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Should labouring women take coffee with their steroids?

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Apnoea is the transient cessation of breathing that may be accompanied by oxygen desaturation and bradycardia. The incidence increases with increasing neonatal prematurity. Caffeine is effective in reducing the number of apnoeic attacks and the use of mechanical ventilation in the two to seven days after starting treatment in premature neonates. There is also decreased apnoea in the immediate peri-extubation period for ventilated infants born at less than 32 weeks gestation receiving caffeine. The target concentration range is 10–20 mg/l. Due to immaturity of the renal and hepatic systems, the half-life in premature infants (100 h) is longer than in term infants (24 h) and adults (3.5 h). It has been suggested that maternal caffeine ingestion may be protective of apnoea in preterm infants. However, ingestion of approximately 1500 ml coffee (500 mg caffeine) would be required to achieve a peak concentration of 10 mg/l in a woman at third trimester. Despite reduced clearance in the premature neonate, concentrations at postnatal day 2 (the usual timing of apnoea onset) would be below target concentration in a typical individual. The maternal use of caffeine, if chronic and excessive, may be associated with an increased incidence of intrauterine growth retardation and cot death as well as maternal and neonatal arrhythmias. Encouraging coffee intake immediately prior to delivery in labouring women is not a practical solution to reduce the incidence of apnoea of prematurity during days 2–7.

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Introduction

Apnoea is the transient cessation of breathing that may be accompanied by oxygen desaturation and bradycardia[1]. Neonates are at risk of apnoea because they have immature respiratory control. Apnoea may be of central, obstructive or mixed origin. Apnoea of prematurity and apnoea of infancy are commonly treated with methylxanthines (e.g. caffeine and theophylline)[2,3]. These methylxanthines can also be used to treat infantile apnoea associated with respiratory illness[4] and anaesthesia for surgery[5,6]. Caffeine has been used for over 20 years to treat apnoea, and is generally well tolerated with few reported adverse events[7]. Caffeine binds to adenosine receptors, antagonising the effect of adenosine which is a potent central inhibitor of respiration. Apnoeic episodes generally do not occur immediately following birth, but rather during the first week of life. It is possible that caffeine ingested by the mother, after crossing the placenta, may prevent apnoea in the first few days of life. Antepartum glucocorticoid treatment helps prevent the respiratory distress syndrome in premature infants[8]; should these steroids be taken in conjunction with strong coffee?

Physiology

Apnoea

Apnoea of prematurity is defined as the cessation of breathing for at least 20 seconds, or for a shorter duration if accompanied by bradycardia and/or oxygen desaturation in an infant of less than 37 weeks gestational age[9]. Apnoea of infancy (idiopathic apnoea with an onset in infants after 37 weeks gestation) is defined as the cessation of breathing for at least 20 seconds, or associated with bradycardia, oxygen desaturation, pallor and/or hypotonia[9,10]. Central apnoea results from a lack of respiratory drive or diaphragm movement resulting in complete cessation of airflow. Obstructive apnoea results from a blockage of the airway that despite continued respiratory effort stops airflow. Mixed apnoea occurs when the airway is obstructed and this occurs in association with a central pause in respiratory effort[2].

Apnoea is a consequence of immature respiratory control. The inspiration centre in the medulla oblongata of the brain stem generates the oscillatory respiratory pattern depending on input from a number of feedback elements from the lungs, upper airway and chemoreceptors. Chemoreceptors in the brain, aortic arch and carotid arteries are sensitive to changes in oxygen, carbon dioxide (CO_2) and pH changes. Neuronal impulses are carried to the respiratory centre where respiration is altered to adjust for these changes. There are also chemoreceptors in the laryngeal mucosa that inhibit respiration in response to chemical or mechanical stimulation. Output signals are sent back to the respiratory muscles to constantly adjust the breathing pattern[10].

Respiratory maturation

The incidence of apnoea increases with decreasing birth weight and gestational age. Almost all infants born weighing less than 1000 g suffer apnoea, compared to 25% born weighing less than 2500 g. For infants born at less than 29 weeks gestation the incidence of apnoea is approximately 50% whereas for those born at 34 to 35 weeks gestational age the incidence is only 7%[1].

The maturation of respiration is incomplete at birth. The respiratory pattern of the neonate resembles that of the fetus. The fetus responds to hypoxia by decreasing breathing activity and to hypercapnia by increasing the depth of breathing. Adults respond to hypoxia and hypercapnia by increasing ventilation[11]. Adults increase ventilation through both increased tidal volume and frequency in response to increased CO_2. Premature neonates do not appear to increase their frequency of breathing in response to increased CO_2; instead the neonate exhibits prolonged expiratory time. Animal studies have suggested that this prolonged expiratory time associated with hypercapnia is mediated by the brainstem[12]. Neurotransmitters such as GABA, adenosine, serotonin and prostaglandin either stimulate or inhibit the respiratory centre[10]. Preterm infants have an enhanced sensitivity to the inhibitory neurotransmitters, GABA and adenosine[13,14]. GABAergic neurons are thought to inhibit the inspiratory drive generated in response to hypercapnia[12,15] and so instead of increasing respiration frequency in response to increased CO_2, the neonate exhibits a prolonged expiratory time. The preterm infant's response to hypercapnia may resolve with maturation changes in the distribution of CO_2 and pH sensitivity among medulla structures and the second messenger systems involved in the modulation of ventilation responses to CO_2[12,15].

Both preterm and term neonates initially respond to hypoxia in the same way as the fetus, with hypoventilation and apnoea. The neonate must reset the threshold for the activation of peripheral and arterial chemoreceptors so that it can survive in the oxygen rich environment after birth. This gradually develops over the first 2 weeks after birth. When the hypoxic sensitivity is mature the infant is less likely to have apnoeic episodes in response to hypoxia[10,12]. Central apnoea may also result as a reflex to stimulation of receptors, such as the mucosal laryngeal receptors.

Upper airway muscles are also implicated in neonatal apnoea; they should dilate in coordination with the diaphragm and chest wall muscles to allow inspiration[16,17]. Preterm infants lack the coordination between the upper airway muscles and the diaphragm and this predisposes the infant to obstructive apnoea[16]. Normally during inspiration the upper airway muscles act to reduce upper airway resistance before the activation of the diaphragm. In preterm infants this sequence can be disrupted and the diaphragm may activate prior to the upper airway muscles, causing pharyngeal collapse and obstruction[18]. Airway closure occurs in up to 47% of central apnoea, and in all central apnoea lasting more than 20 seconds[10,19]. There is a close relationship between central apnoea and apnoea of mixed origin, suggesting that there is a continuum of airway closure instead of two separate events. This explains, in part, the success of continuous positive airway pressure (CPAP) techniques for the management of apnoea in neonates.

Pharmacology

Caffeine (1,3,7-trimethylxanthine) and theophylline (1,3-dimethylxanthine) are the two most commonly used methylxanthines for the treatment of apnoea[20]. Theophylline acts as a prodrug for caffeine[21] with steady state concentrations of caffeine averaging about 30% those of theophylline[22] in the very young. Caffeine has a more favourable pharmacokinetic profile compared to theophylline[23] with a wider therapeutic index, more predictable plasma concentrations, earlier onset of action, fewer side effects (particularly tachycardia)[24,25] and the long term elimination half-life in the neonate allows dosing either once a day or once every two days[26,27].

Pharmacodynamics

A target theophylline concentration of 10 mg/l has been proposed for relief of bronchospasm in adults[28,29]. Similar target concentrations have been used for the management of apnoea in neonates[30]. Plasma concentrations of theophylline greater than 15 mg/l have been shown to be associated with adverse effects such as tachycardia.

There are no concentration-response relationships described for caffeine. Aranda proposed that a clinically effective plasma concentration was 5–50 mg/l, but that there were minimal gains for ventilation drive and apnoea control above 20 mg/l[26]. Steer et al. have demonstrated benefits with increased dose (5 vs 20 mg/kg/day) of caffeine citrate for neonates born at less than 30 weeks gestation in the peri-extubation period[31], suggesting that there is a concentration-response relationship. Unfortunately, that study did not include plasma concentration measures. Toxic effects of caffeine include jitteriness, tremor, hypertonia, tachycardia, sweating, gastric dilatation, rhabdomyolysis, hyperglycaemia, metabolic acidosis, cardiac failure, cardiovascular collapse and death[32]. In premature infants, caffeine is generally well tolerated up to a serum level of 60 mg/l[26,32-35].

Mechanism of action

Caffeine acts through central respiratory centre stimulation, adenosine receptor blockade and improved respiratory muscle function. Caffeine binds to adenosine A_1 and A_{2A} receptors, and it is thought that most of the pharmacological actions of caffeine are mediated through the action of caffeine at adenosine receptors[14,36]. Adenosine and its analogues are potent central inhibitors of respiration. Adenosine is formed as a consequence of neural and metabolic activity and this is increased in response to hypoxia, which is associated with increased ATP breakdown. Animal studies have shown that adenosine antagonists attenuate respiratory depression and thus the therapeutic effect of caffeine may be due to its antagonising action at adenosine receptors[14,36].

GABAergic pathways are known to contribute to the inhibition of inspiration[37]. A_{2A} receptors expressed in areas of the piglet brain contain GABAergic neurons[14]. Activation of adenosine A_{2A} receptors induced the prolongation of expiratory duration and this response was blocked by the presence of a $GABA_A$ receptor antagonist[14]. This suggests that the activation of adenosine A_{2A} receptors produces the release of GABA within the respiratory centre of the CNS and that the activation of $GABA_A$ receptors by GABA results in prolonged expiratory time and inhibition of respiratory drive[14]. It is possible that the responses elicited by adenosine A_1 receptors may also have GABAergic mechanisms. Benzodiazepines have the potential to increase the incidence of apnoea through their action on the $GABA_A$ receptor.

Metabolism

Hepatic metabolism is the major clearance pathway in adults. Caffeine undergoes substantial reabsorption in the kidneys, with 98% tubular reabsorption and only 0.5–2% of an ingested dose of caffeine is excreted unchanged in the urine. Smoking, exercise, disease and pregnancy affect clearance. CYP1A2 accounts for approximately 95% of caffeine metabolism[38]. The N3-demethylation of caffeine to paraxanthine, the major metabolite, is mediated by CYP1A2. Xanthine oxidase and N-acetyltransferase also contribute to caffeine metabolism. Hepatic clearance of caffeine occurs via five metabolic pathways; N3-demethylation to paraxanthine (1,7-dimethylxanthine), N1-demethylation to theobromine (3,7-dimethylxanthine), N7-demethylation to theophylline (1,3-dimethylxanthine), CYP3A4 catalysed 8-hydroxylation to 1,3,7 trimethyluric acid (1,3,7-TMU) and C8–N9 bond scission to 6-amino-5-(N-formylmethylamino)-1,3-dimethyluracil (1,3,7-TAU)[39,40]. Paraxanthine, theobromine and theophylline account for approximately 80%, 11% and 4% of caffeine metabolism respectively[39].

Adult clearance is estimated at 3.6–5.9 l/h/70kg, with a volume of distribution of 46.2 l/70kg and a half-life in adults of 2–4.5 h[41].

Maturation of clearance

There is undetectable CYP1A2 mRNA in the fetal liver[42]. The activity of CYP1A2 remains very low after birth with noteworthy *in vitro* activity detectable by 1 to 3 months of age[43]. These

developmental changes are predicted by age and are independent of size which is predicted by weight. There is a paucity of data regarding mechanisms for the onset of extrauterine expression or specific mechanisms determining temporal switches[44,45]. Caffeine pharmacokinetics can be estimated using a single compartment, first order elimination model. Caffeine is well absorbed enterally and its oral bioavailability approaches unity in preterm neonates[26]. Due to immaturity of the renal and hepatic systems, the half-life in premature infants (100 h) is longer than in term infants (24 h) and adults (3.5 h)[32,33,46]. The volume of distribution is 63 l/70 kg. Standardising estimates of caffeine clearance from the literature to a 70 kg human using the allometric 3/4 power model[47] (Table 1) shows that the clearance of caffeine in infants seems to approach that of adults by 3 months of age[32]. Inter-individual variability of 25% for clearance and 11% for volume of distribution has been estimated for premature neonates.

The increase in clearance of caffeine by three months is attributable to maturing renal function and hepatic CYP1A2 activity. The kidneys excrete drugs and their metabolites by two processes – glomerular filtration and tubular secretion. Glomerular filtration rate (GFR) is commonly normalised to body surface area and GFR in the term infant is approximately 10–15 ml/min/m^2. This increases to approximately 20–30 ml/min/m^2 after 2 weeks[43] and reaches adult values at 3–5 months postnatal age[48]. Proximal tubular secretion reaches adult levels by 7 months of age.

Hepatic elimination of caffeine is almost absent in premature neonates[33]. Even in term neonates more than 85% of a caffeine dose is found in the urine[49]. The maturation of the hepatic system to adult rates occurs by 60 weeks postconception age[46,50] and the percentage cleared renally decreases gradually to the adult value of less than 2% by 7–9 months of age[49].

Polymorphism

There is large inter-individual variability for caffeine clearance reported in adults. The half-life can be as long as 12 h[41]. Individuals can be slow or fast acetylators of caffeine, depending on the allelic variant of CYP1A2. CYP1A2 has been detected only in the liver, where it seems to be regulated by at least two mechanisms, one controlling constitutive levels of expression and another regulating inducibility[51]. Approximately 50% of Caucasians have been shown to be slow or intermediate CYP1A2 metabolisers[51], but the frequency in Japanese subjects is much lower. There have been no nucleotide variations that can explain this phenotypic variability, however two single nucleotide polymorphisms (SNPs) have been identified in the CYP1A2 gene, which appear to be associated with CYP1A2 inducibility. It has been shown that the CYP1A2 164A·C polymorphism (CYP1A2*1F), common in Caucasians, can decrease CYP1A2 activity in smokers[52]. Another SNP found more frequently in Japanese subjects, CYP1A2 3858G·A (CYP1A2*1C) causes a significant decrease in CYP induction by smoking[52,53].

Table 1 Literature estimates of caffeine pharmacokinetic parameters.

Age (yr)	Weight (kg)	Clearance (l/h/kg)	CLstd [a] (l/h/70kg)
Premature neonate	2	0.004	0.06
Term neonate	3.5	0.004	0.13
0.25	6	0.091	3.46
0.5	7.5	0.119	4.8
1.0	10	0.126	5.5
Adult	70	0.057–0.085	3.6-5.9

[a]CLstd is the clearance standardised to a 70 kg human using the allometric 3/4 power model.

From Anderson BJ et al. Anaesth Intensive Care 1999;27:307-311, with permission[32] .

Dosing

In adults, a dose of caffeine of 1 mg/kg produces peak plasma concentrations of 1–2 mg/l. This concentration is not associated with any adverse effects. Doses of 5–8 mg/kg (plasma concentrations of 8–10 mg/l) are associated with some adverse effects including mild anxiety, excessive urinary output and increased gastric secretion. A lethal dose of caffeine in adults is estimated at 5–10 g[34].

A loading dose of caffeine of 10 mg/kg, followed by a daily maintenance dose of 2.5 mg/kg has been shown to reduce the incidence of apnoea in premature infants[26]. The maintenance dose required to achieve the target concentration will vary depending on maturation clearance changes with postconception age. Romagnoli et al.[54] have demonstrated that a maintenance dose of 5 mg/kg has better effect than 2.5 mg/kg in 37 preterm infants born before the 32nd week of gestation. Steer et al.[31] have demonstrated that caffeine citrate 20 mg/kg was superior to 5 mg/kg in the peri-extubation period for neonates born at less than 30 weeks gestation in terms of successful extubation and adverse effects. The target concentration remains undefined and therapeutic drug monitoring of caffeine is not routine.

Prophylactic caffeine administration and prevention of neonatal apnoea

Methylxanthines are effective for treating apnoea of prematurity[55]. Their role as prophylaxis was debated[54,56] but it is now established that they are effective in reducing the number of apnoeic

attacks and the use of mechanical ventilation in the two to seven days after starting treatment in premature neonates[57]. There is also decreased apnoea in the immediate peri-extubation period for ventilated infants born at less than 32 weeks gestation receiving caffeine[1]. The higher dose of 20 mg/kg/day is more effective than a lower dose of 5 mg/kg/day for peri-extubation management[31]. A concentration-response relationship for apnoea prevention has not been established, but serum concentrations in the range 10–20 mg/l appears to be effective[27].

A 10 oz (approximate 300 ml) drip brewed cup of coffee typically contains 100 mg caffeine. A 10 oz cup of tea brewed for more than 3 min contains 42 mg caffeine[58]. These amounts vary enormously per serving. Maternal concentrations after ingestion are dependent on coffee consumption and clearance. Genetic poly-morphism in the CYP1A2 gene cause altered inducibility of this major clearance enzyme. Pregnancy slows caffeine metabolism by 50% in the third trimester[59]. Environmental factors such as smoking can almost double metabolism. Caffeine crosses the placenta readily and maternal serum concentrations mirror those in the fetus[60]. Caffeine concentrations in cord blood are higher than expected, possibly because the fetal liver can methylate theophylline to caffeine as early as the twelfth week of gestation[26]. This caffeine is cleared slowly with progression to the extra-uterine environment.

There are few data relating caffeine ingestion to concentration in pregnant women. Maternal caffeine concentrations in a group of high caffeine consumers (>500 mg/day) were 1.0–3.5 mg/l compared to low caffeine consumers (<200 mg/day) 0.2–1.2 mg/l after an overnight fast of at least 10 h[61]. Fetuses of mothers with high caffeine ingestion spent much greater mean time in arousal state than in a sleep state[61].

It has been suggested that maternal caffeine ingestion may be protective of apnoea in preterm infants[62]. Episodes of apnoea often do not occur immediately after birth and it has been postulated that transplacentally acquired caffeine may be responsible for the delayed onset of apnoea[62]. The amount of apnoea, bradycardia, and periodic breathing experienced before 2 weeks of age in seven preterm infants with detectable cord blood caffeine was not different from that in 14 similar infants without caffeine. Unfortunately detectable caffeine concentrations only ranged from 1.1 to 3.7 mg/l, suggesting maternal access to caffeine was limited due to perinatal interventions.

The relationship of antecedent maternal smoking and caffeine consumption habits on the occurrence of apnoea (using polysonography) in their offspring were analysed in a cohort of mother-infant pairs. Multiple linear regression analysis determined that smokers tended to be younger (1.5 yr) and have lower birth weight infants who presented earlier with apnoea than infants of non-smokers. Increased rates of central apnoea occurred in infants of smokers compared with infants of non-smokers. Both central and obstructive apnoea rates associated positively with increasing maternal caffeine consumption, but smoking habits and caffeine ingestion were correlated[63]. It is difficult to quantify caffeine's effect on neonatal apnoea in this study because of the powerful association between smoking (during and after pregnancy) and apnoea.

Simulation

Apnoeic episodes generally do not occur immediately following birth, but rather during the first week of life. Methylxanthines are effective in reducing the number of apnoeic attacks and the use of mechanical ventilation in the 2–7 days after starting treatment in premature neonates[57]. It is unlikely that the maternal ingestion of coffee is protective against apnoea in the first few days of neonatal life. Neonatal caffeine concentrations are dependent on the caffeine concentration at birth and the postconception age of the infant. Predicted concentrations in an adult and neonate if 500 mg caffeine is ingested 2 h before birth (Figure 1) and 5 h before birth (Figure 2) are shown. This is equivalent to a very large single coffee (1500 ml) resulting in concentrations of only 5.7–7 mg/l at 48 h (Figure 1) in a premature neonate born 2 h after maternal ingestion.

Toxicity

Maternal caffeine ingestion is not without side effects. Chronic maternal caffeine ingestion has been postulated to increase the risks of apnoea in the neonate[64]. Khanna reported a premature infant with high concentrations of transplacentally acquired caffeine. The mother drank 24 cups of coffee/day during pregnancy. The infant developed apnoea, and not having known the above maternal history, was started on caffeine therapy. Serum caffeine concentration was found to be 40.3 mg/l prior to caffeine administration on the fifth day of age. Caffeine concentration at birth was probably much higher based on a pharmacokinetic extrapolation using a neonatal $t_{1/2}$ of 100 h, although it is also possible that this infant had a longer $t_{1/2}$ ($t_{1/2}$ range 40–230 h in premature neonates). It is suggested that manifestation of apnoea in this infant may have been related to caffeine withdrawal[64]. McGowan has reported eight infants born to mothers who

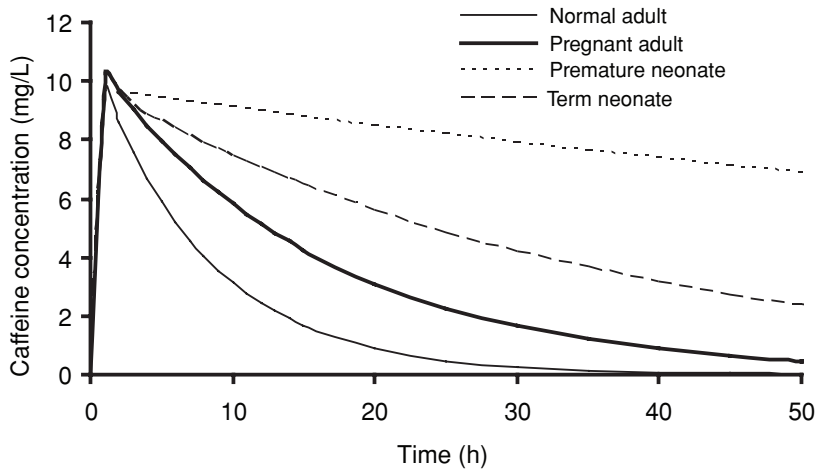

Figure 1 Predicted plasma concentrations of caffeine following delivery 2 h after 500 mg caffeine. Parameter estimates were CLadult 5.8 l/h, absorption half-life 10 min, CLpregnant 2.9 l/h, $t_{1/2}$preterm neonate 100 h, $t_{1/2}$term neonate 24 h

were heavy users of caffeine during pregnancy who all exhibited a withdrawal syndrome after delivery[65]. Apnoea can also be a manifestation of undiagnosed seizure activity associated with high neonatal caffeine concentration. Infants whose mothers have heavy caffeine consumption throughout their pregnancy may have increased risk for sudden infant death syndrome (SIDS). Data from New Zealand[66] suggest increased risk, although this risk was not reproduced in a Nordic population[67].

Chronic consumption was associated with an increased risk of intrauterine growth retardation (birth weight less than the 10th percentile for sex and gestational age). For women whose average daily caffeine consumption was 0–10, 11–150, 151–300, or ≥300 mg, the adjusted odds ratios for delivering a newborn with growth retardation were 1.00, 1.28 (95%CI 1.04–1.59), 1.42 (95% CI 1.07–1.87) and 1.57 (95% CI 1.05–2.33) respectively[68]. Caffeine ingestion during the third trimester was inversely related to birth weight[69,70]. Mean birth weight was reduced by reported caffeine consumption (–28 g per 100 mg of caffeine consumed daily, 95% CI: –0.10, –0.46, P = 0.001) but not mean gestational age. This small decrease in birth weight, observed for maternal caffeine consumption, is unlikely to be clinically important except for women consuming ≥600 mg of caffeine daily[71].

Growth retardation might, in part, be caused by the caffeine's impact on placental blood flow[72]. There is a decrease of placental blood supply and increased maternal serum epinephrine levels associated with maternal coffee ingestion. Animal work suggests that these effects are mediated through myometrial calcium receptor signalling[73,74] and interference with prostaglandin synthesis[75].

Maternal caffeine use during pregnancy is associated with maternal[76] and neonatal arrhythmias[77]. Coffee also promotes gastro-oesophageal reflux, a situation exacerbated by hormone changes during pregnancy. Coffee stimulates gastrin release and gastric acid secretion, although studies on the effect on lower oesophageal sphincter pressure

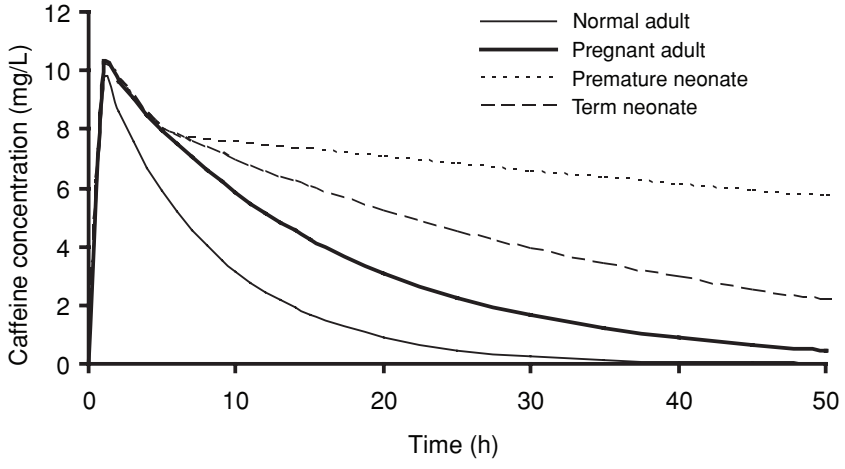

Figure 2 Predicted plasma concentrations of caffeine following delivery 5 h after 500 mg caffeine. Parameter estimates were CLadult 5.8 l/h, absorption half-life 10 min, CLpregnant 2.9 l/h, $t_{1/2}$preterm neonate 100 h, $t_{1/2}$term neonate 24 h

yield conflicting results. Coffee also prolongs the adaptive relaxation of the proximal stomach, suggesting that it might slow gastric emptying[78].

Conclusion

The effects of maternal caffeine ingestion are as difficult to evaluate as those effects on perinatal outcomes[79,80]. There are few data investigating neonatal respiratory effects attributable to maternal coffee ingestion immediately before birth. Simulation suggests that maternal coffee ingestion will have little effect on apnoea on days 2–7. Approximately 1 g of coffee, a dose associated with toxic effects, would be required to be ingested by the mother before birth to achieve concentrations above 10 mg/l on postnatal day 2.

There is large inter-individual variability of predicted concentrations in both mother (coffee dose, delayed gastric absorption, smoking, polymorphism) and child (postconception age, delay between maternal coffee intake and birth) and encouraging coffee intake immediately prior to delivery is not a practical solution to reduce the incidence of apnoea of prematurity during days 2–7. Only a limited number of mothers will give birth within hours of coffee ingestion and the incidence of neonatal apnoea mainly depends on the gestational age at birth. Apnoea is most often observed on postnatal day 2 and beyond and therefore, the administration of caffeine can be initiated after birth in neonates who display symptoms or preventively shortly after birth. In addition, maternal coffee ingestion is associated with negative outcome variables for the mother, fetus and neonate. It is unsurprising that signals of early pregnancy include an aversion to coffee in addition to nausea and vomiting, which results in decreased caffeine consumption. These symptoms often interfere with daily life and last beyond the first trimester for many[81].

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