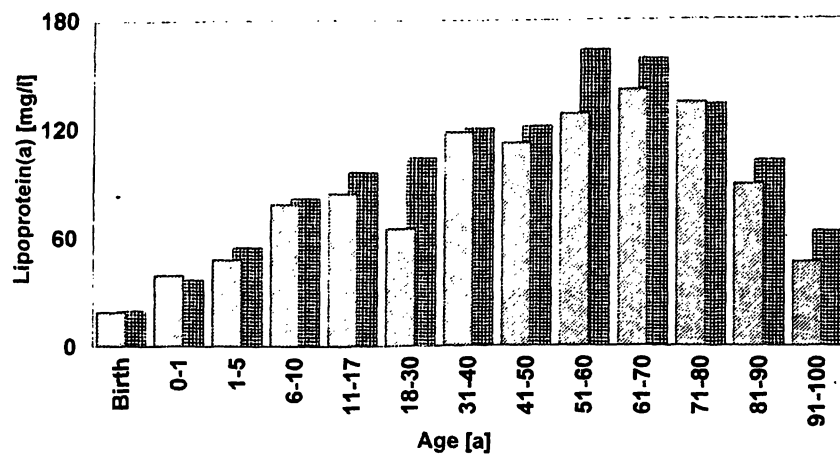


Fig. 1 Median lipoprotein(a) concentrations in subjects at birth and aged between 2 weeks and 100 years of age. Data from 3159 males \square and 3886 females \blacksquare were used.

partum and 786 non-pregnant women aged between 18 and 96 years of age. In addition, data from 1090 males aged between 18 and 100 years of age and 1414 newborns were used for comparison. Lipoprotein(a) was measured with an in-house immunoluminometric assay using two polyclonal antibodies directed against apolipoprotein(a). The method has been published elsewhere (20) and has been used for extensive studies (21–23) as well as for routine purposes. A single lot of reagents has been used throughout the study and thus allows for comparison of results over the whole observation period.

Statistics

Non-parametric statistics have been used throughout. The median has been used as the measure of central tendency, relevant percentiles as measure of dispersion. For comparison of two groups, the *Mann-Whitney* U-test was used for independent samples; for comparison of several groups, the *Kruskal-Wallis* one way analysis of variance was followed by the *Nemenyi* test to check for differences between groups.

Results

Figure 1 shows the distribution of lipoprotein(a) values throughout life in 7045 subjects. Table 1a shows the same for children aged 2 weeks to 17 years. Table 1b also shows the detailed data for women aged 18–59 years, who have been depicted in figure 1. Table 2 shows the correlation between maternal serum lipoprotein(a) and birth weight for all mother child pairs, and for mother child pairs where maternal lipoprotein(a) was in excess of 300 mg/l (300–3150 mg/l). Data are sorted according to sex of the child.

From figure 1 and table 1 a it can be clearly seen that lipoprotein(a) peaks occur in females at puberty (tab. 1 a) and after the menopause (fig. 1). In girls aged between 10 and 12 years of age, lipoprotein(a) concentrations are significantly higher ($p < 0.05$) than in boys of the corresponding ages. Between the ages of 0 and 9, and 13 and 17 years of age, no statistically significant sex-linked difference in lipoprotein(a) levels was found. In adults, lipoprotein(a) was significantly higher in women aged 50 to 59 years of age ($p = 0.05$) than in men of the corresponding age group.

Table 1b shows the lipoprotein values in age matched females, for healthy hospital staff attending a routine check-up, for non-selected in-patient women and for women directly after the birth of a child. Although the median values are different, these are not significant (healthy women vs hospitalised women $p = 0.45$, healthy women vs postpartal women $p = 0.11$, hospitalised

Tab. 1a Median lipoprotein(a) concentrations in serum of children aged 2 weeks to 17 years of age divided into age and sex. Median concentrations are given in mg/l.

Age group (years)	Male children		Female children	
	Lipo-protein(a) (mg/l)	n	Lipo-protein(a) (mg/l)	n
2 weeks–1 year	38.9	167	36.4	161
1	30.8	97	41.7	96
2	45.5	97	44.7	80
3	53.0	76	44.7	55
4	61.5	83	68.6	56
5	59.0	81	80.5	71
6	80.2	104	79.8	57
7	75.7	76	92.7	59
8	69.5	64	76.3	82
9	76.7	62	73.8	73
10	97.4	86	118	76
11	88.2	66	146	60
12	79.4	60	93.0	71
13	74.1	69	83.9	60
14	103	51	73.0	53
15	117	34	102	44
16	74.3	40	95.0	39
17	66.9	19	101	30
1–5 years	47.5	434	54.0	358
6–10	78.1	396	81.4	342
11–17	84.3	339	95.8	357
All	66.5	1336	67.6	1218

The corresponding mean values for all subjects was 175 mg/l (boys 167 mg/l, girls 183 mg/l) showing the extreme skewness of the data (mean: median = 2.61). The median value stabilises first after the number of subjects in a group exceeds at least 100 persons, and so groups from children aged between 1 and 17 years were constructed as in the lower part of the table. Only the group values were used in figure 1.

Tab. 1b Lipoprotein(a) data for healthy, postpartum and sick females aged 18–59 years of age. Median concentrations are given in mg/l.

Age group (years)	Healthy		Postpartum		Sick	
	Lipoprotein(a) (mg/l)	n	Lipoprotein(a) (mg/l)	n	Lipoprotein(a) (mg/l)	n
18–29	87.0	104	111	876	79.5	56
30–39	87.5	112	121	320	121	54
40–49	97.0	55	^a		130	56
50–59	146	93			190	110

^a As there were only 13 mothers over 40 years of age, these were not included in the table. The median lipoprotein(a) concentration of this group was 184 mg/l.

women vs post partal women $p = 0.96$), thus allowing all women of a given age-group to be included in one group in figure 1.

Table 2 shows that there was no correlation between maternal serum lipoprotein(a) and birth weight in full term babies (38th–43rd week of pregnancy). This was true before and after logarithmic transformation of lipoprotein(a) concentrations. The correlation between postpartal maternal and neonatal lipoprotein(a) concentrations after logarithmic transformation was $r = 0.592$ ($n = 1209$).

Relevant assay data, represented by the mean and inter-assay coefficient of variation (in parentheses) for four control sera were as follows:

Serum A: mean 105 mg/l (5.66%) $n = 172$,

Serum B: mean 377 mg/l (5.55%) $n = 62$,

Serum C: mean 808 mg/l (4.30%)

[declared content 800 mg/l] $n = 31$ and

Serum D: mean 37.4 mg/l (7.86%) $n = 61$.

Discussion

Many conflicting reports have been published on the behaviour of lipids and lipoproteins during puberty (24),

Tab. 2 Correlation between maternal lipoprotein(a) and birth weight according to sex of the baby and lipoprotein(a) concentration of the mother at birth. Only full-term newborns are included.

	n	Linear correlation	Log correlation
<i>Lipoprotein(a) less than 300 mg/l</i>			
Male offspring	420	-0.014	0.020
Female offspring	367	0.007	-0.028
<i>Lipoprotein(a) above 300 mg/l</i>			
Male offspring	137	-0.018	0.035
Female offspring	150	0.085	0.033

The data for the linear correlation was calculated from the birth weight (x) and the lipoprotein(a) concentration in mg/l (y).

The data for the logarithmic correlation was calculated from the birth weight (x) and the decadian logarithm of the lipoprotein(a) concentration (y).

pregnancy (7, 10–14), under the influence of drugs (19, 25), oral contraceptives (17) and hormones (19, 26, 27), including gonadotropins (15, 16). Results from animal studies (28) cannot be compared directly with results from humans (5) without due consideration of animal physiology. Other results come from studies in which the number of subjects is too small for comparison (5), even when 'statistically significant' differences have been found.

Reports of behaviour of lipoprotein(a) during pregnancy are also conflicting, some authors not seeing an increase (10, 12, 29), others reporting significant increases (11, 13, 14). In a study of smoking and non-smoking pregnant women, *van Wersch* et al. (30) showed that the lipoprotein(a) levels in non-smoking pregnant women were on average twice as high as in women who smoked, the latter having the same concentrations as non-pregnant women.

Association of high levels of lipoprotein(a) in maternal serum have been associated with severe pre-eclamptic pregnancy (31) and foetal growth retardation due to insufficient placental circulation (32). Peripartur reductions in total cholesterol, high density lipoprotein cholesterol and apolipoprotein A-I, when compared with levels in the 35th week of pregnancy have also been published (5), as have observations in reduction of triacylglycerols, cholesterol and apolipoprotein B measured 6 weeks postpartum, when compared with levels in the 35th and 36th weeks of pregnancy (10, 12). *Chiang* and co-workers (12), however reported no change in apolipoprotein A-I during pregnancy.

In a study covering 232 women during pregnancy (114 Caucasians, 118 Africans/Afro-Caribbeans), *Koukou* et al. (6) found lower levels of total cholesterol, low-density lipoprotein cholesterol, triacylglycerols and apolipoprotein B, but higher levels of high-density lipoprotein cholesterol and lipoprotein(a) in Africans/Afro-Caribbeans, when compared with Caucasians. The differences were not due to weight, age, parity or post-load plasma glucose levels.

Muñoz et al. (33) have observed decreased apolipoprotein A and triacylglycerols in pregnancies with intra-uter-

ine growth retardation. Rheological changes were seen in this group of patients which were due to the inhibition of fibrinolysis by increased levels of apolipoprotein B.

Zechner and co-workers (7) reported a steady increase of lipoprotein(a) in pregnant women up until the 19th week, where the values were on average 2.8 times higher than before the pregnancy, after which values fell to pre-pregnant values at birth. Apolipoprotein B and total cholesterol increased during pregnancy, the time courses being independent of that of lipoprotein(a).

Soma et al. (11) reported that steroid sex-hormones were capable of reducing lipoprotein(a) concentrations in postmenopausal women, and after cessation of hormone-substitution, that the levels returned to pre-treatment concentrations. In men undergoing orchidectomy for prostatic cancer, the same workers observed increases in lipoprotein(a) of 20%, whereas treatment with oestrogens resulted in a reduction of lipoprotein(a) by 50%. Similar results have been reported by *Habiba* et al. (34). In hormone replacement therapy using a combination of oestriol, oestrone, oestradiol and norethisterone a reduction of serum lipoprotein(a) concentrations and protein-S activity was seen over the observation period of one year.

Radwanska (18) has presented data in a review article which implies different effects of sex-steroids and synthetic oestrogens on lipoprotein levels, and that these effects differ with age, sex, pregnancy, body weight and smoking habits. Moreover, the route of application and whether the hormones are endogenous or exogenous appear to influence lipoprotein levels, thus complicating the picture. Similar results have recently been published by *Stone* (19).

Results from the Burgos study on high density lipoproteins during the second decade of life (24) noted increases in high density lipoprotein phospholipids in girls after puberty, but not in boys. In another Spanish study girls and boys between 13–14 years of age from *Alcoy* (35), 38% were classified as having elevated lipoprotein(a) and were classified as 'at-risk'. Further comparisons with values obtained in our observations were not possible, due to the use of parametric statistics.

In the Atherosclerosis Risk in Communities (ARIC) study (36) carried out on men and women aged between 45–64 years of age, women, both black and white, had higher lipoprotein(a) levels than men. In addition, in postmenopausal women on hormone replacement therapy lipoprotein(a) as well as apolipoprotein B and low density lipoprotein cholesterol levels were lower than in non-replacement women.

Stevenson et al. (37) conclude from a study on the influence of age and menopause on serum lipids and lipoproteins, that 'the menopause is associated with potentially

adverse changes in lipids and lipoproteins, independent of any effects of aging. These changes may in part explain the increased incidence of coronary heart disease seen in postmenopausal women'.

The observations made by different groups must first be classified exactly before attempting to extract data for support of the hypothesis that gonadotropins directly influence levels of lipoprotein(a) in serum.

The results from the Burgos study (24) show that changes in the phospholipid content of high-density lipoproteins only occurred in girls during and after puberty. In our study, significant increases in serum lipoprotein(a) occurred in girls during puberty, but decreased afterwards.

In postmenopausal women several groups (34–37) have reported changes in lipid and lipoprotein profiles, including an increase in lipoprotein(a), which can be reversed by sex-steroid therapy. The review of *Radwanska* (18) has shown that certain sex-steroids are capable of changing the lipid and lipoprotein levels, including the reduction of lipoprotein(a). From our data, there is a significant increase in lipoprotein(a) after the menopause, which is seen until the end of the eighth decade of life.

The Austrian group of *Zechner* et al. (7) observed increases in lipoprotein(a) during the first half of pregnancy, values then returning to normal at birth. Other cholesterol fractions increased well into the second half of pregnancy. The first half of pregnancy is 'governed' by gonadotropins, the second by sex-steroids.

The above results show that gonadotropins increase lipoprotein(a), as seen in the results from pubertal girls, but not boys, and in postmenopausal women, but not in age-matched men. Reduction of post-menopausal gonadotropins by steroid sex-hormones results in a fall in serum lipoprotein(a). The different time courses of different lipids and lipoprotein fractions during pregnancy and after the menopause point to an independent pathway for lipoprotein(a), and which may very well support the observations and theory of *Stevenson* et al. (37).

The peak of lipoprotein(a) levels at puberty in girls may reflect the gonadotropin activity, the reduction after puberty to the interaction between gonadotropins and sex-steroids during the menstrual cycle.

The results from the postmenopausal women can only support a hormone replacement therapy to reduce the increased risk of cardiovascular problems in this group.

From our results and those from other groups we may infer that an increase in gonadotropins may contribute to an adverse effect, namely an increase, in lipoprotein(a), which may be reversed by sex-hormone steroid substitu-

tion. From the results from oestrogen therapy on orchidectomised men (11), the lowering of lipoprotein(a) is not sex-linked. Further indirect evidence for a link between gonadotropins and lipoprotein(a) may be seen in the fact that long-term hormone replacement therapy in postmenopausal women reduces the incidence of myocardial infarction by up to 50% during the therapeutic period (38). After cessation of therapy there is less consensus as to whether this protective effect is retained.

From the data in table 1b there is no support to the claim that high maternal lipoprotein(a) levels were correlated with lower birth weight due to placental insufficiency (31, 32) at least in full-term babies.

An interesting postulation for future therapy is whether steroids with an aromatic A-ring may be 'designed' to reduce lipoprotein(a), without having the unwanted side effects, at least in men, of feminisation.

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