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EFFECT OF 25-HYDROXYVITAMIN D3 AND DIVALENT CALCIUM ION SUPPLEMENTATION IN SOWS' DIETS ON TRACE ELEMENTS IN BLOOD AND MILK

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ABSTRACT

This study is designed to evaluate the effect of 25-hydroxyvitamin D3 (25(OH)D3) and divalent calcium ion (Ca^{2+}) supplementation in sows' diets on trace elements in blood and milk to assess whether it is beneficial to pig growth or not. A total of 40 sows of 7 to 8 gestational age with good health and nutritional condition were divided into four groups: control group, low calcium group, 25(OH)D3 group and low calcium with 25(OH)D3 group. The blood and milk from sows and neonatal piglets' blood were collected on the day of parturition. Changes in the content of Cr, Mn, Cu, As, Se and Cd were analyzed. The results showed that there was no significant change in the content of Cr, Mn, Se and Cd in sows' blood by changing calcium content or adding 25(OH)D3 alone, while adding 25(OH)D3 alone can significantly reduce the content of copper in sows' blood. Under the combined action of low calcium and 25(OH)D3, the Cr, Mn and Cd content in piglets' blood were significantly lower than that of control group ($P<0.05$), and the content of copper was significantly increased compared to control group ($P<0.01$). Low calcium group and 25(OH)D3 group significantly increase the content of Cr, Cu and Se in sows' milk compared to control group ($P<0.05$), but has no effect on the content of arsenic. Altogether, our results suggest that addition of 25(OH)D3 to sows' diet is beneficial to maintain the balance of trace elements in sows and their fetuses, so 25(OH)D3 may be helpful for the health of mother and normal development of fetus during pregnancy.

Keywords: 25-hydroxyvitamin D3; Divalent calcium ion; Trace elements; Blood and milk; Piglets; Sows

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INTRODUCTION

Calcium is an important component of mineral in animals, and its absorption is closely related to bone development (Hu *et al*., 2007). Animals need to ingest an appropriate a+ mount of calcium every day to maintain normal physiological functions such as the expansion of smooth muscle and increased enzyme activity in the body (Deng, 2007). In late pregnancy, fetal uptake of nutrients gradually increased and it is easy to lead to sow induce hypocalcemia (Feng, 2009). Typical clinical symptoms of the disease including hypothermia, abnormal breathing, limp and skeletal deformation. It has serious effect on the production performance of sows along with the growth and development of piglets (Li, 2018).

Supplementation of vitamin D3 during pregnancy has important physiological effects on pregnant women and fetuses. When vitamin D3 enters the body, it is first converted into 25(OH)D3 by the liver, and then converted into 1,25(OH)2D3 with biological activity by hydroxylase CyP27b1 produced by the kidney, thus promoting the absorption of calcium (Christakos and Sylvia, 2012; Hirota *et al*., 2017). Previous study has shown that maternal vitamin D3 level can affect fetal growth and bone development (Abrams and Steven 2007; Xu *et al*., 2019). In addition, vitamin D3 can also regulate the maternal fat metabolism during pregnancy to avoid difficult labor caused by obesity (Kang *et al*., 2015). However, the effects of eating 25(OH)D3 directly on the changes of other trace elements in the body have not been clearly studied.

The absorption and metabolism of various trace elements in the body are interrelated (Zhang *et al*., 2010), insufficient of calcium in pregnant women lead to imbalance of other trace elements in the body which may lead to the occurrence of hypertension, diabetes and other diseases during pregnancy (Liu *et al*., 2016). The growth and development of the fetus is also related to the trace element levels of the mother, abnormal trace elements in the mother can affect the transport of nutrients from the placenta and umbilical cord to the fetus, which results in fetal developmental disorders (Kucukaydin *et al*., 2018; Liu *et al*., 2009). Maternal trace element levels can also directly affect the quality of milk (Wang *et al*., 2015). After the birth, the baby is mainly feed on breast milk as the source of nutrition, at the same time, the baby can also obtain the protection of immune factors from breast milk to prevent the occurrence of disease. Therefore, the content of trace elements in milk can directly affect the health of the newborn. So, we raised the concern whether the body after absorbing 25(OH)D3 directly will intervene the balance of trace elements in the body of the mother and fetus, or better maintain the homeostasis of trace elements compare with traditional calcium supplements.

MATERIALS AND METHODS

Experimental grouping: Total 40 landrace sows of 7 to 8 gestational age (the average age was 5 years) with good health and nutritional condition were divided into four groups (n=10). The formula for the feed is formulated as recommended by the National Research Council, the nutrients in feed is shown in the table S1. According to table S2, the contents of calcium, phosphorus and 25(OH)D3 in the feed were adjusted and animals were divided into control group, low calcium group, 25(OH)D3 group and low calcium 25(OH)D3 group. The animal trials and procedures in this experiment were approved by the South China Agricultural University Animal Care Committee, Guangdong, China.

Sample collection: All the groups were fed from day 85 of gestation to day 114 of parturition. Blood and milk from sows were collected on the day of parturition, selected one piglet from each litter for study and their blood was collected before feeding. The blood and milk were stored in liquid nitrogen immediately after collection.

Determination of trace elements: 100 microliters of blood (from each sow and piglet) and milk were taken, while 1 ml of nitric acid and hydrogen peroxide, respectively were added. Digestion of samples were done in water bath at 100℃ until seen clear and transparent, then all the samples were resized to 10 ml with deionized water for testing. Then samples were detected by inductively coupled plasma atomic emission spectrometry (Agilent 7700X icp-ms). The regression value of the standard curve for all element detection was above 0.999 to ensure accurate detection.

Statistical analysis: Data were analyzed as a 2 × 2 factorial design by using the SPSS 19.0 to calculate the mean value, standard deviation, standard error and conducted analysis of variance and LSD Duncan to analyze the difference between groups. The results were expressed as the mean ± standard error (SE). Bar charts were made by GraphPad Prism 5.0. *P<0.05* set for statistically significant.

Table S1: Composition and nutrient levels of the basal diet.

Ingredients	Contents (%)	Nutritional level	Contents (%)
Corn (7.8%)	58.97	Dry material, %	87.33
Soybean meal (48%)	20.1	Sodium (Na), %	0.21
Wheat bran (16.5%)	10	Chlorine (Cl), %	0.301
Fish powder (67%)	3	Crude protein, %	18.527
Soybean	2		
Soybean oil	1.5		
Palm oil	1.5		
Premix*	1		
NaCl	0.4		
Total	100		

*The premix provided the following per kg of diets: V_A 10500 IU, V_E 70 IU, V_{K3} 3 mg, V_{B1} 3 mg, V_{B2} 7.5 mg, V_{B6} 4.5 mg, V_{B12} 0.03 mg, V_{B3} 30 mg, V_{B5} 15 mg, V_{B9} 1.5 mg, V_H 0.12 mg, V_{D3}800 IU, Cu 20 mg, Fe 100 mg, Zn 100 mg, Mn 20 mg, I 0.08 mg, Se 0.30 mg and Cr 0.20 mg.

Table S2: Composition levels of Ca/P and 25(OH)D_3 in the basal diet.

Groups	Ca/P (%)	25(OH)D_3
Control group (CG)	0.75/0.592	0 μg
Low calcium group (LCa)	0.65/0.513	0 μg
25(OH)D_3 group (VD)	0.75/0.592	50 μg
Low calcium + 25(OH)D_3 group (LCa+VD)	0.65/0.513	50 μg

RESULTS

Inclusion of 25(OH)D3 and Ca^{2+} in sows' diets and effect on trace elements in sows' blood: The copper content of 25(OH)D3 group was the lowest, and the difference was significant (*P<0.05*) compared with that of low calcium + 25(OH)D3 group, as shown in Fig 1C. The arsenic content of low calcium + 25(OH)D3 group were significantly higher (*P<0.01*) than that of the other three groups which was shown in Fig 1D. Whereas, no significant (*P>0.05*) changes in the content of other trace elements.

Effects of 25(OH)D3 and Ca^{2+} on trace elements in piglets' blood: The low calcium + 25(OH)D3 group significantly reduced (*P<0.05*) the level of chromium in piglets' blood compared with control group as shown in Fig 2A. The changing trend of manganese content was the same as that of chromium which was shown in Fig 2B. The copper content in low calcium + 25(OH)D3 group was significantly higher (*P<0.01*) than that in the other three groups which was shown in Fig 2C. The arsenic content in 25(OH)D3 group was significantly higher (*P<0.05*) than that in low calcium group and low calcium + 25(OH)D3 group (Fig 2D). The content of selenium was significantly elevated (*P<0.01*) in low calcium + 25(OH)D3 group compared to low calcium group which was shown in Fig 2E. The level of cadmium in low calcium + 25(OH)D3 group dramatically declined (P<0.05) compared to control group and 25(OH)D3 group (Fig 2F).

Effects of 25(OH)D3 and Ca^{2+} on trace elements in milk: The control group, low calcium group and 25(OH)D3 group had significant differences (*P<0.01*) in chromium content which was shown in Fig 3A. The chromium content in low calcium + 25(OH)D3 group was significantly lower than that in low calcium group and significantly higher than that in control group respectively (*P<0.01*). The content of manganese in 25(OH)D3 group dramatically declined (P<0.05) compared to low calcium group as shown in Fig 3B. The content of copper in low calcium and 25(OH)D3 group were significantly higher (*P<0.05*) than that in control group, and the copper content in low calcium + 25(OH)D3 group also increased significantly (*P<0.01*) compared to control group (Fig 3C). The level of selenium in control group was significantly lower (*P<0.01*) than that in low calcium group and low calcium + 25(OH)D3 group, and the selenium content in low calcium group was significantly higher (*P<0.05*) than that in low calcium + 25(OH)D3 group which were shown in Fig 3E. The content of cadcium in 25(OH)D3 group was significantly lower (*P<0.05*) compared to control group as shown in Fig 3F, while there was non significantly (*P>0.05*) change in arsenic content.

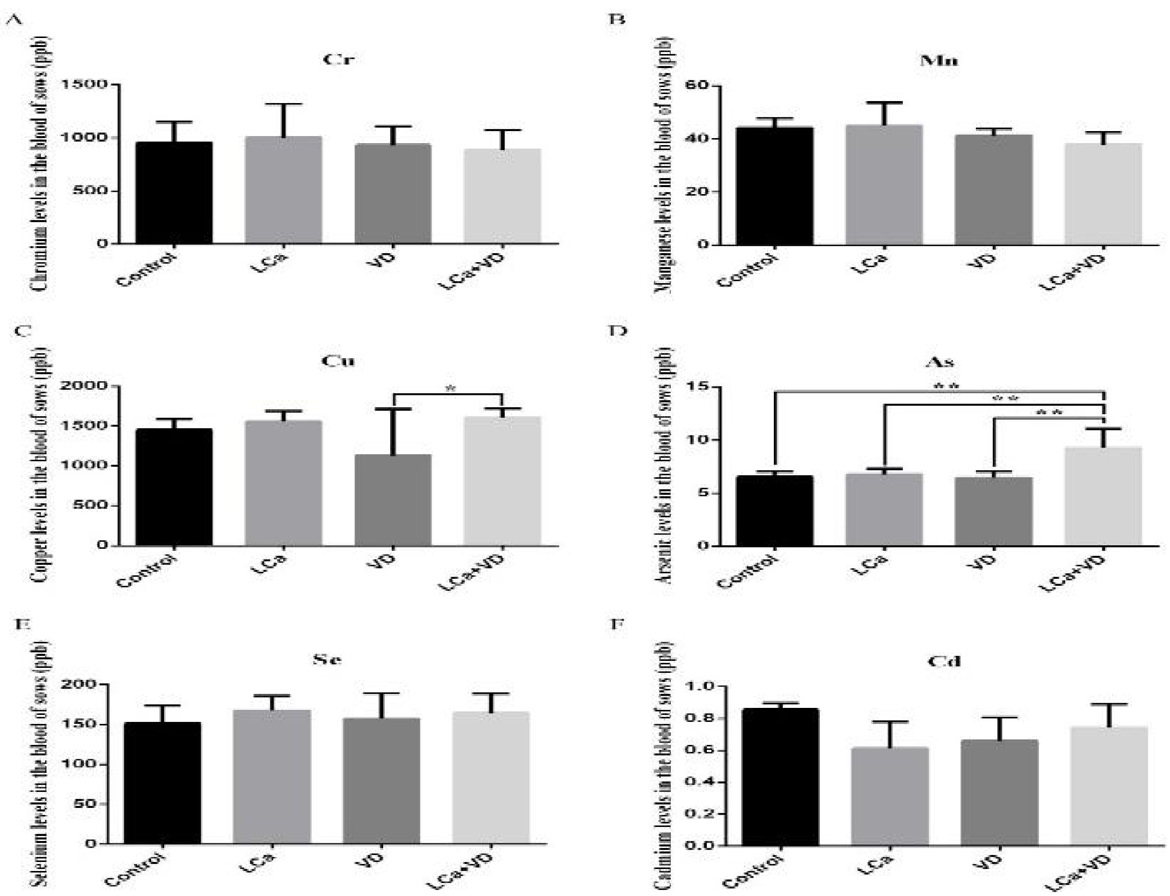

Figure 1: The trace elements of sows' blood. Chromium content in sows' blood (A); Manganese content in sows' blood (B); Copper content in sows' blood (C); Arsenic content in sows' blood (D); Selenium content in sows' blood (E); Cadmium content in sows' blood (F). (Control), (LCa), (VD) and (LCa+VD) represent control group, low calcium group, 25(OH)D3 group and low calcium + 25(OH)D3 group, respectively. "*" indicates statistically significant difference between corresponding group (**P<0.05,* ***P<0.01*).

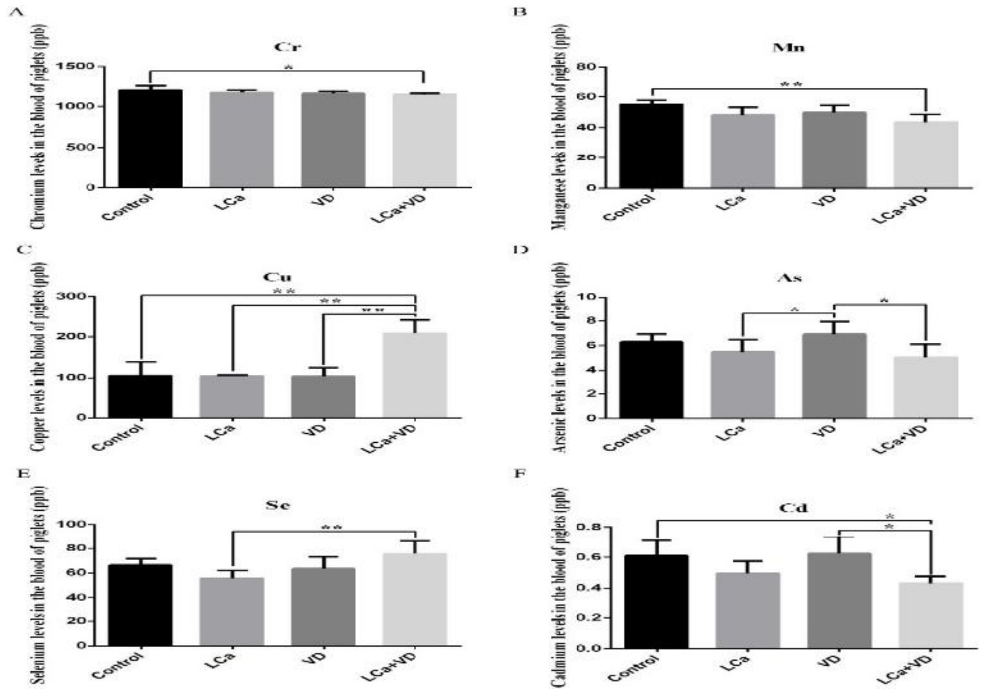

Figure 2: The trace elements of piglets' blood. Chromium content in piglets' blood (A); Manganese content in piglets' blood (B); Copper content in piglets' blood (C); Arsenic content in piglets' blood (D); Selenium content in piglets' blood (E); Cadmium content in piglets' blood (F). (Control), (LCa), (VD) and (LCa+VD) represent control group, low calcium group, 25(OH)D3 group and low calcium + 25(OH)D3 group, respectively. "*" indicates statistically significant difference between corresponding group (P<0.05, **P<0.01*).**

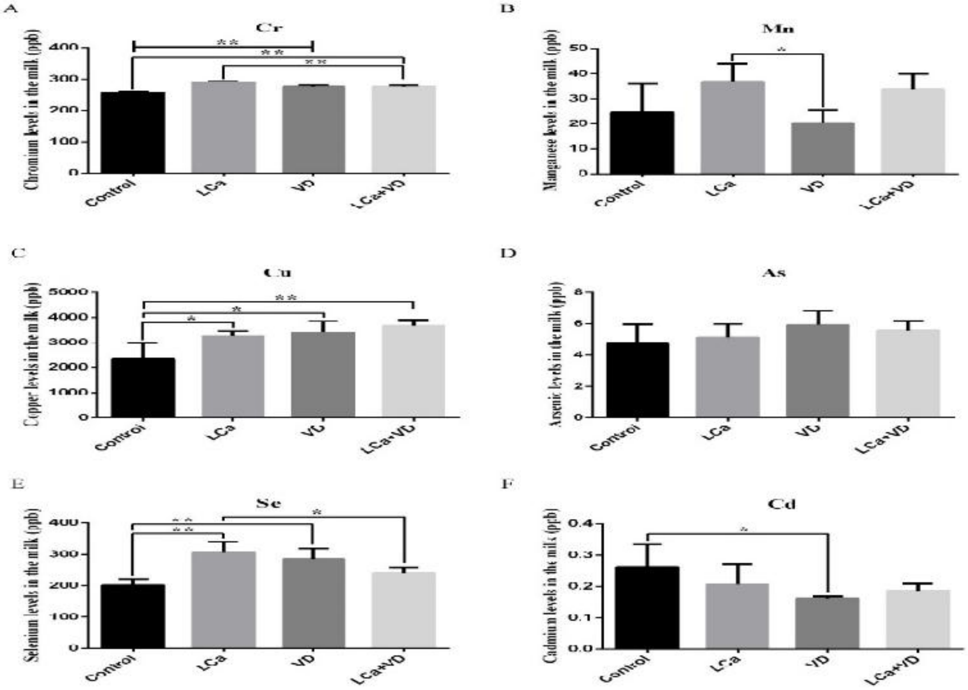

Figure 3: The trace elements of sows' milk. Chromium content in milk (A); Manganese content in milk (B); Copper content in milk (C); Arsenic content in milk (D); Selenium content in milk (E); Cadmium content in milk (F). (Control), (LCa), (VD) and (LCa+VD) represent control group, low calcium group, 25(OH)D3 group and low calcium + 25(OH)D3 group, respectively. "*" indicates statistically significant difference between corresponding group (P<0.05, **P<0.01*).**

DISCUSSION

Although the body needs little chromium, but it plays an important physiological role in health. Studies have found that chromium is essential for glucose metabolism, and the chromium content in pregnant women is related to the occurrence of diabetes during pregnancy (Jiang *et al*., 2004). For pigs, the proper addition of chromium in the feed can accelerate the sugar, fat, protein and nucleic acid metabolism of sows, promote follicular development and increase the litter size of sows, and promotes the secretion of milk (Liu *et al*., 2017). Therefore, maintaining a proper amount of chromium in the blood of sows is beneficial to improve the reproductive performance of sows and the growth performance of piglets. Some scholars also believe that right amount of chromium can improves the meat quality of pigs, which can boost the sales value (Jin *et al*., 2018). According to the results of present study, the addition of low calcium and 25(OH)D3 had no significant effect on chromium content in sows' blood, but had a significant impact on chromium content in milk, it proved that reducing calcium content and adding 25(OH)D3 in diets can increase the content of chromium in sows' milk, but the increase of chromium in low calcium group may be unhealthy. 25(OH)D3 can also significantly reduce the chromium content in milk of low calcium group, it shows that 25(OH)D3 can inhibit the abnormal increase of chromium due to low calcium diet. On the other hand, the change of chromium content in piglets' blood may be caused by maternal level. Therefore, the addition of 25(OH)D3 can improve the content of chromium in sows' milk.

Manganese is the activator of various enzymes and participates in the transport of nutrients and scavenge free radicals through the effect of manganese superoxide dismutase, ultimately provide antioxidant protection (Yang *et al*., 2019). Maternal manganese deficiency or excess can easily lead to fetal nerve damage (Xu *et al*., 2013), In addition, it is the key for the synthesis of chondroitin sulfate, thus affecting the development of bone, and it is worth mentioning that excessive manganese is likely to reduce the litter number of sows and the survival rate of weaned pigs (Xu *et al*., 2010). Excessive manganese will also lead to the occurrence of iron deficiency anemia because of antagonistic relationship between manganese and iron. Studies have shown that the combination of active vitamin D3 with zinc-manganese complex can significantly improve the reproductive performance of sows and increase the piglets' weight gain during lactation (Zhang *et al*., 2018). Therefore, it has great significance to control the balance of manganese content in pregnant sow. According to the analysis of results, the diet of low calcium and 25(OH)D3 did not have a significant effect on the blood manganese content of sows, but manganese content in milk of low calcium group had a rising trend, which may be caused by the antagonism of calcium and manganese. The content of manganese in 25(OH)D3 group was significantly lower than that in low calcium group, however, there was no difference between the other two groups, indicating that low calcium can increase manganese content in milk. Under the combination of low calcium and 25(OH)D3, piglets had much less manganese in their blood compared to control group, due to the antagonistic relationship between calcium and manganese, this change is more likely to be caused by 25(OH)D3.

Copper-containing enzymes plays an important physiological role in the body, such as formation of hemoglobin, maintaining cellular respiration, balancing sugar and lipid metabolism, and affecting immune function (Stern *et al*., 2007). In recent years, copper has been widely used in animal husbandry, increase of copper content can promote the growth of pigs, improve the carcass quality of fattening pigs and the production performance of sows (Zhu *et al*., 2013; Coble *et al*., 2017). Copper can also enhance the humoral immunity of piglets and the oxidation resistance of blood. However, excessive copper can lead to copper poisoning, causing liver and kidney damage, while the piglets suckling milk with high copper content can affect the development of bone, viscera and nervous system. It can be seen from the experimental results that reducing the calcium content alone did not affect the copper content in sows' blood, but adding 25(OH)D3 alone could significantly reduce the copper content in sows' blood. Both low calcium and 25(OH)D3 had the effect of increasing copper content in milk. In terms of copper content in piglets' blood, copper content in low calcium group and 25(OH)D3 group did not change, but under the combined action of the two, copper content was significantly higher than that in the other three groups, this may be due to maternal inheritance.

Arsenic was known to be highly toxic and excessive levels can cause serious damage to the body, exposure to excessive amounts of arsenic in pregnant women may have an impact on the brain development of the fetus (Caldwell *et al*., 2015). On the other hand, arsenic is one of the essential trace elements in the body. Arsenic in moderation is good for hemoglobin synthesis, growth and development, and immunity. Some studies have found that adding a certain amount of organic arsenic in basic diet can significantly increase the daily weight gain of pigs, improve skin quality and reduce the rate of diarrhea (Long *et al*., 2000). The dietary changes of calcium and 25(OH)D3 alone did not affect the blood arsenic level in sows, however, arsenic content increased significantly under the combined action. Compared with control group, the blood arsenic content of piglets in low calcium group showed a decreasing trend, but there was no significant difference yet, the blood arsenic content in

25(OH)D3 group was significantly higher than that of low calcium group and low calcium + 25(OH)D3 group, indicating that 25(OH)D3 may have effect on increasing arsenic content in blood of piglets.

Selenium is involved in the formation of many enzymes, especially the component of glutathione, the amount of selenium in the body is closely related to the antioxidant mechanisms (Brumaghim *et al.,* 2009). At the same time, selenium can antagonize heavy metal elements such as lead, arsenic, chromium, and promotes the absorption of vitamin A and vitamin E (Schrauzer *et al*., 2009). The lack of selenium in pigs can affect sperm quality in boars, which can reduce the conception rate of sows (Zhou *et al*., 2017), selenium deficiency in sows can easily lead to irregular estrus and an increase the number of stillborn and weak fetuses (Zhao *et al*., 2008). In addition, selenium deficiency in newborn piglets will affect the development of skeletal muscle and physiological metabolism, which can cause death (Song *et al*., 2005). The study has found that adding an appropriate amount of organic selenium in sows' diet could promote the growth of embryos in the early stage of pregnancy and improve the reproductive performance of sows (Eleanor and McCartney *et al*., 2006). In this experiment, there was no significant change in blood selenium levels of sow. In the blood of piglets, adding 25(OH)D3 with low calcium can significantly improve selenium content, proving that 25(OH)D3 may have the effect on increasing selenium content. Although, the selenium content in sow's blood did not change much, but selenium content in milk of each group had significant differences. Firstly, the selenium content in milk of low calcium group and 25(OH)D3 group were significantly higher than that of control group, which indicated that low calcium may lead to the increase of selenium content in sows' milk to compensate the deficiency of calcium. 25(OH)D3 can significantly increase selenium content in milk, while adding 25(OH)D3 to low calcium group could inhibit the excessive increase of selenium in milk. This prove that 25(OH)D3 is not only a single factor that increases selenium levels but also play a role in maintaining selenium balance.

Cadmium is a kind of environmental pollutant, which is not a necessary trace element for the body. Cadmium can affect the level of progesterone in sows, reduce pregnancy rate, inhibit growth hormone and lead to developmental disorders. Cadmium can also induce apoptosis of renal tubular epithelial cells thus cause kidney damage (Ren *et al*., 2004). Other studies have found that cadmium can reduce the activity of oxidase in testis supporting cells of pigs and affect reproductive function of boars (Zhang *et al*., 2019). Excessive amounts of cadmium can lead to starvation, diarrhea, anemia and even death in pigs. We can observe that there was no significant difference in cadmium content in sows' blood, 25(OH)D3 could effectively reduce cadmium content in milk. The addition of low calcium and 25(OH)D3 alone did not change cadmium content in piglets' blood, but the combination of the two can effectively reduce the cadmium level.

Changes in calcium content and the addition of 25(OH)D3 can affect the trace element levels in the blood and milk of sows, which lead to changes in the trace element of the fetus, and various physiological reactions of the fetus. It has great value to detect the content of other trace elements for exploring the role of calcium and 25(OH)D3 in maintaining the balance of trace element. Based on the results of this study, it is concluded that changes in calcium content may directly affect the content of other trace elements, especially in the fetus and milk. Altogether, adding appropriate amount of 25(OH)D3 is beneficial to improve the performance of sows along with fetal growth and development.

Novelty of this study: Changes in calcium content and the addition of 25(OH)D3 can affect the trace element levels of sows and their milk, which lead to changes in the trace element of the fetus, and various physiological reactions of the fetus. This study examined the changes of six trace elements, but still has great value to detect the content of other trace elements to explore the role of calcium and 25(OH)D3 in maintaining the balance of trace element environment. Altogether, adding appropriate amount of 25(OH)D3 is beneficial to improve the performance of sows along with fetal growth and development.

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