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Meta-analysis–Effect of bypass fat supplementation on productivity, blood parameters and reproductive performance in ruminant

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ABSTRACT

Fat supplementation in cattle has shown variable results across studies. The objective of this meta-analysis was to evaluate the effects of bypass fat supplementation compared to control on productivity, blood parameters, and reproduction in cattle. This meta-analysis evaluated data from studies examining reproductive performance (n=47), productivity (n=41), and blood parameters (n=65) in cattle receiving bypass fat supplementation. The methodological approach used included systematic literature research, selection criteria, data extraction, and comprehensive statistical analysis consisting of heterogeneity, effect size, publication bias, trimfill, and meta-regression tests using R Studio. The results of the meta-analysis showed significant effects of blood parameters, productivity, and reproductive parameters in response to bypass fat supplementation. Analysis of blood parameters showed changes in profile, decreased triglyceride and glucose concentrations, and significantly increased cholesterol levels. Production parameters showed variable responses, with significant increases in body condition scores, while body weight was unaffected. Reproductive parameters showed variable results, with significant increases in service per conception (S/C) and days open, while conception rates showed no significant changes. The study concluded that bypass fat supplementation effectively improves cattle performance through improving reproductive parameters, production, and blood profile.

Introduction

In early lactation, nutrient requirements increase rapidly to support milk production, while feed intake decreases. The latter condition results in a negative energy balance, which causes low blood parameters such as glucose to compensate for the energy deficit (Sundrum, 2015). Nutrient requirements for lactogenesis in early lactation increase because cows experience a period of negative energy balance, which has a direct impact on decreased body condition due to the mobilization of body reserves (Rutherford *et al*., 2016). Negative energy balance is a metabolic energy condition that affects reproductive efficiency and productivity. Energy requirements after the calving phase in cows increase up to 2.5 times (Macmillan *et al*., 2020). Energy balance in high-producing cows has a significant effect on follicle growth and development, which is associated with measurable changes in energy metabolites and hormones (Song *et al*., 2021). Lack of available energy in the diet not only often limits milk production and milk component production, but also reduces reproductive performance and prevents weight replacement (Folnožić *et al*. 2019; Đuričić *et al*. 2020). Supplementation with dietary fat has been identified as an energy requirement for cows. Dietary supplementation with fat improves reproductive parameters by stimulating follicle growth and increasing steroid secretion (Leroy *et al*., 2018).

Bypass fat is a solution to avoid negative energy balance to improve the performance of high-yielding cows without affecting rumen microorganisms which are cellulolytic bacterial activities and are resistant to rumen lipolysis but assimilated in the lower intestine (Sarkar *et al*., 2022). Dietary bypass fat doesnt affect the rumen pH (Cho *et al*. 2024). A stable pH has a positive impact by improving the balance of microorganisms and enhance fermentation efficiency, so that increasing cattle productivity. Bypass fat can reduce the byproducts of feed fermentation in the rumen, such as methane, and improve the efficiency of energy utilization through long-chain fatty acids that can be directly absorbed by the rumen (Park *et al*., 2010). Bypass fat also helps reduce the mobilization of body reserves in early lactation ruminants, resulting in increased body weight and body condition score (BCS) scores (Ranaweera *et al*., 2020). Supplementation of bypass fat in the ration will increase the productivity of lactating cows by reducing the negative energy balance (Singh *et al*., 2014). Bypass fat supplementation increases the transfer of proteins carried by cholesteryl esters, which enhances cholesterol transport and increases HDL cholesterol levels, thus increasing blood cholesterol levels (Lytle *et al*., 2023; de Lima *et al*., 2023). Dietary fat in the diet can increase follicle development by increasing nutrients in the ovarian microenvironment (Guo *et al*., 2017; Grazul-Bilska *et al*., 2019).

In studies discussing bypass fat supplementation, there are differing conclusions as seen in Moriel *et al*. (2012), who reported that bypass fat supplementation had no significant effect on BCS, with a BCS of 4.7 in all groups, while Satapathy *et al*. (2019) reported that bypass fat supplementation had a significant effect on increasing BCS scores at different levels, namely 0 (control), 50, and 100 g, with BCS scores of 3.89, 3.93, and 2.98, respectively. Furthermore, Kang *et al*. (2019) stated that administering rumen-protected fat increased blood cholesterol from 140.4 mg/dl in the control group to 152.9 mg/dl in the treatment group, while the study by Sallam *et al*. (2021) stated that Protected Fat supplementation decreased blood cholesterol levels from 255.64 in the control group to 211.28 in the treatment group.

The results regarding bypass fat supplementation from previous studies have shown inconsistencies in research findings. These inconsistent results make it difficult to draw clear conclusions, which in turn negatively impacts the accuracy of applying these studies in the community and reduces the effectiveness of dairy cow management practices. Therefore, an appropriate method is needed to provide comprehensive conclusions, thus improving the accuracy of research results and providing benefits for the development of practices in the community, as well as for scientific knowledge. Meta-analysis is a solution to evaluate the effect of bypass fat supplementation compared to control and to determine its long-term effects on productivity parameters, blood parameters, and reproduction of ruminant livestock comprehensively.

Materials and methods

Search strategy

Meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. The systematic literature search included international journals were published in leading scientific databases including Scopus, Science Direct, and other relevant academic repositories published from 1990 to 2025 with journals containing related keywords the effect of bypass fat supplementation. The search included combinations of "bypass fat", "rumen protected fat", "calcium soap fatty acids" for the treatment; "services per conception", "days open", "conception rate", "artificial insemination per conception" for reproduction parameters; while "triglycerides", "cholesterol", "glucose" for blood parameters; and "body condition score (BCS)", "body weight" for productivity parameters.

Selection criteria

Studies used in the meta-analysis must meet the inclusion criteria, namely, international journals published between 1990 and 2025 that contain data in the form of mean values for control and treatment groups involving bypass fat supplementation and standard deviation, including the moderator of bypass fat supplementation duration. The meta-analysis included journals with study designs of randomized controlled trials (RCTs) that were divided into two or more groups, with the control group receiving no bypass fat supplementation and the treatment group receiving bypass fat supplementation. The number of subjects was not a limitation in the meta-analysis, but only studies using cattle as research subjects, including dairy cattle, crossbred cattle, and beef cattle, were included in the criteria.

The exclusion criteria were journals published before 1990 and those that were not international journals, journals with review and meta-analysis study designs were included in the excluded journals. This was intended to avoid data duplication and to use only journals with primary data according to the inclusion criteria. Journals with research subjects other than cattle, those lacking control data (i.e., cattle not supplemented with bypass fat), those with only treatment data (i.e., cattle supplemented with bypass fat), and journals that did not include means and standard deviations were excluded. The inclusion and exclusion criteria for this meta-analysis are shown in the PRISMA diagram in Fig 1.

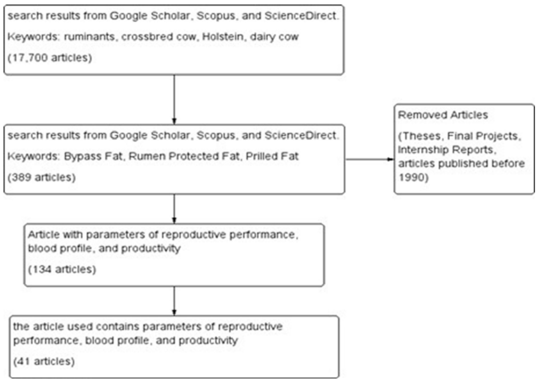

Fig. 1. PRISMA diagram.

Data extraction

Data extraction was carried out by collecting data such as author, mean, standard deviation, and moderators in the form of the duration of bypass fat administration that met the inclusion criteria. The collected data were compiled in a single Excel folder, which was then meta-analyzed using R Studio for statistical analysis. The effect size was assessed using the standardized mean difference (SMD), and heterogeneity in the study was assessed using I^2. The I^2 statistic was used to assess the degree of heterogeneity, which was evaluated using the Cochran's Q test. This assessment involved computing the weighted sum of the squared deviations between the effects observed in individual studies and the overall pooled effect across all studies. The I^2 values range from 0% to 100%. The summary effect is a pooled estimate derived from the effect sizes across multiple independent studies included in the meta-analysis. The summary effect was calculated using a random effects model by calculating the variability in the distribution of the true effect size across the different study populations and settings. Random effects model was used to calculate the within- and between-study variance values and calculate the effect size differences among all studies. Egger's regression test to evaluated publication bias in meta-analysis. The trimfill test serves to estimate missing or unpublished studies by eliminating studies with extreme values and re-estimating the combined effect based on empirical and imputed data. Moderator analysis using meta regression to evaluate duration of supplementation bypass fat in cattle.

Results

Meta-analysis integrated data from multiple studies was discuss effect supplementation bypass fat across reproduction parameters, blood parameters and productivity parameters. A total of 45 journals met the inclusion criteria, comprising 153 studies across all parameters. Reproduction using 47 studies consisting of days open (n=14), service per conception (n=11), conception rates (n=10) and ai per conception (n=12). Blood parameters were evaluating 65 studies consisting of glucose (n=27), cholesterol (n=21), and triglyceride (n=17). Productivity parameters were analysed using 41 studies containing body weight (n=22) and body condition score (n=19). Included studies are listed in Table 1.

BCS and Body Weight

Body weight

Meta-analysis result showed significant effect the supplementation of bypass fat on body weight (ES = -0.0392, 95% CI: -0.1825 to 0.1041, p = 0.5918), with low heterogeneity (I^2 = 4.52%) indicating study in meta-analysis is homogeneous. Potentially 5 missing study in meta-analysis, with trimfill adjusted to no significant effect (ES = -0.1492; 95% CI: -0.4429 to 0.1445; P = 0.3194) supplementation bypass fat in body weight. Meta regression result showed no significant effect (Slope = 0.0055 ± 0.00475; P=0.25), this indicated that duration of bypass fat supplementation has no effect on the body weight cow. The results of the meta-analysis are presented in Table 2 and forest plot are presented in Fig. 2.

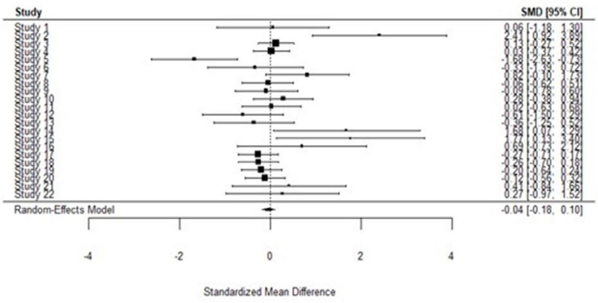

Fig. 2. Forest plot body weight parameters.

BCS

The analysis showed a significant effect of the supplementation of bypass fat on BCS (ES = 0.3803, CI: 0.0278 to 0.7328, p = 0.0345). High heterogeneity was detected indicated study in meta-analysis is various. Publication bias showed potentially 2 missing studies detected (SE = 2.4622), adjusted with trimfill to significant effect (ES = 0.3803; 95% CI: 0.0278 to 0.7328; P = 0.0345), indicated that bypass fat supplementation increases the BCS of cow. The meta regression suggests no effect (slope = 0.0055, SE = 0.00475; P = 0.25) of duration of bypass fat supplementation on cow. The results of the meta-analysis are presented in Table 2 and forest plot are presented in Fig. 3.

Table 1. Summarizing the characteristics of the included studies.

Author	Year	Treatment	Duration of Treatment
Khalil *et al*.	2012	Magnapac	141 days
Chavda *et al*.	2022	Rumen Protected Fat	90 days
Filley *et al*.	2000	calcium salts of fatty acids	30 days
Moriel *et al*.	2012	Megalac-R	30 days
Aguilar-Pérez *et al*.	2009	calcium salts of palm fatty acids	98 days
Satapathy *et al*.	2019	bypass fat	60 days
Garcia *et al*.	2011	Megalac-E®6	56 days
Ylioja *et al*.	2018	BergaFat T-300, Berg	21 days
Liu *et al*.	2020	calcium salts of soybean FA Megalac-E,	28 days
de Souza *et al*.	2017	calcium salts of palm FA Magnapac	91 days
DeFrain *et al*.	2005	Ca soaps of long-chain fatty acids (LCFA, Megalac)	92 days
Jolazadeh *et al*.	2019	Ca-salts of soybean oil	119 days
Burke *et al*.	1997	Menhaden Fish Meal (sea-lac)	88 days
Kang *et al*.	2019	Prilled form of palm oil	10 days
Brzóska	2006	calcium salts of soybean FA Megalac-E and calcium salts of palm FA Magnapac	21 days
Tyagi *et al*.	2010	Bypass Fat	210 days
Woo *et al*.	2024	Protected Fat	112 days
El-Zaiat *et al*.	2020	calcium soap of palm FA	105 days
Sallam *et al*.	2021	Megalac-E®6	84 days
Gandra *et al*.	2014	Calcium salts of fatty acids	112 days
Harvatine *et al*.	2006	LCFA	21 days
Liu *et al*.	2020	BergaFat T-300	28 days
Mohammed *et al*.	2024	extruded flaxseed and salmate	214 days
Bernal-santos *et al*.	2003	Ca-salts of palm fatty acid distillate	154 days
Chen *et al*.	2002	Prilled Fat	21 days
lohrenz *et al*.	2010	Rumen Protected Fat	28 days
Gowda *et al*.	2013	Protected fat	195 days
Schingoethe and Casper	1991	Extruded soybeans and Extruded sunflower	305 days
El-Hamd *et al*.	2012	CSFA	180 days
Badiei *et al*.	2014	Optomega (Optivite Co., Worksop, UK) - rumen protected fish oil	56 and 35 days
Gonzalez *et al*.	2015	Extruded soybeans and Extruded linseed	77 days
Jahani-Moghadam *et al*.	2015	Magnapac	77 days
Roodbari *et al*.	2016	Palm oil (Energizer-RP10, IFFCO, Malaysia) and CLA protected rumen (Lutrell Pure, BASF, Ludwigshafen, Germany)	63 and 42 days
Rahbar *et al*.	2021	Palm oil (unsaturated fattyacids/UFA) and Rumen protected CLA (Lutrell Pure, BASF	81 days
Akhlaghi *et al*.	2019	CSFA and high-palmitic acid (PA)	90 days
Wafa *et al*.	2022	Protected Fat	120 days
Lloyd *et al*.	2002	calcium salts of long-chain fatty acids and megalac	54 days and 123 days
Shike *et al*.	2013	OmegaFlax	108 days
Burke *et al*.	1997	Menhaden Fish Meal (sea-lac)	88 and 82 days
Dirandeh *et al*.	2013	Omegalin	189 days
Moallem *et al*.	1997	CSFA	150 days

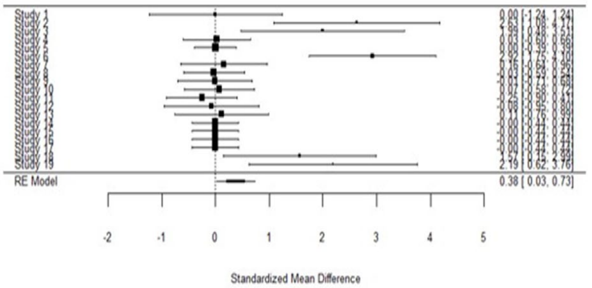

Fig. 3. Forest plot BCS parameters.

Table 2. Meta-analysis body weight and BCS parameters.

Parameters	N	Estimates	P-value[1]	Slope	SE Slope	P-value Slope
BCS	19	0.38	0.38	0.38	0.38	0.38
Body Weight	22	-0.15	-0.15	-0.15	-0.15	-0.15

[1] P-value of meta-analysis

Cholesterol, triglycerides and glucose

Cholesterol

Bypass fat supplementation significantly increased levels of cholesterol (ES = 1.2509; CI: 0.3335 to 2.1682; P = 0.0075) in the blood of cow, with high heterogeneity was detected. No publication bias was observed, with trimfill was adjusted (ES: 1.2509; CI: 0.3335 to 2.1682, p = 0.0075) indicating that bypass fat supplementation effectively increases blood cholesterol in cow. Meta regression showed no significant effect (slope = -0.0038 ± 0.0095 (P=0.691)) of duration of bypass fat supplementation on cholesterol blood cow. The results of the meta-analysis are presented in Table 3 and forest plot are presented in Fig. 4.

Table 3. Meta-analysis cholesterol, triglyceride and glucose parameters.

Parameters	N	Estimates	P-value[1]	Slope	SE Slope	P-value Slope
Cholesterol	21	1.25	0.01	-0.00	0.01	0.69
Triglyceride	17	-0.60	0.06	-0.01	0.00	0.01
Glucose	27	0.12	0.01	-0.00	0.00	0.5

[1] P-value of meta-analysis

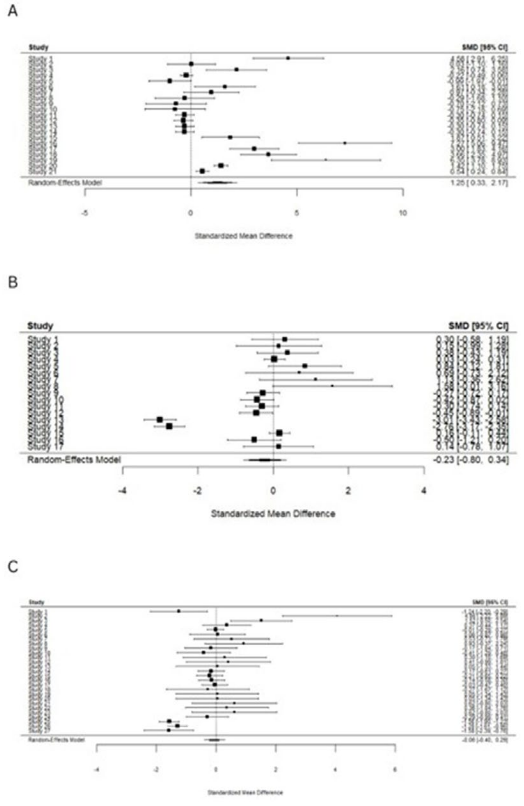

Fig. 4. Forest plot cholesterol, triglyceride and glucose parameters.

Triglycerides

No significant effect of bypass fat supplementation on triglyceride levels (ES = -0.2267; 95% CI: -0.7968 to 0.3434; P = 0.4358). Various studies were observed in heterogeneity (I^2 = 94.73%, P < 0.0001), with trimfill analysis adjusted to significant effect (adjusted ES = -0.6015 CI: -1.1439 to -0.092; P = 0.0592), indicating that bypass fat supplementation reduced triglyceride levels in cow. Significant effect (slope = -0.012 ± 0.0048 (P=0.008)) of duration of bypass fat supplementation on blood triglyceride of cow, suggesting that longer supplementation decrease triglyceride levels in the blood of cow. The results of the meta-analysis are presented in Table 3 and forest plot are presented in Fig. 4

Glucose

No significant effect of bypass fat supplementation on glucose levels in the blood of cow (ES = -0.0551, 95% CI: -0.3982 to 0.2879, p = 0.75), with high heterogeneity was detected in the study (I^2 = 84.22%, p < 0.0001) indicated various across studies. Publication bias detected potentially 8 missing study (SE = 3.3950), with trimfill analysis adjusted to significant effect of supplementation bypass fat (-0.3975, CI: -0.7850 to -0.0099, p = 0.0444) indicating effectively decrease glucose blood levels in cow. No significant effect (slope = -0.002 ± 0.0031 (P=0.509)) of duration of the bypass fat supplementation on glucose blood levels of cow. The results of the meta-analysis are presented in Table 3 and forest plot are presented in Fig. 4.

Service per Conception (S/C), days open and conception rates

Service per Conception

The result of the meta-analysis showed significant effect of bypass fat supplementation on S/C (ES = -1.0160, 95% CI: -1.6759 to -0.3560, p = 0.0026). Heterogeneity test results showed a high of heterogeneity in S/C (I^2 = 97.68%, P<0,0001), suggesting there is considerable variation in treatment effects. Publication bias showed no missing study in S/C (estimate 1 study, SE = 3.0339) in the meta-analysis, with trimfill analysis adjusted to significant effect of bypass fat supplementation 1.2509 (ES = -0.9001, 95% CI: -1.6098 to -0.1903, p = 0.0129) indicating effectively decrease S/C in cow. The analysis indicated supplementation bypasses fat in cow effectively decreasing service of conception that suggest improvement of fertility in cow. No significant effect of the duration of bypass fat supplementation in S/C of cows (slope = 0.00156, SE = 0.0044; P = 0.72). The results of the meta-analysis are presented in Table 4 and forest plot are presented in Fig. 5.

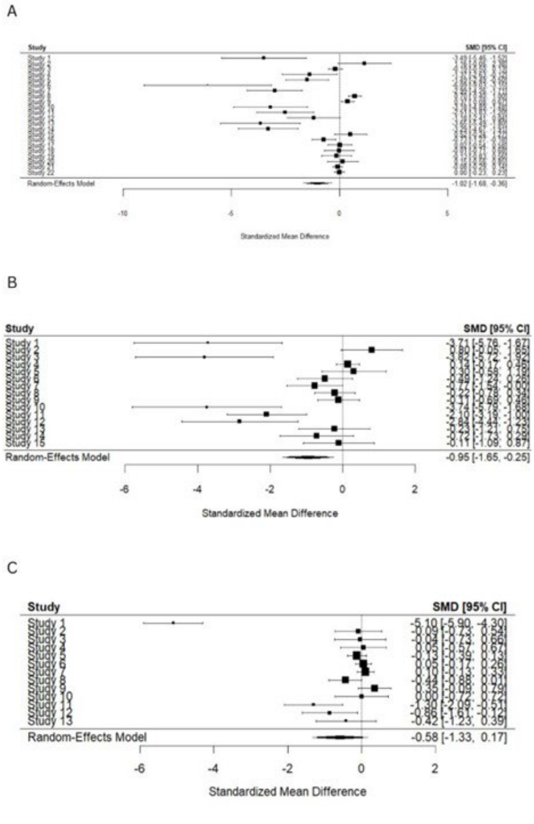

Fig. 5. Forest plot s/c, days open and conception rates parameters.

Days open and conception rate

Meta-analysis result indicates no significant effect of bypass fat supplementation on days open (ES = -0.951, 95% CI: -1.6525 to -0.2486, p = 0.008) and conception rate (ES = -0.5817, 95% CI: -1.5199 to 0.1285, p = 0.1285) of cows, with all treatment detected high heterogeneity suggesting variation study in the analysis. No missing study (estimated missing studies = 0) in days open and conception rate. Duration of bypass fat supplementation has no effect on days open (slope = 0.0060, SE =

0.0096; P = 0.535) and conception rate (slope = 0.045, SE = 0.035; P = 0.201). The results of the meta-analysis are presented in Table 4 and forest plot are presented in Fig. 5.

Table 4. Meta-analysis S/C, days open and conception rates parameters.

Parameters	N	Estimates	P-value[1]	Slope	SE Slope	P-value Slope
Days Open	14	-0.95	0.01	-0.00	0.01	0.42
Service Per Conception	22	-0.90	0.01	0.00	0.00	0.73
Conception rate	13	-0.58	0.13	0.01	0.01	0.39

[1] P-value of meta-analysis

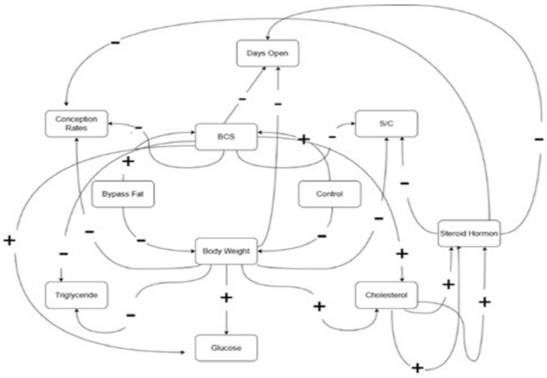

Fig. 6. Causal Loop Meta-Analysis.

Discussion

The results of the meta-analysis showed that bypass fat supplementation significantly improved reproductive, blood and production parameters through comprehensive metabolic processes to increase productivity, improve blood metabolites and improve reproductive performance efficiency.

The route of bypass fat begins in the small intestine, in which fat is absorbed by crossing the apical membrane of enterocytes from the lumen of the small intestine, while endogenous lipids in the bloodstream are transported across the basolateral membrane (Porter *et al.*, 2007). The absorbed fatty acids will be transported between the apical membranes of enterocytes by diffusion or facilitated using CD36 (cluster of differentiation 36) or FATP (fatty acid transport protein) (Niot *et al.*, 2009). Fatty acids will be activated by long-chain acyl-CoA synthetase (ACSL) where ACSL will bind fatty acid binding protein 3 (FABP3) (Yen *et al.*, 2019). Acyl-CoA is then incorporated into triacylglycerol via glycerol-3-phosphate acyltransferase (GPAT), 1-acylglycerol-3-phosphate O-acyltransferase (AGPAT), and diacylglycerol acyltransferase (DGAT) (Wang *et al.*, 2017; Jiang and Feingold, 2011). The synthesized triacylglycerol accumulates between the membrane layers of the endoplasmic reticulum, eventually forming lipid droplets. These lipid droplets remain in the cytoplasmic storage organelles or undergo lipolysis based on cellular energy needs, representing a dynamic mechanism for cellular lipid homeostasis.

Fatty acids are also converted into cholesterol through the main pathway of fatty acid (FA) catabolism, namely β-oxidation located in mitochondria and peroxisomes (Sun *et al.*, 2020). This β-oxidation process will produce acetyl-CoA. Acetyl-CoA is converted into 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) mediated by 3-hydroxy-3-methylglutaryl-CoA synthase and reduced to melanovate catalyzed by 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) (Nayeri and Stothard, 2016; Viturro *et al.*, 2009; Berg *et al.*, 2002). Mevalonate is converted to 3-isopentenyl pyrophosphate, which undergoes three steps to form farnesyl pyrophosphate, followed by reductive dimerization of two molecules of farnesyl pyrophosphate to form squalene through catalysis by the endoplasmic reticulum enzyme squalene synthase, after which squalene undergoes oxidative cyclization by oxidosqualene cyclase to form lanosterol, and the final step involves the conversion of lanosterol to cholesterol.

MTP is responsible for transporting triglycerides and cholesterol to apob-48 and continues by wrapping the phospholipid and cholesterol layers (Giammanco *et al.*, 2015). Apolipoprotein (apo) B48 in the intestine meets triglycerides (TG) in the endoplasmic reticulum (ER) through the action of microsomal triglyceride transfer protein together with cholesterol, phospholipids, and ApoAIV, to form pre-chylomicrons (Stone, 2022). Pre-chylomicrons will be sent to the cis-Golgi to meet ApoAI to produce chylomicrons where each chylomicron will contain 1 ApoB48 (Gugliucci, 2024). Chylomicrons will undergo exocytosis causing them to exit the basolateral enterocytes and head to the lymphatic capillaries through the lamina propria (Gugliucci, 2023). Chylomicrons together with VLDL-ApoB48 consisting of phospholipids, cholesterol esters and liposoluble vitamins will be carried to the lymph, veins until they enter the arterial circulation (Desmarchelier *et al.*, 2019; Mangat *et al.*, 2007). Chylomicrons will be hydrolyzed by Lipoprotein Lipase (LPL) so that triglycerides change into glycerol + 3 fatty acids. Some fatty acids will be used by cells for fuel by interacting with cell surface receptors such as CD36 or stored in lipid droplets when not in use (Goldberg *et al.*, 2009; Frayn *et al.*, 1998). The hydrolysis process by LPL causes chylomicrons to change into remnant chylomicrons and be carried to the liver. This is because the liver receptor binds to ApoE. Apolipoprotein E functions as a binder for various liver receptors such as LDLR and LRP1 so that it can facilitate the endocytosis process. Chylomicron remnants will be used as material for the liver to synthesize VLDL to be released into circulation where triglycerides will be released so that they change into IDL and finally into LDL (Caldari-Torres *et al.*, 2016). Free cholesterol in the lysosomal compartment is exported out through the action of NPC1 and NPC2 (Sleat *et al.*, 2004).

Free cholesterol that has been released from the lysosome to the cytoplasm which then goes to the endoplasmic reticulum (ER). Cholesterol will go through 2 pathways, namely ABCA1 and ACAT2. ABCA1 facilitates the formation of new high-density lipoprotein (HDL) for blood circulation, while Acyl coenzyme A: cholesterol acyltransferase 2 (ACAT2) catalyses the esterification of excess cholesterol into cholesteryl ester (CE), which is packaged into VLDL particles to be secreted into the bloodstream (Yang *et al.*, 2013). Apolipoprotein B100 (ApoB100) has an important role as a scaffold protein for TG incorporation during the maturation of VLDL particles (Chen *et al.*, 2008; Zhang *et al.*, 2019). Sortilin (SORT1) functions as an intracellular ApoB100 receptor that regulates the synthesis and transport of lipid particles while also regulating low-density lipoprotein-cholesterol (LDL-C) levels (Amengual *et al.*, 2018).

Free cholesterol is transported by binding to the steroidogenic acute regulatory protein (stAR) into the mitochondria through the outer and inner mitochondria to the mitochondrial matrix (Selvaraj *et al*, 2018). Cholesterol is converted by the cytochrome P450 family amily 11 member 1 (CYP11A1) to pregnenolone (Mitani *et al.*, 1982; Hanukoglu *et al.*, 1980; Hanukoglu *et al.*, 1981; Hanukoglu and hanukoglu, 1986). Pregnenolone is transported out of the mitochondria to the endoplasmic reticulum and converted to progesterone by the enzyme hydroxyl-5-steroid dehydrogenase, 3 beta and steroid delta isomerase 1 (HSD3B1) (Labrie *et al.*, 1992). Pregnenolone is also converted to DHEA facilitated by cytochrome P45017α, which then undergoes a transformation catalysed by 3β-HSD to produce androstenedione. Androstenedione in theca cells is transported into granulosa cells where cytochrome P450 aromatase facilitates the aromatization of androstenedione to estrone. The 17β-HSD will facilitate estrone to be converted to oestradiol where this process is regulated at the mitochondrial level during early steroidogenesis and through modulation of aromatase activity.

Liver has a important role in central metabolism hub. The liver not only the sites of cholesterol synthesis but also regulated the homeostasis of cholesterol (Luo *et al.*, 2020). Chylomicron degradation products which is free cholesterol convert to cholesteryl esters were regulated by AcetylCoA acetyltransferase (ACAT) stored in cells (Chang *et al.*, 1997). Intracellular cholesteryl esters constitutes part of lipid droplets along with perilipins and phospholipids (Chang *et al*., 2001; Horton *et al*., 2003). This finding explains why in the present study supplementation bypass fat improve BCS score and enhance recovery of body weight in high yield cow because requirement nutrition to milk production were met, resulting in excess cholesterol from metabolism being stored in adipose tissue in lipid droplet. Chylomicron was enter to the liver. Chylomicron was breakdown to acetyl coa and cholesterol by lipoprotein lipase. Acetyl-CoA converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) which is mediated by 3-hydroxy-3-methylglutaryl-CoA synthase and reduced to melanovat which is catalyzed by 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) (Nayeri and Stothard, 2016; Viturro *et al*., 2009; Berg *et al*., 2002). Mevalonate is converted to 3-isopentenyl pyrophosphate, which goes through three steps to form farnesyl pyrophosphate, followed by the reductive dimerization of two farnesyl pyrophosphate molecules to form squalene via catalysis by the endoplasmic reticulum enzyme squalene synthase, after which the squalene is oxidative cyclization by oxidosqualene cyclase to form lanosterol, and the final step involves the conversion of lanosterol to cholesterol via a multi-step process. Intracellular cholesterol collected from uptake of chylomicron residues and de novo synthesis via the mevalonate pathway collects in the endoplasmic reticulum (ER). Cholesterol will go through 2 pathways, namely ABCA1 and ACAT2. ABCA1 facilitates the formation of nascent high-density lipoprotein (HDL) for blood circulation, while Acyl coenzyme A:cholesterol acyltransferase 2 (ACAT2) catalyzes the esterification of excess cholesterol into cholesteryl ester (CE), which is packaged into VLDL particles for secretion into the bloodstream (Yang *et al*., 2013).

Apolipoprotein B100 (ApoB100) has an important role serving as a scaffold protein for TG incorporation during VLDL particle maturation (Chen *et al*., 2008; Zhang *et al*., 2019). Sortilin (SORT1) functions as an intracellular ApoB100 receptor that regulates the synthesis and transport of lipid particles while also regulating low-density lipoprotein-cholesterol (LDL-C) levels (Amengual *et al*., 2018). In addition, LDL was binding to LDL receptor (LDLR) which is triggered receptor to mediated endocytosis process (Brown *et al*., 1986). The endosome was combined with lysosome is separated from receptor to breakdown to free cholesterol (Grummer and Carroll, 1988). Free cholesterol in lysosomal compartment export out by action of NPC1 and NPC2 (Sleat *et al*., 2004). Free cholesterol is transported by binding of steroidogenic acute regulatory protein (stAR) into mitochondrial pass through outer and inner mitochondrial to matrix mitochondrial (Selvaraj *et al*., 2018). Cholesterol is converted by cytochrome P450 family 11 member1 (CYP11A1) to pregnenolone (Mitani *et al*., 1982; Hanukoglu *et al*., 1980; Hanukoglu *et al*., 1981; Hanukoglu and Hanukoglu, 1986). Pregnenolone transported out from mitochondria to endoplasmic reticulum and convert to progesterone by enzyme hydroxydelta-5-steroid dehydrogenase, 3 beta- and steroid delta isomerase 1 (HSD3B1) (Labrie *et al*., 1992). Pregnenolone is also converted to DHEA facilitated by cytochrome P45017α, which then undergoes a transformation catalyzed by 3β-HSD to produce androstenedione. Androstenedione in theca cells are transported into granulosa cells where cytochrome P450 aromatase facilitated the aromatization of androstenedione to estrone. 17β-HSD will facilitated estrone to convert to make estradiol which this process were regulated at the mitochondrial level during early steroidogenesis and through modulation of aromatase activity.

This study showed that supplementation bypass fat significantly enhance cholesterol concentration in cow. The improving of cholesterol concentrations might facilitate enhanced progesterone biosynthesis via the steroidogenic pathway, where pregnenolone converts to progesterone in endoplasmic reticulum, leading to improved reproductive efficiency. Progesterone functions as a critical regulatory hormone to increase successful conception, which prepares embryo implantation in the uterus (Rahbar *et al*., 2021). Increasing progesterone can improve intensity of estrous expression and increase fertility (Madureira *et al*., 2021).

The improvement of cholesterol concentrations might also facilitate enhanced estradiol biosynthesis via the steroidogenic pathway, where estrone is converted to make estradiol by 17β-HSD enzyme, leading to improvement in reproductive efficiency. Estradiol functions as a critical endocrine modulator, which is hypothalamic GnRH secretory and gonadotrophic LH secretion (Kadokawa, 2020). GnRH will release the hormones FSH and LH (Thatcher *et al*., 1993). Estradiol has 2 pathways to produce GNRH. First, estradiol will binding to ESR2. Estradiol-ESR2 signaling in GnRH neurons leads to a rapid gene regulatory response via CREB phosphorylation (Ábrahám *et al*., 2003), followed by increasing cAMP production and activation of calcium signals, resulting in the release of the hormone GnRH (Hu *et al*., 2008). Estradiol also regulating secretion GnRH via kisspeptin-mediated pathway in the hypothalamus (Amstalden and Williams, 2019). Specifically via neurons in the anteroventral periventricular nucleus (AVPV) that regulate positive feedback responses (Dedes, 2012). AVPV kisspeptin neurons will increase ESR2 expression (Kanaya *et al*., 2019), so that ESR1 and ESR2 will provide signals to modulate GnRH release via AVPV-derived kisspeptin signals (Papaoiconomou *et al*., 2011). Hypothalamic GnRH stimulates anterior pituitary FSH secretion, which then exerts pleiotropic effects on ovarian function, including growth, development, maturation, and follicle maintenance, while activating several intrafollicular signaling pathways that are important for oocyte quality and ovulatory follicle function until they are ready to be released (Amin *et al*., 2023). The rapid increase in estradiol levels, due to advanced follicular development, triggers hypothalamic neurons to release high frequency GnRH signals as a result of positive feedback from estradiol, which in turn stimulates a surge in LH secretion from anterior pituitary gonadotrophs, which ultimately initiates the ovulatory cascade. GnRH secreted by the hypothalamus will be transported in a pulsatile pattern into the pituitary portal system, where the rhythmic release aims to be the main regulator of the pulsatile LH secretion pattern (Wakabayashi *et al*., 2010).

This surge in estradiol also provides a negative feedback effect, namely a decrease in FSH secretion by the pituitary. The LH-mediated luteinization process regulates post-ovulatory follicular transformation, characterized by the formation of a corpus luteum in which the corpus luteum secretes progesterone switch from estradiol (Murphy, 2000). Bypass fat supplementation modulates reproductive hormones through increasing the concentration of cholesterol, a major precursor of steroidogenesis, maximizing direction in the secretion patterns of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). This synchronized endocrine regulation manifests in increased follicular development, increased circulating concentrations of estradiol and progesterone, and improved corpus luteum function, ultimately resulting in a significant reduction in days open and services per conception. Meta-analytic evidence suggests that ruminants supplemented with bypass fat show improved reproductive parameters through direct effects on ovarian function and indirect mechanisms through improved energy status by optimizing reproductive efficiency through proper temporal coordination of the hypothalamic-pituitary-ovarian axis so it can be concluded that supplementation bypass fat in diets can improve reproductive performance. The decrease in conception rates in fat bypass studies can be caused by several factors, such as poor semen quality parameters, less than optimal mating management, inadequate inseminator skills, and inappropriate timing of artificial insemination due to human error. Specifically, reduced sperm motility, morphology, and viability significantly impact fertilization potential and inappropriate timing of insemination relative to the time of ovulation decreases fertilization success. In addition, inseminator proficiency, particularly in terms of proper semen handling and insemination techniques, plays an important role in fertility outcomes, which if effect can significantly reduce conception rates.

To the best of our knowledge, this is the first meta-analysis on bypass fat to specifically discuss bypass fat in detail. This was chosen to fill the gap in meta-analysis that have examined dietary fat in relation to certain parameters. In the journal published by Rodman *et al*. (2015), it was stated that there was a 27% increase in pregnancy to service, but there was no significant difference in the calving to pregnancy interval parameter. This indicates an improvement in the reproductive efficiency of this journal. This aligns with the results of our study, which showed a decrease in days open of -0.951 (95% CI: -1.6525 to -0.2486, p = 0.008) and an increase in service per conception of 1.2509 (ES = -0.9001, 95% CI: -1.6098 to -0.1903, p = 0.0129). This suggests that the increase in reproductive efficiency is influenced by the advancement in technology used, namely, the shift from dietary fat to bypass fat, as reflected in the decreased number of days open, increased service per conception, and supported by an increase in cholesterol levels of 1.2509 (CI: 0.3335 to 2.1682, p = 0.0075) to support the process of steroidogenesis and the synthesis of reproductive hormones, which are positively correlated with reproductive efficiency.

In this meta-analysis, several parameters exhibited heterogeneity values that fell within a high range. This is because of several factors, such as differences in research locations, which have varying environmental conditions. The use of different feed compositions in each journal could have influenced the heterogeneity values in this meta-analysis. In addition to causing high heterogeneity, this also led to increased publication bias values for several parameters in this study. The use of different cattle breeds also affected the heterogeneity values and publication bias. To address these limitations, we used trimfill to ensure that there was no publication bias in this meta-analysis in order to prevent studies on bypass fat supplementation containing the established parameters from remaining unpublished by researchers. Trimfill represents the potential value of missing studies and estimates the correction for the effect estimate.

Conclusion

The results of our meta-analysis have a significant effect on dairy cattle management by improving ruminant performance through enhanced reproductive efficiency, increased production parameters, and improved blood metabolism profile efficiency. This can increase profitability in dairy cattle maintenance with bypass fat supplementation by boosting reproductive efficiency, including shortening the cycle and increasing the success rate of artificial insemination, which is supported by increased cholesterol levels that aid reproductive hormone synthesis. Future studies comparing different types of bypass fat sources and their specific effects on reproductive performance, productivity, and blood parameters are needed to regulate more appropriate types of bypass fat sources.

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Conflict of interest

The authors have no conflict of interest to declare.

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