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Research Article
Multinutrients from Local Cattle Bone Marrow in Central Sulawesi of Indonesia Have the Potential to Improve the Successful Pregnancy Rate and Prevent Slowing of Fetal Kidney Growth

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Abstract
Background and Objective: The results of previous studies have indicated that undernutrition that occurs during pregnancy can result in the slowing of fetal growth. Intrauterine growth retardation (IUGR) caused by malnutrition will have a negative effect on organogenesis, including kidney growth (nephrogenesis). This study aimed to evaluate the potency of bone marrow obtained from a local beef livestock practice in Central Sulawesi of Indonesia to increase the success of pregnancy and to prevent the slowing of fetal kidney growth during pregnancy. **Materials and Methods:** This experimental laboratory study with animal models used a complete randomized design (CRD) with a single factor. The bone marrow was obtained from the Tawanjuka Palu slaughterhouse of Central Sulawesi in Indonesia. A standard feed, an intrauterine growth retardation feed and a substitution isocaloric feed with bone marrow were formulated. The intervention was applied to rats during pregnancy with the feed available *ad libitum*. After birth, the offspring underwent lactation until the age of 22 days and then weaned and given standard feed. At the age of 30 days, the kidneys were removed and weighed. The kidney weight data were analyzed using a descriptive statistical test and a Wilcoxon test using SPSS version 23. **Results:** The results of the descriptive analysis indicate that there was a positive trend in response to the feed with the bone marrow but Wilcoxon analysis showed no significant difference in kidney weight between the control and intervention groups. **Conclusion:** Feed formulations containing bone marrow from local cattle have the potential to prevent slowing of kidney growth during pregnancy and increase the success of pregnancy.

Key words: Local beef, local cattle bone marrow, mother's nutrition, slowing kidney growth, successful pregnancy

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

The quality and quantity of the mother's nutritional intake will affect her fertility, duration of pregnancy and the health of the child to be born[1]. In addition, researchers have studied the relationship between nutrition during early pregnancy and intrauterine growth with the health of the offspring throughout childhood and adulthood. Previous animal models have shown that providing mice with less nutrition during pregnancy has an impact on the growth of their fetuses. The impact of malnutrition causes the fetus to adapt to the environment. Malnutrition in utero can affect organ/tissue growth and the altered organs and tissues that form will be present throughout adulthood; this event is called programming[2]. Although, adaptations occurring during fetal growth make it possible for the offspring to survive, the disruption of growth during pregnancy results in long-term consequences for the cardiovascular, renal, metabolic, respiratory and endocrine systems[3,4].

Wang *et al.*[5] found no apparent malformations in renal samples from a fetal growth restriction (FGR) group but the mean renal weight was significantly lower between the FGR and standard feeding groups because FGR contributed to increased apoptosis and decreased renin and angiotensinogen expression during kidney development[5]. Maternal protein restriction can reduce the number of nephrons in offspring whose mothers are fed a low-protein formula during pregnancy but this does not affect blood pressure or cause hyperfiltration in adulthood. These deficits can lead to the kidneys being more susceptible to kidney disease and diabetes[6].

Hypertension in adulthood is something that can be programmed during prenatal growth due to an environment that does not support proper growth of the fetus and this has been observed in both humans and experimental animals. Obstructed fetal growth causes a decrease in the number of nephrons, which in turn leads to increased pressure on glomerular capillaries and the development of glomerular sclerosis. This sclerosis leads to loss of nephrons and ongoing hypertensive cycles and progressive cell injury[7]. Research on animals and humans have shown that low intrauterine growth rates are associated with a reduced numbers of nephrons.

Prenatal hypertension is associated with abnormal patterns of intrarenal renin-angiotensin system (RAS) ontogeny that may play roles in the pathogenetic state, for example, by altering renal hemodynamics or Na-reabsorption[8]. The renin-angiotensin system is mediated by a group of proteins that show their highest expression in the developmental phase of the kidney and play a role in kidney growth. The number of nephrons is positively correlated with fetal weight at termination and the kidneys in fetal growth restrictions (FGR) groups exhibit more apoptotic cells than in the non-FGR groups, while the concentrations of renin and angiotensinogen are both decreased in the FGR groups. In addition, evaluation with ultrasound indicates that the kidney size in FGR groups is smaller than in the non FGR [9]. The analysis of the bone marrow composition of Donggala and Bali's semi-intensive and traditional cattle industry indicated that marrow from both breeds of cattle raised in either way contains sufficient nutrients to support the growth of a fetus during pregnancy. The main components of the marrow are total fat 82.35-94.71%, protein 1.93-3.64% and carbohydrates 0.78-4.09%. Bone marrow fat is a source of essential fatty acids such as omega 3 fatty acids (0.55-0.63%), omega 6 (1.41-1.57%), AA (0.04-0.06%), DHA (0.008-0.012%), EPA (0.00974-0.017%), oleic acid (23.67-33.72%), linoleic acid (1.33-1.49%), linolenic acid (0.53-0.62%) and cholesterol (461-769 mg/100 g). Previous research has suggested that fatty acids are essential in the process of growth and cell metabolism, maintaining the fluidity and permeability of cell membranes. Fatty acids are also involved in the processes of energy metabolism, synthesis of protein and carbohydrates and regulation of gene expression in cells. Other functions of fatty acids that have been identified are acting as precursors of prostacyclin, prostaglandin, thromboxane and leukotriene[10].

Bone marrow contains amino acids such as histidine, threonine, proline, tyrosine, leucine, aspartic acid, lysine, glycine, arginine, alanine, valine, isoleucine, phenylalanine, glutamic acid and serine. Amino acids are needed during pregnancy for the translation process (protein synthesis), the process of interconverting proteins into other substrates and the oxidation process[11].

Micronutrients such as vitamins and minerals are also contained in bone marrow; they include vitamins A, D, E, K and the minerals Ca, Mg, Fe, P, Zn, Se and Mn. Vitamins and minerals are needed during pregnancy to support maternal health and fetal development through an integrated process throughout the parent compartment, placenta and fetus[12].

The macro and micronutrient content of marrow, as mentioned above, has potential if substituted into the feed to stimulate the fetal nephrogenesis process. This study evaluated the effect of a local beef bone marrow substitution intervention feed during pregnancy on kidney growth in Sprague Dawley rat offspring.

MATERIALS AND METHODS

Design, place and time: This study is an experimental study that uses an animal model and a complete randomized design. The grouping of mother rats was based on the type of feed provided: normal food formulation (NFF), intrauterine growth retardation feed formulation (IUGRFF), semi-intensive Donggala bone marrow feed formulation (SIDFF), traditional Donggala bone marrow feed formulation (TDFF), semi-intensive Bali bone marrow feed formulation (SIBFF) and traditional Bali bone marrow feed formulation (TBFF). The offspring used for each group were selected as those from rats who gave birth to 12 pups.

The bone marrow was obtained from the Tawanjuka Palu slaughterhouse of Central Sulawesi in Indonesia on February 2, 2017. Its nutrient composition were analyzed at Saraswanti Indo Genetech (SIG)-Bogor on March 15, 2017; isocaloric feed formulation was carried out in the nutrition laboratory of the Formulation Faculty of Fisheries Bogor Agricultural University. The intervention of the study was conducted at the Laboratory of Animal Assay, Animal Hospital of Bogor Agricultural University, from December 2017 until April 2018. The stages were an adaptation period of ten days followed by breeding, pregnancy, birth and 30 days postnatal. When the offspring reached 30 days of age, their kidneys were removed for analysis.

This study received approval from the Ethics Commission of the Faculty of Veterinary Medicine Bogor Agricultural University with SKEH Number: 077/KEH/SKE/XII/2017.

This experimental study used Sprague-Dawley male (20) and female rats (50), aged eight weeks with a weight between 150-200 g, from the Tropical Biopharmaca Study Center of Bogor Agricultural University (the number: F-RM/ UKHP-15/02/00).

In addition, the other materials used in the study were mineral water, feed from Indo Feed Bogor, the feed intervention, ketamine-xylazine and a 10% BNF (buffer normal formaldehyde) solution. The tools included 35 rat cages, bedding (sterile wood shavings obtained through an oven process), rat drinking bottles, metal surgical equipment (stainless steel), tubes to hold organs and electronic weight scales.

Preparation of the normal and intervention feed: In this study, the feed formulation referred to a previous study[13] and considered the total fat concentration of the bone marrow, the daily total fat requirement of Indonesian women during pregnancy[14] and the daily fat requirement in the pregnant rat. Both the normal and treatment feeds during pregnancy were made to be isocaloric. The feed formulations in this study were as follows:

Preparation of experimental animals: The number of female rats chosen to be mated in this study was selected using the Federer formula on Purwanto (2016), which was (t-1) (n-1) $\geq$15, where t was the number of the groups and n was the number of experimental animals per group[15].

Base on the equation, the number of mother rats that must be pregnant and give birth is five for each treatment. In this study, there were six groups (one control and five treatments) so the number of female rats was at least thirty. In addition, with anticipation of failures in the process of breeding and pregnancy the number of rats prepared for this study were fifty females and twenty males. The method of breeding was divided into three stages; the first stage was conducted on December 19th, 2017, when twenty-four females were mated with twelve male rats. After that, the second stage was held on December 26th, 2017, when we mated sixteen females and eight males and the third stage on January 8, 2018, when we mated ten females and five males. The process of mating is conducted by combining the females and males in 1 cage with a ratio of 1 male: 2 females. The weight when mated was 165-205 g for the female and 236-280 g for the male.

Considering Federer's terms and the progress of the mating process in this study, the experimental rats consisted of nine females for the control (NFF), nine females for the IUGRFF treatment, eight females for the SITFF treatment, eight females for the TDFF treatment, eight females for the SIBFF treatment and the remaining females for the TBFF treatment. The feed was given *ad libitum*, starting on the day the female was positively pregnant (the vagina closed) and continuing throughout the pregnancy. The mother rats were weighed every three days to monitor their growth until birth occurred. After the lactation process for 22 days, the offspring were weaned and then dissected at the age of 30 days.

The rat's dissection was carried out by randomly taking three rat pups from the control and each treatment group. The kidney weights were recorded. The kidney weights of the offspring were analyzed descriptively and the significance of the differences between the control and treatments were examined by nonparametric Wilcoxon tests (SPSS version 23).

RESULTS

Successful pregnancy and number of offspring born: The success of the rat breeding program was determined by the ratio of the number of female rats mated to the number of rats that successfully became pregnant and gave birth. Based on these calculations, the success of mating for the control and treatment groups in this study were as follows:

Table 1: The formulation and composition of the normal and intervention feed

	Feed composition at g kg^{-1} during pregnancy					
Composition	Control/NFF	IUGRFF	SIDFF	TDFF	SIBFF	TDFF
Casein	180	90	178.07*	177.58*	176.97*	176.36*
Marrow protein	0	0	1.93	2.42	3.03	3.64
Folic acid	1	1	1	1	1	1
Cornstarch	425	482	424.37*	424.36*	422.305*	421.46*
Marrow carbohydrate	0	0	0.63	0.64	2.695	3.54
Sucrose	213	243	213	213	213	213
Choline	2	2	2	2	2	2
DL-Methionine	5	5	5	5	5	5
Vitamins[1]	5	5	5	5	5	5
Minerals[2]	20	20	20	20	20	20
Cellulose	50	50	50	50	50	50
Corn oil	100	100	18.31*	18.22*	15.51*	13.4*
Marrow	0	0	81.63	81.78	84.49	86.60

The composition of these formulations were developed based on previous research[13].*Determined based on the protein, carbohydrate and fat in the bone marrow, 1: Vitamin mix, 2: Mineral mix, NFF: Normal feed formulation, IUGRFF: Intrauterine growth retardation feed formulation, SIDFF: Semi-intensive Donggala bone marrow feed formulation, TDFF: Traditional Donggala bone marrow feed formulation, SIBFF: Semi-intensive Balinese bone marrow feed formulation, TBFF: Traditional Balinese bone marrow feed formulation (TBFF)

Table 2: The success of breeding and the average number of offspring born

Treatments	No. mated	No. of successful pregnancies and delivery	The success of breeding (%)	No. of offspring (mean±SD)
NFF	9	7	77.77	11.14±1.9587
IUGRFF	9	6	66.66	11.66±0.4364
SIDFF	8	6	75.00	12.83±0.6362
TDFF	8	7	87.50	12.16±0.9880
SIBFF	8	7	87.50	12.14±1.2454
TBFF	8	7	87.50	12.37±2.6692

NFF: Normal feed formulation, IUGRFF: Intrauterine growth retardation feed formulation, SIDFF: Semi-intensive Donggala beef bone marrow feed formulation, TDFF: Traditional Donggala beef bone marrow feed formulation, SIBFF: Semi-intensive Bali beef bone marrow feed formulation, TBFF: Traditional Bali beef bone marrow feed

As shown in Table 2, the normal and intervention feeds affected the success of mating rats and the number of offspring. Mothers that were given the semi-intensive and traditional bone marrow feed formulation of Donggala and Bali cattle had higher successful mating rates and a larger average number of offspring than the normal feed and IUGRFF groups.

The weight of the kidneys at 30 days old: The mean kidney weights of the offspring whose mothers were fed with NFF, SIDFF, TDFF, SIBFF and TBFF are shown in Table 3.

The results of the normality tests (Shapiro-Wilk) of the differences in renal weight are shown in Table 3. The data are not normally distributed, namely, the differences in the weights of the kidneys from offspring whose mothers were fed IUGRFF and TDFF had a significant value <0.05. Therefore, a comparative analysis was performed using the Wilcoxon nonparametric test.

According to the Wilcoxon analysis shown in Table 4, there were no significant differences in the mean kidney weights (α>0.05). Although the nonparametric statistical test did not show a significant difference, the descriptive-test showed a positive trend of the feed formulations given to the mother rat on the growth of these organs (Fig. 1).

Figure 1 shows that the heaviest 30-day kidneys occurred in pups whose mothers were fed SIBFF, followed by offspring from mothers fed with SIDFF, TDFF, TBFF and FMN and the lowest weights were found in the pups whose mothers were fed IUGRFF.

In Fig. 1, it can be seen that feeding the mothers with IUGRFF (low casein 9%) affected kidney growth compared with the offspring of rats fed normal feed (casein 18%). Meanwhile, the offspring whose parents were given the formulations containing bone marrow from Donggala and Balinese cattle influenced kidney growth and therefore, their kidney weights were higher than the kidney weights of offspring from mothers given normal feed or IUGRFF.

DISCUSSION

The formulation and composition of the normal and intervention feeds: The normal feed and intervention feed formulations are shown in Table 1. Their composition was based on the development of formulations done previously[13]. The normal feed formulation (NFF) and the intrauterine growth retardation feed formulation (IUGRFF) differ primarily in the amount of protein. The composition of NFF contains 180 g of protein per kg (18%) while the IUGRFF contains 90 g of protein per kg (9%). The results of previous studies have shown that a low-protein feed has an adverse effect on kidney cell proliferation[16]. The feed formulations (SIDFF, TDFF, SIBFF, TDFF) are the semi-intensive and traditional feed substitutes using the Donggala and Balinese beef bone marrow from Central Sulawesi-Indonesia. The substitution was done by referring to the highest nutritional component in the marrow, namely, total fat. The amount of marrow added is based on the total fat requirements of Indonesian pregnant women[14] and the total fat concentration of each marrow.

After obtaining the amount of marrow that is needed, it is converted into the feed needs of the model rat/day. Based on these calculations, we arrived at the composition and formulation of the feed as presented in Table 1.

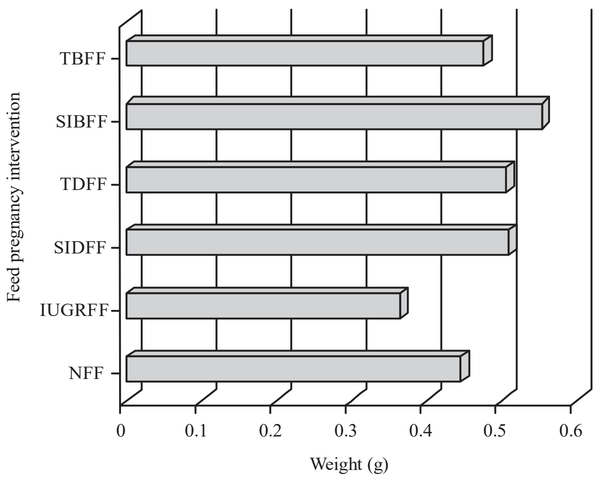

Fig. 1: The average kidney weights of 30-day-old offspring whose mothers were fed NFF: Normal feed formulation, IUGRFF: Intrauterine growth retardation feed formulation, SIDFF: Semi-intensive Donggala beef bone-marrow feed formulation, TDFF: Traditional Donggala beef bone marrow feed formulation, SIBFF: Semi-intensive Bali beef bone marrow feed formulation and TBFF: Traditional Bali beef bone marrow feed formulation

Table 3: Mean weights of the kidneys of offspring whose mothers were fed NFF, SIDFF, TDFF, SIBFF, or TBFF

Treatments	Mean±SD
NFF	0.436±0.0472
IUGRFF	0.363±0.0115
SIDFF	0.510±0.0300
TDFF	0.506±0.0230
SIBFF	0,553±0.0208
TBFF	0.486±0.0152

The role of marrow macro and micronutrients in increasing pregnancy success and fetal kidney growth: As previously mentioned, researchers have shown that a diet enriched in saturated or unsaturated fatty acids can alter serum steroid concentrations in some species including rodents, food animals and humans[17]. PUFA supplementation can increase the length of pregnancy[18], change the composition of the ovarian follicles and increase the number of follicles[19,] induce ovulation[20] and increase mitochondrial synthesis[21]. During pregnancy, the accumulation of omega-3 fatty acids in the mother will continue to decrease as they are selectively transferred to the fetus for brain and retina growth during pregnancy[22]. The composition of food ingredients consumed during pregnancy, especially fatty acids, will affect some aspects related to the reproductive process such as the maturation process of the oocytes and the timing of ovulation[23], t he production of chemoattractants[24] and

Table 4: Analysis of the average weight of kidneys from the offspring of mothers fed NFF, SIDFF, TDFF, SIBFF, or TBFF

The average weights of the kidneys compared		Asymp. Sig.	
NFF	IUGRFF	0.102	Not significant
	SIDFF	0.109	Not significant
	TDFF	0.109	Not significant
	SIBFF	0.109	Not significant
	TBFF	0.157	Not significant
IUGRFF	SIDFF	0.109	Not significant
	TDFF	0.102	Not significant
	SIBFF	0.109	Not significant
	TBFF	0.102	Not significant
SIDFF	TDFF	1.000	Not significant
	SIBFF	0.102	Not significant
	TDFF	0.157	Not significant
TDFF	SIBFF	0.102	Not significant
	TDFF	0.109	Not significant
SIBFF	TDFF	0.102	Not significant

prostaglandin synthesis, the properties of the reproductive tract and the ability to achieve fertilization and the offspring's sex ratio[25].

The bone marrow contains a high amount of oleic acid (23.6-34.69%) and previous studies have indicated that oleic acid has several potential uses, such as decreasing renal and hepatic dysfunction and reducing nonesterified triglycerides in septic rats[26]. Essential fatty acids contained in the marrow are indispensable components in the process of organogenesis because the process of growth requires the process of cell proliferation and each division is followed by the formation of cell membranes and new organelles. According to Swanson *et al.*[27], DHA is a key component of all cell membranes and is found in abundance in the brain and retina.

Amino acids contribute to the translation process to produce important proteins such as receptors, hormones and enzymes needed during growth. One of the amino acids that contributes to fetal growth is arginine. This amino acid is the precursor of the synthesis of nitrogen oxide (NO) after catalysis by the nitric oxide synthase enzyme and NO is a potent vasodilator that causes relaxation in the blood vessels, thus optimizing blood flow to the placenta[28]. During pregnancy, NO plays an important role in the adaptation of the heart and vasodilation of the blood flow circulation system within the uterus and fetoplacental unit and modulates the myogenic tone in the mesenteric and uterine arteries. In addition, NO is also responsible for reducing peripheral resistance in pregnant women[29]. According to Al-Bayati[30], NO produced from cellular enzymatic catalysis can increase the blood supply, repair and improve some phenotypes in animal reproduction models and increase fetal viability. Histologic and stereological profiles that describe the activity and enlargement of the placental layer are associated with enhancement of maternal blood circulation, angiogenesis and vasodilation processes that have implications for increasing the placental weight[30].

Recent studies have shown that vitamin A participates in signaling mechanisms to initiate meiosis in female gonads during embryogenesis[31]. Vitamin D plays a vital role in CYP27B and VDR expression during placental development in early stages of pregnancy and then vitamin D and Ca are needed during pregnancy to prevent or reduce the risk of preeclampsia[32]. Vitamin E deficiency (α-tocopherol) may cause an early failure of pregnancy because it is used to protect essential fatty acids from oxidative damage during embryogenesis, as shown in *in vitro* and animal model studies. Vitamin E plays a role in increasing enzyme induction, cellular signaling and cellular membrane integrity. The possibility of α-tocopherol phosphorylation has been considered to promote placental vascularization and is also suspected to improve the expression of angiogenetic molecules such as vascular endothelial factor (VEGF)[33]. In this study, the bone marrow of Donggala and Bali cattle contained vitamin E between 0.74-1.55 mcg/100 g (Tangkas, 2017 not yet published) and this would be expected to contribute to optimizing the growth and development of the fetus during pregnancy.

Although, vitamin K deficiency rarely occurs, it can lead to fetal bleeding, especially intracranial hemorrhage, because all vitamin K in the fetus is obtained from the mother. When the mother has a nutritional disorder that results in vitamin K deficiency, the fetus will also have vitamin K deficiency[34]. The results of bone marrow analysis of Donggala and Bali cattle show it contains vitamin K between 19.64-34.73 mcg/100 g (Tangkas, 2017 not yet published). The content of vitamin K is expected to enhance the concentration of vitamin K available to the mother and fetus during pregnancy.

Moreover, some micronutrients are known to play an essential role in lowering oxidative stress levels during pregnancy, for example, selenium is known to be an activator of glutathione peroxidase and it has antioxidant properties that can reduce the risk of miscarriage and preeclampsia. Cu, Zn and Mn are essential activators of superoxide dismutase (SOD) enzymes that eliminate pathologies in pregnancy[29].

Previous studies support the results of this study, Hoppe *et al.*[35] found that offspring from Sprague-Dawley parents who were fed a low-protein diet (8%) two weeks before, during and two weeks after pregnancy had a lower renal weight at 19 weeks of age than the weight of kidneys of the offspring from parents fed normal diets (casein 20%). Meanwhile, Lim *et al.*[36] found that the offspring of Wistar-Kyoto fed a low-protein feed (casein 8.7%) 2 weeks before, during and two weeks after pregnancy had a lower renal weight at 32 weeks of age than offspring whose mothers were fed a protein feed normal (casein 20%). Male Wistar-Kyoto offspring whose mothers were given a low-protein feed (casein 8.7%) two weeks before, during and two weeks after pregnancy had a lower renal volume and a lower number of nephrons at four weeks of age than offspring from mothers who consumed normal feed (casein 20%)[37]. The results of these previous studies are indicative that a low-protein feed intervention induces the slowing of kidney growth. When compared with the results on Table 3 and Fig. 1 of the research obtained in this study, it can be seen that the macro- and micronutrient content of Donggala and Bali cattle bone marrow obtained from animals kept under semi-intensive or traditional practices has the potential to prevent kidney intrauterine growth retardation.

CONCLUSION

A feed formulation substituted with the bone marrow of Donggala and Bali cattle raised under semi-intensive or traditional methods has the potential to improve the success rate of pregnancy and prevent the slowing of kidney growth during pregnancy.

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