Decrease in birth weight and gestational age by arsenic among the newborn in Shanghai, China

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Objectives To assess the effects of trace metals on birth weight and gestational age among newborn babies of mothers without occupational exposure.

Methods The subjects examined were 142 newborn babies (71 males and 71 females) delivered at two university hospitals in Shanghai, China and their parents. Relationships of newborn birth weight and gestational age to concentrations of arsenic, lead, cadmium, manganese, zinc, and cobalt in maternal and cord blood were investigated.

Results Birth weight was 3379.5 ± 440.8 (2090–4465) g and the gestational age was 39.7 ± 1.3 (35–43) weeks. Stepwise regression analysis indicated that, in the male newborn, birth weight and gestational age were inversely related to the logarithm arsenic concentration (4.13 ± 3.21 μg/l) in mothers' whole blood.

Conclusion Arsenic might have a negative influence on newborn birth weight and gestational age at a relatively low exposure level. This effect was observed in male but not female babies, suggesting a sex differential in susceptibility to arsenic at an early stage of development. Although birth weight is believed to be related to gestational age, arsenic may directly affect both birth weight and gestational age.

Key words: arsenic, birth weight, gestational age, Shanghai

1. Introduction

Environmental contamination with trace metals has become a global problem, especially in developing countries. Arsenic (*As*), for example, is a well-documented environmental contaminant in Bangladesh[1], India[2,3], and Taiwan[4]. Major sources of human exposure to *As* are natural geological resources, drinking water, ambient air pollution and food[5]. Recent epidemiological studies have demonstrated that exposure to trace metals including *As* during pregnancy may affect birth outcomes: *As* exposure is associated with spontaneous abortion, still birth, low birth weight and neonatal/infant death[2～4]. Hopenhayn et al.[6] reported that consumption of drinking water with a high level of *As* (up to 40 μg/l) by mothers leads to low birth weight of their newborn. Recently, exposure to lead (*Pb*) during pregnancy was also found to be associated with decreased gestational period and increased risk of preterm birth and low birth weight[7,8]. *Pb* might disturb placental function, as shown by our previous observation that *Pb* caused preeclampsia and pregnancy hypertension in women without occupational exposure[9,10]. Cadmium (*Cd*) also has been thought to adversely affect gestational age, fetus growth, and birth weight[11～13], although a study on Swedish women failed to demonstrate significant effects on birth outcome[8].

Deficiency of metals may also cause problems, as documented for zinc (*Zn*)[14], manganese (*Mn*)[15] and cobalt (*Cb*)[16] with negative pregnant outcomes in animal experiments. Our recent study[17] demonstrated *Mn* concentrations in mothers' whole blood to be significantly lower in cases demonstrating intrauterine growth retardation than in those with weights ap-

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propriate for gestational age. Supplementation with *Zn* during pregnancy is associated with offspring growth and increasing in birth weight[18]. In animal experiments, *Co* deficiency leads to abnormality in neonatal behavior although effects on birth weight and gestational age remain to be clarified[19]. As low birth weight is believed to affect development of the fetus[20~22] and increase the risk of various diseases in adulthood[23], the influence of trace metals on birth weight is an important health issue throughout the world.

In China, it is reported that low birth weight is a major risk for death of newborn babies[24]. In the present study, we surveyed birth outcome among subjects without occupational exposure to arsenic in Shanghai, China. Although Shanghai is a megalopolis with a population of 18.58 million, levels of trace metals in water and ambient air are reported to be very low[25]. Concentrations of *As* and other trace metals in maternal and cord blood samples were here measured to assess dose-effect relationships with birth weight, gestational age, and other birth outcomes.

2. Subjects and Methods

2.1 Subjects

The study was conducted as a joint research project between Mie University, Juntendo University and Shanghai Jiaotong University, from October 2006 to April 2007. Among 12 hospitals affiliated with Shanghai Jiaotong University, representatives of two agreed to participate in the study. One, with approximately 1600 beds, was located in Puxi and the other, with approximately 600 beds, in Pudong. During the study period, a total of 850 pregnant women without abortion, stillbirth, or other accidents were asked to participate in the study by university staff. One hundred and eighty-six women (mothers) and their husbands (fathers) agreed, but 20 pairs were excluded from the study because the mothers had chronic conditions such as heart disease, renal failure, or hepatitis. Thus, 166 mother and father pairs and their newborn babies served as study subjects.

The study protocol was approved by the Research Ethics Committee of Mie University Graduate School of Medicine and the Research Ethics Committee of Medical School of Shanghai Jiaotong University, and the survey was conducted under their supervision. The purpose and procedures of the study were explained to all subjects, and the study was conducted with their informed consent.

2.2 Questionnaire

Each subject was asked questions by face to face structured interview conducted by hospital staff. The questionnaire included socio-demographic characteristics of mothers and fathers and mothers' pregnancy and reproductive histories.

2.3 Collection and analysis of blood samples

Mothers' whole blood (MWB) samples were collected just before delivery. Umbilical cord blood (UCB) samples were collected at the time of delivery. All blood samples were collected using EDTA-K2 anticoagulant tubes and were stored at −80℃ until analysis. Frozen blood was thawed at room temperature and 200 μl samples were mixed in tubes with 400 μl aliquots of 69% nitric acid. Subsequently, the mixed samples were digested by heating in a microwave oven and diluted with deionized water to 4.5 g. Concentrations of metals (*As*, *Pb*, *Cd*, *Mn*, *Zn* and *Co*) in the samples were measured using an inductively coupled plasma mass spectrometer (Model ICP-MS, Agileng 7500CE, Agilent Technologies, USA)[10,17,26,27]. Standard reference blood (Contox Co. Ltd., USA) was used for calibration in the measurement. All measurements were conducted in duplicate; if the results were below the detection limits or 5 times greater than the norm, a repeat measurement was made. Detection limits for *As*, *Pb*, *Cd*, *Mn*, *Zn*, and *Co* were 0.1, 0.1, 0.05, 0.1, 0.1, and 0.1 μg/l, respectively.

2.4 Statistical Analysis

Pearson's correlation analysis or one-way analysis of variance were performed to examine associations of newborns' birth weight and gestational age with metal concentrations in MWB and UCB and parents' characteristics. To reduce the influence of outliers and normalize the residual distribution, common logarithms of blood metal concentrations were used in the analysis. Relationships of birth weight or gestational age (a dependent variable) with metal concentrations and parents' characteristics were examined by multiple regression with a stepwise method, using the probability of F-values of the regression coefficient as the criterion for entry ($p<0.05$ or $p=0.05$) or removal ($p>0.05$) from the regression equation. Independent variables examined were those significantly related to the dependent variable by simple correlation analysis or one-way analysis of variance: i.e. as described in the Results section, they were logAs (MWB), logCd (MWB and UCB), gestational age, and mother's height and income for birth weight and logAs (MWB and UCB) for gestational age. As described below (Table 2), some subjects showed Cd concentrations below the detection limit (0.05 μg/dl); calculation was therefore performed using half of the detection limit for the correlation and stepwise regression analyses. The Student t-test was employed to compare gestational ages, birth weights, blood metal concentrations and parents' characteristics separately for male and female newborn babies. SPSS 14.5 for Windows was employed for statistical calculations.

3. Results

Blood samples from 24 subjects were excluded because of technical problems with measurement of metal concentrations. Thus, a total of 142 parents and their newborn were investigated. Age, body weight, height,

Table 1　Demographic characteristics of 142 parents

	Mother	Father
	Mean±SD	Mean±SD
Age (years)	27.2±4.4	29.9±5.6
Height (cm)	161.0±4.4	173.9±5.1[a]
Weight		
Before pregnancy (kg)	53.4±6.6[b]	—
At delivery (kg)	71.0±9.0[c]	72.0±12.4[d]
	No. (%)	No. (%)
Education		
Unschooled	3(2.1)	1(0.7)
≦Middle school	41(28.9)	30(21.6)
≦High school	38(26.8)	52(36.6)
≧College	60(42.3)	59(41.5)
Monthly income (RMB*)		
<1000	49(34.5)	4(2.8)
1000～3000	54(38.0)	64(45.1)
3000～5000	28(19.7)	27(19.0)
>5000	11(7.7)	47(33.1)
Source of drinking water		
Tap water	75(52.8)	75(52.8)
Well	1(0.7)	1(0.7)
Water purifier	59(41.5)	64(45.1)
Bottled water	7(4.9)	2(1.4)
Milk drinking		
None	11(7.7)	54(38.0)
Sometimes	23(16.2)	44(31.0)
Always	18(12.7)	11(7.7)
Every day	90(63.4)	33(23.2)

* RMB: the symbol of Chinese currency
Number of missing data: [a]3, [b]5, [c]8, [d]8.

Table 2　Metal concentrations in umbilical cord blood and mother's whole blood (UCB and MWB, respectively) in 142 newborns

	UCB mean±SD (range)	MWB mean±SD (range)
As (μg/l)	3.82±3.81 (0.31–33.54)	4.13±3.21 (0.63–30.45)
Pb (μg/dl)	4.25±2.51 (1.05–18.99)	6.68±2.92 (2.07–22.40)
Cd (μg/l)	0.93±1.60 (0.00[a]–12.10)	1.14±0.87 (0.00[b]–4.12)
Mn (μg/l)	79.93±27.45 (25.67–174.10)	58.71±22.55 (23.56–187.50)
Zn (mg/l)	2.58±1.08 (1.33–7.07)	6.32±1.23 (1.85–10.20)
Co (μg/l)	43.65±15.70 (6.83–68.01)	46.10±15.62 (8.01–74.36)

[a,b] Lower than detection limit (9 and 8 subjects, respectively).

Table 3　Pearson's correlation coefficients of newborn birth weight and gestational age with metals in umbilical cord blood (UCB) and mother's whole blood (MWB) in 71 male and 71 female newborns

	Male newborns		Female newborns	
	UCB	MWB	UCB	MWB
Birth weight				
logAs	−0.215	−0.288*	0.153	−0.001
logPb	0.152	0.099	0.136	0.140
logCd[a]	0.309**	0.289*	−0.090	−0.136
logMn	0.122	0.147	−0.019	0.029
logZn	−0.073	0.184	0.164	−0.166
logCo	−0.195	−0.219	0.071	0.065
Gestational age				
logAs	−0.259*	−0.342*	0.153	−0.001
logPb	−0.085	0.175	0.136	0.140
logCd[a]	0.106	0.217	−0.137	−0.102
logMn	−0.026	−0.005	−0.019	0.029
logZn	0.187	−0.182	0.164	−0.166
logCo	−0.076	−0.031	0.071	0.065

* $P<0.05$　** $P<0.01$
[a] Correlation coefficients were calculated using the half of detection limit (0.025 μg/dl) for subjects with Cd concentration lower than the detection limit.

and other demographic characteristics of parents are listed in Table 1. Among 142 newborn babies, 71 were males and 71 were females. Their aerage gestational age was 39.7±1.3 (35–43) weeks and birth weight was 3379.5±440.8 (2090–4465) g. With regard to their parents, one mother (0.7%) and 73 fathers (51%) were smokers, whereas 2 mothers (1.4%) and 24 fathers (29.4%) consumed alcohol beverages, respectively, before pregnancy. There were no significant differences in gestational ages, birth weights, or parents' characteristics between male and female newborn (p>0.05).

Concentrations of metals in UCB and MWB are shown in Table 2. There were no significant differences in measured values between male and female newborn cases (p>0.05). Correlations of birth weight and gestational age with those metal concentrations were as shown in Table 3. In males, both birth weight and gestational age were correlated inversely with log *As* in MWB and positively with log *Cd* in MWB; gestational age was also correlated inversely with log *As* in UCB. By contrast, in females, no significant correlations were observed between birth weight or gestational age and blood metal concentrations.

In male newborn, birth weight was significantly correlated with gestational age and mothers' height (r=0.354 and r=0.242, p<0.05, respectively). In addition, one way analysis of variance showed birth

Table 4　Results of stepwise regression analysis for 71 male newborns[a]

Independent variables	Birth weight[b]		Gestational age[c]	
	β_0	β(95%CI)	β_0	β(95%CI)
logAs in MWB	−0.254*	−354.405(−677.527～−31.284)	−0.342**	−1.507(−2.499～−0.514)
gestational age	0.269*	84.111(11.746～156.476)	NS	NS
mother's height	0.257*	24.307(3.769～44.844)	NS	NS
Adjusted R^2	0.208*		0.104*	

* $P<0.05$, ** $P<0.01$;

[a] Stepwise method used the probability of F-values of the regression coefficient as criteria for its entry to ($P<0.05$ or $P=0.05$) or removal from ($P>0.05$) the regression equation (SPSS 14.5 for Windows).
Independent variables examined: [b] logAs (MWB), logCd (MWB and UCB), gestational age, and mother's height and income for birth weight; [c] logAs (MWB and UCB) for gestational age. Calculation was performed using the half of detection limit (i.e. 0.025 μg/dl) for Cd concentration if it was lower than the detection limit.

β_0, β = standardized and non-standardized regression coefficient, respectively.
95%CI = 95% confidence interval.
NS = Not selected.

weight to significantly vary among the classes of mothers' income (Table 1) ($F=3.304$, $p<0.05$).

Results of the stepwise multiple regression analysis with birth weight or gestational age as the dependent variables for male newborn are shown in Table 4, where independent variables were those significantly related to birth weight or gestational age as above. Both birth weight and gestational age were inversely related to log *As* in MWB. Birth weight was also significantly related to mothers' height. Relationships of birth weight and gestation age to *As* in MWB in 71 male newborn are illustrated in Fig 1.

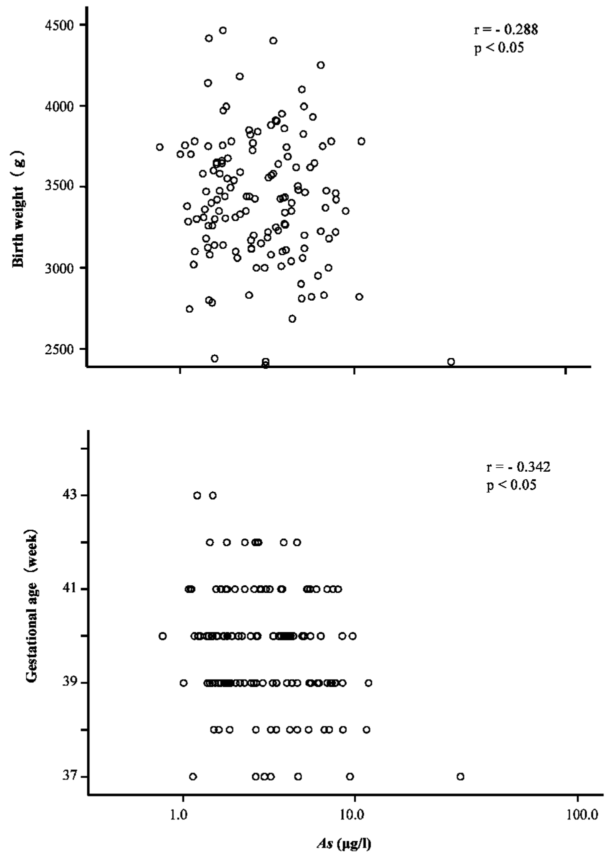

Fig 1.　Significant correlations of birth weight and gestational age with arsenic (*As*) in mother's whole blood among 71 male newborns.

4. Discussion

In the present study, *As* was found to be a risk factor for both low birth weight and decreased gestational age in male newborn, in agreement with the previous observation of adverse effects of *As* on birth outcome[1,2,4,6]. Multiple regression analysis indicated that the effects of *As* on birth weight and gestational age were independent of each other, indicating that low birth weight is a direct effect of low level fetal exposure to *As*, rather than a result of decreased gestational age. Also, mothers' height should be the indicator for nutritional status of mothers, which may affect the infant directly. *As* concentrations in cord blood and maternal blood in a population exposed to high levels in drinking water showed that were found to be similar and correlate with each other[28], so *As* can readily permeate through the placenta barrier leading to exert toxic effects on the fetus. The fetus is mostly likely to be exposed to inorganic *As* acting as an immunosuppressive factor[29] in early gestation, before induction of arsenic methyltransferase, a key enzyme of detoxification[30]. Thus, direct effects of *As* on fetus seem significant and critical.

Adverse effects of *As* were only demonstrated in male newborn in the present study, i.e. no significant relationship of *As* with birth weight or gestational age was observed for female babies, suggesting that males are more susceptible to *As* at an early stage of development. The reason is unclear, although sex differences in health effects of *As* have been observed in previous studies, as pointed out in the review of Vahter et al.[31] For example, males appear to demonstrate more *As*-related skin effects including skin cancer than females, possibly related to sex differences in biotransformation of *As* by methylation. In contrast, Ahmad et al[32] reported females to be more susceptible to toxic effects of chronic arsenic exposure (arsenicosis) in Nilkanda, Bangladesh. Thus, further studies should be necessary on sex differences in the effects of *As* on birth outcome. Smoking is also believed to be a risk factor for low birth weight in the newborn[33], but in the present study only one mother was a smoker.

Non-occupational human exposure to *As* in the environment is primarily through ingestion of food and water[34]. Of these, food is generally the principal contributor to the daily intake of total *As*, including organic and inorganic forms, whereas drinking water is a significant source of inorganic *As* exposure[34]. Although Shanghai is a metropolis in China, there are only few factories in the city area; polluted water from industries located outside of the city, if any, drains into the sea rather than the river system. Owing to the law and supervision, tap water in Shanghai is of good quality as reported by Shanghai Local Government with a concentration of *As* as low as 1 μg/l in 2009[35], which is very different from reported well water values of 40 μg/l and above in severe *As* polluted areas[36]. In fact, almost all mothers were likely to drink bottled water instead of tap water during their pregnancy (data not shown), so that *As* exposure from drinking water could be neglected. It is therefore appeared that significant source of exposure of mothers was food intake in the present study. As the location was on the east coast of China, *As* exposure from seafood should be considered. However, most *As* in seafood is in organic forms, which are believed not to be toxic[37]. On the other hand, most food stuffs as meat, poultry, dairy products and cereals have higher levels of inorganic *As*. Thus, a survey on food intake, together with measurement of organic and inorganic forms of *As* in blood separately, should be carried out to identify the environmental sources of *As* exposure which might affect birth outcome as observed in the present study.

Cd exposure has been reported to be related to decreased gestational age and low birth weight[11,12]. In China, Zhang et al.[13] observed that in a highly polluted area (DaYe city, Hu Bei Province) the maternal serum concentration of *Cd* was negatively related to neonatal birth height. In the present study, *Cd* concentration in maternal blood, averaged 1.14 μg/l and therefore was lower than that in the ealier report (1.72 μg/l), showing a positive correlation with birth weight. However, on multiple regression analysis, the *Cd* concentration did not significantly relate to birth weight. Jelliffe-Pawlowski et al.[7] reported that, at maternal blood *Pb* levels above 10 μg/l, the risk of preterm birth and low birth weight in the newborn is increased. In the present study, the average maternal blood *Pb* concentration was 6.68 ± 2.92 μg/dl (max 22.40 μg/l), and was not significantly related to gestational age or birth weight. However, it is reported that hypertension[9] and preeclampsia[10] were observed among pregnant mothers with blood *Pb* concentrations of 5.7 ± 2.0 and 5.09 ± 2.01 μg/dl, respectively. *Pb* might thus affect the maternal environment. Our recent study[17] showed *Mn* concentrations in maternal whole blood to be significantly lower in intrauterine growth retardation newborn (16.7 ± 4.8 μg/l) than that in appropriate-for-gestational age cases (19.1 ± 5.9 μg/l). Supplementation with *Zn* in small-for-gestational age infants has proved to be beneficial for offspring development[38], and deficiency of *Zn* is reported to be related to low birth weight and decreased gestational age[39]. In animal experiments, it was found that deficiency of *Co*/VitB12 leads to aberrant ovarian function and malnutrition of the fetus[19]. In the present study, maternal blood levels were within normal ranges for *Mn* (58.71 ± 22.55 μg/l), *Zn* (6.32 ± 1.23 mg/l), and *Co* (46.10 ± 15.62 μg/l)[40] and no significant reproductive effects were noted. As supplementation of several vitamins and minerals may protect pregnant mothers against *As* toxicity[41], preventive effects of supplementation of vitamins should be investigated in future studies.

The hospitals surveyed in the present study were public ones, i.e. operated by Shanghai City, the same as other hospitals in China which are administered by local or central government, the expense of delivery being covered by national insurance. According to the statistics data from Shanghai City[42], the average annually income of white collar workers in Shanghai was 46,426 RMB (3,869/month) while that of blue collar counterparts was 19,244 RMB (1,603/month), with a total average annual income of 34,707 RMB (2,892/month). In the present study, the monthly income range was 1000–3000 RMB, suggesting a typical socioeconomic profile for the subjects, although exact data were not available. However, the educational level was relatively high (i.e. more that 40% had attended college or higher), considering that education levels of Shanghai citizens were reported as follows: unschooled of 4.33%, middle school 48.3%, high school 26.1%, and college 21.3%[43].

The study might have some flaws. The sample size should be increased to achieve statistically more accurate results. Concentrations of heavy metals in blood and urine, together with their chemical forms, should be investigated to clarify the effects that depend on chemical status of metals. To generalize the findings in the present study, a more carefully designed epidemiological study will be necessary to control possible sampling bias and confounding effects of socio-economical factors.

5. Conclusions

The present study on newborn babies delivered at two university hospitals in Shanghai, China, and their parents suggested that *As* has negative influence on newborns' birth weight and gestational age despite the fact that Shanghai is a low *As* contamination area. As effects were observed only in males, a gender differential in susceptibility to *As* may exist at an early stage of development. Although birth weight is believed to be related to gestational age, *As* may directly affect both independently. Further studies with a larger number of subjects is now necessary to confirm the effects of low level exposure to *As* and other trace metals on birth outcome.

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References

1) Rahman A, Vahter M, Ekstro EC, et al. Association of arsenic exposure during pregnancy with fetal loss and infant death: a cohort study in Bangladesh. American Journal of Epidemiology 2007; 165: 1389–1396.
2) Rahman MM, Sengupta MK, Ahamed S, et al. The magnitude of arsenic contamination in groundwater and its health effects to the inhabitants of the Jalangi-one of the 85 arsenic affected blocks in West Bengal, India. Science of the Total Environment 2005; 338: 189–200.
3) von Ehrenstein OS, Guha-Mazumde DN, Hira-Smith M, et al. Pregnant outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. American Journal of Epidemiology 2006; 163(7): 662–669.
4) Yang CY, Chang CC, Tsai SS, et al. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. Environmental Research 2003; 91: 29–34.
5) Matschullat J. Arsenic in the geosphere- a review. Science of the Total Environment 2000; 249: 297–312.
6) Hopenhayn C, Ferreccio C, Browning SR, et al. Arsenic exposure from drinking water and birth weight. Epidemiology 2003; 14(5): 593–602.
7) Jelliffe-Pawlowski LL, Miles SQ, Courtney JG, et al. Effect of magnitude and timing of maternal pregnancy blood lead (Pb) levels on birth outcomes. Journal of Perinatology 2006; 26(3): 154–62.
8) Osman K, Akesson A, Berglund M, et al. Toxic and essential elements in placentas of Swedish woman. Clinical Biochemistry 2000; 33(2): 131–138.
9) Vigeh M, Yokoyama K, Mazaher M, et al. Relationship between increased blood lead and pregnancy hypertension in woman without occupational lead exposure in Tehran, Iran. Archives of Environmental Health 2004; 59(2): 70–5.
10) Vigeh M, Yokoyama K, Ramezanzadeh F, et al. Lead and other trace metals in preeclampsia: a case-control study in Tehran, Iran. Environmental Research 2006; 100(2): 268–75.
11) Nishijo M, Nakagawa H, Honda R, et al. Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. Occupational and Environmental Medicine 2002; 59(6): 394–6.
12) Salpietro CD, Gangemi S, Minciullo PL, et al. Cadmium concentration in maternal and cord blood and infant birth weight: a study on healthy non-smoking women. Journal of Perinatal Medicine 2002; 30(5): 395–9.
13) Zhang YL, Zhao YC, Wang JX, et al. Effect of environmental exposure to cadmium on pregnancy outcome and fetal growth: a study on healthy pregnant women in China. Journal of Environmental Sscience and Health. Part A, Toxic/hazardous Substances & Environmental Engineering 2004; 39(9): 2507–15.
14) Golub MS, Gershwin ME, Hurley LS, et al. Studies of marginal zinc deprivation in rhesus monkeys: III. Pregnancy outcome. American Journal of Clinical Nutrition 1984; 39: 879–887.
15) Hansen SL, Spears JW, Lloyd KE, et al. Feeding a low manganese diet to heifers during gestation impairs fetal growth and development. American Dairy Science Association 2006; 89: 4305–4311.
16) Dwyer CM. Genetic and physiological determinants of maternal behavior and lamb survival: Implications for low-input sheep management. Journal of Animal Science 2008; 86(E. Suppl.): E246–E258.
17) Vigeh M, Yokoyama K, Ramezanzadeh F, et al. Blood manganese concentrations and intrauterine growth restriction. Reproductive Toxicology 2008; 25(2): 219–23.
18) Islam MN, Ullah MW, Siddika M, et al. Serum zinc level in preterm low birth weight babies and its comparison between preterm AGA and preterm SGA babies. Mymensingh Medical Journal 2008; 17(2): 145–8.
19) Mitchell LM, Robinson JJ, Watt RG, et al. Effect of cobalt/vitamin B12 status in ewes on ovum development and lamb viability at birth. Reproduction, Fertility and Development 2007; 19: 553–562.
20) Spinillo A, Capuzzo E, Egbe TO, et al. Pregnancies complicated by idiopathic intrauterine growth retardation. Severity of growth failure, neonatal morbidity and two-year infant neurodevelopmental outcome. The Journal of Reproductive Medicine 2005; 40: 209–215.
21) McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. The New England Journal of Medicine 1985; 312: 82–90.
22) Osmond C, Barker DJP. Fetal infant and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. Environmental Health Perspectives 2000; 108(Suppl 3): 545–553.
23) Wilcox AJ. On the importance-and the unimportance-of birth weight. International Journal of Epidemiology 2001; 30: 1233–1241.
24) Lin XZ, Liu ZH, Zheng H, et al. The study of risk factors of low birth weight and death in newborn. HeNan Journal Prevention Medical 2001; 12(1): 16–7.

25)　Shanghai Environmental Protection Bureau: [http://www.shanghaiwater.com/]. Accessed Aug. 20, 2008.
26)　Chen XL, Zhang ZY, Feng LX, et al. Contents of trace elements in blood of healthy old people assayed by ICP–MS. Medical Journal of the Chinese People's Armed Police Force 2006; 17(3): 166–168.
27)　Xu ZG, Shang W, Shen YZ, et al. Analysis of trace elements in human hair, human serum and cancer by ICP–MS. Journal of ZheJiang University. 2000; 34(5): 479–482.
28)　Concha G, Vogler G, Lezcano D, et al. Exposure to inorganic arsenic metabolites during early human development. Toxicology Science 1998; 44(2): 185–190.
29)　Ferrario D, Croera C, Brustio R, et al. Toxicity of inorganic arsenic and its metabolites on haematopoietic progenitors ''in vitro'': Comparison between species and sexes. Toxicology 2008; 249: 102–108.
30)　Vahter M. Health effects of early life exposure to arsenic. Basic & Clinical Pharmacology & Toxicology 2008; l02(2): 204–211.
31)　Vahter M, Akesson A, Liden C, et al. Gender differences in the disposition and toxicity of metals. Environmental Research 2007; 104: 85–95.
32)　Ahmad SK, Sayed MHSU, Khan MH, Jail MA, Ahmed R, Faruquee MH: Arsenicosis: sex differentials. Journal of Preventive & Social Medicine 18: 35–40, 1999.
33)　Nafstad P, Fugelseth D, Qvigstad E, et al. Nicotine Concentration in the Hair of Nonsmoking Mothers and Size of Offspring. American Journal of Public Health 1998; 88(1): 120–124.
34)　IPCS: Environmental Health Criteria 224: Arsenic and Arsenic Compounds (Second Edition), World Health Organization, Geneva, 2001.
35)　Shanghai Environmental Protection Bureau: [http://www.shanghaiwater.com/]. Accessed Jun. 25, 2010.
36)　Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. International Epidemiological Association 1998; 27: 561–569.
37)　Borak J, Hosgood HD. Seafood arsenic: Implications for human risk assessment. Regulatory Toxicology and Pharmacology 2007; 47: 204–212.
38)　Krebs NF, Westcott JL, Rodden DJ, et al. Exchangeable zinc pool size at birth is smaller in small for gestational age than in appropriate-for-gestational-age preterm infants. The American Journal of Clinical Nutrition 2006; 84: 1340–1343.
39)　Elizabeth KE, Krishnan V, Vijayakumar T. Umbilical cord blood nutrients in low birth weight babies in relation to birth weight & gestational age. Indian Journal of Medical Research 2008; 128: 128–133.
40)　Matthew JE, Donald GB. Metals and Related Compounds: Medical Toxicology. Elsevier Science Publishing Company, 1998; 1022–1065.
41)　Gamble MV, Liu XH, Slavkovich V, et al. Folic acid supplementation lowers blood arsenic. American Journal of Clinical Nutrition 2007; 86(4): 1202–1209.
42)　Shanghai Statistics Yearbook 2008: Table 9–4 average annual income. China Statistics Press, 2008: 132.
43)　China Statistics Yearbook 2008: Table 3–12 Population by Sex, Educational Attainment and Region (2007). China Statistics Press, 2008: 69.

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