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An exploratory study on the influence of maternal age on human milk polyamines during lactation

Tengku Norbaya Tengku Azhar[1,2*], Nursyuhada Abdul Aziz[3], Nhawal Aminie Saidon[1] & Puteri Shafinaz Abdul-Rahman[4,5]

[1]*Centre of Foundation Studies, Universiti Teknologi MARA, UiTM Selangor Dengkil Campus, Selangor, Malaysia*; [2]*Maternal, Infant and Young Child Nutrition Research Group (MiChild), Faculty of Health Sciences, Universiti Teknologi MARA, Bandar Puncak Alam, Selangor, Malaysia,* [3]*Science Biology Programme, School of Postgraduate, Faculty of Applied Sciences, Universiti Teknologi MARA, Selangor, Malaysia;* [4]*Department of Molecular Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur Malaysia;* [5]*Universiti Malaya Centre of Proteomics Research, Universiti Malaya, Kuala Lumpur Malaysia.*

ABSTRACT

Introduction: Polyamines are essential bioactive compounds involved in cell proliferation, differentiation, and immune maturation during early life. Human milk serves as a dynamic source of polyamines, with their concentration influenced by maternal physiological and demographic factors. This study aimed to examine the effect of maternal age on concentrations of three major polyamines – putrescine, spermidine, and spermine – in human milk collected from breastfeeding mothers across a lactation period of 0–24 months. **Methods:** A cross-sectional study was conducted using 30 human milk samples collected from three categorised lactation stages: 0-3 months, 4-6 months, and 7-24 months. Participants were categorised into two maternal age groups: 21–29 years and 30–39 years. Polyamine concentrations were quantified using validated high-performance liquid chromatography with fluorescence detection (HPLC-FLD) following derivatisation with dansyl chloride. **Results:** Putrescine concentrations were significantly higher in milk samples from older mothers (30–39 years) compared with younger mothers (21–29 years) (p<0.05). In contrast, spermidine and spermine concentrations did not differ significantly between maternal age groups. **Conclusion**: Maternal age appeared to selectively influence putrescine levels in human milk, whereas spermidine and spermine concentrations remained relatively stable across age groups. No significant correlations were observed in this small cohort, and findings were independent of maternal dietary intake and lactation stage. Future studies with larger, longitudinal cohorts that include crucial confounding factors are needed to clarify these associations and their clinical relevance.

Keywords: human milk, maternal age, polyamines, putrescine, spermidine, spermine

*Corresponding author:
Dr Tengku Norbaya Tengku Azhar
Centre Foundation Studies, Universiti Teknologi MARA,
UiTM Selangor Dengkil Campus, Selangor, Malaysia.
Tel: (6)019-9620539; E-mail: tengku2888@uitm.edu.my
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INTRODUCTION

According to Muñoz-Esparza *et al.* (2021a) and Sagar *et al.* (2021), polyamines are aliphatic organic bases that belong to a larger group of amines containing two or more amino groups called bioactive amines. Dietary polyamines, particularly putrescine, spermidine, and spermine, are absorbed into the maternal circulation and secreted into milk, while the mammary gland can synthesise them through the ornithine decarboxylase (ODC) pathway. Although the mechanisms regulating polyamine secretion into milk are multifactorial, evidence suggests maternal nutritional status, including habitual dietary patterns, and body composition can influence polyamine levels in milk (Ali *et al.*, 2013). Amino acids, such as arginine and ornithine, are substrates in the polyamine biosynthetic pathway (Ali *et al.*, 2014); thus, protein status has been linked to polyamine content in milk and other biological matrices in some studies.

Based on Figure 1, ornithine is converted to putrescine by ODC, and putrescine is subsequently metabolised to spermidine and spermine by spermidine and spermine synthases using aminopropyl groups from decarboxylated S-adenosylmethionine (dcSAM). This dual supply from dietary intake and *de novo* synthesis enables the mammary gland to modulate milk polyamine levels in response to maternal physiological conditions. Rather than being completely independent of dietary influences, endogenous synthesis can partly compensate for fluctuations in nutrient availability, while polyamine levels may also be influenced by other

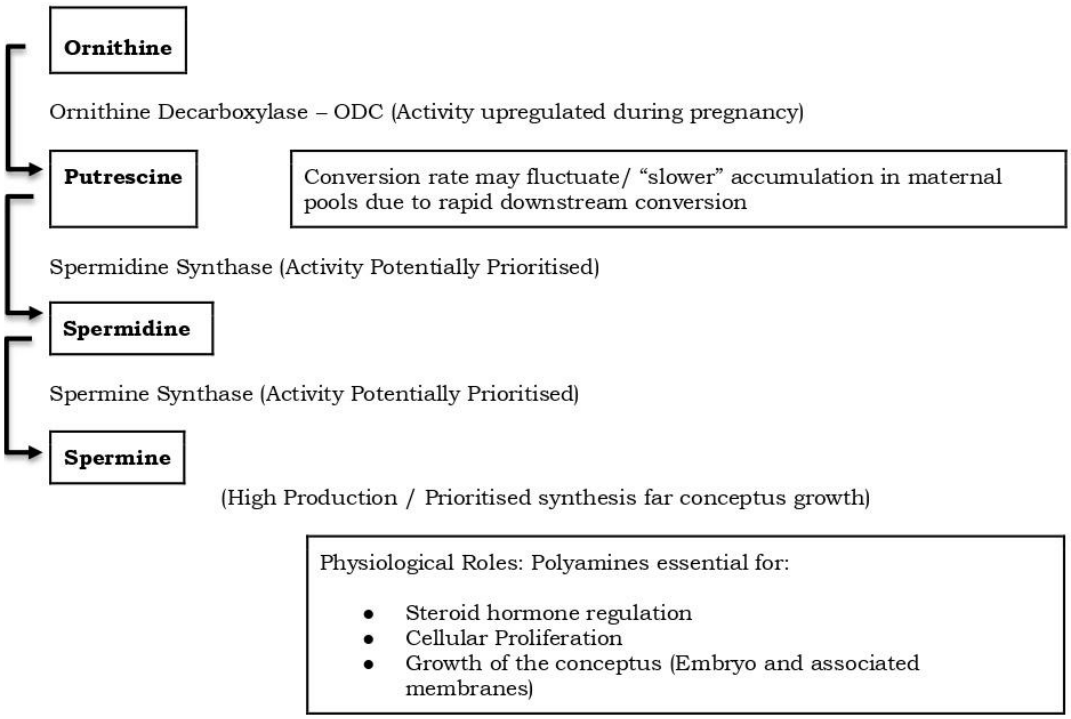

Figure 1. Overview of the canonical polyamine biosynthesis pathway and its prioritisation during pregnancy

factors such as age, lactation stage, delivery mode, and environmental exposures (Favara *et al.,* 2025; Muñoz-Esparza *et al.,* 2022).

Polyamines are essential for cellular processes such as DNA stabilisation, gene expression, proliferation, and apoptosis (Schibalski *et al.,* 2024; Sagar *et al.,* 2021). In infancy, they support gastrointestinal (GI) maturation by promoting mucosal integrity, differentiation, and microbiota balance (Nakamura & Matsumoto, 2025). They also shape immune development through inflammation control, tolerance induction, and lymphocyte maturation (Hesterberg, Cleveland & Epling-Burnette, 2018; Lian *et al.*, 2022). However, neonates have limited capacity for endogenous polyamine synthesis, making them reliant on external sources, with human milk being the primary source. Insufficient intake during early life may impair gut and immune function, predisposing infants to later infections, allergies, or metabolic issues (Nance *et al.*, 2020).

Maternal biological characteristics, including age, may influence polyamine composition in human milk. As reported by Lin *et al.* (2023), increasing maternal age is associated with physiological and hormonal changes that may elevate oxidative stress, potentially altering cellular signalling pathways that regulate the biosynthesis and secretion of milk constituents. Although several maternal factors influence milk polyamine variability, maternal age remains underexplored. Understanding how age shapes polyamine profiles is especially relevant as delayed childbearing becomes more common (Muñoz-Esparza *et al.*, 2024). While some studies reported no significant associations, others have not directly examined maternal age despite collecting demographic data (Lemas *et al.*, 2023). Given that maternal metabolic states such as obesity alter milk polyamine content (Ali *et al.,* 2014; Ellsworth *et al.,* 2020), it is plausible that age-related physiology exerts similar effects. Addressing this gap may clarify how maternal age affects infant development by altering milk polyamine composition.

METHODOLOGY

The study employed an observational cross-sectional design involving lactating mothers with infants aged 0–24 months, recruited from four Malaysian states (Melaka, Negeri Sembilan, Selangor, and Kuala Lumpur). In this study, eligible participants were mothers aged 18 to 45 years who gave birth to full-term infants between 37 and 42 weeks of gestation. Eligible infant feeding methods encompassed both exclusive breastfeeding (infants aged 0–6 months receiving no formula, solids, or other fluids) and mixed feeding (infants receiving formula, solid foods, or other fluids). Additionally, the study included mothers who gave birth either via vaginal delivery or Caesarean section. Participants were required to be healthy with no prior history of chronic diseases. Individuals were excluded from the study if they were outside the specified age range (under 18 or over 45 years old), experienced a preterm birth of less than 37 weeks of gestation, and had pre-existing chronic diseases or medical complications. Specific exclusionary conditions included asthma, diabetes, obesity, autoimmune disorders, cardiovascular diseases, and thyroid disorders. Ethical approval was obtained from the Faculty Ethics Review Committee (FERC) of the Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), with ethical reference number R1/FERC/FSG/073.

Sample size was calculated using a single-proportion formula with a 95% confidence level and a precision of 0.05 (d), yielding a minimum of 95 participants. Given the exploratory nature of this study, which primarily aimed to generate preliminary data and assess methodological feasibility, recruitment was limited

to 30 eligible lactating mothers. The smaller sample size was due to feasibility constraints, including recruitment (difficulty enrolling sufficient participants within the study time frame), time (deadlines and limited study duration), and geographical/access challenges (participants dispersed across different areas, making it difficult to arrange meetings for sample collection).

Participants were provided with a detailed explanation of the study procedures and instructed to manually express approximately 30–45 mL of human milk into sterile zip-lock storage bags. To account for potential variability in milk composition, samples were collected twice from different expressions from each participant within the same day in the morning under standardised conditions. Repeated sampling has been recommended to improve representativeness of human milk composition (Muñoz-Esparza *et al.*, 2021a). While human milk composition is dynamic, collection in the morning provides a consistent baseline while minimising the impact of the mother's daily circadian rhythm, hormones, and nutrient fluctuations throughout the day. The collected samples were then transported on the same day, aliquoted into 1 mL portions, and stored at –20°C until further analysis.

Polyamine standards (putrescine, spermidine, and spermine) and analytical-grade reagents were obtained from Sigma-Aldrich and Fisher Scientific. All buffer solutions were prepared according to the methods described by Kamaruzzaman *et al.* (2018). Perchloric acid working solutions (0.2 M and 0.6 M) were prepared by dilution of 70% stock solution. Sodium carbonate buffer (pH 10.5) was adjusted using 5 M HCl. L-proline solution (10 mg/mL) was prepared in distilled water.

A stock solution of the internal standard, 1,7-diaminoheptane (0.001 M), was prepared in 0.2 M perchloric acid and further diluted to 0.005 mM for use. Polyamine stock solutions (5 mM each) were also prepared in 0.2 M perchloric acid and subsequently mixed and diluted to obtain working standards ranging from 0 to 5.0 nmol/200 µL. All standard solutions were spiked with 0.01 mL of the internal standard before derivatisation. A solution of dansyl chloride (15 mg/mL in acetonitrile) was freshly prepared, incubated at 37°C for 1 hour, and centrifuged to remove undissolved particles before use.

Milk samples (1 mL) were centrifuged at 13,000 rpm for 15 minutes, treated with perchloric acid, and supernatants processed for dansylation. After overnight incubation with sodium carbonate and dansyl chloride, the excess reagent was quenched with L-proline. Extracts were cleaned with toluene, dried, reconstituted in acetonitrile, and transferred to HPLC vials.

Analysis was performed using an Agilent 1200 Series HPLC (Agilent Technologies, Santa Clara, CA, USA), with a C18 column and fluorescence detection (excitation 254 nm, emission 360 nm). The mobile phase consisted of 40% acetonitrile and 60% water at 1 mL/min, with 20 µL injections in duplicate.

Polyamine concentrations (putrescine, spermidine, spermine, and total polyamines) were compared across maternal age groups. Welch's *t*-test was used to compare young adults (21–29 years, n=11) with adults (30–39 years, n=19). Analysis of variance (ANOVA) was also conducted across all maternal age groups (21–39 years). Significance was set at $p<0.05$, with effect sizes (Cohen's d) classified as negligible (<0.2), small (0.2–0.5), medium (0.5–0.8), or large (>0.8). Analyses were performed using IBM SPSS Statistics version 29.0.1 (IBM Corp., Armonk, NY, USA). Before parametric analysis, the distributions of continuous variables were evaluated for normality using graphical methods (histograms and Q–Q plots) and the Shapiro–Wilk test.

RESULTS

Polyamine concentrations were measured in human milk samples collected from 30 lactating women aged 21–39 years. Based on Table 1, mean maternal BMI differed between age groups, with younger mothers (21–29 years) having a lower average BMI (20.9±3.1 kg/m²) compared to older mothers (30–39 years) (22.6±4.6 kg/m²). The distribution of lactation stage varied across age groups. Among women aged 21–29 years, 45.5% were within 0–3 months postpartum, 36.4% were between 4–6 months postpartum, and 18.2% were between 7–24 months postpartum. In contrast, women aged 30–39 years were more evenly distributed, with 26.3% in both the 0–3 and 4–6 months categories, and 47.4% in the 7–24 months category. Although lactation stage was available, it was not included as a covariate in the inferential analyses due to the limited sample size (N = 30), which could result in unstable parameter estimates, wide confidence intervals, and reduced reliability and statistical power of the findings. Lactation stage was therefore reported descriptively to provide clinical context but was not included in the statistical models to maintain statistical robustness. Regarding mode of delivery, vaginal birth was more common in both groups (81.8% in younger women and 73.7% in older women), while Caesarean section accounted for 18.2% and 26.3%, respectively.

Table 1. Characteristics of participating mothers (N=30)

Characteristic	*21-29 years (n=11)*	*30-39 years (n=19)*
Body mass index (kg/m²), mean±*SD*	20.9±3.1	22.6±4.6
Lactation stage (months postpartum), *n* (%)		
0-3	5 (45.5)	5 (26.3)
4-6	4 (36.4)	5 (26.3)
7-24	2 (18.1)	9 (47.4)
Mode of delivery, *n* (%)		
Normal	9 (81.8)	14 (73.7)
Surgery (Caesarean section)	2 (18.2)	5 (26.3)

Polyamine concentration and distribution

The descriptive statistics for putrescine, spermidine, and spermine are presented in Table 2. Among the three polyamines, spermine exhibited the highest mean concentration (5.34±5.87 nmol/L), followed by putrescine (1.74±3.34 nmol/L) and spermidine as the lowest (0.58±0.89 nmol/L). Notably, putrescine showed the widest concentration range (0.00–8.97 nmol/L), indicating considerable inter-individual variability.

Table 2. Descriptive statistics of polyamine levels in maternal samples (N=30)

Polyamine	*Mean±SD (nmol/L)*	*Range*
Putrescine	1.74±3.34	0.00-8.97
Spermidine	0.58±0.89	0.00-3.42
Spermine	5.34±5.87	0.20-17.67

In Table 3, correlation analysis was performed on polyamine concentrations measured in milk samples from women aged 21-39 years. However, no polyamine

correlations reached statistical significance at the α=0.05 level. Some negative correlations were observed between putrescine and spermidine and between putrescine and spermine.

Table 3. Spearman correlation coefficients between polyamine types in maternal samples (*N*=30)

Polyamine pair	*95% CI*	*p-value*	*Spearman ρ*	*p-value*
Putrescine-Spermidine	-0.461, 0.241	0.512	-0.227	0.228
Putrescine-Spermine	-0.612, 0.038	0.077	-0.248	0.188
Spermidine-Spermine	-0.094, 0.576	0.142	0.280	0.134

Age-related differences in polyamine levels

In Table 4, putrescine levels were significantly different between age groups (p=0.016), with the 30-39 years age group exhibiting a substantially higher mean concentration (2.648±3.892 nmol/L) compared to the 21-29 years age group (0.183±0.218 nmol/L). The median values (0.143 vs. 0.099) further confirmed this trend, although the difference was less pronounced than for means, suggesting the influence of extreme values in the older age group. Indeed, the older age group displayed a considerably wider range (8.969 vs. 0.760) and greater variability, as evidenced by a coefficient of variation of 147.0% compared to 119.1% in the younger age group.

Table 4. Comparison of human milk polyamine levels(nmol/L) between young adult (21-29 years) and adult (30-39 years) age groups

Polyamine	*Mean±SD [95% CI]*		*Mean difference*	*t-value*	*p-value*	*Effect size*
	21-29 years (n=11)	*30-39 years (n=19)*				
Putrescine	0.183±0.218	2.648±3.892	-2.465	-2.649	0.016*	0.889
	[0.039, 0.327]	[0.769, 4.526]				
Spermidine	0.478±0.701	0.641±0.986	-0.163	-0.520	0.608	0.193
	[0.015, 0.940]	[0.167, 1.115]				
Spermine	6.876±6.499	4.683±5.517	2.193	0.959	0.346	0.365
	[2.571, 11.180]	[2.025, 7.341]				
Total Polyamines	7.536±6.798	7.972±5.824	-0.436	-0.188	0.853	0.069
	[3.022, 12.050]	[5.159, 10.785]				

Values are presented as mean±standard deviation (*SD*)
Statistical analysis was performed using Welch's t-test due to unequal variances
*Statistical significance at p<0.05

Spermidine concentrations were moderately higher in the 30-39 years age group (mean: 0.641±0.986 nmol/L; median: 0.021 nmol/L) compared to the 21-29 years age group (mean: 0.478±0.701 nmol/L; median: 0.054 nmol/L), though with substantial overlap in distributions. Both groups exhibited high variability, with coefficients of variation exceeding 145%, indicating substantial inter-individual differences in spermidine levels across age groups.

In contrast, spermine levels were higher in the younger age group (mean:

6.876±6.499 nmol/L; median: 3.269 nmol/L) compared to the older age group (mean: 4.683±5.517 nmol/L; median: 1.808 nmol/L). This pattern was particularly interesting as it ran counter to the age-related increases observed for putrescine and spermidine. The 95% confidence intervals for spermine levels showed considerable overlap between age groups, suggesting substantial within-group variability.

Total polyamine levels were comparable between the two age groups (21-29 years: 7.536±6.798 nmol/L; 30-39 years: 7.972±5.824 nmol/L), with distributions largely overlapping. The coefficient of variation was slightly lower in the older age group (73.1% vs. 90.2%), indicating more consistent polyamine levels among mothers in their 30s. Although total polyamine levels did not differ significantly between the two maternal age groups, the effect size was negligible (Cohen's d = 0.07), suggesting that maternal age had minimal impact on total polyamine concentration. According to Cohen's criteria, a d value <0.2 reflects a very small effect size, indicating limited practical significance even if minor differences are observed.

Overall, the descriptive analyses revealed a pattern of age-related changes across polyamine profiles, with putrescine showing the most pronounced age-related increases, moderate increases in spermidine, and a contrary trend of higher spermine levels in younger adults. These differential patterns suggest age-specific regulation of individual polyamines rather than a uniform change in the entire polyamine system with advancing age.

DISCUSSION

The involvement of polyamines in reproductive health and pregnancy has been increasingly recognised, yet the interrelationships among polyamine types in human milk remain incompletely understood. Our findings partially align with existing literature on polyamine metabolism. Previous studies (Wu *et al.,* 2025; Zhang *et al.*, 2025) have demonstrated that polyamine levels are tightly regulated through biosynthesis, catabolism, and transport systems. However, the specific relationships among polyamines in human milk have been less extensively characterised.

Enzymatic conversion and metabolic flux

The lack of significant inter-polyamine correlations observed in this study suggests that polyamine metabolism in human milk may not be tightly coordinated under the conditions examined. Although hormones such as oestrogen, progesterone, and human chorionic gonadotropin (Niu *et al.,* 2021) are known to regulate key enzymes involved in polyamine biosynthesis and turnover during pregnancy, their influence may not translate into synchronised changes in individual polyamine levels in human milk. This shift may be attributed to increased spermidine and spermine synthase activity during pregnancy, which accelerates the conversion of putrescine into higher-order polyamines like spermine to support foetal and placental development (Guleroglu *et al.*, 2025). Metabolically, hormonal changes in pregnancy, particularly increased oestrogen and progesterone, may further modulate polyamine enzyme expression, such as ornithine decarboxylase (ODC) and polyamine oxidase (PAOX) (Cable & Grider, 2020). However, in this human milk study, factors beyond maternal hormonal regulation are likely to play more prominent roles in determining polyamine interrelationships.

Distinct regulatory pathways or responses to postpartum shifts

This metabolic changes in polyamines synthesise encompasses the mammary gland's remarkable ability to adjust its pathways, such as *de novo* lipogenesis (DNL), to maintain optimal milk composition despite fluctuations in maternal nutrient, immune, and oxidative stress status. Polyamines dynamically respond to environmental and physiological stimuli, participating in antioxidant defence, inflammatory regulation, and tissue remodelling (Xuan *et al.,* 2023; Zhang *et al.,* 2025). Their selective regulation indicates a finely tuned system that can adjust individual polyamine levels without uniform changes across all types. Factors, such as maternal age (Muñoz-Esparza *et al.,* 2021b), parity, placental efficiency, and environmental exposures (Soda, 2022), further shape maternal polyamine profiles, underscoring their distinct roles and regulation through interconnected but separate pathways.

Overall, the absence of significant correlations may be attributed to several methodological and biological factors. The relatively small sample size likely limited statistical power to detect subtle associations between polyamines; therefore, the findings should be interpreted with caution. In addition, polyamine metabolism is a complex and multifactorial process that extends beyond hormonal regulation. Age-related changes in hormone levels and endocrine sensitivity (Biagetti & Puig-Domingo, 2023) may further alter enzyme activity in a polyamine-specific manner. Together, these mechanisms likely contribute to the modest correlations between putrescine, spermidine, and spermine in human milk, reflecting a partially uncoupled system shaped by maternal endocrine status.

Research on polyamines in human milk is relatively well established, whereas biomarker-based investigations remain largely exploratory; moreover, data specific to this cohort are limited. Notably, several polyamine studies have employed small cohort designs, consistent with approaches used in exploratory metabolomic research, such as Lemas *et al.* (2023). In that study, potential biomarkers were identified using only ten human milk samples, demonstrating that preliminary analyses with limited sample sizes can yield meaningful results. Despite constrained sample size, such studies provide valuable insights into emerging trends and associations, thereby establishing a foundation for subsequent large-scale investigations.

Age-related differences in polyamine levels

The finding of significantly higher putrescine levels in mothers aged 30–39 years compared to those aged 21–29 years, with a large effect size, indicates an age-related difference in milk polyamine concentrations. This observation raises important questions regarding the biological or environmental mechanisms that may drive this variation. This may reflect physiological changes with age, such as altered hormonal regulation affecting ODC activity, the key enzyme in putrescine synthesis. Differences in metabolism, stress responses, or diet between older and younger mothers may further influence polyamine production. Lifestyle factors, including parity, breastfeeding experience, and environmental exposures, such as pollution or tobacco smoke, could also contribute to this variation.

Age-related increases in putrescine have been documented in other biological matrices, and the observed increase in milk putrescine may reflect similar metabolic shifts. These could involve increased biosynthetic activity or reduced catabolic processing in the mammary gland or in the systemic circulation. Previous studies have shown that ageing can affect ODC activity, potentially leading to elevated tissue levels of putrescine, including in mammary tissues (Soda, 2022).

Furthermore, decreased expression or activity of catabolic enzymes such as spermidine/spermine N1-acetyltransferase (SSAT) with advancing age may result in greater polyamine retention (Muñoz-Esparza *et al.,* 2024; Tse *et al.,* 2022). These enzymatic adaptations may influence the local synthesis and secretion of polyamines into milk, even in the absence of significant changes in circulating levels.

Despite the higher putrescine levels, no significant differences in spermidine, spermine, or total polyamines were observed across age groups, suggesting stronger regulation of these metabolites. The overall consistency in polyamine distribution across age groups reinforces that age exerts limited influence on overall milk polyamine profiles in early lactation, though variability from diet, genetics, or unmeasured lactation stage may explain individual outliers. These findings support the hypothesis that age-related physiological changes may not significantly affect polyamine levels during early lactation, though further research is needed to examine other contributing factors. It should be noted that the lactation stage was not explicitly controlled for in this analysis. As polyamine levels vary across the course of lactation, the observed age-related differences may in part reflect unmeasured variability in lactation stage.

The presence of spermine across all age groups aligns with evidence that maternal diet, genetics, and lactation stage may shape milk polyamines more than age. Spermine supports mucosal integrity, immune tolerance, and cytokine suppression (Nakamura & Matsumoto, 2025) and regulates T-cell function in older adults (Fischer *et al.,* 2020; Lian *et al.,* 2022). In systemic tissues, spermine has been implicated in age-related enhancement of autophagy and neuroprotection. However, the current study did not observe a significant increase in milk spermine levels with maternal age. This may be attributed to the unique regulatory mechanisms of the mammary gland, which may tightly control milk composition to ensure a consistent nutritional and immunological environment for the infant. It is also plausible that spermine levels vary later in lactation, whereas the current data are limited to early lactation. Thus, spermine may behave differently in milk compared with systemic circulation. While increased systemic spermine may serve age-specific functions in immune modulation, milk spermine is more likely involved in infant development and thus tightly regulated across all maternal ages (Soda, 2022).

The correlation patterns observed in this study offer several potential implications for both clinical practice and future research. Firstly, the near-significant negative correlation between putrescine and spermine suggests that the ratio of these two polyamines could potentially serve as a novel biomarker for evaluating maternal health status during pregnancy. Secondly, the relative independence observed among different types of polyamines suggests that an intervention aimed at modulating specific polyamines may be feasible without broadly disrupting the entire polyamine pool, potentially offering a more targeted approach.

Limitation and future directions

Despite the valuable findings, one limitation should be considered. The sample size was relatively small (N=30), but the large effect sizes suggest that the results remain statistically significant and reflect wider trends. Emerging evidence suggests that maternal nutritional quality may influence milk polyamine levels. Therefore, future studies should incorporate comprehensive dietary assessments, including evaluation of protein quality and amino acid profiles, with larger

cohorts. Other maternal and infant factors, such as lactation stage, gestational age, maternal health and nutritional status, should also be considered, while cell-based or animal-based models are needed to further elucidate the biological mechanisms underlying these associations and their implications for maternal and infant health.

CONCLUSION

The absence of significant correlations may reflect the involvement of multiple, interacting metabolic pathways beyond those examined, as well as the continuity of maternal polyamine changes from pregnancy into lactation. Polyamine metabolism is complex and interconnected with broader processes, including amino acid metabolism, oxidative stress, and microbial-derived pathways, which may independently influence milk polyamine levels. These factors, combined with small cohort size, may obscure simple correlations. Our findings highlight the intricate regulation of polyamines in maternal physiology and suggest that demographic factors, such as maternal age, should be carefully considered in future studies with larger, longitudinal cohorts to clarify their clinical relevance.

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Authors' contributions

Tengku Norbaya TA, principal investigator, conceptualised and designed the study, prepared the draft of the manuscript, performed data analysis and interpretation, and reviewed the manuscript; Nursyuhada AA, conducted the study, led data collection, assisted in drafting the manuscript; Nhawal Aminie S, formatted the manuscript; Puteri Shafinaz AR, reviewed the manuscript.

Conflict of interest

Authors have no conflict of interest to disclose.

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