

ORIGINAL ARTICLE

Ubiquinol-10 and ubiquinone-10 levels in umbilical cord blood of healthy fetuses and the venous blood of their mothers

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Abstract

Despite their being good markers of oxidative stress for clinical use, little is known about ubiquinol-10 (reduced coenzyme Q₁₀) and ubiquinone-10 (oxidized coenzyme Q₁₀) levels in fetuses and their mothers. This study investigates oxidative stress in 10 healthy maternal venous, umbilical arterial and venous bloods after vaginal delivery by measuring ubiquinol-10 and ubiquinone-10 levels. Serum ubiquinol-10 and ubiquinone-10 levels were measured by HPLC with a highly sensitive electrochemical detector. Maternal venous ubiquinol-10 and ubiquinone-10 levels were significantly higher than umbilical arterial and venous levels (all $p < 0.001$). However, the ubiquinone-10/total coenzyme Q₁₀ (CoQ₁₀) ratio, which reflects the redox status, was significantly higher in umbilical arterial and umbilical venous blood compared to maternal venous blood (all $p < 0.001$). The ubiquinone-10/total CoQ₁₀ ratio was higher in umbilical arterial than in umbilical venous blood ($p < 0.01$). The present study demonstrated that fetuses were under higher oxidative stress than their mothers.

Keywords: Coenzyme Q₁₀, oxidative stress, maternal blood, ubiquinol-10, ubiquinone-10, umbilical cord blood

Abbreviations: BMI, body mass index; CoQ₁₀, coenzyme Q₁₀; LDL, low density lipoprotein; HDL, high density lipoprotein; free fatty acids, FFAs.

Introduction

Oxidative stress is critical under some conditions, such as during the neonatal and pregnant periods. Normal pregnancy is a physiological condition in which an increase of free radicals is produced because of high energy demands and the tissue oxygen requirements of many bodily functions, such as increasing lipid metabolism and the growing placenta and foetus with an increase in lipid peroxidation [1–4]. Abnormal pregnancy states, such as pre-eclampsia [5–7] and gestational diabetes [8,9], are also conditions

where there is a significant increase in free radicals and, consequently, an increase in oxidative damage.

Not only the mothers, but also their fetuses and neonates are susceptible to oxidative stress because of their deficient antioxidant capacity [10], with lower CoQ₁₀ levels in the umbilical cord than in maternal blood [11]. Increased free radicals are a feature of most neonatal diseases [10]. Therefore, to identify oxidative stress, including the oxidant and antioxidant status of fetuses and their mothers, an oxidative stress marker, such as CoQ₁₀, is needed for clinical use.

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About 95% of total CoQ₁₀ is present in the human circulation as ubiquinol-10 and the remaining 5% exists as ubiquinone-10 [12]. Ubiquinol-10, the reduced form of ubiquinone-10, is a potent lipophilic antioxidant present in all human tissue [13–15]. Meanwhile, ubiquinone-10 is an oxidative product that is most recognized for its role in energy production by mitochondria, where it functions as an essential proton-electron carrier in the lipid phase of the inner mitochondrial membrane [16]. Previous studies reported that, in the plasma of patients with hyperlipidemia [17], hypercholesterolemia [18] and diabetes [19], ubiquinol-10 levels were low and ubiquinone-10 levels were high because of increased oxidative stress.

Ubiquinol-10 and ubiquinone-10 levels, as well as the ratio of ubiquinol-10/ubiquinone-10 and ubiquinone-10/total CoQ₁₀ are therefore good markers of oxidative stress, which is defined as a disturbance in the pro-oxidant–antioxidant balance in favour of the pro-oxidant state [8,20]. However, no study has measured ubiquinol-10, ubiquinone-10 and the ubiquinone-10/total CoQ₁₀ oxidation ratio redox status to clarify oxidative stress in fetuses and their mothers.

The aim of this study was to evaluate oxidative stress in umbilical cord blood of the fetuses and the venous blood of their mothers by measuring ubiquinol-10 and ubiquinone-10 levels at childbirth. The findings are then discussed in the context of oxidative stress in fetuses and their mothers.

Methods

Participants and survey methods

This cross-sectional study was performed between February and March 2007 at a hospital in Tokyo, Japan. Ten healthy Japanese pregnant women with no obstetrical complications at admission to the obstetric ward for delivery were recruited. All pregnant women initially had an early dating ultrasound scan at 10–12 weeks' gestation to allow accurate gestational dating. Information on individual characteristics and lifestyle factors was obtained by questionnaire at recruitment. Maternal peripheral venous blood and umbilical cord venous and arterial blood samples were obtained immediately after vaginal delivery.

In addition, healthy non-pregnant women of similar ages were recruited as a control group at the university. The non-pregnant women also completed the same questionnaire and their peripheral venous blood samples were drawn at the time of recruitment after obtaining their agreement.

The study protocol was approved by the Institutional Review Board of the University of Tokyo. Written, informed consent was obtained from all participants.

Participants' characteristics and lifestyle factors

Age (years), pre-pregnancy body mass index (BMI; kg/m²), obstetrical history and perinatal outcomes were obtained from the participants' medical records. Several factors potentially important for CoQ₁₀ levels *in vivo* were considered in our study in both the pregnant and non-pregnant women, including vitamin supplement intake, current alcohol habit and current smoking habit.

Blood collection and processing

Umbilical cord blood reflects foetal–placental status. Umbilical venous blood is the blood that has circulated through the placenta and umbilical arterial blood is the blood that has circulated through the foetus. Therefore, we sample blood from the umbilical arteries (transporting blood from the foetus to the placenta) and blood from the umbilical veins of newborns (transporting blood from the placenta to the foetus) to determine foetal status *in utero*.

Immediately after delivery, an umbilical cord segment was double clamped, blood was drawn gently from the umbilical arteries and veins and maternal peripheral venous blood was obtained with a 21-gauge needle and syringe. To avoid the impact of oxidation on CoQ₁₀ levels at the time of sampling, blood samples were first taken from the umbilical cord vein and then from the umbilical cord artery in the first five infants, while in the next five infants, the blood samples were first taken from the umbilical cord artery and then from the umbilical cord vein.

Whole blood was collected in 7 ml serum separator tubes (Venoject[®] II Autosep[®] Gel+Clot Act, Terumo Corp., Tokyo, Japan). The sample tubes were centrifuged at 1610 g for 10 min, after which the whole blood samples were immediately placed on ice for 10 min. Although haemolysis was assessed by visual inspection, no samples had extreme red cell lysis and fibrin deposition due to insufficient exposure time after blood collection. In addition, we confirmed that the haemolysis did not affect the serum levels of CoQ₁₀ among adults by another test, because there were small quantities of endoglobular CoQ₁₀. After freeze–thawing of the serum, problems with fibrin clot formation did not occur in any samples.

Serum specimens were immediately transferred to relabelled, 1.5-ml, screw-capped, polypropylene tubes (Nunc Cryo Tube No. 37535, 1.0 ml, Roskilde, Denmark) and stored at –80°C until analysis. The centrifugation steps involved in serum preparation were performed at room temperature. Therefore, whole blood samples were immediately placed on ice for 10 min and the time between blood sampling and freezing of the all sera was not more than 20 min. All analyses were performed within 2 months.

We tested the stability of ubiquinol-10 and ubiquinone-10 of pooled serum during sample storage at -80°C for 318 days ($n=13$). The mean levels (2 SD) of ubiquinol-10 (ng/ml) and ubiquinone-10 (ng/ml) were 771 (56.5) and 53.0 (4.3), respectively. The CVs were 7.3% for ubiquinol-10 and 8.2% for ubiquinone-10, which were within 9.7% of the inter-assay CV. Serum ubiquinol-10 and ubiquinone-10 were stable for at least 10 months when stored at -80°C without repeated sample thawing and refreezing.

Measurement of serum lipid markers

Serum lipid markers, such as total cholesterol (mg/dl), low density lipoprotein (LDL)-cholesterol (mg/dl), high density lipoprotein (HDL)-cholesterol (mg/dl), triglycerides (mg/dl) and free fatty acids (FFAs, mEq/l) were determined by SRL, Inc (Tokyo, Japan). Since CoQ₁₀ is known to bind to lipoproteins, the amount of CoQ₁₀ in blood is related to the amount of cholesterol and differences in total CoQ₁₀ may be normalized to total cholesterol [21].

Measurement of serum CoQ₁₀ content (ubiquinol-10 and ubiquinone-10)

The standard sample of CoQ₁₀ was kindly provided by KANEKA Co. Ltd. (Osaka, Japan) through Shiseido Co., Ltd. (Tokyo, Japan). Other chemicals were purchased and used; namely, high performance liquid chromatography (HPLC) grade isopropanol, methanol (Nacalai Tesque Inc. Kyoto, Japan, catalogue no. 29128-31 and 21929-23, respectively), and sodium periodate (Sigma-Aldrich Co. St Louis, MI, catalogue no. 410241-100G). An internal standard such as CoQ₉ was not used. Although we previously tested from CoQ₀ to CoQ₁₁ as internal standards, the quinol was oxidized by all of the quinone in the internal standard. Therefore, pooled serum was used as the internal standard.

Simultaneous detection of ubiquinol-10 (ng/ml) and ubiquinone-10 (ng/ml) was performed with the method reported by Yamamoto and Yamashita [22] with a slight modification. The serum CoQ₁₀ content (ubiquinol-10 and ubiquinone-10) was measured using HPLC (NANOSPACE SI-2, Shiseido Co., Ltd, Tokyo, Japan) with an electrochemical detector (ECD, NANOSPACE SI-2 3016, Shiseido Co., Ltd, Tokyo, Japan) [23]. First, 20 μl of serum were mixed with 180 μl of isopropanol, which we previously found resulted in lower oxidation than ethanol and methanol. Then, after centrifugation at 2000 g for 10 min at 4°C , 20 μl of the mixture was injected directly into HPLC with ECD. The oxidation potential for ECD was 650 mV. When the samples were loaded, the mobile phase 1 was 50 mM sodium perchlorate in methanol/distilled water (95/5, v/v) with a flow rate 0.2 ml/min. Second, after 1.5 min, using a

column-switching system, CoQ₁₀ was eluted from the concentration column (CQ-C ID 2.0 mm \times 35 mm, Shiseido Co., Ltd, Tokyo, Japan; catalogue no. 21221) by mobile phase 2 (50 mM sodium perchlorate in methanol/isopropanol (95/5, v/v)) with a flow rate of 0.4 ml/min. The column oven was set to 40°C . A CQ-S ID 2.0 mm \times 150 mm (Shiseido Co., Ltd, Tokyo, Japan, catalogue no. 21222) and a CQ-R ID 2.0 mm \times 20 mm (Shiseido Co., Ltd, Tokyo, Japan, catalogue no. 21223) were used as a separating column and a reducing column, respectively. For calibration of the CoQ₁₀ level of an unknown specimen, a linear regression formula was calculated based on the peak area of CoQ₁₀ standards that were prepared in every assay. The intra-assay CVs of ubiquinol-10 (two samples, $n=9$) and ubiquinone-10 (two samples, $n=9$) were within 5.7% and 9.7%, respectively. The inter-assay CVs of ubiquinol-10 (one sample, $n=20$) and ubiquinone-10 (one sample, $n=20$) were 7.7% and 18.3%, respectively. The recovery rates for ubiquinol-10 (two samples, two concentration levels) and ubiquinone-10 (one sample, three concentration levels) were 94.0–115% and 83.2–97.4%, respectively. Thus, since there was no standard for ubiquinol-10, a mixed standard of total levels of known and unknown samples was used for recovery rates.

In our experience, when up to nine samples were analysed at a time, the intra-assay CV was within 9.7%. Therefore, up to nine samples, including two samples of standard and pooled serum, were analysed at a time with HPLC-ECD to keep automatic oxidation at minimal levels as follows. A standard curve was prepared based on the peak area once a batch. Then, a pooled serum sample was measured. It was confirmed that the CV of the ubiquinol level of pooled serum was within 9.7%. After that, seven unknown samples were measured. Finally, 200 ng/ml of standard were measured with HPLC-ECD. If this peak area had variability greater than 5%, the reduction column was replaced with a new one and the electrode was cleaned to obtain variability below 5%. All samples were measured repeatedly using this procedure.

The redox status of CoQ₁₀ was expressed by the ubiquinone-10/total CoQ₁₀ ratio. The ratio of total CoQ₁₀/total cholesterol was also reported to the adjusted lipid level, because the serum levels of ubiquinone-10 depend mostly on the amount of ubiquinone-10-containing lipoproteins in circulation [24].

Statistical analysis

The statistical significance of differences between the pregnant group and non-pregnant group or umbilical arterial blood of newborns was determined by the non-parametric Mann-Whitney U-test or Fisher's exact test and comparisons for results within the foetuses in umbilical venous blood and arterial blood

were performed using the Wilcoxon matched pairs test.

The relationships between CoQ₁₀ levels of maternal blood and CoQ₁₀ levels of umbilical cord arterial and venous blood were analysed using Spearman's correlation coefficient. The statistical package for the Social Sciences Version 13.0 (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analysis. All *p*-values were two-sided; *p* < 0.05 was considered statistically significant.

Results

Participant's characteristics

As shown in Table I, the characteristics and lifestyle factors were not significantly different between the 10 pregnant and the 10 non-pregnant women. All pregnant women had a full-term vaginal delivery without epidurals and healthy newborns. Five pregnant women received oxytocin treatment during labour and immediately after vaginal delivery. None of the participants took vitamin supplements regularly and none smoked.

Serum lipid marker levels

As shown in Table II, the levels of total cholesterol, LDL-cholesterol and triglycerides were significantly higher in maternal blood than in non-pregnant women's blood. HDL-cholesterol and FFAs were not significantly different between maternal blood and non-pregnant women's blood. The total cholesterol,

LDL-cholesterol, HDL-cholesterol, triglyceride and FFA levels were significantly lower in umbilical cord venous blood than in their mothers' venous blood (all *p* < 0.001).

Serum ubiquinol-10 and ubiquinone-10 levels in mothers, their fetuses and in non-pregnant women

As shown in Table III, the levels of total CoQ₁₀, ubiquinol-10 and ubiquinone-10 and the ratio of total CoQ₁₀/total-cholesterol were significantly higher in maternal blood than in non-pregnant women's venous blood and umbilical cord arterial blood (all *p* < 0.001). However, the ratio of ubiquinone-10/total CoQ₁₀ was not significantly different between maternal and non-pregnant women's blood. The ratio of ubiquinone-10/total CoQ₁₀ was significantly lower in maternal blood than in umbilical arterial cord blood (*p* < 0.001).

Umbilical arterial and venous cord blood

As shown in Table III, the total CoQ₁₀ levels were not significantly different between umbilical cord arterial and venous blood. However, the ubiquinol-10 level was significantly lower in umbilical cord arterial blood than in umbilical cord venous blood (*p* < 0.05). The ubiquinone-10 level was significantly higher in umbilical cord arterial blood than in umbilical cord venous blood. The ratio of ubiquinone-10/total CoQ₁₀ was significantly higher in umbilical arterial cord blood than in umbilical venous cord blood (*p* < 0.01).

Table 1. Description of clinical characteristics.

Women	Pregnant women (n=10)	Non-pregnant women (n=10)	p-value
Age (years) [†]	32.5, 9.5 (23.0–37.0)	32.5, 8.0 (27.0 – 44.0)	0.7
Prepregnancy BMI (kg/m ²) ^{*†}	20.3, 3.9 (16.6–24.6)	19.6, 2.3 (16.6 – 23.2)	0.6
Primipara [‡]	5	8	0.4
Use of oxytocin during labour	4		
Use of oxytocin during after birth	1		
Lifestyle factors			
Vitamin supplements intake [‡]	3	4	0.5
regular intakes	0	0	
irregular intakes	10	10	
Alcohol habit	4	7	0.2
Smoking habit	0	0	
Newborn			
Gastational week at delivery (weeks)	39.0, 1.5 (38.0–41.0)		
Birth weight (g)	3026.0, 263.0 (2614.0–3206.0)		
Apgar score at delivery	9.0, 1.0 (8.0–10.0)		
Fetal bradycardia or meconium staining	3		
Placenta weight (g)	537.5, 73.3 (481.0–729.0)		

Data are shown as the median, interquartile range (range; max - minimum) or n.

[†]Mann - whitney U test.

[‡]Fisher's exact test.

^{*}Body mass index.

Table II. Levels of lipid markers in non-pregnant women and maternal venous blood and umbilical venous blood.

	Non-pregnant women venous blood (n=10)	Maternal venous blood (n=10)	Umbilical venous blood (n=10)
Total cholesterol (mg/dl)	202.0, 62.8 (149.0–240.0)	318.5, 75.3 (241.0–374.0)***	70.5, 16.8 (49.0–79.0)†††
Low-density lipoprotein cholesterol (mg/dl)	98.5, 40.5 (54.0–121.0)	191.5, 73.0 (119.0–246.0)***	17.5, 19.0 (8.0–27.0)†††
High-density lipoprotein cholesterol (mg/dl)	78.0, 42.3 (63.0–113.0)	96.5, 18.0 (70.0–109.0)	34.0, 10.3 (18.0–41.0)†††
Triglyceride (mg/dl)	53.0, 27.3 (25.0–132.0)	239.0, 111.5 (144.0–366.0)***	20.0, 18.5 (9.0–59.0)†††
Free fatty acid (mEq/l)	0.5, 0.7 (0.07–1.02)	0.9, 0.7 (0.33–1.50)	0.2, 0.1 (0.08–0.27)†††

Data are shown as the median, interquartile (range; max - minimum). Maternal venous blood was taken immediately after delivery.

Statistical analysis was performed by Mann-Whitney U test.

*** $p < 0.001$: non-pregnant women venous blood vs maternal venous blood.

††† $p < 0.001$: maternal venous blood vs umbilical venous blood.

Correlation of the ratio of ubiquinone-10/total CoQ₁₀ between maternal blood and umbilical cord blood

There were no significant correlations between the maternal blood ubiquinone-10/total CoQ₁₀ ratio and the umbilical cord arterial and venous blood ratios (respectively; $rp = -0.02$, $p = 0.96$; $rp = 0.1$, $p = 0.78$). As shown in Figure 1, there was a significant correlation between the umbilical cord arterial and venous blood ubiquinone-10/total CoQ₁₀ ratios ($rp = 0.9$, $p < 0.001$).

Discussion

There was no significant difference in oxidative stress measured by ubiquinol-10 and ubiquinone-10 blood levels between mothers and non-pregnant women. Then, healthy foetuses were exposed to higher oxidative stress than their healthy mothers.

Previous studies have reported that total CoQ₁₀ levels were higher in healthy pregnant women than in non-pregnant women. However, no studies have reported the blood ubiquinol-10 and ubiquinone-10 levels in healthy foetuses and their healthy mothers.

Oxidative stress and CoQ₁₀ in maternal venous blood

We found that the ubiquinone-10 level was ~ 2.8-fold higher in maternal venous blood than in non-pregnant women's blood. However, the ratio of ubiquinone-10/total CoQ₁₀, which reflects the redox status, was not significantly different between maternal venous blood and non-pregnant women's blood. Meanwhile, the ubiquinol-10 level was higher by ~ 2.6-fold in maternal blood compared to non-pregnant women's blood. Previous studies have reported that healthy pregnant women had increased oxidative products such as biopyrrin [25], lipid hydroperoxides [3] and MDA [1], as well as antioxidants such as total CoQ₁₀ [26,27], Vitamin E [2] and uric acid [3]. The present study results clearly showed that pregnant women with no complications maintained their pro-oxidant-antioxidant balance and the redox status by increased levels of the antioxidant ubiquinol-10.

Serum CoQ₁₀ levels in maternal and umbilical cord blood

In maternal venous blood, total CoQ₁₀ and ubiquinol-10 levels were 10-fold higher than in umbilical

Table III. Levels of ubiquinol and ubiquinone in non-pregnant women and maternal venous blood and umbilical venous blood.

	Non-pregnant women venous blood (n=10)	Maternal venous blood (n=10)	Umbilical arterial blood (n=10)	Umbilical venous blood (n=10)
Total Coenzyme Q ₁₀ (ng/ml)	6230, 237 (466–1020)	1480, 689 (1250–2550)***	158, 31.5 (134–198)†††	153, 28.0 (127–192)
Ubiquinol-10 (ng/ml)	596, 230 (446–996)	1420, 672 (1190–2450)***	128, 40.0 (103–166)†††	135, 35.5 (102–164)‡
Ubiquinone-10 (ng/ml)	24.2, 8.6 (19.6–35.7)	72.0, 25.5 (52.4–104)***	26.3, 11.5 (18.6–41.9)†††	20.6, 11.2 (11.4–27.9)‡‡
Total Coenzyme Q ₁₀ /Total cholesterol ratio (%)	3.4, 1.0 (2.3–4.3)	5.1, 1.1 (3.9–7.2)***	no data	2.4, 0.6 (1.9–2.7)‡‡‡
Ubiquinone-10/Total Coenzyme Q ₁₀ ratio (%)	4.3, 0.6 (2.4–5.2)	4.6, 0.8 (3.6–5.3)	16.0, 10.4 (11.5–25.4)†††	13.7, 9.0 (6.8–19.7)‡‡

Data are shown as the median, interquartile range (range; max - minimum). Maternal venous blood was taken immediately after delivery.

*** $p < 0.001$: non-pregnant women vs maternal venous. Mann-whitney U test.

††† $p < 0.001$: maternal venous umbilical arterial blood. Mann-whitney U test.

‡ $p < 0.05$, ‡‡ $p < 0.01$, ‡‡‡ $p < 0.001$: umbilical arterial blood vs umbilical venous blood. Willcoxon test.

‡‡‡ $p < 0.001$: Total Coenzyme Q₁₀/Total cholesterol ratio (%) maternal vs venous vs umbilical arterial blood. Mann-whitney U test.

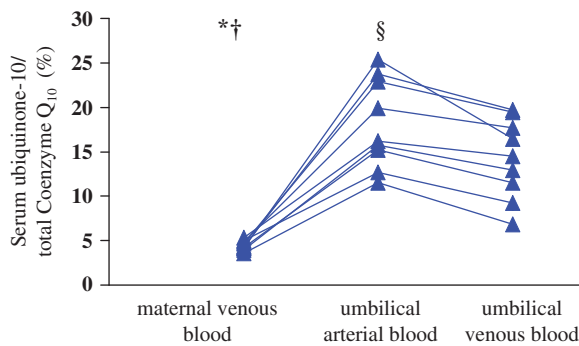


Figure 1. The ratios of serum ubiquinone-10/total coenzyme Q_{10} (%) in maternal venous blood ($n=10$) and the umbilical arterial and venous blood ($n=10$). * $p < 0.001$ vs umbilical arterial blood by Mann-Whitney U-test. † $p < 0.001$ vs umbilical venous blood by Mann-Whitney U-test. § $p < 0.01$ vs umbilical arterial blood by Wilcoxon test. There are no significant correlations between the maternal blood ubiquinone-10/total CoQ_{10} ratio and the umbilical cord arterial and venous blood ratios (respectively; $rp = -0.02$, $p = 0.96$; $rp = 0.1$, $p = 0.78$). There is a significant correlation between the umbilical cord arterial and venous blood ubiquinone-10/total CoQ_{10} ratios ($rp = 0.9$, $p < 0.001$).

cord arterial blood and the ubiquinone-10 level was 2.7-fold higher than in umbilical cord arterial blood. These results support previous studies reporting that absolute CoQ_{10} levels were higher in maternal blood than in fetuses or neonates [28–30]. Noia et al. also reported that level of CoQ_{10} among pregnant women had increased throughout pregnancy [27], but level of CoQ_{10} among fetuses was unchanged throughout pregnancy [11]. The large difference in total CoQ_{10} levels between mothers and their fetuses may suggest that the plasma cholesterol increase during pregnancy contributes to increased CoQ_{10} production.

CoQ_{10} and cholesterol share part of a common synthesis pathway [31]. The serum levels of ubiquinone-10 depend mostly on the amount of ubiquinone-10 contained in lipoproteins in circulation [24]. Maternal hyperlipidemia is one of the most consistent and striking changes to take place in lipid metabolism during pregnancy. As shown in Table II, the lipid profile was significantly lower in umbilical cord venous blood and in non-pregnant women than in mothers' venous blood (all $p < 0.001$). Furthermore, a previous study reported that there is no direct placental transfer of maternal lipoproteins [32]. Maternal lipoproteins may be involved in the large difference in total CoQ_{10} levels between mothers and their fetuses.

The present study found that the ratio of ubiquinone-10/total CoQ_{10} was 3.9-fold higher in fetuses than in their mothers, which suggests that newborns and fetuses are easily susceptible to oxidative stress because of their low level of antioxidants [10].

We next compared the ubiquinone-10/total CoQ_{10} ratio (%) and ubiquinol-10 and ubiquinone-10 levels between umbilical cord arterial and venous blood

to understand the role of placental function under oxidative stress. In umbilical cord arterial blood, the ubiquinone-10/ CoQ_{10} ratio and ubiquinone-10 levels were higher than in umbilical cord venous blood. However, the present study found that higher ubiquinol-10 levels were observed in umbilical cord venous blood than in umbilical cord arterial blood. In addition, the level of ubiquinone-10 and the ubiquinone-10/total CoQ_{10} ratio were not correlated between maternal blood and umbilical cord blood. These results suggest that oxidative stress of a healthy foetus is independent from that experienced by its mother.

This study has some limitation. First, the number of participants was small, which may have reduced statistical power. Second, we had not considered other oxidative stress markers, because we had considered ubiquinol-10 (reduced coenzyme Q_{10}) and ubiquinone-10 (oxidized coenzyme Q_{10}) levels to represent a disturbance in the pro-oxidant–antioxidant balance in favour of the pro-oxidant state. However, other markers may be needed to clarify the oxidative stress of fetuses and their mother. Further research needs to measure lipid peroxidation or some other measure of damage to clarify oxidative stress of fetuses and their mothers. In this study, participants had a normal pregnancy, normal delivery without epidurals and healthy newborns. Therefore, further research needs to compare the ubiquinol-10 and ubiquinone-10 among babies of diabetic mothers, mothers with pre-eclampsia and mothers in whom epidurals were used, as well as in pre-term infants.

In conclusion, the present study found that CoQ_{10} is not transferred from mothers to their fetuses, since the CoQ_{10} levels of mothers and their fetuses differed. In addition, healthy pregnant women who are under increased oxidative stress maintain the pro-oxidant–antioxidant balance by increasing levels of ubiquinol-10, which is an antioxidant. On the other hand, fetuses are exposed to higher oxidative stress than their mothers, as indicated by the results. Further research needs to measure some other measure of damage to clarify oxidative stress of fetuses and their mother and to compare the ubiquinol-10 and ubiquinone-10 among babies and their mothers who had complications, such as diabetes, pre-eclampsia and pre-term delivery, and used treatments, such as epidurals and oxytocin.

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References

- [1] Arikan S, Konukoglu D, Arikan C, Akcay T, Davas I. Lipid peroxidation and antioxidant status in maternal and cord blood. *Gynecol Obstet Invest* 2001;51:145–149.
- [2] De Vriese R, Dhont M, Christophe B. Oxidative stability of low density lipoproteins and vitamin E levels increase in maternal blood during normal pregnancy. *Lipids* 2001;36:361–366.
- [3] Toescu V, Nuttall L, Martin U, Kendall J, Dunne F. Oxidative stress and normal pregnancy. *Clin Endocrinol* 2002;57:609–613.
- [4] Gitto E, Reiter J, Karbownik M, Tan X, Gitto P, Barberi S, Barberi I. Causes of oxidative stress in the pre- and perinatal period. *Biol Neonate* 2002;81:146–157.
- [5] Barton R, Sibai M. Prediction and prevention of recurrent preeclampsia. *Obstet Gynecol* 2008;112:359–372.
- [6] Hubel A, McLaughlin K, Evans W, Hauth A, Sims J, Roberts M. Fasting serum triglycerides, free fatty acids, and malondialdehyde are increased in preeclampsia, are positively correlated, and decrease within 48 hours post partum. *Am J Obstet Gynecol* 1996;174:975–982.
- [7] Palan R, Shaban W, Martino T, Mikhail S. Lipid-soluble antioxidants and pregnancy: maternal serum levels of coenzyme Q₁₀, alpha-tocopherol and gamma-tocopherol in preeclampsia and normal pregnancy. *Gynecol Obstet Invest* 2004;58:8–13.
- [8] Biri A, Onan A, Devrim E, Babacan F, Kavutcu M, Durak I. Oxidant status in maternal and cord plasma and placental tissue in gestational diabetes. *Placenta* 2006;27:327–332.
- [9] Chen X, Scholl O. Oxidative stress: changes in pregnancy and with gestational diabetes mellitus. *Curr Diab Rep* 2005;5:282–288.
- [10] Saugstad D. Mechanisms of tissue injury by oxygen radicals: implications for neonatal disease. *Acta Paediatr* 1996;85:1–4.
- [11] Noia G, Romano D, De Santis M, Mariorenzi S, Caruso A, Mancuso S. Coenzyme Q₁₀ fetal plasma levels. *Fetal Diagn Ther* 1998;13:127–130.
- [12] Miles V, Horn S, Morrison A, Tang H, DeGrauw T, Pesce J. Plasma coenzyme Q₁₀ reference intervals, but not redox status, are affected by gender and race in self-reported healthy adults. *Clin Chim Acta* 2003;332:123–132.
- [13] Feher J. The preventive role of coenzyme Q₁₀ and other antioxidants in injuries caused by oxidative stress. *Arch Med Sci* 2007;3:305–314.
- [14] Bentinger M, Brismar K, Dallner G. The antioxidant role of coenzyme Q. *Mitochondrion* 2007;7(Suppl):41–50.
- [15] Teran E, Racines-Orbe M, Vivero S, Escudero C, Molina G, Calle A. Preeclampsia is associated with a decrease in plasma coenzyme Q₁₀ levels. *Free Radic Biol Med* 2003;35:1453–1456.
- [16] Mitchell P, Moyle J. The role of ubiquinone and plastoquinone in chemiosmotic coupling between electron transfer and proton translocation. In: Lenaz G, editor. *Coenzyme Q*. Chichester: John Wiley and Sons Ltd; 1985. p 145–163.
- [17] Kontush A, Reich A, Baum K, Spranger T, Finckh B, Kohlschutter A, Beisiegel U. Plasma ubiquinol-10 is decreased in patients with hyperlipidaemia. *Atherosclerosis* 1997;129:119–126.
- [18] Mabuchi H, Higashikata T, Kawashiri M, Katsuda S, Mizuno M, Nohara A, Inazu A, Koizumi J, Kobayashi J. Reduction of serum ubiquinol-10 and ubiquinone-10 levels by atorvastatin in hypercholesterolemic patients. *J Atheroscler Thromb* 2005;12:111–119.
- [19] Lim C, Tan H, Goh K, Subramaniam T, Sum F, Tan K, Lee L, Ong N. Oxidative burden in prediabetic and diabetic individuals: evidence from plasma coenzyme Q(10). *Diabet Med* 2006;23:1344–1349.
- [20] Sies H. Oxidative Stress. In: Sies H, editor. London: Academic Press; 1985. p 1–8.
- [21] Menke T, Niklowitz P, De Sousa G, Reinehr T, Andler W. Comparison of coenzyme Q₁₀ plasma levels in obese and normal weight children. *Clin Chim Acta*. 2004;349:121–127.
- [22] Yamamoto Y, Yamashita S. Plasma ratio of ubiquinol and ubiquinone as a marker of oxidative stress. *Mol Aspects Med* 1997;18(Suppl):79–84.
- [23] Barshop A, Gangoiti A. Analysis of coenzyme Q in human blood and tissues. *Mitochondrion* 2007;7:89–93.
- [24] Laaksonen R, Riihimaki A, Laitila J, Martensson K, Tikkanen J, Himberg J. Serum and muscle tissue ubiquinone levels in healthy subjects. *J Lab Clin Med* 1995;125:517–521.
- [25] Matsuzaki M, Haruna M, Ota E, Watanabe E, Murayama R, Tsukamoto H. Urinary biopyrrin as a possible oxidative stress marker during pregnancy. *J Jpn Acad Midwife* 2006;20:40–49.
- [26] Althaus J, Szymanski L, Blakemore K. Co-enzyme (CoQ₁₀) levels and preterm delivery. *Am J Obstet Gynecol* 2007;197:49.
- [27] Noia G, Littarru P, De Santis M, Oradei A, Mactromarino C, Trivellini C, Caruso A. Coenzyme Q₁₀ in pregnancy. *Fetal Diagn Ther* 1996;11:264–270.
- [28] Teran E, Vivero S, Racines-Orbe M, Castellanos A, Chuncha G, Enriquez G, Moya W. Coenzyme Q₁₀ is increased in placenta and cord blood during preeclampsia. *Biofactors* 2005;25:153–158.
- [29] Compagnoni G, Lista G, Giuffrè B, Mosca F, Marini A. Coenzyme Q₁₀ levels in maternal plasma and cord blood: correlations with mode of delivery. *Biol Neonate* 2004;86:104–107.
- [30] Todoroki Y, Tsukahara H, Ohshima Y, Shukunami K, Nishijima K, Kotsuji F, Hata A, Kasuga K, Sekine K, Nakamura H, Yodoi J, Mayumi M. Concentrations of thioredoxin, a redox-regulating protein, in umbilical cord blood and breast milk. *Free Radic Res* 2005;39:291–297.
- [31] Folkers K, Langsjoen P, Willis R, Richardson P, Xia LJ, Ye CQ, Tamagawa H. Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci USA* 1990;87:8931–8934.
- [32] Herrera E, Lasuncion MA. Maternal-fetal transfer of lipid metabolites. In: Polin RA, Fox WW, Abman SH, editors. *Fetal and neonatal physiology*. 3rd ed. Philadelphia: W.B. Saunders Co.; 2004. p 375–388.

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