Maternal plasma leptin levels in relation to the duration of the active phase of labor

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Carlhäll, S., Källén, K., Thorsell, A., Blomberg, M., (2018), Maternal plasma leptin levels in relation to the duration of the active phase of labor, *Acta Obstetricia et Gynecologica Scandinavica*, 97(10), 1248-1256. https://doi.org/10.1111/aogs.13380

Original publication available at:
https://doi.org/10.1111/aogs.13380

Title

Maternal plasma leptin levels in relation to the duration of the active phase of labor.

Running headline: Maternal leptin and duration of labor.

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Conflicts of interest statement: The authors declare no conflicts of interest.

Abstract

Introduction: Obese women have increased leptin levels and longer duration of labor compared to normal weight women. Leptin has an inhibitory effect on myometrial contractility *in vitro*. Our purpose was to examine whether maternal leptin levels in active labor were associated with the duration of the active phase of labor.

Material and methods: This prospective cohort study included 914 women. Maternal blood samples were collected in active labor. The plasma-leptin concentration was obtained using a direct sandwich-based ELISA. Bivariate and multiple linear regression analyses were used to study the association between leptin levels and the duration of labor.

Results: A one ng/ml increase in maternal plasma leptin was associated with a 0.015 hour increase in duration of labor ($p<0.007$). This association was not statistically significant in the adjusted analyses or when analyzing nullipara and multipara separately. In women with spontaneous labor (n=766) leptin was not associated with an increase in duration of labor in the adjusted analyses.

Conclusions: There was no significant association between leptin levels and duration of the active phase of labor. Leptin *in vivo* might display a similar dose-response effect on myometrial contractility as demonstrated in *in vitro* studies. Future studies need to explore the association between leptin levels and time in labor in obese women with high leptin levels to evaluate a possible dose-response effect.

Key words: Leptin, duration of labor, active phase of labor, obesity, delivery.

Abbreviations: BMI=body mass index, GWG=gestational weight gain, GDM=gestational diabetes mellitus.

Key message: Duration of the active phase of labor increased with maternal leptin levels measured in active labor, however the increase was not significant in the adjusted analyses.

Introduction

The increasing worldwide prevalence of maternal obesity is concerning considering the strong association with complications for the obese mother and her child (1-3). As regards the majority of obesity-related complications during pregnancy and labor, the risks seem to increase with a higher degree of obesity (2-4). Obese women more often have a dysfunctional labor pattern compared to normal weight women and the duration of labor increases with maternal body mass index (BMI) (5, 6). Many studies have demonstrated that there are no associations between BMI and the length of second stage of labor suggesting that the effect of maternal overweight and obesity on time in labor is restricted to the active phase of labor (6-8). Post-dated pregnancies and induction of labor are more common in obese women, who also require more oxytocin for augmentation than normal weight women (9, 10).

The exact mechanism of dysfunctional labor in obese women is not fully understood and presumably is multifactorial. Impaired myometrial contractility has been proposed to be of importance. It has been demonstrated that the myometrium of obese women contracts with less force and frequency *in vitro* than myometrial fibers of normal weight women (11).

Adiposity-related hormones such as leptin, an adipokine mainly produced by white adipose tissue, might affect uterine contractility. Leptin receptors have been identified in the myometrium as well as in other reproductive tissues (12). During pregnancy, the placenta is a major source of leptin production and contributes to the elevated levels seen in all pregnant women (13). Maternal leptin levels increase during gestation, peak in late second or early third trimester, decrease towards the end of the pregnancy in normal weight women and decline drastically postpartum, suggesting an important role during gestation (13-15). Obese pregnant women seem to have increased leptin levels compared to normal weight women (16) and morbidly obese women have

the highest leptin values (17). Leptin has been reported to depress human myometrial contractility *in vitro* (18, 19) and to maintain uterine quiescence by inducing myometrial proliferation (20). These findings have led to speculations about whether leptin could be used as a tocolytic agent (20, 21).

Since pregnant obese women display elevated levels of leptin, and seem to have less effective myometrial labor contractions, we hypothesized that high leptin values might contribute to the dysfunctional labor often observed in obese women. To our knowledge, there are no previous published studies on the predictive effect of maternal plasma leptin on the duration of labor. In this study we therefore aimed to examine whether maternal leptin levels were associated with the duration of the active phase of labor in the total study population as the primary outcome, and in women restricted to a spontaneous start of labor as a secondary outcome.

Materials and methods

Study design and participants

This prospective cohort study, including 914 pregnant women who delivered between April 1, 2014 and December 10, 2015, was conducted at Linköping University Hospital, Sweden. At the first antenatal visit in gestational weeks six to ten, all pregnant women in Linköping aged 18 years or older, were informed and asked to participate by attending a local biobank (register number 185, at the department of Obstetrics and Gynecology, Östergötland County Council) for collection of maternal blood samples during pregnancy and labor. In Sweden, 95 % of all women attend an antenatal clinic during the first trimester. After giving informed written consent the women, consecutively recruited to this biobank in early pregnancy, were included in the present study. Women with multiple pregnancies, diabetes mellitus, intrauterine fetal death, premature

labor (gestation week < 37+0), elective caesarean section, missing leptin value or incomplete information on the time estimates of the active phase of labor, were excluded. Hence, all women who had undergone an emergency cesarean section during the active phase of labor (before pushing efforts started) were excluded (Figure 1).

Variables and parameters included in study

Maternal height and weight were measured at the baseline visit in gestation weeks six to ten. Maternal socio-demographic data, medical history, pregnancy complications, maternal weight on admission to the delivery ward, and data on labor and birth were prospectively recorded in standardized medical records (Obstetrix®, Cerner) by midwives or doctors at the department of Obstetrics and Gynecology, Linköping University Hospital. BMI was calculated using maternal weight and height data, which were recorded in early pregnancy. Gestational weight gain (GWG) was defined as maternal weight gain in kg from weight at the baseline visit in early pregnancy to measured weight on admission to the delivery unit. The study population was sub-classified into three GWG groups; below recommended, recommended, or excessive weight gain based on the American Institute of Medicines guidelines on weight gain during pregnancy, in relation to pre-pregnancy BMI (22). Onset of active labor was, at the time of the study, defined as regular painful uterine contractions, three to four per ten minutes, and a cervical dilatation of three cm or more. The midwife at the delivery ward prospectively recorded the time when active labor and pushing efforts started. The active phase of labor was defined as from the start of active labor until the start of the pushing efforts.

Analysis of plasma leptin

Maternal plasma was collected shortly after the women had arrived to the delivery ward as soon as she was assessed to be in active labor. For leptin analyses blood was collected in a test tube with a clot activator and gel for plasma separation. One hour after sampling, the blood was

centrifuged, aliquoted, and plasma was stored at -70 degrees Celsius in the local biobank (register number 185, at the department of Obstetrics and Gynecology, Östergötland County Council) until further analyses.

The plasma leptin concentration was obtained using a direct sandwich-based ELISA (Catalogue # EZHL-80SK; Merck-Millipore, Solna, Sweden) according to the manufacturer's instructions. Human leptin was captured by a polyclonal antibody on a 96-well microtiter plate, followed by addition of a secondary monoclonal biotinylated antibody. Streptavidin-horseradish peroxidase was then added to the biotinylated antibodies, and in the final step prior to measuring enzyme activity. The enzyme activity was measured spectrophotometrically (Victor 3, PerkinElmer, Waltham, MA, USA) at 450 nm after acidification of the sample products stopping the enzymatic reaction. In between each step the wells were washed three to five times to eliminate unbound material. Increased absorbance was directly proportional to the amount of captured human leptin in unknown samples, and quantification was derived from a generated reference curve with reference calibrators of known concentrations. In a sample size of 25 µL, the limit of sensitivity of the assay was 0.17 ng + 2 SD. The within and between assay variation was 3.8 and 6.2 %, respectively. The specificity of the assay was 100 % for human leptin. No cross-reactivity was found for human pro-insulin, insulin, insulin-growth factor – I and – II, or glucagon. All samples were run in duplicates and a CV cut-off of 15% was set for each duplicate.

Data management and statistical analyses

Time in the active phase of labor in relation to leptin levels and maternal and fetal characteristics were analyzed in the total study population as well as in nulliparous and multiparous women separately. Furthermore, 766 women with a spontaneous start of labor were analyzed separately after excluding women with induced labor. Maternal BMI in early pregnancy, GWG, parity, maternal age, birth-weight, gestational week at delivery, smoking, pre-eclampsia, gestational

diabetes mellitus (GDM), induction of labor, epidural anesthesia and usage of oxytocin (for either induction or augmentation of labor) were regarded as potential confounding factors. Bivariate and multiple linear regression analyses were used to study the association between maternal leptin levels and duration of the active phase of labor. The first multivariable model included leptin levels and variables considered as possible confounding factors with $p < 0.2$ in the bivariate analyses and the final restricted multivariable model included leptin levels and variables with $p < 0.2$ in the first full multivariable model. The dataset was restricted to case records with known leptin levels and length of the active phase of labor. Missing data on GWG were handled using multiple imputation (number of imputed data sets =20). A Kaplan-Meier analysis was performed and a graph produced in order to illustrate the association between maternal BMI, leptin levels in active labor and time in the active phase of labor. Women who were normal-weight or underweight with levels below or similar to/above the leptin value of the third quartile (37 ng/ml) were compared to women who were overweight or obese with leptin levels below or similar to/above the third quartile leptin value (37 ng/ml).

All analyses were performed using IBM SPSS version 23 (IBM Inc, Armonk, NY). A p-value < 0.05 was considered statistically significant.

Ethical approval

The Regional Ethical Committee in Linköping, Sweden approved this study (Dnr 2010/296-31 date of approval 2010-10-13, Dnr 2013/378-32 date of approval 2013-09-27).

Results

The study-population included 914 women with information on maternal plasma leptin levels in active labor and duration of the active phase of labor. In this study population 48.8% of the

women were nulliparous and 51.3% were multiparous, 24.5% were overweight and 8.8% were obese. Labor started spontaneously in 83.8% (766) of the women. The mean time and 95% confidence interval (CI) in the active phase of labor was 8.7 (CI; 8.3-9.2) hours in nulliparous women and 4.6 (CI; 4.3-4.9) hours in multiparous women. Descriptive data on maternal and fetal characteristics during pregnancy and labor and maternal leptin levels (ng/ml) in median and quartiles are presented in Table 1. The median leptin values were higher with increasing maternal BMI. The median leptin levels were lower in women with a GWG below recommendations compared to women with recommended GWG, and increased in women with excessive GWG. Figure 2 shows a Kaplan-Meier graph, illustrating the cumulative chance to end the active phase of labor at a certain time point, by maternal BMI category and leptin value in active labor. There was no overall statistically significant difference between the groups ($p = 0.296$). However, from the figure a difference is seen between the groups after 10 hours duration of active labor, when normal-weight/underweight women with lower leptin levels (below the third quartile/ <37 ng/ml) had a greater chance to end the active phase of labor at a given time point compared to overweight/obese women with high leptin levels (≥ 37 ng/ml).

The time in the active phase of labor in relation to maternal leptin levels, and maternal and fetal characteristics in the total study population are presented in Table 2. A one ng/ml increase in maternal plasma leptin was associated with a 0.015 hour increase in duration of labor ($p<0.007$) in the unadjusted analyses. In women with morbid obesity (BMI ≥35) the median leptin value were 50 mg/ml, which would mean that time in the active phase of labor increased 0.75 hours. Nulliparous women, those who used epidural anesthesia and those who received oxytocin during labor had statistically significantly longer duration of the active phase of labor compared to their counterparts in the unadjusted analyses. Furthermore, the time in labor increased statistically significantly with gestational age and birth-weight. GWG but not BMI was associated with time

in the active phase of labor in the unadjusted analyses. In addition, the active phase of labor was statistically significantly shorter in women with induced labor compared to those with spontaneous onset of labor.

In the adjusted analyses the statistically significant association between leptin levels and duration of the active phase of labor did not persist. In the final multivariable analyses nulliparity, birth-weight and usage of epidural anesthesia or oxytocin were statistically significantly associated with increased duration of the active phase of labor and induction of labor was statistically significantly associated with a shorter duration of the active phase of labor (Table 2).

When nulliparous and multiparous women were analyzed separately, no significant associations between the time in the active phase of labor and maternal leptin levels were found in any of the groups. Results not shown.

In the 766 women with a spontaneous onset of labor, a one ng/ml increase in maternal leptin level was associated with a 0.016 hours increase in duration of the active phase of labor ($p<0.005$) in the unadjusted analyses (Table 3). However, this association was not significant when adjusting for confounding factors or when analyzing nulliparous and multiparous women with spontaneous labor separately. Results not shown.

Discussion

Here, we present a first study examining correlations between plasma leptin levels from mothers in early active labor and duration of the active phase of labor. At the onset of this study we anticipated that high leptin levels would have an antagonistic effect on the duration of the active phase of labor. In this study population of 914 women, with a low prevalence of obesity, we found a significant effect of leptin on time in the active phase of labor in the bivariate analyses but not in the multivariate adjusted analyses. This could mean that in our study-population, other

birth related factors were of more importance than leptin, in influencing the time in the active phase of labor.

To our knowledge there are no previous published reports on maternal leptin levels measured in active labor in relation to labor duration. Logan et al found a significant association between the increased duration of labor and higher cord blood leptin levels. Maternal leptin levels were not included in the analyses (23). In the same cohorts with a smaller number of participants, maternal leptin levels were measured 24 hours postpartum and correlated with cord blood leptin levels (24). However, as maternal leptin levels decrease rapidly after delivery (13), and we do not know how maternal leptin levels during active labor differ from maternal leptin levels shortly after delivery, our results are difficult to compare.

There are several *in vitro* studies suggesting that leptin might play a role in the regulation of myometrial activity (12, 18-20, 25). Two separate studies demonstrated an *in vitro* inhibitory effect of leptin on contractions in myometrial biopsies from non-laboring pregnant women (18, 19). Leptin may also prevent remodeling of myometrial extracellular matrix, which is necessary for effective uterine contractions during labor (25), and inhibit myometrial apoptosis, which is of importance for uterine smooth muscle to change from a proliferative to contractile status (12). Leptin has also been shown to be able to induce human myometrial proliferation and maintain uterine quiescence and thereby oppose the mechanisms that trigger labor and myometrial contractions (20). It has been speculated that if leptin has the same function in the uterine smooth muscle cells as in vascular smooth muscle and reduce intracellular calcium [Ca^{2+}] release, it could impair the contractile ability if the myometrium (26). This idea was supported by Zang et al. who demonstrated reduced frequency and amplitude of contractions in myometrium

from obese pregnant women *in vitro*. The tocolytic effect was explained by less [Ca^{2+}] flux observed in the myometrium of obese women compared to normal weight women (11).

With this large number of preclinical studies demonstrating a tocolytic activity by leptin, one might speculate why no association between maternal leptin levels in early active labor and duration of active labor was found in the present study.

Perhaps the results would be different if more obese women were included, as median levels were higher in the obese women and maybe there were too few women with high leptin levels to demonstrate a statistically significant effect in the adjusted analyses. Several authors demonstrate that the *in vitro* myometrial relaxant effect of leptin is cumulative and more pronounced with increasing leptin concentrations (18, 19). This raises the question of whether the inhibitory effect of leptin on uterine contractility only exists at high leptin levels, as is observed in obese women?

In normal weight women, maternal leptin concentrations increase from early pregnancy but start to decrease towards the end of pregnancy (14). Considering the *in vitro* relaxant effect of leptin, high leptin levels at the time of delivery would have an antagonistic effect on the myometrium. It is possible that although placental production of leptin decreases close to parturition, leptin levels derived from adiposity tissue in obese women might still be high enough to affect the myometrial contractility.

In our study population, a number of birth related factors other than maternal leptin were significantly associated with duration of the active phase of labor. Parity, birth-weight and the use of epidural anesthesia and oxytocin had the most pronounced effect on time in labor. Being nulliparous or delivering a large for gestational age child are known risk factors for increased duration of labor. Those strongly correlated factors to duration of labor might have concealed the effects of leptin. Another possibility is that a longer duration of the active phase of labor

influenced the decision to use oxytocin or to give an epidural anaesthesia and therefore could explain the association between those factors and duration of labor. In contrast to several other studies, maternal BMI in our study-population was not significantly associated with duration of the active phase of labor (5-8). This could be explained by the low prevalence of obese women in our study-population.

The strength of this present study is the large number of participants with information on the actual maternal leptin value when the outcome, time in the active phase of labor, was measured. We chose to restrict the analyses on the association between leptin levels and duration of labor to the active phase of labor, as previous studies indicate that the dysfunctional part of labor in obese women seem to be restricted to the active phase of labor (7, 8). Furthermore, uterine contractility and maternal pushing ability during the second stage do not seem to be dependent on maternal BMI (27). The prospective design enabled us to follow the cohort from early pregnancy, with a thorough baseline evaluation on maternal co-morbidity and socio-economic factors and continuous registration of maternal complications during pregnancy, consequently adjusting the statistical analyses for possible confounding factors. The size of the study population also enabled us to analyze subgroups based on parity and onset of labor.

Information on GWG was missing in 27.8% of the women. Multiple imputation was used to deal with missing information in the adjusted analyses which included GWG as a potential confounding factor.

There are certain limitations. Our study population, restricted to those who agreed to participate in the biobank, may not be representative of the total population. The women in the biobank have so far not been described elsewhere. The number of obese women in the present study (BMI>30)

was 8.8% compared to 13.6% in the total pregnant population in Sweden 2015 (28). This may limit the generalizability of our results.

As it is unknown whether maternal leptin levels change during active labor, the sample time of maternal plasma might be an important potential confounding factor. Unfortunately, we had no information on the exact time of maternal plasma sampling. For most women sampling was done as soon as they arrived to the delivery-ward and were assessed to be in active labor.

Since we only included women with information on the active phase of labor and the end of the active phase of labor was defined as the start of pushing efforts, 67 women with missing information on the time when pushing phase started were excluded. This could have biased our results since all women with an emergency cesarean section during the active phase of labor were thus excluded. The small number of cesareans performed after pushing has begun is a result of the implementation of a “nine-item list” of structured organizational and cultural changes at the delivery unit, where one of the efforts was to increase the staff confidence in handling instrumental delivery (29). The measurement of cervical dilatation and defining the start of regular contractions were subjective. If the study population is large, the estimation of these parameters may not be uniform across the study population, but the variation is probably not related to maternal leptin levels. Another limitation is our definition of the start of active labor. We have used the definition that was nationally accepted in Sweden at the time of this study. However, recent studies have shown that latent labor may last until up to six centimeters of cervix dilatation has occurred, and that there can be great variation in the duration of latent labor (30). This may limit the generalizability of the present study.

In conclusion, this study could not demonstrate a significant association between leptin levels and duration of the active phase of labor. A positive association between increasing maternal leptin

levels and longer time in the first stage of active labor in the total study population as well as in women with a spontaneous onset of delivery was found in the bivariate analyses. However, this association was not statistically significant when adjusting for confounding factors or when analyzing nulliparous- and multiparous women separately. It is possible that leptin, as a single putative factor, may not cause a clinical negative effect on the contractile ability of the myometrial fibers during the active phase of labor, such as the inhibitory effect of leptin on myometrial contractility demonstrated in *in vitro* studies. On the other hand, leptin *in vivo* might display a similar dose-response effect as *in vitro*, which not could be demonstrated in this study population, with a low prevalence of obese women. Whether the association between maternal leptin levels and duration of labor is different in obese women needs to be investigated in future studies.

Funding: This study was supported by a grant from the Östergötland County Council.

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Table 1. Maternal and fetal characteristics during pregnancy and labor and maternal plasma leptin levels in active labor. (N = 914)

	N	%	Maternal leptin levels (ng/ml) – median and quartiles		
			25%	Median	75%
Maternal characteristics					
Age < 25 (years)	88	9.6	18.1	25.4	43.2
Age ≥ 35 (years)	173	18.9	12.7	23.4	35.1
Para 0	445	48.6	15.4	25.0	40.9
Para 1+	469	51.3	13.6	21.8	34.5
Smoking yes	18	2.0	18.0	27.4	33.3
Smoking no	896	98.0	14.3	23.4	37.1
BMI <18.5 (kg/m^2)	17	1.9	6.04	13.8	22.5
BMI 18.5-24.9 (kg/m^2)	591	64.7	13.2	20.2	30.8
BMI 25.0-29.9 (kg/m^2)	224	24.5	19.9	30.9	42.5
BMI 30.0-34.9 (kg/m^2)	61	6.7	20.5	36.2	51.1
BMI ≥35 (kg/m^2)	19	2.1	30.5	50.0	65.0
Missing BMI	2	0.2			
Below recommended GWG	141	15.4	10.6	16.4	25.6
Recommended GWG	256	28.0	14.5	23.1	34.6
Above recommended GWG	263	28.8	21.4	33.0	48.4
Missing GWG	254	27.8	12.6	20.1	33.1
Pre-eclampsia yes	19	2.1	21.6	29.4	55.6
Pre-eclampsia no	895	97.9	14.2	23.2	36.9
GDM yes	12	1.3	22.5	25.8	46.9
GDM no	902	98.7	14.3	23.3	37.0
Delivery					
Gestational age 37-38 weeks	147	16.1	13.5	21.5	35.0
Gestational age 39-40 weeks	515	56.3	14.1	23.3	37.8
Gestational age ≥41weeks	252	27.6	16.0	23.9	37.8
Induction yes	148	16.2	15.4	24.9	36.8
Induction no	766	83.8	14.3	23.1	37.0
Epidural yes	419	45.8	15.6	24.9	38.8
Epidural no	495	54.1	13.3	22.0	36.1
Oxytocin yes	442	48.4	16.0	25.8	38.3
Oxytocin no	472	51.9	13.3	21.4	36.1
Vaginal, non-instrumental	846	92.6	14.2	23.1	36.8
Instrumental delivery	65	7.1	17.3	30.0	46.1
Emergency cesarean section	3	0.3	20.9	22.7	24.7
Fetal characteristics					
Birth-weight <2500g	12	1.3	14.4	25.3	33.4
Birth-weight ≥4500g	28	3.1	16.7	27.0	37.5
Female gender	449	49.1	14.4	22.6	55.6
Male gender	465	50.9	14.4	23.8	59.8

	Apgar score 5 min <7	11	1.2	14.4	23.1	46.4
	Apgar score 5 min ≥7	903	98.8	14.3	23.4	36.9

BMI= body mass index in early pregnancy
GWG = gestational weight gain according to IOM recommendations
GDM = gestational diabetes mellitus

Table 2. Time in the active phase of labor (h) in relation to maternal and fetal characteristics and maternal leptin levels (ng/ml). Results from bivariate and multiple linear regression analyses. N=914

Characteristics	Crude estimate		Estimates from first multivariable model[a]		Estimates from final restricted multivariable model [b]	
	Beta-coefficient[c]	p-value	Beta-coefficient[c]	p-value	Beta-coefficient[c]	95% confidence interval
Age (per one year increment)	-0.19	<0.001	-0.03	0.259		
Parity (0 vs. 1+)	4.05	<0.001	2.08	<0.001	2.19	1.68-2.69
Smoking (yes vs. no)	0.39	0.711				
Maternal BMI (per one kg/m^2 increment)	0.04	0.235				
Pre-eclampsia (yes vs. no)	0.04	0.970				
GDM (yes vs. no)	-0.72	0.575				
GWG (per one kg increment)	0.10	0.002	-0.01	0.819		
Gestational age (per one week increment)	0.08	<0.001	0.03	0.068	0.03	0.00-0.06*
Induction (yes vs. no)	-2.15	<0.001	-3.37	<0.001	-3.37	-4.02 to -2.72
Epidural (yes vs. no)	4.03	<0.001	2.38	<0.001	2.39	1.89-2.89
Oxytocin (yes vs. no)	3.55	<0.001	2.65	<0.001	2.63	2.10-3.16
Birth-weight (per 100g increment)	0.06	0.041	0.10	<0.001	0.09	0.04-0.14
Leptin levels (per one ng/ml increment)	0.015	0.007	0.004	0.326	0.004	-0.004 to 0.013

[a] Includes leptin levels and variables with $p < 0.2$ in the bivariate analyses.
[b] Includes leptin levels and variable with $p < 0.2$ in the first full multivariable model.
[c] The beta coefficients represents the slope, the change in maternal duration of labor per one unit increment of each evaluated factor (as specified above).
BMI = body mass index

GDM = gestational diabetes mellitus
GWG = gestational weight gain
*Non significant

Table 3. Time in the active phase of labor (h) in relation to maternal and fetal characteristics and maternal leptin levels (ng/ml) in women with a spontaneous start of labor. Results from bivariate and multiple linear regression analyses. (N=766)

Characteristics	Crude estimate		Estimates from first multivariable model [a]		Estimates from final restricted multivariable model [b]	
	Beta-coefficient[c]	p-value	Beta-coefficient[c]	p-value	Beta-coefficient[c]	95% confidence interval
Age (per one year increment)	-0.20	<0.001	-0.05	0.123	-0.05	-0.11to 0.01
Parity 0 vs. 1+	4.08	<0.001	1.73	<0.001	1.69	1.09-2.27
Smoking (yes vs. no)	1.66	0.179	0.44	0.645		
BMI (per one unit increment)	0.07	0.076	0.04	0.204		
Pre-eclampsia (yes vs. no)	-0.61	0.734				
GDM (yes vs. no)	-0.16	0.920				
GWG (per one kg increment)	0.10	0.003	0.01	0.647		
Gestational age (per one week increment)	0.10	<0.001	0.06	0.001	0.06	0.03-0.09
Epidural (yes vs. no)	4.47	<0.001	2.41	<0.001	2.43	1.88-2.98
Oxytocin (yes vs. no)	4.74	<0.001	2.79	<0.001	2.82	2.26-3.39
Birth-weight (per 100g increment)	0.04	0.21				
Leptin levels (per one unit increment)	0.016	0.005	0.003	0.564	0.005	-0.004 to 0.013

[a] Includes leptin levels and variables with p<0.2 in the bivariate analyses.
[b] Includes leptin levels and variable with p<0.2 in the first full multivariable model
[c] The beta coefficients represents the slope, the change in maternal duration of labor per one unit increment of each evaluated factor (as specified above).

BMI = body mass index
GDM = gestational diabetes mellitus
GWG = gestational weight gain

Figure 1: Flow chart of the included and excluded women in the cohort.

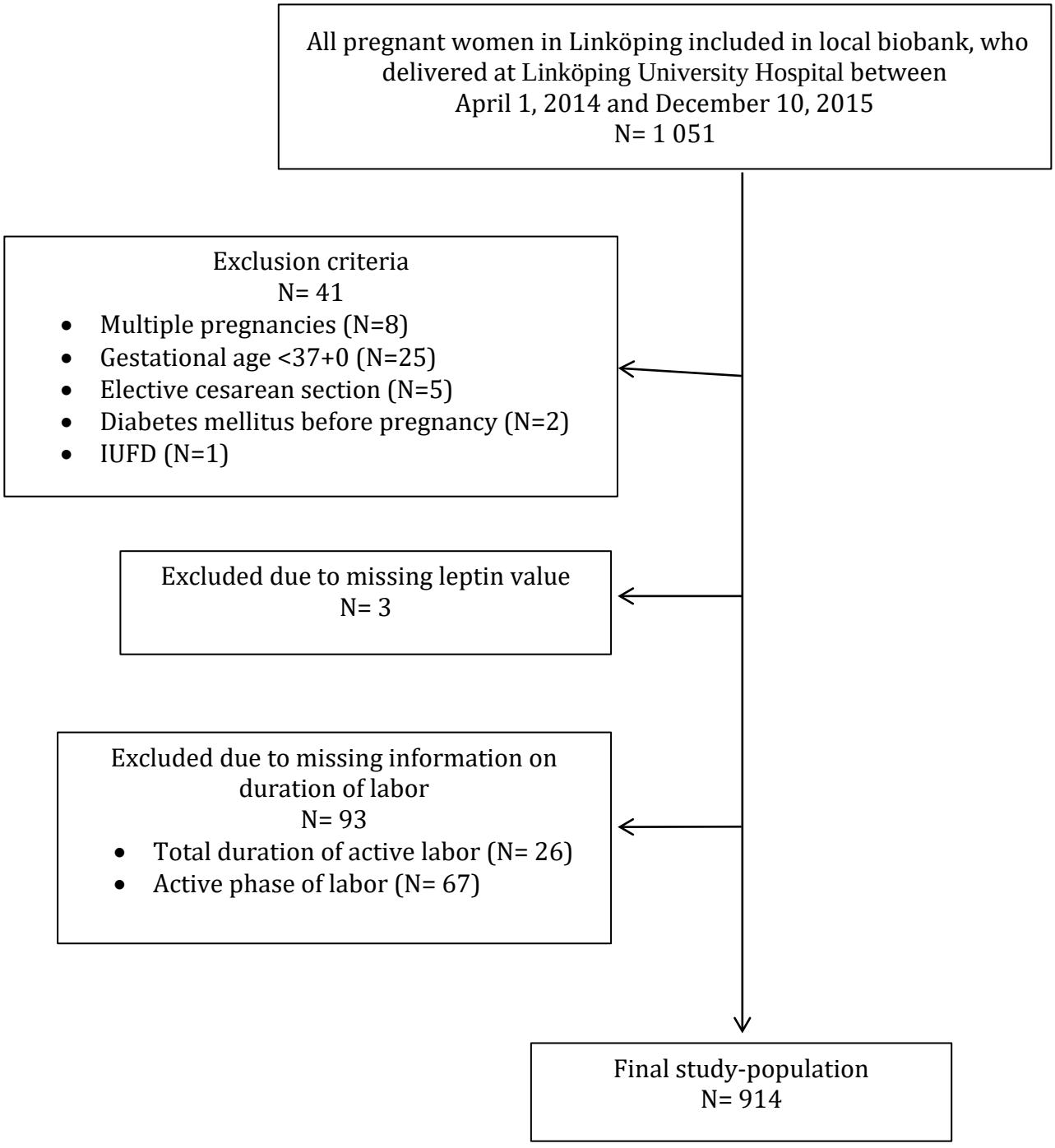

Figure 2: Cumulative hazard plot of the study population (N=914). The chance to end the active phase of labor at certain time point, in relation to early maternal BMI and leptin value in active labor, below or similar to/above the third quartile of leptin (37 ng/ml) in all women. Event was defined as end of active phase of labor. p=0. 296).