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Comparison of frequency of tachycardia of Caffeine versus Aminophylline for Apnea of Prematurity

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Abstract

Background: Apnea of prematurity (AOP) is a common condition in preterm neonates, managed primarily with methylxanthines. Aminophylline has traditionally been used but is associated with adverse effects such as tachycardia. Caffeine, with a wider therapeutic index and more predictable pharmacokinetics, is increasingly preferred. **Objective:** To compare the frequency of tachycardia in preterm neonates treated with caffeine versus aminophylline for apnea of prematurity. **Methods:** This randomized controlled trial was conducted in the Department of Pediatrics, Neonatal Intensive Care Unit (NICU), at Fauji Foundation Hospital, Lahore, from 18 January 2025 to 18 july 2025 . A total of 60 preterm neonates (<36 weeks + 7 days gestation, weight <2.5 kg) with apnea of prematurity were enrolled using non-probability consecutive sampling and randomized into two groups: Group A received aminophylline (n=30) and Group B received caffeine citrate (n=30). **Results:** Baseline characteristics including gestational age, birth weight, and gender were comparable between groups (p>0.05). Tachycardia occurred in 12 neonates (40.0%) in the aminophylline group compared to 3 neonates (10.0%) in the caffeine group, a statistically significant difference (p=0.01). Stratification showed higher tachycardia rates among low birth weight (<1.5 kg) and <32 weeks gestation neonates treated with aminophylline. **Conclusion:** Caffeine therapy is associated with a significantly lower frequency of tachycardia compared to aminophylline in preterm neonates with apnea of prematurity. These findings support caffeine as the safer first-line pharmacological therapy.

Introduction

Apnea of prematurity is the most common diagnosis in Neonatal Intensive Care Unit (NICU) due to immature respiratory centers. Premature babies have immature respiratory systems which are less capable of exchange of gasses hence resulting in apnea [1]. Apnea is defined as an interruption of breathing for >20 seconds or less respiratory pause with hypoxia or bradycardia, which causes potential damage to brain tissue [2]. Apnea is higher in neonates between 30–31 weeks [1, 3]. In premature infants, methylxanthines (include caffeine, theophylline, and pentoxifylline) are used to cure episodic apnea until they complete a post-conceptional age of 34–35 weeks [4]. Apnea of prematurity (AOP) is defined as a cessation of breathing for twenty seconds or less than twenty seconds as accompanied by bradycardia (heart rate less than 100 bpm) or desaturation. AOP could be classified into central, obstructive, and mixed types. The mixed type is the most common among premature infants [5, 6]. Premature infants are delivered earlier than after 36+6 gestational weeks [7, 8]. Caffeine and aminophylline were administered to treat apnea on ground of the following reasons: Prematures who develop apnea or those at an increased risk of apnea. Caffeine proves equally effective as theophylline (intravenous version called aminophylline) in the reduction of apnea occurrence. Nonetheless, caffeine compared to theophylline (aminophylline) has a wide therapeutic range and limited side effects, as well as a long half-life. Thus, caffeine emerged as the treatment of AOP of choice [9]. The decision regarding which of the two drugs to use is made after reviewing various modalities of oxygen delivery devices (where applicable, either low flow nasal cannula, CPAP or BiPAP, or the use of a mechanical ventilator) [10]. In this research we evaluated the effectiveness of caffeine and aminophylline in the management of infants with apnea based on the rates of recurrent apneic incidences [11].

Caffeine does produce tachypnea, tachycardia, irritability and hypertonicity as well as tonic-clonic movements which signify that the patient experiences seizures and aminophylline produces tachycardia, dysrhythmia, and seizures [11]. Aminophylline is known as less effective in treating apnea of prematurity than caffeine causes, and tachycardia [10, 12]. In an evaluation of the impact of heart rate in newborns, beat-to-beat rate variability of the newborns indicates that maintenance administration of caffeine does not produce any effect on the heart rate [13]. The results of the study published earlier revealed that there was rate of tachycardia >160 bpm being 8.3 and 34.4 in caffeine and aminophylline group respectively when tachycardia was defined as an increased rate of heart rate by more than 10 beat/min above baseline, 41.7 and 63.5 in caffeine and aminophylline groups respectively [14].

The purpose of this study is to compare the frequency of tachycardia the of caffeine versus aminophylline in apnea of prematurity treatment. I want to investigate this as data is relatively scarce on this topic in Pakistan.

Objective

To compare the frequency of tachycardia after caffeine vs. aminophylline for treatment of apnea of prematurity.

Methodology

This Randomized controlled trial was conducted in the Department of Pediatrics, Neonatal Intensive Care Unit (NICU), at Fauji Foundation Hospital, Lahore from 18 January 2025 to 18 July 2025. A total of 60 cases (30 in each group) were enrolled. The sample size is calculated using 80% power of the test, 5% level of significance, and the expected frequency of tachycardia in caffeine group (8.3%) and

aminophylline group (39.4%) [14]. Non-probability consecutive sampling technique was used to collect the data.

Inclusion Criteria:

Babies born <36 weeks + 7 days of gestational age
Weight <2.5 kg
Both genders with apnea of prematurity

Exclusion Criteria:

Babies presenting >48 hours after onset of apnea
Babies who have already received caffeine or aminophylline
Babies with congenital anomalies, congenital heart disease, chromosomal malformations, or metabolic disorders

Data Collection:

After approval from the ethical committee and review board of Fauji Foundation Hospital, Lahore Eligible neonates admitted with apnea of prematurity (gestational age <36 weeks + 7 days confirmed by ultrasonography) were enrolled after obtaining informed written consent from parents or guardians. Patients were randomized into two groups using a blocked randomization technique:

Group A: Aminophylline therapy

Group B: Caffeine citrate therapy
Medications were administered as per operational definitions, and neonates were closely monitored for seven days. The occurrence of tachycardia was documented daily and managed according to hospital protocol.

Data Analysis:

Data were analyzed using SPSS version 20.0. Qualitative variables such as gender and presence of tachycardia were presented as frequencies and percentages, while quantitative variables such as age and weight were summarized as mean ± standard deviation. Stratification was performed with respect to age, gender, and weight to control for confounders. Post-stratification, the chi-square test was applied to compare outcomes between the groups, with a p-value <0.05 considered statistically significant.

Results

Data were collected from 60 patients. The mean gestational age was 32.1 ± 2.1 weeks in the aminophylline group and 32.5 ± 1.9 weeks in the caffeine group. Similarly, the mean birth weight was 1.48 ± 0.32 kg and 1.52 ± 0.28 kg in the aminophylline and caffeine groups, respectively. Male neonates comprised 60.0% of the aminophylline group and 56.7% of the caffeine group. No statistically significant differences were observed between the groups in terms of gestational age, birth weight, or gender distribution ($p > 0.05$).

Table 1: Baseline Characteristics of Study Participants (n = 60)

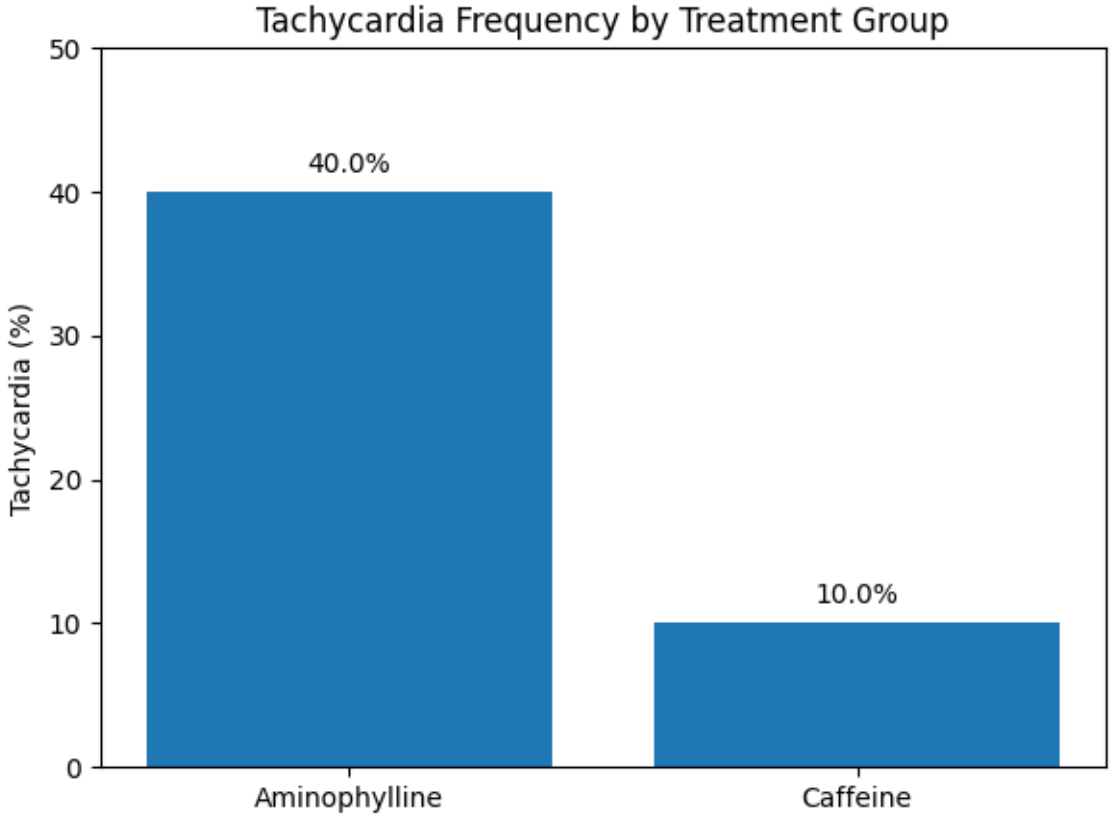
Variable	**Aminophylline Group (n=30)**	**Caffeine Group (n=30)**	**p-value**
Mean gestational age (weeks)	32.1 ± 2.1	32.5 ± 1.9	0.48
Mean birth weight (kg)	1.48 ± 0.32	1.52 ± 0.28	0.62
Gender: Male n (%)	18 (60.0%)	17 (56.7%)	0.79
Gender: Female n (%)	12 (40.0%)	13 (43.3%)	

Tachycardia occurred in 12 neonates (40.0%) in the aminophylline group compared to only 3 neonates (10.0%) in the caffeine group. This difference was statistically significant (p = 0.01). Overall, tachycardia was documented in 15 out of 60 neonates (25.0%), with the majority occurring in those treated with aminophylline.

Table 2: Frequency of Tachycardia in Both Groups (n = 60)

Group	**Tachycardia Present n (%)**	**Tachycardia Absent n (%)**	**Total**	**p-value**
Aminophylline	12 (40.0%)	18 (60.0%)	30	0.01*
Caffeine	3 (10.0%)	27 (90.0%)	30	
Total	15 (25.0%)	45 (75.0%)	60	

(*Significant at p < 0.05)

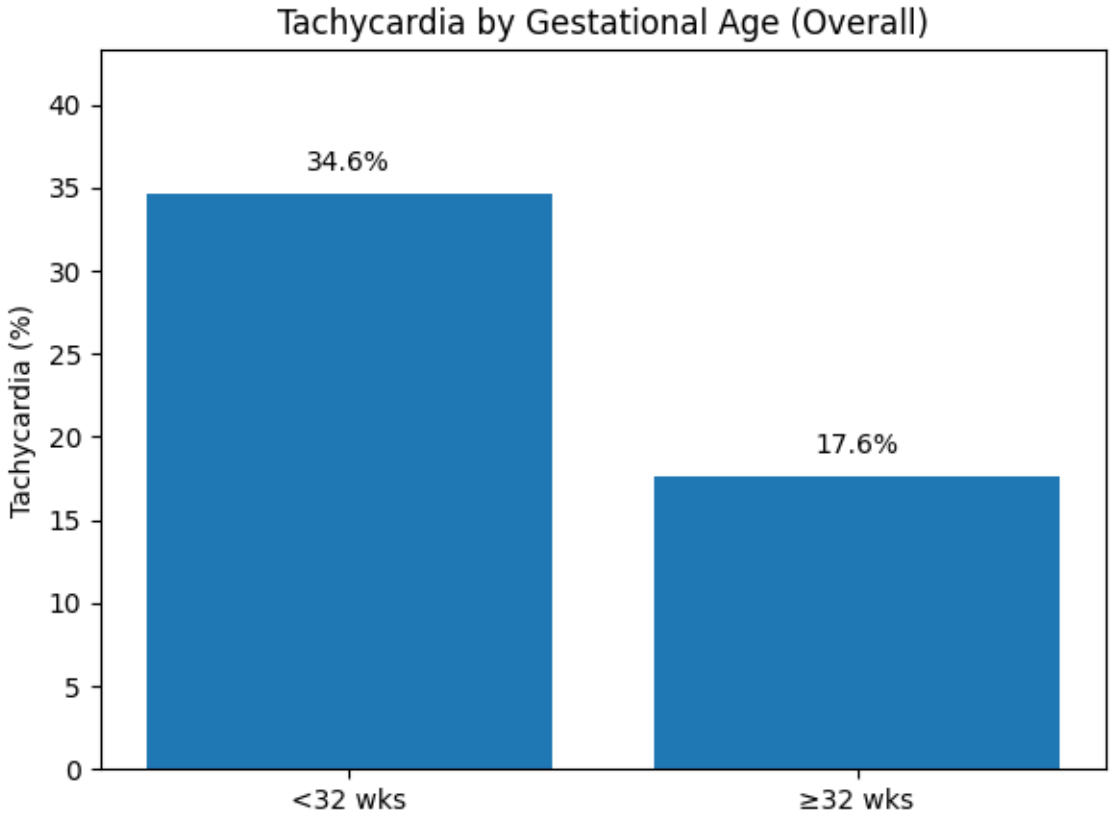


When stratified by gender, tachycardia was more common in males (28.6%) compared to females (20.0%), although the difference was not statistically significant (p = 0.42). With respect to birth weight, neonates weighing <1.5 kg had a higher frequency of tachycardia (32.1%) compared to those weighing ≥1.5 kg (18.8%), but again this difference was not statistically significant (p = 0.18). Similarly, tachycardia was more frequent among neonates born at <32 weeks gestation (34.6%) compared to those born at ≥32 weeks (17.6%), though the difference did not reach statistical significance (p = 0.21).

Table 3: Stratification of Tachycardia by Gender and Weight (n = 60)

Variable	**Tachycardia Present n (%)**	**Tachycardia Absent n (%)**	**p-value**
Gender			
Male (n=35)	10 (28.6%)	25 (71.4%)	0.42
Female (n=25)	5 (20.0%)	20 (80.0%)	

Birth Weight			
<1.5 kg (n=28)	9 (32.1%)	19 (67.9%)	0.18
≥1.5 kg (n=32)	6 (18.8%)	26 (81.2%)	
Gestational Age	**Tachycardia Present n (%)**	**Tachycardia Absent n (%)**	**p-value**
<32 weeks (n = 26)	9 (34.6%)	17 (65.4%)	0.21
≥32 weeks (n = 34)	6 (17.6%)	28 (82.4%)	



Within the aminophylline group, tachycardia occurred in 38.9% of male neonates and 41.7% of female neonates. In the caffeine group, tachycardia was observed in 11.8% of males and 7.7% of females. The difference between genders was not statistically significant (p = 0.84), indicating that gender did not play a major role in modifying the risk of tachycardia within treatment groups.

Table 4: Stratification of Tachycardia by Treatment Group and Gender (n = 60)

Group	**Male Tachycardia n (%)**	**Female Tachycardia n (%)**	**Total Tachycardia n (%)**	**p-value**
Aminophylline	7/18 (38.9%)	5/12 (41.7%)	12/30 (40.0%)	0.84
Caffeine	2/17 (11.8%)	1/13 (7.7%)	3/30 (10.0%)	

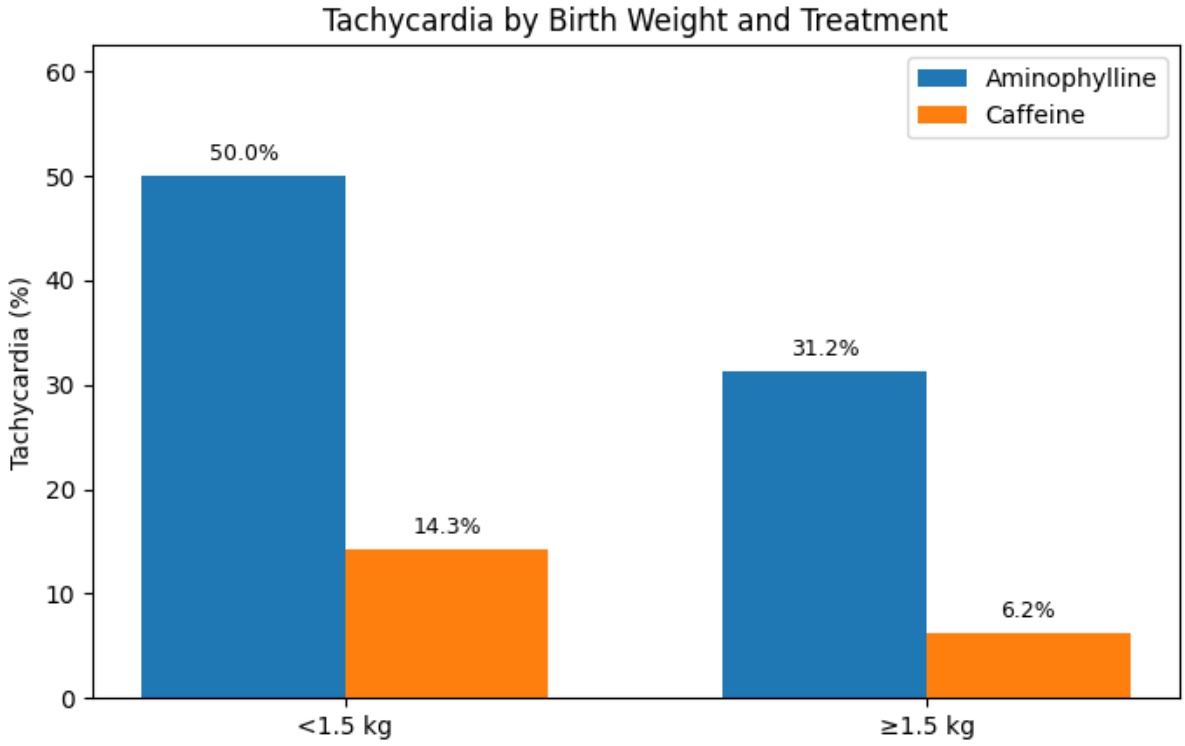
In the aminophylline group, tachycardia was markedly higher among neonates with birth weight <1.5 kg (50.0%) compared to those weighing ≥1.5 kg (31.3%). Conversely, in the caffeine group, only 14.3% of low birth weight neonates and 6.3%

of higher birth weight neonates developed tachycardia. The difference between groups was statistically significant (p = 0.03).

Table 5: Stratification of Tachycardia by Treatment Group and Birth Weight (n = 60)

Group	**<1.5 kg Tachycardia n (%)**	**≥1.5 kg Tachycardia n (%)**	**Total Tachycardia n (%)**	**p-value**
Aminophylline	7/14 (50.0%)	5/16 (31.3%)	12/30 (40.0%)	0.03*
Caffeine	2/14 (14.3%)	1/16 (6.3%)	3/30 (10.0%)	

(*Significant at p < 0.05)



Discussion

Apnea of prematurity (AOP) is a frequent complication among preterm neonates, and pharmacological therapy with methylxanthines remains the cornerstone of management.

This study was undertaken to assess the incidence of tachycardia in the preterm baby treated with aminophylline and compared with incidence in the baby treated with caffeine. Our data show that tachycardia was significantly more prevalent with aminophylline (40%) as opposed to caffeine (10%). This would support the fact that caffeine possesses safety benefits in the setting of neonatal intensive care. The findings of the present study are in agreement with other studies that have several times asserted the cardiovascular safety of caffeine relative to aminophylline [15]. Inherent with a more limited therapeutic window and variability in serum levels, aminophylline has a higher reported incidence of tachycardia in earlier trials conducted in both developed and developing countries, possibly because aminophylline must be monitored more often. Compared to placebo, caffeine has a longer half-life and predictability of pharmacokinetics mitigating variability that predisposes to adverse effects [16].

Another old study indicated that the rates of tachycardia were about 35-40 with aminophylline and caffeine was less than 10 thus akin to our findings. Another study also returned emphasis to the likelihood of caffeine in reducing the tachyarrhythmias

as well as the extubation and the risk of bronchopulmonary dysplasia [17]. These results support the superiority in terms of efficacy and safety of caffeine in preterm infants with apnea of prematurity. In our study, tachycardia was mainly evident in neonates with lower birth weights (<1.5 kg) and in those whose gestational age was <32 weeks and especially the aminophylline group. This finding is clinically important, as neonates that are at high risk of having hemodynamic instability because they were born extremely early and weigh less than average are already at risk. Such heightened incidences of tachycardia amongst the at-risk groups drive home the significance of grasping the process of drug selection [19]. There was no significant impact of the gender on the frequency of tachycardia, reflecting most likely that the differences result more likely as a result of the pharmacodynamics of the drug and maturity of the newborn and not of the sex differences. The results have direct implications on the neonatal practice in Pakistan. Caffeine is not always cheap and readily accessible as aminophylline, which makes its usage prevalent to some extent in most of the NICUs. Nonetheless, this increased incidence of tachycardia in relation to aminophylline is of specific concern regarding its own safety profile. In resource-poor settings, the treatment option needs to be cost-effective, available and safe [21]. The magnitude of difference in effects highlights the need to use caffeine as the first-choice agent in AOP, even in low- and middle-resource regions, to enhance better outcomes in neonates and minimal effect adverse events. The major strong point in this study is that it is randomized controlled; in this way, we minimize selection bias and increase the validity of comparisons between the two drugs. The calculation of the sample size was founded on an anticipated effect size, so that adequate power is available to determine clinically significant differences. Nonetheless, there are some limitations that one should consider. First, the study is located in one tertiary NICU and the findings may not be extrapolated to other facilities that may have different patient populations and treatment guidelines. Second, and importantly, serum drug levels were not collected and this would have given further information regarding pharmacokinetic variability. Three, the duration of follow-up covered a 7-day period and a long-term cardiovascular outcome was not measured.

Conclusion

It is concluded that caffeine therapy is associated with a significantly lower frequency of tachycardia compared to aminophylline in preterm neonates with apnea of prematurity. Both groups were comparable in baseline characteristics, indicating that the difference observed was attributable to the intervention itself. Stratified analysis further highlighted that tachycardia was more common in low birth weight and extremely preterm neonates treated with aminophylline. These findings support the preferential use of caffeine as a safer first-line therapy in neonatal intensive care units. Wider availability of caffeine in resource-limited settings such as Pakistan should be encouraged to optimize outcomes and reduce cardiovascular complications in this vulnerable population.

References

Zhao J, Gonzalez F, Mu D. Apnea of prematurity: from cause to treatment. Eur J Pediatr. 2011;170(9):1097-105. doi:10.1007/s00431-011-1409-6.

Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354(20):2112-21. doi:10.1056/NEJMoa054065.

Atik A, Harding R, De Matteo R, Kondos-Devcic D, Cheong JL, Doyle LW, Tolcos M. Caffeine for apnea of prematurity: Effects on the developing brain. Neurotoxicology. 2017;58:94-102. doi:10.1016/j.neuro.2016.11.012.

Vliegenthart RJ, Christine H, Onland W, van Kaam AH. Doxapram treatment for apnea of prematurity: a systematic review. Neonatology. 2017;111(2):162-71. doi:10.1159/000448941.

Du L, Tong X, Chen C, Gao X, Gagnatelli A, Li J, et al. Caffeine citrate for apnea of prematurity: a prospective, open-label, single-arm study in Chinese neonates. Front Pediatr. 2020;8:76. doi:10.3389/fped.2020.00076.

Sajjadian N, Taheri PA, Jabbari M. Is early preventive caffeine safe and effective in premature neonates? A clinical trial. Int J Pediatr. 2022;2022:8701598. doi:10.1155/2022/8701598.

Scala M, Marchman VA, Brignoni-Perez E, Morales MC, Dubner SE, Travis KE. Impact of the COVID-19 pandemic on developmental care practices for infants born preterm. Early Hum Dev. 2021;163:105483. doi:10.1016/j.earlhumdev.2021.105483.

Hassan S, Romero R, Vidyadhari D, Fusey S, Baxter J, Khandelwal M, et al. Vaginal progesterone reduces preterm birth rate in women with a short cervix: a randomized trial. Ultrasound Obstet Gynecol. 2011;38(1):18-31. doi:10.1002/uog.9017.

Jobe AH. Caffeine therapy—when and why? J Pediatr. 2017;190:2. doi:10.1016/j.jpeds.2017.09.032.

Zhang CY, Liu DJ, Hua SD, Guo S, Li XY, Zhang B, et al. Caffeine versus aminophylline with oxygen therapy for apnea of prematurity: a retrospective cohort study. Exp Ther Med. 2020;20(1):1-1. doi:10.3892/etm.2020.9175.

Lin YC, Tan YL, Yen TA, Chen CY, Tsao PN, Chou HC. Specific premature group have better benefits when treating apnea with caffeine than aminophylline/theophylline. Front Pediatr. 2022;10:817624. doi:10.3389/fped.2022.817624.

Prakash R, Pournami F, Prabhakar J, Nandakumar A, Jain N. Duration of caffeine for apnea of prematurity—A randomized controlled trial. Indian J Pediatr. 2021;88(11):1174-9. doi:10.1007/s12098-021-03659-y.

Lenasi H, Rihar E, Filipic J, Klemenc M, Fister P. The effect of caffeine on heart rate variability in newborns: a pilot study. MDPI. 2023;13(7).

Lin YC, Tan YL, Yen TA, Chen CY, Tsao PN, Chou HC. Specific premature groups have better benefits when treating apnea with caffeine than aminophylline/theophylline. Front Pediatr. 2022;10.

Miao Y, Zhou Y, Zhao S, Liu W, Wang A, Zhang Y, Li Y, Jiang H. Comparative efficacy and safety of caffeine citrate and aminophylline in treating apnea of prematurity: A systematic review and meta-analysis. PLoS One. 2022 Sep 19;17(9):e0274882. doi: 10.1371/journal.pone.0274882. PMID: 36121807; PMCID: PMC9484669.

Miao Y, Zhou Y, Zhao S, Liu W, Wang A, Zhang Y, et al. (2022) Comparative efficacy and safety of caffeine citrate and aminophylline in treating apnea of prematurity: A systematic review and meta-analysis. PLoS ONE 17(9): e0274882. https://doi.org/10.1371/journal.pone.0274882

Ho FCh, Duh TH, Chung HW, Yang ShT, Chen HL. Comparison of Caffeine and Aminophylline in Treating Apnea of Prematurity with Historical Data: A Single Center, Observational Study in Taiwan. Iranian Journal of Neonatology. 2025 Jan: 16(1). DOI: 10.22038/IJN.2024.75703.2458

Mueni E, Opiyo N, English M. Caffeine for the management of apnea in preterm infants. Int Health. (2009) 1:190–5. doi: 10.1016/j.inhe.2009.09.005

Dobson NR, Hunt CE. Caffeine: an evidence-based success story in VLBW pharmacotherapy. Pediatr Res. (2018) 84:333 40. doi: 10.1038/s41390-018-0089-6

Rostas SE and McPherson C. Caffeine therapy in preterm infants: the dose (and timing) make the medicine. Neonatal Netw 2019; 38: 365 374.
Kumar VHS and Lipshultz SE. Caffeine and clinical outcomes in premature neonates. Chil dren (Basel) 2019; 6: 118.