A meta-analysis of relationship between birth weight and cord blood leptin levels in newborns

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Context: Low cord blood leptin concentration is implicated as a risk factor for small for gestational age (SGA) babies. However, the association of strength, consistency, independence, and confounding factors of this affliction has not been systematically examined.

Objective: To determine if there is a difference in cord blood leptin concentration between SGA and appropriate for gestational age (AGA) newborns, and to observe whether the sample origins, GA, pregnancy-induced hypertension (PIH) and congenital malformation (CM) are confounding factors of the meta-analysis.

Data sources and study selection: Relevant studies published between 1996 and 2007 were identified through literature searches using Ovid, Medline, PubMed, Web of Science, National Knowledge Infrastructure, Wanfang Data, and VIP China Scientific Journal Database, based on the following key words: leptin, intrauterine growth restriction, intrauterine growth retardation, fetal growth restriction, and small for gestational age.

Data extraction: A meta-analysis was conducted to analyze the difference of the cord blood leptin concentrations between SGA and AGA newborns. Then the stratified meta-analyses were repeated with a multivariate model to adjust for potential confounders, i.e., samples origin (Chinese newborns *vs.* non-Chinese newborns), GA (the term-newborns *vs.* the mixed GA newborns), PIH or CM (the newborns excluding PIH or CM *vs.* the newborns not excluding PIH or CM).

Data synthesis: Twenty articles including 514 SGA newborns and 1006 AGA newborns were collected. The cord leptin concentrations of SGA newborns were lower than those of AGA newborns [WMD (95%CI), -4.42 (-5.54, -3.29) ng/ml; *P*<0.01; *n*=1520 newborns]. The results of stratified meta-analyses showed similar results in Chinese *vs.* non-Chinese newborns and term *vs.* mixed GA newborns, respectively. However, the newborns not excluding PIH or CM had a wider 95%CI than the newborns excluding PIH or CM [WMD (95%CI), -4.17 (-5.00, -3.33) ng/ml *vs.* -4.47 (-9.61, 0.67) ng/ml)], and there was no significant difference in cord blood leptin concentrations between SGA and AGA newborns in the newborns not excluding PIH or CM (*P*=0.09).

Conclusions: SGA babies have low cord leptin concentrations. Other factors that may influence cord leptin levels are maternal PIH and CM.

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Introduction

Small for gestational age (SGA) babies are those whose birth weight is below the 10th percentile of the mean birth weight for those gestational age (GA) babies. SGA is associated with increased risks of neonatal death, necrotizing enterocolitis, and respiratory distress syndrome.[1] In 1996 leptin was first measured in the cord blood of newborns. As a protein encoded by the *obese(ob)* gene, it appears to play a role in early human development and pregnancy.[2-4] In addition, leptin serves as a feedback signal from fat cells to the central nervous system in the regulation of food intake, energy balance and fat storage. Since leptin may play a role in the regulation of infant weight gain, SGA babies are more likely to be obese in childhood.[5,6]

Some investigations have demonstrated that there is no correlation between cord blood leptin levels and maternal peripheral blood leptin levels, but the former were lower than the latter.[7-9] On the contrary there is a significant positive correlation between the cord blood leptin levels and the maternal peripheral blood leptin levels in women with pregnancy-induced hypertension (PIH).[10-11]

Recent studies have shown a positive correlation between cord blood leptin levels and birth weight in

the newborns.[12-14] Other studies reported the difference in cord blood leptin levels between SGA newborns and appropriate for gestational age (AGA) newborns, but the sample sizes of the studies were too small to determine the relationship between birth weight and cord blood leptin level.[8-9,15-32] Therefore, a meta-analysis was made in the present study to determine the difference in cord blood leptin level between SGA and AGA newborns, and to observe whether the sample origins, GA, PIH and congenital malformation (CM) are confounding factors of the meta-analysis.

Methods

Collection of studies

The cord blood leptin level in newborns was first reported in 1996, hence the literature search was concentrated on articles published between 1996 and 2007. Ovid, Medline, PubMed, Web of Science, National Knowledge Infrastructure, Wanfang Data, and VIP China Scientific Journal Database were searched by two authors independently with the help of an experienced librarian, based on the following key words: leptin, intrauterine growth restriction, intrauterine growth retardation, fetal growth restriction, and small for gestational age. The full-text articles both in Chinese and English and the Chinese theses were obtained from the library of our university.

The studies included comparison of cord blood leptin levels between SGA and AGA newborns. The quality of the included studies depended on the following conditions: 1) the cord blood was immediately collected after birth; 2) the GA should have no difference between SGA and AGA newborns, i.e., the SGA group and AGA group in the same study were all full-term newborns or newborns without significant difference in GA; 3) the cord blood leptin levels of newborns were measured by the same method of radioimmunoassay (kits from Linco Research or Diagnostic Systems Laboratories, USA).

Statistical analysis

Trial heterogeneity was estimated using the Cochrane Q statistic.[33] When the hypothesis of heterogeneity was rejected, a fixed-effects model was used to calculate weighted mean difference (WMD) and 95% confidence interval (CI). When the hypothesis of heterogeneity was not rejected, a random-effects model was used to calculate WMD and 95%CI.[34]

At first, an analysis was made to compare the cord blood leptin levels of AGA newborns with those of SGA newborns.

Then, the stratified meta-analyses were repeated with a multivariate model. The included studies were divided into subgroups according to the potential confounders: samples origin (Chinese newborns vs. non-Chinese newborns), GA (term-newborns vs. mixed GA newborns; the mixed GA newborns including preterm newborns, term newborns and overdue newborns while the newborns with no significant difference in gestational age), PIH or CM (newborns excluding PIH or CM, i.e., PIH or CM excluded vs. newborns not excluding PIH or CM, i.e., PIH or CM not mentioned). Then meta-analysis was made in subgroups respectively, while comparing whether their results are different. If the results are significantly different, the grouping factor may be a confounder in the present meta-analysis.

At last, sensitivity analysis was conducted. Cumulative meta-analysis was made on WMD and 95%CI of the cord blood leptin levels between SGA and AGA newborns by adding one article at a time according to the date of publication during 1996-2007. To determine whether each article could impact the results of meta-analysis, WMD and 95%CI were observed when eliminating just one article (All induced articles were eliminated in turn).

Review Manager Program software (version 4.2) and Stata Program software (version 10) were used for statistical analysis.

Results

Of 331 studies identified by literature search, 130 were reviewed and 20 were included in this analysis. Nineteen of the 20 studies demonstrated significant differences in cord blood leptin levels between SGA and AGA newborns. The characteristics of the newborns in the 20 studies are shown in Table. A total of 1520 newborns were recruited, with 367 and 23 newborns in the largest and smallest studies, respectively. Random sampling was used in 3 studies; blind method was mentioned in none of the 20 studies.

The asymmetry plot shows the possibility of publication bias for the 20 studies. However, the capacity of funnel plot to detect bias is associated with the sample sizes.[35] The sample sizes of most studies in the present analysis were small. Hence the funnel plot may not be a definitive proof of publication.

Meta-analysis

The hypothesis of homogeneity was rejected (Q=375.34, P<0.00001) after 1520 newborns were identified in the 20 studies. WMD (95%CI) of the cord blood leptin levels between SGA and AGA newborns in the 1520 newborns was -4.42 (-5.54, -3.29) ng/ml

(Fig. 1), indicating that the levels of cord blood leptin in SGA newborns were significantly lower than those in AGA newborns (*P*<0.00001).

Stratified meta-analysis
By a random-effects model, similar results were observed in Chinese newborns vs. non-Chinese newborns [WMD (95%CI): -4.15 (-5.16, -3.14) ng/ml vs. -4.78 (-5.54, -3.29) ng/ml], i.e., the cord blood leptin levels of SGA newborns were significantly lower than those of AGA newborns for both Chinese and non-Chinese newborns (*P*<0.00001 and *P*=0.001 respectively).

The results of the meta-analysis in term newborns vs. mixed GA newborns were observed [WMD (95%CI): -5.36 (-7.05, -3.66) ng/ml vs. -2.49 (-3.92, -1.05) ng/ml], i.e., the leptin levels in cord blood of the SGA newborns were significantly lower than those of the AGA newborns for both term and mixed GA newborns (*P*<0.00001); the results of the term-newborns were similar to the results of all newborns. However, WMD of the term newborns was lower than that of the mixed GA newborns, with no significant difference.

The newborns not excluding those with PIH or CM showed a wider 95%CI than the newborns excluding those with PIH or CM [-4.17 (-5.00, -3.33) ng/ml vs.

-4.47 (-9.61, 0.67) ng/ml]. In the former, there was no significant difference in cord blood leptin levels between SGA and AGA newborns (*P*=0.09) while in the latter, the levels in SGA newborns were significantly lower than those in AGA newborns (*P*<0.00001) (Fig. 2).

Sensitivity analysis
The results of cumulative meta-analysis are shown in Fig. 3. The studies were added one by one from the top down. The dots and horizontal lines represent the WMD and 95%CI, respectively. When the number of studies increased, WMD values were adjacent to -4.35 ng/ml and 95%CI diminished. Since adding the fourth study, both the upper and lower bounds of 95%CI were <0. WMD and 95%CI of SGA and AGA newborns were estimated after eliminating one study. The minimum and maximum values of WMD were -4.69 ng/ml and -3.79 ng/ml, respectively. The minimum upper and lower bounds of 95%CI were -3.51 ng/ml and -6.15 ng/ml, respectively. The maximum upper and lower bounds of 95%CI were -3.00 ng/ml and -4.58 ng/ml, respectively. It was exhibited that WMD and 95%CI did not change obviously after eliminating any study, i.e., there was a significant difference in the levels of cord blood leptin between SGA and AGA newborns (*P*<0.001).

Table. The study characteristics of the newborns included in the present report

No. of references	Author	Year	Country	The number of newborns			GA	PIH	CM	Random sampling
				Total	SGA	AGA				
8	Lepercq J	2003	France	22	13	9	Mixed*	–	–	No
9	Arslan M	2004	Japan	44	25	19	Mixed*	–	–	No
15	Liu H	2004	China	110	30	80	Mixed*	excluded	–	No
16	Gao Y	2000	China	63	19	44	Mixed*	–	–	No
17	Wang L	2007	China	36	10	26	Term newborns	excluded	–	Yes
18	Li T	2003	China	48	16	32	Term newborns	–	excluded	No
19	Liu T	2001	China	80	16	64	Term newborns*	excluded	–	No
20	Han SP	2001	China	78	31	47	Term newborns	excluded	–	Yes
21	Zhu QY	2004	China	44	15	29	Term newborns	–	excluded	Yes
22	Zhang J	2004	China	67	23	44	Term newborns	–	excluded	No
23	Sun QM	2004	China	110	30	80	Term newborns*	excluded	–	No
24	Fan XA	2005	China	72	9	63	Term newborns	excluded	excluded	No
25	Li HN	2004	China	47	10	37	Term newborns	excluded	excluded	No
26	Chen LQ	2004	China	30	14	16	Term newborns	excluded	–	No
27	Koistinen HA	1997	Finland	41	13	28	Term newborns*	–	–	No
28	Valūniene M	2007	Russia	367	80	287	Term newborns*	–	excluded	No
29	Cetin I	2000	Italy	23	6	17	Mixed*	–	excluded	No
30	Jaquet D	1999	France	105	70	35	Mixed*	–	excluded	No
31	Akcakus M	2007	Sweden	70	30	40	Term newborns*	excluded	excluded	No
32	Martínez-Cordero C	2006	Mexico	100	50	50	Term newborns	–	excluded	No

SGA: small for gestational age; AGA: appropriate for gestational age; GA: gestational ages; PIH: pregnancy-induced hypertension; CM: congenital malformation; *: AGA newborns were compared with SGA newborns for gestational age, *P*>0.05; Mixed: The newborns included premature newborns, term newborns and post-term newborns.

Study or sub-category	SGA cases	SGA Mean (SD)	AGA cases	AGA Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Koistinen HA	13	3.30 (0.50)	28	14.50 (2.80)		5.66	-11.20 [-12.27, -10.13]
Jaquet D	70	4.48 (6.70)	35	7.96 (8.30)		4.06	-3.48 [-6.65, -0.31]
Cetin I	6	1.80 (0.70)	17	3.80 (2.20)		5.60	-2.00 [-3.19, -0.81]
Gao Y	19	3.60 (1.10)	44	6.40 (3.00)		5.69	-2.80 [-3.82, -1.78]
Han SP	31	5.55 (3.79)	47	9.47 (5.97)		4.89	-3.92 [-6.09, -1.75]
Liu T	16	2.79 (1.54)	65	7.40 (4.45)		5.52	-4.61 [-5.93, -3.29]
Lepercq J	13	2.50 (0.70)	9	2.60 (0.90)		5.83	-0.10 [-0.80, 0.60]
Li T	16	1.13 (1.98)	32	3.06 (0.96)		5.68	-1.93 [-2.96, -0.90]
Arslan M	25	6.80 (2.20)	19	10.60 (3.60)		5.15	-3.80 [-5.63, -1.97]
Chen LQ	14	3.73 (1.74)	16	9.84 (3.64)		5.02	-6.11 [-8.11, -4.11]
Li HN	14	7.27 (3.05)	37	11.50 (5.24)		4.76	-4.23 [-6.55, -1.91]
Liu H	30	5.74 (2.60)	80	9.29 (3.11)		5.62	-3.55 [-4.70, -2.40]
Sun QM	30	5.74 (2.92)	38	8.09 (5.08)		5.08	-2.35 [-4.27, -0.43]
Zhang J	23	6.79 (4.59)	44	16.30 (11.60)		3.48	-9.51 [-13.42, -5.60]
Zhu QY	15	3.29 (1.24)	29	6.81 (4.67)		5.17	-3.52 [-5.33, -1.71]
Fan XA	9	3.33 (1.58)	63	10.50 (4.96)		5.32	-7.17 [-8.77, -5.57]
Martinez-Cordero C	50	15.32 (12.78)	50	23.44 (14.36)		2.56	-8.12 [-13.45, -2.79]
Akcakus M	30	11.70 (5.60)	40	20.30 (7.60)		4.12	-8.60 [-11.69, -5.51]
Valūniene M	80	4.30 (0.66)	287	7.10 (0.48)		5.96	-2.80 [-2.95, -2.65]
Wang L	10	10.34 (2.30)	26	13.70 (4.48)		4.83	-3.36 [-5.60, -1.12]
Total (95% CI)	514		1006			100.00	-4.42 [-5.54, -3.29]

Test for heterogeneity: Chi=375.34, df = 19 (P<0.001), I²=94.9%
Test for overall effect: Z=7.67 (P<0.001)

-10 -5 0 5 10
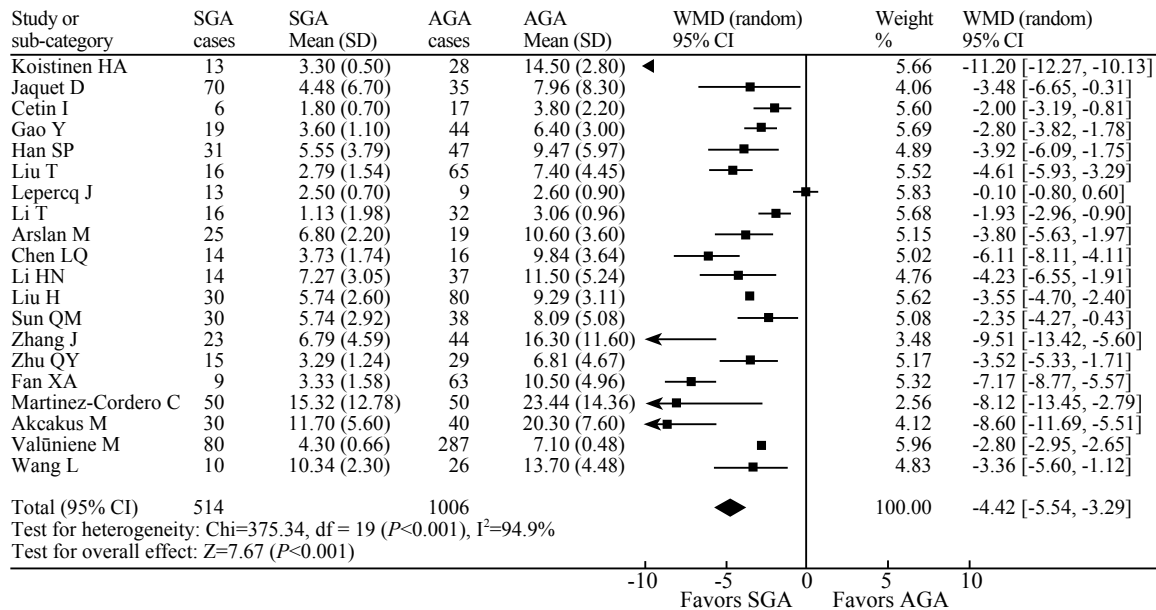Favors SGA   Favors AGA

Fig. 1. The weighted mean difference (WMD) and 95% confidence intervals (CI) of cord blood leptin concentrations between small for gestational age (SGA) and appropriate for gestational age (AGA) newborns.
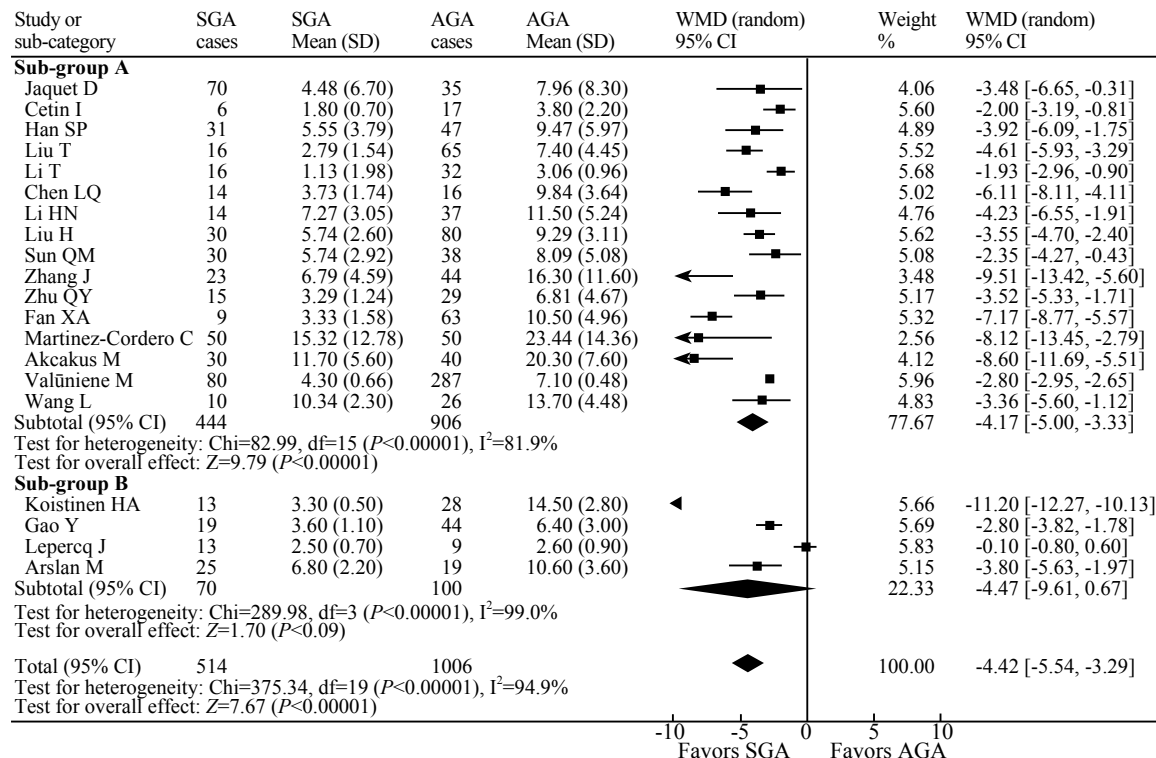
Study or sub-category	SGA cases	SGA Mean (SD)	AGA cases	AGA Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Sub-group A							
Jaquet D	70	4.48 (6.70)	35	7.96 (8.30)		4.06	-3.48 [-6.65, -0.31]
Cetin I	6	1.80 (0.70)	17	3.80 (2.20)		5.60	-2.00 [-3.19, -0.81]
Han SP	31	5.55 (3.79)	47	9.47 (5.97)		4.89	-3.92 [-6.09, -1.75]
Liu T	16	2.79 (1.54)	65	7.40 (4.45)		5.52	-4.61 [-5.93, -3.29]
Li T	16	1.13 (1.98)	32	3.06 (0.96)		5.68	-1.93 [-2.96, -0.90]
Chen LQ	14	3.73 (1.74)	16	9.84 (3.64)		5.02	-6.11 [-8.11, -4.11]
Li HN	14	7.27 (3.05)	37	11.50 (5.24)		4.76	-4.23 [-6.55, -1.91]
Liu H	30	5.74 (2.60)	80	9.29 (3.11)		5.62	-3.55 [-4.70, -2.40]
Sun QM	30	5.74 (2.92)	38	8.09 (5.08)		5.08	-2.35 [-4.27, -0.43]
Zhang J	23	6.79 (4.59)	44	16.30 (11.60)		3.48	-9.51 [-13.42, -5.60]
Zhu QY	15	3.29 (1.24)	29	6.81 (4.67)		5.17	-3.52 [-5.33, -1.71]
Fan XA	9	3.33 (1.58)	63	10.50 (4.96)		5.32	-7.17 [-8.77, -5.57]
Martinez-Cordero C	50	15.32 (12.78)	50	23.44 (14.36)		2.56	-8.12 [-13.45, -2.79]
Akcakus M	30	11.70 (5.60)	40	20.30 (7.60)		4.12	-8.60 [-11.69, -5.51]
Valūniene M	80	4.30 (0.66)	287	7.10 (0.48)		5.96	-2.80 [-2.95, -2.65]
Wang L	10	10.34 (2.30)	26	13.70 (4.48)		4.83	-3.36 [-5.60, -1.12]
Subtotal (95% CI)	444		906			77.67	-4.17 [-5.00, -3.33]

Test for heterogeneity: Chi=82.99, df=15 (P<0.00001), I²=81.9%
Test for overall effect: Z=9.79 (P<0.00001)

Sub-group B							
Koistinen HA	13	3.30 (0.50)	28	14.50 (2.80)		5.66	-11.20 [-12.27, -10.13]
Gao Y	19	3.60 (1.10)	44	6.40 (3.00)		5.69	-2.80 [-3.82, -1.78]
Lepercq J	13	2.50 (0.70)	9	2.60 (0.90)		5.83	-0.10 [-0.80, 0.60]
Arslan M	25	6.80 (2.20)	19	10.60 (3.60)		5.15	-3.80 [-5.63, -1.97]
Subtotal (95% CI)	70		100			22.33	-4.47 [-9.61, 0.67]

Test for heterogeneity: Chi=289.98, df=3 (P<0.00001), I²=99.0%
Test for overall effect: Z=1.70 (P<0.09)

Total (95% CI)	514		1006			100.00	-4.42 [-5.54, -3.29]

Test for heterogeneity: Chi=375.34, df=19 (P<0.00001), I²=94.9%
Test for overall effect: Z=7.67 (P<0.00001)

-10 -5 0 5 10
Favors SGA   Favors AGA

Fig. 2. The weighted mean difference (WMD) and 95% confidence intervals (CI) of cord blood leptin concentrations between small for gestational age (SGA) and appropriate for gestational age (AGA) newborns in sub-group A (excluding pregnancy-induced hypertension (PIH) or congenital malformation (CM)) and sub-group B (not excluding PIH or CM).

Discussion

In the present study, there were differences in cord leptin levels among the 20 studies, for instance, the mean value (1.13 ng/ml) of the cord leptin level in SGA newborns was lower in the study of Li[18] than that (15.32 ng/ml) of the cord leptin level of SGA newborns in Martínez-Cordero's study;[32] the latter was almost 15 times that of the former. On the basis of Cochrane Q statistic test in the present analysis, there was significant heterogeneity in the 20 studies, which may be due to the data from different studies.[36]
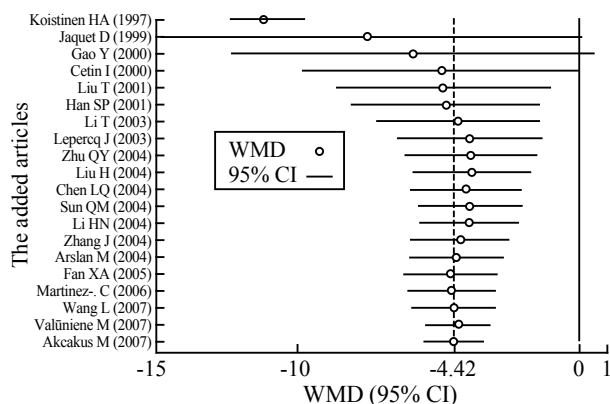
The present meta-analysis showed that the cord

Fig. 3. Cumulative meta-analysis of the 20 studies. WMD and CI indicate the weighted mean difference (WMD) and 95% confidence intervals (CI) of cord blood leptin concentrations between AGA and SGA newborns, respectively. The cumulative studies increased with years during 1996-2007.

leptin levels of the AGA newborns were significantly higher than those of the SGA newborns. Thus the sample origin and GA are not the confounder of the meta-analysis. It is worth noticing that in the newborns not excluding PIH or CM, the cord blood leptin levels of SGA newborns were not significantly different from those of the AGA newborns, indicating that PIH or CM may be the confounders of the meta-analysis. However, the mechanism underlying the increased cord blood leptin levels in AGA newborns is still unclear.[37]

The meta-analysis showed the importance of detecting the levels of cord blood leptin for the health of newborns. Since the cord leptin levels of SGA newborns are lower than those of AGA newborns, low leptin may predict the increased possibility of neonatal death, necrotizing enterocolitis, and respiratory distress syndrome. Both SGA and AGA newborns with low levels of cord blood leptin should be given adequate care.

In the present meta-analysis, stratified meta-analysis, cumulative meta-analysis, and meta-analysis after eliminating one study were conducted. According to the results of the stratified meta-analysis, PIH and CM were identified as two factors influencing the levels of cord blood leptin, and the influence of GA and study population on the cord blood levels was eliminated. Moreover, cumulative meta-analysis and meta-analysis after eliminating one reference strengthened the result that the cord leptin levels of AGA newborns were significantly higher than those of SGA newborns.

The major limitation of the present meta-analysis include the enhanced instability of the results. Random sampling was present in only 3 of the 20 studies and it was unclear whether blinding was used. The sample sizes in 8 studies were ≤15. Also, the types of congenital anomalies were unavailable.

Since SGA babies show low levels of cord leptin,

the relationship between SGA and cord blood leptin should be further investigated. Other factors that may influence cord leptin levels including maternal PIH and CM also await further investigation.

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