RELATION BETWEEN REPORTED MATERNAL CAFFEINE CONSUMPTION DURING PREGNANCY AND NEONATAL STATE AND HEART RATE

by

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(ABSTRACT)

The prenatal period is a time of rapid development during which the fetus adapts to a wide range of experiences that may alter the infant's developmental course. These experiences include exposure to conditions such as maternal stress, disease and the ingestion of a wide range of drugs. While great attention has focused, recently, on the effects of prenatal exposure to such drugs as cocaine and alcohol on newborn behavior, little is known about the effects of prenatal exposure to caffeine. Despite the widespread consumption of caffeine by mothers during pregnancy, recent investigations have suggested that caffeine may indeed function as a physical and behavioral teratogen. In addition to consistent findings of adverse physical outcomes such as prematurity and fetal growth retardation in both animals and humans, adverse effects of maternal caffeine consumption during pregnancy on behavioral development in the fetus have also been suggested by both comparative and human studies. For example, assessment of rodents prenatally exposed to caffeine generally show behavioral patterns of increased activity. Studies with humans using the Neonatal Behavioral Assessment Scale (NBAS) have shown that maternal caffeine consumption

is related to differences in the ability of infants exposed to caffeine to regulate their level of arousal. The purpose of this study was to explore the relation between prenatal exposure to caffeine and newborn regulation of arousal, as measured by variations in neonatal heart rate and behavioral state. The heart rates and behavioral states of 50 healthy, full-term one to two-day-old neonates were assessed every 30 seconds for one hour between feedings. Measures of fetal growth and dysmorphology were also collected for each infant. Mothers were then interviewed about their caffeine consumption during pregnancy. When maternal nicotine and alcohol use during pregnancy were statistically controlled, results showed that infants who were prenatally exposed to higher amounts of caffeine had higher heart rates, both overall and during quiet and active sleep. In addition, these infants had experienced a higher number of obstetrical complications and were more likely to be from a lower socioeconomic background than infants prenatally exposed to smaller amounts of caffeine. These findings suggest that maternal caffeine consumption during pregnancy is related to altered levels of arousal among exposed infants. Since heart rate is an indicator of autonomic nervous system functioning, heavier maternal caffeine consumption during pregnancy may have subtle effects on nervous system (NS) development among exposed infants. These observed behavioral outcomes may, in turn, have long-term consequences for social and cognitive development.

DEDICATION

I would like to dedicate this dissertation to my fiance and best friend, David Pizarro. His unwaivering love and support was my one constant through the many high and low points that occurred during this long and challenging process. For his enduring patience, love, and belief in me, I am grateful.

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Introduction

The developmental period prior to birth is a time of rapid growth and development which sets the stage for future developmental processes. During the prenatal period of development, the fetus is sensitive to a wide range of influences, including chemical, physical and electrical experiences and is susceptible to subtle changes in the uterine environment (Hofer, 1981). Recent evidence suggests that developmental influences such as prenatal malnutrition, prenatal exposure to drugs, and maternal hormones have complex effects on nervous system development which may, ultimately, alter behavioral development (Hofer, 1981). In other words, alterations in the prenatal environment such as externally influenced biochemical changes may result in individual differences as the affected organism develops along different trajectories.

The past several decades have witnessed an increasing awareness of the potential dangers that exposure to drugs and other chemical substances pose for the developing fetus. The discovery that most substances ingested by the pregnant mother, including both nutritive and pharmacologic substances, readily cross the placental barrier and enter the fetal system has generated countless studies on the effects of those substances on the developing organism (Soyka, 1981). In particular, the unexpected discovery that the supposedly innocuous drug, thalidomide, could drastically alter the structural development of an organism (McBride, 1961) focused

widespread attention on the potential teratogenic effects of a wide range of chemical substances.

Early studies focused primarily on the potential mutagenic effects of a range of drugs such as thalidomide (e.g, McBride, 1961) and morphine (e.g., Friedler & Cochlin, 1972). A substance was generally not considered teratogenic if deleterious physical effects were not observed in the exposed organisms. More recently, a broader conceptualization of teratology has included any drugs or other chemical substances that have morphological, physiological, biochemical or behavioral effects on the developing fetus (Coyle, Wayner, & Singer, 1976; Hollenbeck & Scanlon, 1986). A teratogenic agent is now widely accepted to be any "drug, chemical, virus, physical agent, or deficiency state that, if present during the embryonic or fetal period, alters morphology or subsequent function in the postnatal period (Shepard, 1986, p.237)."

This conceptualization of teratogenicity broadens the range of substances considered to be harmful to a developing organism by recognizing substances which have more subtle adverse effects on the exposed fetus. Sensitive indicators of the prenatal effects of a drug include such effects as intrauterine growth retardation (IUGR) and atypical neonatal behaviors (e.g., frequent or infrequent changes in behavioral states and irritability). This recognition of the more subtle symptoms of teratology has allowed a substance to be identified as a teratogen in the absence of immediately observable morphological or anthropometric effects if physiological,

biochemical, or behavioral effects are present.

The potential danger of teratogenic substances for developing organisms becomes even more salient when the possibility of adverse long lasting consequences is considered. It is conceivable that prenatal exposure to drugs can directly alter behaviors or other functions that may persist into childhood or throughout life (Sonderegger, 1992). Animal studies have begun to provide evidence for such long lasting effects of numerous drugs to which organisms are exposed during gestation. For example, one study found that when rats were exposed to caffeine during the first week of life, which corresponds to the animal model equivalent of the third trimester of human fetal development, they were significantly impaired in spatial learning and their locomotive activity in an open-field test was significantly lower than controls when assessed as adults (Zimmerberg, Carr, Scott, Lee & Weider, 1991).

In addition to such direct effects on development, social interactions between the drug-using mother and the exposed infant may affect neonatal development (Bernstein, Jeremy, & Marcus, 1986). Prenatal exposure to drugs creates biological vulnerability in the infant such as an increased occurrence of dispositional qualities in the young organism that may alter the manner in which the caregiver responds to the infant and, thus, may make the infant more susceptible to poor or inadequate caregiving (Zuckerman & Brown, 1993).

A transactional model of this process was originally described by Sameroff and Chandler (1975) and experimentally tested by Zeskind and Ramey (1978; 1981).

Infants who have been exposed to a wide range of drugs prenatally often display difficulty in regulating their arousal (Zuckerman & Brown, 1993). If these infants do not receive help from caregivers in this process of regulation (e.g., effectively providing or reducing stimulation when needed), the already vulnerable infant may be propelled into a cycle of inadequate interactive behaviors with its caregiver. This ongoing cycle of nonnurturant interactions continue to enhance the possiblity of a nonoptimal developmental outcome for the infant. For example, atypical behaviors in prenatally exposed neonates in conjunction with dysfunctional or insensitive parenting may result in a pattern of circumstances which lead to failure to thrive (Crockenberg, 1981; Zuckerman & Brown, 1993) and insecure and disorganized infant-mother attachment and behavioral disorganization at 18 months of age (Rodning, Beckworth, & Howard, 1990). In conclusion, the specific behavioral and physical effects of prenatal exposure to drugs in conjunction with other nonoptimal environmental and postnatal factors may significantly affect the vulnerability of the developing organism and increase its odds of moving along a nonoptimal developmental trajectory.

The field of behavioral teratology has recently examined the effects of prenatal exposure to teratogens on newborn behavior. For example, a large body of literature has explored the adverse effects of prenatal exposure to alcohol. Although much of this work has focused on the distinct pattern of morphological malformations and behavioral pattern which characterizes the "fetal alcohol syndrome" described by Jones, Smith, Vlleland and Streissguth (1973), other work has studied the more subtle

effects of prenatal exposure to lower doses of alcohol. These adverse effects include poorer habituation (Streissguth, Martin, & Barr, 1983), poorer arousal (Jacobson, Fein, Jacobson, Schwartz, & Dowler, 1984), and significantly lower IQ scores (Streissguth, Sampson, & Barr, 1989) among children exposed prenatally to small to moderate doses of alcohol. Adverse effects of prenatal exposure to other drugs such as nicotine and marijuana have also been well-documented (Abel, 1980; Fried, 1980; Fried, 1983; Fried & Watkinson, 1988; Fried, Watkinson, & Willan, 1984; Greenland, Staisch, Brown, & Gross, 1982; Landesman-Dwyer & Emmanuel, 1979; Linn, Schoenbaum, Monson, Rosner, Stubblefield, & Ryan, 1983; Naeye, 1981; Richardson, Day, & Taylor, 1989; Saxton, 1978; Scher, Richardson, Coble, Day, & Stoffer, 1988).

Perhaps because it is widely viewed as being a relatively innocuous drug, relatively little effort has been concentrated on examining the effects of prenatal exposure to caffeine on the developing fetus. Caffeine is widely recognized as being one of the most frequently consumed drugs in humans (Gilbert, 1976; Weathersbee & Lodge, 1977) and has been argued to be so common that it is considered to be more of a dietary supplement than a drug by most consumers (Zimmerberg et al., 1991). In fact, some studies have found that up to 95% of mothers ingest caffeine during their pregnancy in the form of coffee, tea, colas, cocoa, chocolate or over-the-counter medications such as Doan's pills, Nodoz, Vivarin, cold and allergy tablets, headache tablets, diuretics, and stimulants (Hill, 1973). Despite the popular belief that caffeine

is merely a dietary supplement, by all definitions, caffeine has specific structural and physiological properties which characterize it as a drug.

Physiological Effects of Caffeine

Structure and Mutagenicity of Caffeine.

Caffeine (1,3,7-trimethylxanthine) is a plant alkaloid and a member of the xanthine family of drugs. It is structurally related to both adenine and guanine (see Figure 1), two of the purine DNA base pairs responsible for building genetic material (Weathersbee & Lodge, 1977). Partly as a result of its genetically related structure, the presence of caffeine in developing cells can both decrease DNA polymerase activity (Wragg, Carr & Ross, 1967) and increase the number and appearance of smaller DNA-replicating units (Lehmann, 1972). Since these characteristics of caffeine are so closely associated with genetic processes, they give caffeine the potential to alter the biochemical processes involved in the multiplication and metabolism of cells (Linn, Schoenbaum, Monson, Rosner, Stubblefield, & Ryan, 1982). Consequently, researchers have been prompted to study the mutagenic and physical teratogenic effects of caffeine on the developing fetus (Weathersbee & Lodge, 1977).

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insert Figure 1 about here

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Various studies have indicated that caffeine can be mutagenic in bacteria (Greer, 1968), fungi (Zetterberg, 1959) and Drosophila (Mittler, Mittler & Owens,

1967). At this time, evidence of mutagenic effects of caffeine in more complex organisms is less clear-cut. For example, extremely high doses of caffeine injected into young offspring has been shown to cause physical deformations in the offspring of pregnant mice (Fujii & Nishimura, 1969) but not in the offspring of pregnant rats (Gilbert & Pistey, 1973). Chromosomal breakage in human cell cultures (Kulhmann, Fromme, Heege & Ostertag, 1968) and in human cells in vitro (Ostertag, Duisberg & Sturmann, 1965) has been demonstrated with extremely high doses of experimentally administered caffeine, however, no human malformations have been linked to the natural ingestion of caffeine during pregnancy (Mulvihill, 1973). As a result, little can be concluded concerning the mutagenic potential of caffeine in humans or other mammals. Little is known about any of the teratogenic effects of lower doses of caffeine that correspond to the amounts of caffeine which are conceivably ingested by human beings on a day to day basis.

Pharmacologic Effects of Caffeine. Once a product containing caffeine has been consumed, the caffeine is rapidly and completely absorbed from the gastrointestinal tract into the bloodstream (Blanchard & Sawyers, 1983) and distributed throughout the body to areas including the brain, heart, liver, spleen, testes, muscles, plasma and erythrocytes in proportion to tissue water content (Graham, 1978; Rall, 1985). Peak blood levels of caffeine are typically reached within 30 minutes following ingestion of a caffeinated product in the human adult (Rall, 1985). Because of its low molecular weight and high lipid solubility, which

facilitate placental transfer, caffeine readily crosses the placenta (Morris & Weinstein, 1981) and achieves fetal blood and tissue levels similar to the maternal concentrations (Soyka, 1981).

Adults then metabolize and excrete caffeine through the renal systems in the form of methylxanthine derivatives (see Figure 2 for the metabolic pathways of caffeine), with only 3-6% of the ingested caffeine appearing in the urine in its original trimethylxanthine form (Graham, 1978). Since the metabolic half-life of caffeine is only approximately 3 hours in adults, the pharmacologic effects of caffeine are typically short-lived in the adult human.

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Considering such a short metabolic half-life, the placental transfer of caffeine, theoretically, should not pose significant danger to the developing fetus. There is considerable evidence, however, that the fetus and newborn infant lack the necessary enzymes to metabolize caffeine (Morris & Weinstein, 1981). Up to 85% of the ingested caffeine is excreted in its original form in the newborn's urine, compared to 26% in the maternal urine (Horning, Stratton, Nowlin, Wilson, Horning, & Hill, 1973). The remainder of the caffeine in the maternal system is broken down and excreted as methylxanthine derivatives. Figure 3 shows the excretion of caffeine and its metabolites in both the urine of a mother and the urine of her newborn infant (see

Figure 3). It is clear that the enzymes needed to break caffeine down into paraxanthine (1,7-dimethylxanthine) and, subsequently, monomethylxanthine are absent in the newborn infant. Additional evidence suggests that these enzymes are not present or functional until several days after birth (Weathersbee & Lodge, 1977). Thus, the caffeine that the infant was exposed to during the last days of gestation remain in the newborn's system for several days following birth.

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In addition to the relative inability of the fetus or newborn infant to metabolize caffeine, the caffeine remains in their system for significantly longer periods of time than in the systems of their adult counterparts. The metabolic half-life for caffeine in the newborn infant is 4 days, considerably longer than the average 3-hour half-life in adults (Horning, Butler, Nowlin, & Hill, 1975; Parsons & Neims, 1981). This relatively long half-life allows small amounts of caffeine which, alone may not be harmful to the fetus, to accumulate to potentially toxic levels in the fetus or newborn infant (Bory, Baltassat, Portault, Bethenod, Frederich, & Ananda, 1979). Thus, although the fetus or infant may appear to be exposed to only small amounts of caffeine, their undeveloped metabolic systems allow the accumulation of possibly dangerous levels of the drug.

Effects of Caffeine on the Central Nervous System. One of the primary physiological effects of caffeine is its function as a stimulant which produces excitation at all levels of the central nervous system (Howell, Clozel, & Aranda, 1981; Rall, 1985). Such excitation can be observed in phenomena such as the increase of the transmission of impulses across nerves and synapses and stimulation at the motor-end plates in the presence of small doses of caffeine (Howell et al., 1981). It is widely accepted that these stimulative, behavioral effects of caffeine may be mediated by the blockage of adenosine receptors (Phillis & Kostopoulos, 1975; Rall, 1985). Adenosine is a neurotransmitter/neuromodulator in the central nervous system (CNS) with an essential role in energy metabolism (Phillis & Wu, 1981). It also functions as a potent depressant on the central neurons which prevents the firing of cerebral cortical neurons and, thus, has a generalized inhibitory, depressive action on CNS functioning, blood pressure, catecholamine release and respiration (James, 1991).

When caffeine is introduced to the system, it functions as an antagonist at adenosine receptors (Mumford & Holtzman, 1990; Snyder, Katims, Annau, Bruns, & Daly, 1981) which, subsequently, increases the accumulated levels of cyclic adenosine monophosphate (cyclic AMP). Since adenosine is responsible for regulating a variety of biological processes such as catecholamine release, CNS activity, and respiration, interference with its normal functioning can significantly alter physiological and behavioral processes. In fact, the presence of caffeine in the CNS increases the rate of firing of cerebral cortical neurons by antagonizing the depressant actions of

adenosine (Phillis & Wu, 1981). These stimulative effects do not require large amounts of caffeine to occur. Even what is considered to be moderate doses of 10mg/kg of caffeine (approximately equivalent to 5-6 cups of drip style coffee/day in a 70kg individual) consistently elicit patterns of excitation in the human CNS (Phillis & Wu, 1981).

Hormonal Effects of Caffeine. In addition to its antagonistic effects on adenosine receptors, caffeine has significant hormonal effects in mammals. Evidence suggests that caffeine may significantly increase the serum glucose level of the neonate (Lazaro-Lopez, Colle & Dupont, 1980). Several possible mechanisms have been linked to this increase in blood glucose. One possible explanation is that caffeine functions as a competetive inhibitor of phosphodiesterase which slows the normal metabolic process of the cyclic nucleotides (Weathersbee & Lodge, 1977). An increase in the cyclic nucleotides, specifically cyclic 3',5'-adenosine monophosphate (cyclic AMP) and cyclic 3',5'-guanosine monophosphate (cylic GMP) is produced as a result. These cyclic nucleotides are ubiquitous within the cells of the body and appear to have an inverse relationship to such vital functions as cell division and cellular growth. As the number of circulating cyclic nucleotides increase, cell division and growth is slowed. Consequently, in order for the development of the fetus and newborn infant to occur at its typically rapid rate, the amount of available cyclic nucleotides needs to remain relatively low.

It has been hypothesized that, during gestation, the intracellular level and

sensitivity to cyclic AMP decreases in the developing embryo and remains low until shortly before birth (Robison, 1973). This would allow cell growth and division to occur more rapidly. When caffeine is released into the fetus' bloodstream, caffeine increases the available cyclic nucleotides by inhibiting the metabolic process. The typical rate of cell growth and division is, consequently, slowed. Thus, an increase in the amount of circulating cyclic nucleotides, due to the presence to caffeine, may detrimentally alter important developmental processes such as cell growth and cell division.

This particular phenomenon may explain the high incidence of reduced birth weight typically found in infants exposed to caffeine prenatally (Gilbert & Pistey, 1973). It is not unusual to find a significant decrease in birthweight in both humans (e.g., Hogue, 1981) and other animals (e.g., Gilbert & Pistey, 1973) exposed to caffeine during prenatal development, even at small doses such as 4 mg/kg (approximately equivalent to two cups of drip style coffee per day). In fact, the indirect growth inhibiting properties of caffeine may be dose-related. Since an inverse relationship between cyclic nucleotides and cell growth and division exists, increased amounts of caffeine are hypothesized to act as greater inhibitors of the metabolism of cyclic nucleotides. This, in turn, would proportionally increase the amounts of circulating cyclic AMP and cyclic GMP which would slow the overall cell growth and division.

Caffeine has also repeatedly been shown to increase the amount of

catecholamines, particularly epinephrine and norepinephrine, circulating in the human fetus and newborn (Kirkinen, Jouppila, Koivula, Vuori, & Puukka, 1983). Increases in fetal catecholamines are responsible for altering blood flow in the fetus by constricting the uterine and placental vasculature and have been shown to produce severe fetal asphxia when large doses were administered to pregnant rhesus monkeys (Adamsons, Mueller-Heubach,& Meyers, 1971). When pregnant mice were exposed to caffeine, the altered blood flow resulting from increased fetal catecholamines resulted in higher incidences of cleft palate, brachnathia and digital malformations (Fujii & Nishimura, 1974). Thus, it is hypothesized that caffeine could alter the fetal catecholamine balance in human fetus' in the same manner, thereby altering potential physical and behavioral developmental changes (Weathersbee & Lodge, 1977).

Cardiovascular Effects of Caffeine. Since caffeine is readily absorbed into the bloodstream, it is transported throughout the body to every major organ and system, including the heart. Caffeine acts as a direct cardiac muscle stimulant and can cause cardiac symptoms such as palpitations and arrhythmias in adults (Howell et al., 1981). Caffeine has also been shown to significantly reduce cerebral blood flow in adults (Mathew, Barr, & Weinman, 1983). Considerably less is known about the cardiac effects of caffeine on the exposed fetus or newborn. There is little evidence to suggest that there are any direct detrimental cardiac effects on the fetus exposed to typical doses of caffeine (James, 1991), however, the possibility that decreased cerebral blood flow to the fetus can contribute to fetal hypoxia has not been ruled out.

Although there is, currently, no direct evidence of an association between caffeine and reduced blood flow, impaired fetal development as a consequence of decreased blood flow has been well-documented in the presence of other teratogens such as nicotine (e.g., Abel, 1980). For example, numerous studies have found that smoking during pregnancy is associated with intrauterine growth retardation (e.g., Chase, 1969; Lowe, 1959). Comparative studies that have explored the effects of intrauterine exposure to nicotine, have demonstrated that the primary physiological mechanism responsible for intrauterine growth retardation (i.e., reduced birth weight or birth length) is fetal oxygen deprivation related to nicotine exposure during pregnancy (e.g., Kirschbaum, Dilts, & Brinkman, 1970).

This intrauterine hypoxia appears to occur, in part, as the result of the release of catecholamines (Armitage, 1965). Catecholamines can create uterine vasoconstriction which effectively decreases the blood flow to the placenta. Consequently, the nutrients and oxygen carried to the fetus via the blood flow are limited. Since, as discussed above, caffeine also affects the levels of circulating catecholamines, the potential role of decreased cerebral blood flow in altering developmental outcomes should not be ruled out as a possible teratogenic mechanism.

Summary of the Pharmacologic Effects of Caffeine. In summary, caffeine has various pharmacologic effects which may prove hazardous to the developing fetus. Caffeine is readily transported from the mother to the fetus and remains in the fetus for several days before it is eliminated in its original form. While in the fetus,

caffeine functions as a nervous system stimulant and alters the overall distribution of various hormones in the developing fetus. In addition, caffeine may produce fetal hypoxia by altering placental blood flow. The known biochemical effects of caffeine discussed above, which range from inhibiting cell growth and division to significantly stimulating the central nervous system, suggest that caffeine may affect processes related to the infant's regulation of arousal. As a result, investigators have begun to explore the association between prenatal exposure to caffeine and adverse developmental outcomes in the newborn infant.

The Association of Caffeine with Developmental Outcomes in the Fetus and Newborn

The majority of the work that has been conducted to explore the increased risk for nonoptimal development that stems from prenatal exposure to methylxanthines has used comparative studies which tend to be the most efficient means for collecting data concerning perinatal drug exposure (Weinberg et al., 1992). A variety of methodological issues contribute to the practicality of using comparative studies more frequently than human studies. One such issue concerns the difficulties inherent in studying human subjects who cannot ethically have many types of experimental controls related to substance use imposed upon them. Because there are many confounding variables that may be associated with caffeine in naturally occurring settings, comparative studies are often used to explore the effects of caffeine on prenatal development. Comparative studies permit genetic and environmental controls as well as carefully controlled drug treatment procedures (Weinberg, Sonderegger, &

Chasnoff, 1992) which allows for causal pathways between drug exposure and developmental outcomes to be determined. In addition, the smaller mammals which are typically used in such studies have shorter gestational and infancy periods which enhance the practicality of conducting prospective studies and of exploring the possibility of long-term effects of perinatal drug exposure. Although the ability to draw conclusions between humans and other animals on the basis of comparative studies is somewhat limited, a comparative model is frequently used to study early exposure to potential teratogens because of its ability to provide information on the underlying processes and mechanisms of teratogens on developmental outcomes.

Structural Effects. Early comparative studies focused primarily on the adverse physical effects of caffeine exposure on the developing fetus. In general, caffeine has been linked to increases in the incidence of fetal structural abnormalities such as cleft palate and limb and skeletal abnormalities in the offspring of both mice and rats treated with caffeine during pregnancy (Battig, 1985; Mulvihill, 1973). Many of these findings, however, are based on studies which have administered extremely high doses of caffeine to the animal. For instance, a single intraperitoneal injection of caffeine (250mg/kg body weight) administered to mice produced a variety of congenital malformations (Fujii & Nishimura, 1969). Such a high dose of caffeine administered at one point in time is not equivalent to the lower doses of caffeine consumed at steady intervals by humans (James, 1991).

Gilbert and Pistey (1973) addressed this methodological issue by repeatedly

administering injections of lower doses of caffeine to pregnant rats to determine the physical consequences of chronic exposure to relatively low doses of caffeine during gestational development. The intraperitoneal dose administered on a daily basis (ranging from 4mg/kg to 16mg/kg) approximated the dose consistent with fairly high caffeine consumption in humans (10 to 40 cups of coffee per day). No significant physical malformations were observed in the exposed offspring, however, the average fetal weight of the exposed offspring was significantly decreased in all groups. In fact, the decrease in fetal weight appeared to be dose-related, with the group receiving the largest injections of 16mg/kg of caffeine per day demonstrating the lowest average fetal weight. Thus, it appears that although smaller doses of caffeine do not produce congenital malformations in the offspring exposed to caffeine during gestation, they are responsible for reducing the birth weight of exposed infants.

One shortcoming of the above study is the route of drug administration. A number of studies suggest that the method of administration may play an important role in the effects that caffeine has on the exposed offspring (Concannon, Braughler, & Schechter, 1983; James, 1991). Intraperitoneal injections expose the animal to the concentrated daily dose of caffeine all at once. Since humans repeatedly consume caffeine during the day through beverages and medications which are ingested orally, it is important to consider the route of drug administration when drawing conclusions about the potential teratogenic effects of caffeine based on findings from comparative studies.

To counteract these methodological issues which limit the generalizability to humans, many studies have used methodologies which administer caffeine to animals in patterns which attempt to parallel human consumption of caffeine (Elmazar, McElhatt, & Sullivan, 1982; Nolen, 1981; 1982). For example, when caffeine is administered to pregnant mice orally by gavage to simulate oral ingestion of caffeine by humans, structural teratologic effects are found for high doses of caffeine (200 mg/kg and 300 mg/kg), but not for lower doses of 100 mg/kg (Elmazar, McElhatt, & Sullivan, 1981). This confirms the importance of considering the route of administration when drawing conclusions about the teratologic effects of caffeine. It appears that single intraperitoneal injections of high doses of caffeine are considerably more toxic in young rodent offspring than repeated oral administrations of lower doses. However, even lower doses have been associated with nonoptimal developmental outcomes other than extreme physical defects.

The findings of studies on the effects of maternal caffeine use on physical development in the human fetus and newborn infant are considerably less clear-cut than those of comparative studies. No studies have definitively linked caffeine use to congenital abnormalities in human neonates (Heller, 1987), however, caffeine consumption during pregnancy has been repeatedly associated with increased incidences of prematurity and low birth weight (e.g., Hogue, 1981; Van den Berg, 1977). Many of these studies have failed to control for polydrug use such as alcohol or nicotine. Since both smoking and drinking are positively correlated with caffeine

consumption during pregnancy (Heller, 1987), the failure to account for nicotine and alcohol use severely limits the conclusions that can be drawn about the effects of caffeine on fetal development.

More recent studies have attempted to control statistically for some of these potentially confounding variables (e.g., Linn, Schoenbaum, Monson, Rosner, Stubblefield, & Ryan, 1982). In general, there have been mixed findings which adds to the general confusion concerning the potential teratologic danger of caffeine. For example, in one study, after controlling for smoking, Linn et al. (1982) did not find any associations between low to moderate coffee consumption (0-4 cups/day) during pregnancy and adverse congenital or anthropometric outcomes. As such, they conclude that coffee consumption does not appear to pose any physical danger to the developing fetus.

Other studies, however, have found a significant association between caffeine consumption and low birth weight. One such study controlled for both maternal age and alcohol use, but not smoking (Mau & Netter, 1974). In general, they found that only 4.7% of the mothers who did not drink coffee during their pregnancy had low birth weight infants (<2500 grams) compared to 7.5% of mothers who frequently drank coffee during their pregnancy. However, in addition to the failure to control for smoking, no data are provided concerning the quantity of caffeine consumed by the mothers.

Watkinson and Fried (1985) found a significant correlation between heavy

caffeine use (>300 mg/day which is approximately equivalent to more than 3 cups of drip coffee per day) and low birth weight even after carefully controlling for maternal smoking and alcohol use (Watkinson & Fried, 1985). In addition, unlike other studies of its kind, this study carefully calculated amounts of individual caffeine consumption by considering details such as size of serving and method of coffee preparation. They were able to demonstrate that heavy caffeine use (>300 mg/day) alone is associated with a significant reduction in the mean birth weight and the ratio of the infant's weight for length.

Whereas Watkinson and Fried (1985) examined the relation of heavy caffeine exposure during pregnancy to anthropometric outcomes of the newborn infants, Martin and Bracken (1987) studied the association between a range of exposure to maternal caffeine consumption during pregnancy and the birthweight of her infant. Based on reported caffeine use, mothers and infants were assigned to one of four categories of caffeine consumption: 1) 0 mg/day, 2) 1-150 mg/day (<1.5 cups of coffee per day), 3) 151-300 mg/day (1.5-3 cups of coffee per day) or 4) >300 mg/day (>3 cups of coffee per day). Consistent with the findings of previous studies, they found that low birthweight (<2500 gm) was more likely to occur in the infants of women who consumed heavy amounts of caffeine (>300 mg/day). No evidence of an increased incidence of low birthweight was found for the infants of mothers who consumed low (1-150 mg/day) or moderate (151-299 mg/day) amounts of caffeine. There was, however, a dose-related effect of caffeine on the birthweight of infants in all three

caffeine groups. In other words, even though the infants were not more likely to be low birthweight infants (<2500 grams), low and moderate amounts of prenatal exposure to caffeine were associated with a reduction in neonatal birthweight.

In summary, existing studies on the association of prenatal caffeine exposure and birthweight have shown mixed findings. Exposure to heavy amounts of caffeine during prenatal development is clearly associated with a significant reduction in birth weight in humans, as well as other mammals. As indicated earlier, such effects as altered levels of hormones may result in the increased incidence of IUGR in animals exposed to heavy amounts of caffeine. When the developing organism is exposed prenatally to low to moderate amounts of caffeine, a significant reduction in birthweight is typically only observed when the effects of other confounding variables are removed or statistically controlled. Although the evidence of the anthropometric effects of lower doses of caffeine is presently inconclusive, assessment techniques other than birthweight may provide more sensitive measures of any altered developmental outcomes associated with maternal caffeine consumption during pregnancy.

Behavioral Effects. Although much of the research on the adverse effects of prenatal exposure to caffeine on the developing organism have focused on the physical effects of caffeine, the teratogenicity of caffeine is evident in other types of developmental outcomes as well. These teratogenic effects can be manifested in a number of ways (see Table 1). Investigators have recently begun to recognize that

behavioral tests may be more sensitive indicators of the teratogenicity of drugs than relying on the observation of physical abnormalities alone (Coyle et al., 1976; Vorhees, Brunner, & Butcher, 1979) and increasing numbers of studies have begun to explore these more subtle indications of the teratogenic effects of caffeine. Since behavioral deficits can be observed as a consequence of prenatal drug exposure in the absence of observable morphological changes (Coyle et al., 1976), it has become clear that the assessment of a drug's teratogenicity is not complete without an assessment of its structural and functional effects. As a result, investigators have recently begun, in earnest, to explore the neurobehavioral effects that caffeine may have on the developing organism.

One such study by Sinton, Valatx, and Jouvet (1981) showed adverse behavioral outcomes in mice as a result of early caffeine exposure in the absence of any observable structural deficiencies. In order to isolate the effects of caffeine exposure to those incurred during the fetal stage, Sinton et al., (1981) cross-fostered mice offspring exposed to caffeine to dams that had never received caffeine treatments in their water. Pregnant dams were treated daily with doses of 60mg, 80mg, and 100mg of caffeine in their drinking water. The offspring were then tested for a total of 6 months beginning at 9 months of age. No physical abnormalities were observed, however, increases in passive avoidance latencies in an apparatus consisting of a light and a dark compartment were observed in subjects who had been exposed to caffeine prenatally. Thus, the results of this study indicate that, even when pups are only

exposed to caffeine during gestation, behavioral effects are clearly observed beyond infancy.

The authors concluded that exposure to caffeine gestationally modifies neural systems related to ascending anterior forebrain dopamine systems (Sinton et al., 1981). Decreases in the amount of available dopamine is hypothesized to be responsible for the depressed behavior observed in the exposed pups. Support for this interpretation was provided by Enslen, Milan, and Wurzner (1980) who found a decrease in dopamine in the locus coeruleus in rat pups exposed to caffeine prenatally. Thus, exposure to caffeine during the important prenatal period of development may interfere with neurotransmitter activity which, subsequently, has significant, long-term behavioral consequences.

Long-term behavioral effects of caffeine were also found in a study involving rats (Sobotka, Spaid, & Brodie, 1979). Rats were continually exposed to water containing either 0.0125, 0.025, or 0.05% of caffeine during pregnancy and lactation (Sobotka et al., 1979). The only neurobehavioral change noted in the neonate was a delay in eye-opening among the caffeine exposed pups. However, when tested during adolescence, the rats exposed to caffeine during pregnancy and lactation exhibited increased open-field exploratory activity and enhanced performance in a combined fixed ratio/position discrimination paradigm. Thus, it appears that early exposure to caffeine may be manifested as hyperarousal as late as adolescence in rat pups which suggests that the adverse neurobehavioral effects of caffeine have long-term

developmental consequences. Although chronic exposure to caffeine appeared to be responsible for these altered developmental outcomes, it is not clear from this study whether these behavioral effects were the result of exposure to caffeine prenatally, postnatally (lactation) or as a combination of pre- and postnatal exposure to caffeine.

Although Sinton et al. (1981) and Sobotka et al. (1979) provided important information about the potential long-lasting neurobehavioral effects of caffeine exposure during prenatal development, the scope of their studies did not include detailed information on the more immediate neurobehavioral consequences of early caffeine exposure. Such data was provided by West, Sobotka, Brodie, Beier, and O'Donnell (1986) who explored the potential neurobehavioral effects in newborn and young pups exposed to caffeine during gestation. Pregnant rats were orally administered caffeine in daily doses of 5, 25, 50 and 75 mg/kg (equal to approximately 2 1/2 to 37 1/2 cups of drip style coffee in a 70 kg individual). The physical and behavioral development of the offspring was then measured from birth through 9 weeks of age. Physical effects of prenatal caffeine exposure included decreased neonatal body weights for offspring who were exposed to 50 or 75 mg/kg of caffeine and delayed eye opening for the offspring who had been exposed to 25, 50, and 75 mg/kg of caffeine during gestation.

Behavioral effects included increased performance of a step down avoidance response in a passive avoidance task and decreased active avoidance in a shuttlebox active avoidance task for the offspring who were exposed to the higher doses of

caffeine (50 or 75 mg/kg) than for the control pups. Although the behavioral effects of caffeine were most pronounced in groups exposed to higher doses of caffeine, it is interesting to note that even at the lowest level of caffeine used in this study (5mg/kg), increased auditory startle responses and decreased amounts of active and passive responding to shock were observed. Thus, the authors concluded that there was no safe level of in utero caffeine exposure in this particular study, and that even small amounts of caffeine may be detrimental to the developing fetus.

The above study indicates that prenatal exposure to caffeine, ranging from 5 mg/kg to 75 mg/kg, appears to increase locomotor activity in rats and mice following birth. This excitability is widely believed to be the result of blocked adenosine receptors which effectively reduces the amount of depressive cyclic nucleotides. In fact, the vast majority of the results support the widely held belief that the underlying mechanism for these functional effects is caffeine's antagonism of adensonine receptors which acts as a central stimulant with altered behavioral effects lasting into adolescense or adulthood.

Although, as stated earlier, a few studies on the association between prenatal caffeine exposure and newborn behaviors have found some evidence of hypoarousal (or depressed behaviors), most studies have demonstrated hyperarousal in the exposed infant. It is interesting to note that, while hyperarousal is typically demonstrated in exposed neonates, there is some evidence to suggest that this apparent early hyperarousal ceases to exist by about 2 months of age (Hughes & Beveridge, 1986;

Sobotka et al., 1979). Studies that have examined neurobehavioral effects of prenatal caffeine exposure in older offspring have often found evidence of hypoaroused patterns of behavioral responses (e.g., Sinton, 1981). Thus, although behavioral effects associated with prenatal exposure to caffeine are still observed in older offspring, the manifestation of those altered developmental outcomes change during development. To date, it is unclear what the physiological mechanism is that is responsible for this neurobehavioral shift.

Studies of the behavioral effects of prenatal exposure to caffeine on human infants have also shown differences in the ability of infants exposed to caffeine to regulate their level of arousal. Most of these studies have used the Neonatal Behavior Assessment Scale (Brazelton, 1984) to explore the association between prenatal exposure to caffeine and changes in newborn behavior and regulation of arousal. The Neonatal Behavior Assessment Scale (NBAS) is comprised of 28 behavioral items, scored on 9-point scales, designed to assess the infant's behavioral style when interacting with its environment. Individual items are designed to assess areas such as behavioral state, responsiveness to auditory and visual stimuli, motor maturity, reflexes and changes in arousal. Although the NBAS was originally designed to assess normal, healthy, full-term infants, it has long been used to assess the effects of variations in the prenatal environment (e.g., Lester & Zeskind, 1978; Zeskind, 1981) and has frequently been used with high-risk infants, including those prenatally exposed to behavioral teratogens (Brazelton, Nugent, & Lester, 1987). As such, the NBAS is

one of the most frequently used behavioral assessment techniques in teratologic studies. The NBAS has been used, for example, to assess the effects of prenatal exposure to alcohol (Coles, Smith, Fernhoff, & Falek, 1985; Coles, Smith, Lancaster, & Falek, 1987; Streissguth, Barr, & Martin, 1983), cocaine (Chasnoff, Burns, Schnoll, & Burns, 1985; Coles, Platzman, Smith, James & Falek, 1992; Woods, Eyler, Behnke, & Conlon, 1993), marijuana (Fried, 1980; Fried & Makin, 1987), methadone (Soule, Standley, Copans, & Davis, 1974), heroin (Kaplon & Kron, 1975) and nicotine (Picone, Allen, Olsen, & Ferris, 1982; Saxton, 1978).

The existing studies on the association of maternal caffeine consumption during pregnancy and neonatal behavioral outcomes have, similarly, used the NBAS as their primary assessment technique. In one such study, mothers were interviewed concerning their caffeine consumption as well as their alcohol and nicotine use (Jacobson et al., 1984). When potentially confounding variables, such as exposure to other drugs (including alcohol and nicotine), and maternal stress were statistically controlled, maternal caffeine use during pregnancy was associated with a significantly shorter gestation, poorer neuromuscular development and a higher incidence of abnormal reflexes. Since the finding of an increased number of abnormal reflexes were hypothesized to possibly be the result of the higher incidence of preterm infants among the sample exposed to caffeine, analyses were conducted in which gestational age was controlled statistically. Even with the removal of this potentially confounding variable, caffeine use was associated with a higher score on abnormal reflexes.

Caffeine use prior to pregnancy was also related to poorer orientation and general irritability.

An important finding of this study was the significant relation between prenatal caffeine exposure and a greater range of behavioral states in exposed infants. The Range of State scale score on the NBAS is comprised of four items which reflect the infant's highest level of arousal (excitement), the speed at which the infant achieves this peak, irritability, and how often the infant changes behavioral states during the approximately 20-30 minute examination. Unfortunately, conclusions based on the final score for lability of states are limited by problems inherent in its scoring. A poor score on the Range of State scale could indicate that an infant frequently changed state or seldom appeared to change state. Thus, while these results suggest that behavioral state is an important behavioral outcome of prenatal caffeine exposure, the Range of States score does not provide information about whether the infant appears to hypoaroused or hyperaroused. Further, Jacobson et al. (1984) did not have a direct measure of the amounts of caffeine consumed by the mothers during their pregnancy.

A more recent study explored the association of neonatal behavioral outcomes with more detailed information concerning the amount of maternal caffeine consumption during pregnancy (Hronsky & Emory, 1987). Only nonsmoking mothers and mothers who were not considered to be at high risk due to alcohol abuse or drug addiction were included in the study. Mothers were asked to complete a detailed dietary questionnaire which obtained information about their recent caffeine

consumption (past 3 days) as well as other nutritional habits. The accuracy of this information was confirmed by the results of salivary and cord blood assays from newborn samples collected at birth and at the time of assessment. In general, results showed a dose-related effect of prenatal exposure to caffeine on several behaviors assessed by the NBAS. One significant finding was that maternal caffeine consumption during pregnancy was correlated with an increase in the number of times an infant changed its behavioral state during the exam. Results also showed that infants prenatally exposed to caffeine demonstrated an increase in the number of Behavioral Startles, a decrease in their ability to orient to visual stimuli, and a lower score on the Consolability and Muscle Tone scales than comparison infants. These findings are consistent with those of Jacobson et al. (1984) who also found a greater Range of State in infants prenatally exposed to caffeine.

A third study examined the long-term consequences of prenatal exposure to caffeine (Barr & Streissguth, 1991). Five hundred children of mothers who consumed caffeine during pregnancy were followed for seven years and assessed on a variety of behavioral measures. Maternal caffeine consumption ranged between 0 and 2506 mg/day, with an average of approximately 190 mg/day (equivalent to 2-2 1/2 cups of coffee per day). After variables such as smoking, alcohol, and maternal demographics were statistically controlled, no association between exposure to caffeine and behavioral outcomes on measures such as the NBAS, sucking, the Bayley Scales, IQ at 4 and 7 years of age, Fine Motor Dexterity at 4 years of age, or Vigilance at 7

years of age were found. It was concluded that no short-term or long-term consequences of prenatal caffeine exposure appeared to be present in humans.

These results are inconsistent with the significant behavioral effects of prenatal exposure to caffeine found by Hronsky and Emory (1987) and Jacobson et al. (1984) and may be the consequence of marked differences in the demographic characteristics of the subject populations. Whereas Hronsky and Emory (1987) and Jacobson et al. (1984) studied mothers with a low socioeconomic status (SES), Barr and Streissguth (1991) had older, predominantly white, moderate to high SES subjects. These demographic characteristics have been associated with differences in patterns of caffeine consumption and smoking habits (e.g., Kuzma & Kissinger, 1981) and, therefore, significant differences among subject populations may have important consequences for the results of studies on the association of prenatal caffeine exposure and neonatal outcomes.

Summary. Results of comparative and human studies indicate a relation between prenatal exposure to caffeine and changes in neonatal behavior. Significant differences in activity level and regulation of arousal are not surpising when considering the stimulative effects that caffeine has on physiological systems such as the cardiac system, hormonal system and nervous system. Comparative studies generally show an increase in locomotor activity and behavioral responding in newborns prenatally exposed to caffeine. Within a few weeks of birth, some studies find that this hyperaroused pattern of responding shifts to a hypoaroused pattern of

responding. Although it is unclear why this neurobehavioral shift occurs, comparative studies indicate that changes in level of arousal are consistently found among animals prenatally exposed to caffeine.

Similarly, results of studies on human infants show that differences in the regulation of arousal are associated with prenatal exposure to caffeine. Both Jacobson et al. (1984) and Hronsky and Emory (1987) found an increase in scores on the Range of State item on the NBAS. These higher scores suggest that infants had difficulty in regulating their arousal as measured by behavioral state (Brazelton, Nugent, & Lester, 1987). Thus, variations in the regulation of behavioral state differentiates infants who have been prenatally exposed to various amounts of caffeine. Hronsky and Emory (1987) also found an association between prenatal exposure to caffeine and an increased number of Behavioral Startles and a decreased ability of infants to orient to visual stimuli. Both of these findings can also be conceptualized as reflecting the regulatory capacities of the newborn infant. Behavioral startles are part of the autonomic regulation of newborn infants and have been found to be sensitive to individual differences in infants related to nutritional insult and other obstetric complications (Emory & Mapp, 1988; Huntington, Zeskind, & Weiseman, 1985). Further, infants who have difficulty orienting towards auditory or visual stimuli on the NBAS also have difficulty regulating their behavioral state or level of arousal (Horowitz, 1987). Infants that are highly aroused prefer less intense stimulation, whereas infants that are less aroused prefer more intense stimulation (Karmel,

Gardner, & Magnanon, 1992; Turkewitz, Lewkowicz, & Gardner, 1983). Thus, infants who have difficulty in regulating their arousal as a result of prenatal experience to caffeine will demonstrate differences in their ability to attend to sensory stimulation.

Assessment of Infant Arousal

An infant's ability to regulate its arousal has important implications for how the infant will adapt to the rich array of stimulation present in its complex postnatal environment. In fact, the structural and functional organization and integrity of an infant is reflected in its ability to regulate arousal as measured by differences in behavioral state (Gardner & Karmel, 1983). In the presence of both endogenous and exogenous sources of stimulation, infants must be able to cope with sensory challenges from the external environment as well as adequately perform homeostatic processes (DeGangi, DiPietro, Greenspan, & Porges, 1991). Individual differences in the ability to regulate arousal, therefore, may reflect the impact of a wide range of endogenous and exogenous developmental influences. As discussed above, existing studies on the association between prenatal exposure to caffeine and individual differences in behavioral outcomes have suggested that maternal consumption of caffeine during pregnancy may be an important source of chemically-induced stimulation which may affect an infant's ability to regulate its arousal as measured by behavioral state. Although the NBAS has been shown to be an effective instrument for detecting individual differences in the abilities of infants to regulate their arousal

in response to a range of sensory stimuli, it does not differentiate between infants who may be hyper- or hypoaroused or provide specific information about the degree of variability in the infant's levels of arousal. Two frequently used measures for assessing changes in infant arousal are behavioral state and heart rate.

Behavioral State as an Assessment of the Regulation of Arousal. Behavioral states are temporally organized, qualitatively distinct patterns of behaviors that range from conditions of sleep to crying (Prechtl and O'Brien, 1982). Nominal scales by which behavioral state can be measured have been developed by several researchers including Prechtl and Beintema (1964), Wolff (1966), Thoman (1975) and Brazelton (1973; 1984), among others. Despite some differences among these behavioral state classifications, researchers agree that behavioral states are a collection of recurring patterns of behaviors that are qualitatively different from each other and indicate qualitatively unique levels of arousal (Prechtl & O'Brien, 1982).

These measures of behavioral state have been used to explore individual differences in behavioral organization that are associated with variations in pre- and perinatal experience. As described above, measurement of behavioral state is frequently a part of the NBAS to assess the effects of conditions that alter the regulation of arousal. For example, poor regulation of arousal, as measured by the NBAS, has been found in preterm infants (Brazelton, Als, Tronick, & Lester, 1979), and infants who showed signs of atypical patterns of fetal growth, as indicated by an atypical ponderal index (Lester, Garcia-Coll, Valcarcel, Hoffman, & Brazelton, 1986;

Zeskind, 1981) and low birth weight (Lester, Emory, Hoffman, & Eitzman, 1976). Individual differences in the regulation of arousal, as measured by the NBAS, have also been found in infants who were prenatally exposed to drugs, including marijuana (e.g., Fried & Makin, 1987), alcohol (e.g., Coles, Smith, Fernhoff, & Falek, 1985), and cocaine (Chasnoff, Griffith, MacGregor, Dirkes, & Burns, 1989). While this method of assessing young infants may indicate the presence of differences in the ability to regulate arousal, it does not separate infants who demonstrate atypically high levels of arousal from infants who demonstrate atypically low levels of arousal. (Table 2 shows a description of the 6 categories of behavioral state described by Brazelton (1974; 1984) and frequently used to assess individual differences among infants.)

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Other studies have explored individual differences in temporal organization of behavioral state by measuring how long an infant is observed in individual behavioral states. For example, infants who suffer from brain damage were found to differ from comparison infants in the amount of time they spend in various sleep states (Parmelee & Stern, 1972). The number of 20-second epochs that infants were observed to be in quiet (eyes closed and still and regular respiration) and active (eyes closed, eye movements, frequent body, limb, or face movements, and irregular respiration

patterns) sleep were recorded during a 2-3 hour observation period. Results showed that infants suffering from brain damage spent a significantly larger percentage of time in quiet sleep than comparison infants.

Differences in the amount of time spent in individual behavioral states has also been documented in infants exposed to a wide range of drugs such as opiates (Hans, Marcus, Jeremy, & Auerbach, 1984), alcohol (Rosett et al., 1979), and marijuana (Scher et al., 1988). In one study which examined the association between maternal alcohol consumption during pregnancy and neonatal state regulation, the amount of time each infant spent in active, quiet and indeterminate sleep was continuously recorded between feedings over a 24-hour period via a bassinet sleep monitor with a pressure sensitive mattress (Rosett et al., 1979). Infants of mothers who drank heavily during pregnancy spent less time asleep, were more restless, had more frequent major body movements and demonstrated a poorer quality of quiet sleep than comparison infants. A more recent study assessed individual differences in the regulation of arousal among infants who were prenatally exposed to alcohol and marijuana by obtaining a 2 - 2 1/2 hour EEG-sleep recording for each infant 24 to 36 hours after birth (Scher et al., 1988). The percent of time that each infant spent in awake, active sleep, and quiet sleep states were calculated for the total observation period. In general, infants who were prenatally exposed to marijuana demonstrated increased body movements, and decreased percentages of time spent in both total quiet sleep and trace alternant quiet sleep.

The stability of temporal organization of behavioral state has also been shown to be indicative of individual differences in the regulatory capacities in infants (Thoman, 1986). One way of establishing the stability of temporal organization of behavioral state was developed by Thoman (Thoman & Whitney, 1990). In her longitudinal study, Thoman determined the distribution of each infant's sleep and waking states within each of four consecutive weekly 7-hour observations and then examined the intraperson correlations between these state variables across the four observations (Thoman & Whitney, 1990). In a study of state organization in 22 healthy, full-term infants using this method of assessment, all infants who demonstrated unusually low stability of their behavioral state organization experienced nonoptimal developmental trajectories ranging from severe developmental dysfunctions such as mental retardation, severe hyperactivity and Sudden Infant Death Syndrome (SIDS) to minor developmental delays at 6 months and at 30 months of age (Thoman, Denenberg, Sievel, Zeidner, & Becker, 1981). None of the infants who demonstrated higher stability scores showed any evidence of developmental dysfunctions at 30 months of age suggesting that stability in the organization of behavioral state is predictive of later development.

The number of times that an infant changes behavioral state has also been found to differentiate infants who have been exposed to a wide range of pre- and perinatal experiences. In one study, results indicated that preterm infants who showed a greater number of state changes were more likely to have a poorer overall

performance on the NBAS and were at higher risk for severe medical problems or for early death (Tynan, 1986). The number of observed changes in behavioral state has also been shown to be a useful indicator of developmental outcomes in fullterm infants. Infants who were observed to have a larger number of state transitions were more likely to have "poor clinical outcomes" such as developmental delays, seizures, and epilepsy at 3 to 4 years of age than infants who displayed a smaller number of state transitions (Lombroso & Matsumiya, 1985).

Heart Rate as an Assessment of the Regulation of Arousal. Another approach to assessing differences in the regulation of arousal in newborn infants is to study the activity of autonomic nervous system function evident in heart rate. Unlike behavioral state, which is measured on a nominal scale, heart rate is a continuous variable that can be subjected to parametric analyses. Early in prenatal development, heart rate has little or no variability (Dreyfus-Brisac, 1968). After about 30 weeks of conceptional age, as heart rate is increasingly coordinated with a wide range of central and autonomic systems, heart rate is characterized by a significant increase in variability (Watanabe, Iwase, & Hara, 1973). By birth, the infant's heart rate reflects a summation of a multitude of internal and external sensory systems, including those associated with physiological, cognitive and behavioral processes (Zeskind & Marshall, 1991) as they are mediated by the coordination of the parasympathetic and sympathetic components of the autonomic nervous system (Berg & Berg, 1987). When the sympathetic nervous system is activated by external or internal sources of

stimulation, a heightened level of arousal is reflected in an increased heart rate. The parasympathetic nevous system may subsequently react in equal magnitude to inhibit arousal and decrease the infant's heart rate (Glick & Braunwald, 1965). These normal homeostatic processes may be reflected in a rhythmic pattern of the variability of the infant's heart rate (Porges & Byrne, 1992; Zeskind & Marshall, 1991).

Measures of heart rate variability can be partitioned into short-term variability (beat-to-beat variability) and/or long-term variability. Short-term variability refers to the variability between sequential heart beats and is calculated by obtaining the standard deviation or the mean absolute difference between sequential heart beats (Porges & Byrne, 1992). With this particular method, large amounts of data are collected in relatively short periods of time. Short-term variability is hypothesized to reflect neural control of the heart by the vagus and, thus, provides an indirect measure of the status of the infant's nervous system (Porges, McCabe & Yongue, 1982). This detailed method of assessing small gradations in heart rate as it is modulated by the nervous system via the tone of the vagus nerve is an index called the cardiac vagal tone (Porges & Byrne, 1992). A greater vagal tone is associated with a greater range of organized behaviors in the individual, whereas a lower vagal tone is believed to be indicative of inefficient autonomic and central processes.

Since vagal tone is hypothesized to be sensitive to nervous system insult, it has been used to assess individual differences among infants exposed to a range of prenatal conditions and has consistently been found to differentiate infants with a range of

nervous system dysfunctions from healthy infants. A lower vagal tone has also been found among infants who were at-risk due to being preterm or because they had experienced asphyxia at birth (Fox & Porges, 1985; Porges, 1983). In addition, at both 40 weeks conceptional age and 90 days after birth, infants with respiratory distress syndrome exhibited a decreased short-term variability in their heart rate pattern (Fox, 1983). These findings indicate that measures of short-term heart rate variability (HRV) may be able to differentiate high-risk infants from healthy infants.

In contrast to measures of short-term variability, long-term variability is hypothesized to measure a level of arousal that reflects the effects of relatively more stable timing mechanisms on behavior (Zeskind and Marshall, 1991) and reflects homeostatic processes between sympathetic and vagal influences (Porges & Byrne, 1982). By definition, long-term variability is measured by recording the infant's heart rate over a relatively longer period of time. One useful method by which long-term heart rate variability has been measured has been to time-sample the heart rate of the infant every 30 seconds for extended durations. In one early study, long-term heart rate variability was found to reliably differentiate among infants who also differed in measures of crying believed to reflect autonomic processes (Zeskind & Field, 1981). When heart rate was recorded at 5-minute intervals for 30 minutes, long-term heart rate variability (as measured by the standard deviation of the heart rate) was found to be greater among infants who had a higher threshold for crying which is associated with high-risk infants than among infants with a lower threshold for crying. Building

on the above work, more sophisticated measures of long-term heart rate variability have been used to differentiate infants who show signs of atypical fetal growth, as assess by an atypical ponderal index (PI) (Zeskind, Goff, & Marshall, 1991). For this study, the heart rates of 36 newborn infants were recorded every 30 seconds for 2 continuous hours while infants rested in an isolette midway between scheduled feedings. Spectral analyses of the time-series data showed that infants who showed signs of atypical fetal growth, had less complexity in the rhythmicity of their long-term heart rate variability than infants with typical patterns of fetal growth (Zeskind et al., 1991). In addition, although not statistically significant, the heart rate variability of infants with an average PI was larger than the heart rate variability of infants with an atypical PI.

Other studies support the view that infants with these differences in long-term heart rate variability also differ in other measures of autonomic functioning. Newborn infants with atypical patterns of fetal growth have a higher fundamental frequency in their cry sound and a higher threshold for arousal than infants with average PI's (Lester, 1979; Zeskind & Lester, 1981). Both of these behaviors have been directly linked to the autonomic regulation of arousal (Lester, 1984; Porter, Porges, & Marshall, 1988). Infants with atypical patterns of fetal growth have also been shown to have poorer scores on scales measuring auditory and visual orientation to stimuli, and to have greater difficulty in regulating their autonomic function and state of arousal as measured by the NBAS (Als, Tronick, Adamson, & Brazelton, 1976;

Lester, 1979; Zeskind, 1981; 1983). This population of infants is also at high risk for lower intelligence, a more withdrawn personality and less optimal mother-infant interactions through 3 years of age (Zeskind & Ramey, 1978; 1981) and lower IQ's and attention deficits at 12 years of age (Zeskind, Campbell, & Ramey, 1994).

The method of assessing long-term heart rate variability by recording heart rate every 30 seconds for an extended period of time has also been shown to be sensitive to differences in early postnatal nutrition. The heart rate and behavioral state, as assessed by a 6-point nominal scale consisting of 1) Quiet Sleep, 2) Active Sleep, 3) Drowse, 4) Alert, 5) Active Alert, and 6) Crying states (Brazelton, 1973;1984), of 14 breast-fed and 14 bottle-fed newborn infants was recorded every 30 seconds for 2 hours while the infants rested in an isolette (Zeskind, Marshall, & Goff, 1991). Results showed that breast-fed infants had greater complexity in the rhythmicity of their long-term heart rate variability, a larger amount of variability in heart rate, as measured by statistical variance, and were observed to spend a smaller number of 30 second epochs in Quiet Sleep than were bottle-fed neonates. In addition, when a separate mean heart rate was derived for those 30-second epochs in which each infant was in Quiet and Active Sleep states, breast-fed infants demonstrated a lower mean heart rate in both Quiet Sleep and Active Sleep than bottle-fed infants. In other words, even when infants were observed to be in the same behavioral state, individual differences in heart rate were able to differentiate between infants with different nutritional experiences. Since a lower heart rate has been used as a reliable estimate

of lower energy consumption (Woodson, Field, & Greenberg, 1983), these findings suggest that breast-fed infants are more efficient in their energy utilization, thereby conserving more energy for other developmental processes.

These findings are similar to previous work that has demonstrated that measures of arousal and the regulation of behavioral state differentiate between breast-fed and bottle-fed infants. For example, breast-fed infants have a lower threshold for arousal as indicated by the increased likelihood of crying following stimulation (Alegria & Noirot, 1978). Breast-fed infants have also been found to be more "irritable" and "less consolable", and to have more difficulty in regulating their behavioral state than bottle-fed newborns as measured by the NBAS (DiPietro, Larson, & Porges, 1987). In addition, when heart rate was assessed for a 10-minute period, breast-fed infants demonstrated a lower heart rate, higher vagal tone and higher heart rate variability than bottle-fed infants (DiPietro et al., 1987). These patterns of heart rate activity have been hypothesized to indicate greater autonomic organization (Porges, 1983). Taken together, these findings suggest that various measures of autonomic regulation can reliably differentiate between infants who have been exposed to different early postnatal conditions.

Pilot Data

The sensitivity of measures of the organization of behavioral state to the potential adverse effects of prenatal exposure to caffeine is supported by analyses of pilot data. Data which was collected during a previous study of newborn behavior not

specifically designed to assess behavioral outcomes in newborns prenatally exposed to caffeine were used for these analyses in order to examine the sensitivity of the paradigm and measures to reports of maternal caffeine consumption during pregnancy. Reported maternal caffeine consumption during pregnancy was calculated and used to assign infants to groups of low (0-109 mg/day), moderate (133-316 mg/day) or high (343-850 mg/day) caffeine exposure. Data from infants whose mothers reported alcohol use or who smoked more than ten cigarettes a day were excluded from analyses. Consequently, the group of low caffeine exposure consisted of 7 subjects, the group of moderate caffeine exposure had 16 subjects, and the group of high caffeine exposure had 3 subjects. The behavioral state of the infant, using Brazelton's (1973; 1984) six-point scale, was recorded every 30 seconds for two continuous hours. Oneway analyses of variance (ANOVA) on levels of caffeine exposure were conducted on the number of 30 second episodes that infants were observed in each of the six behavioral states.

Results showed significant effects of caffeine for time spent in active sleep, $F(3,22)=4.24$, $p<.01$, time spent in an alert state, $F(3,22)=7.49$, $p<.001$, and time spent in an active alert state, $F(3,22)=3.26$, $p<.05$. Newman-Keuls post-hoc tests showed that infants who were prenatally exposed to heavy amounts of caffeine during pregnancy spent more time in active sleep and less time in alert and active alert states than infants exposed to low or moderate amounts of caffeine (see Table 4). These results indicate that the behavioral states of neonates are sensitive to prenatal exposure

to caffeine. As such, careful observations of the behavioral states of neonates prenatally exposed to caffeine are expected to serve as sensitive indicators of the adverse effects of intrauterine exposure to caffeine on the developing fetus.

Purpose of the Study

The purpose of this study was to examine how prenatal exposure to caffeine is related to neonatal regulation of arousal, as assessed by measures of behavioral state and heart rate. In addition, measures of atypical patterns of fetal growth were closely examined to explore their potential role as moderator variables which determine, in part, how an infant will develop in response to early exposure to caffeine.

Method

Subjects

Fifty subjects were selected from a sample of 1- to 2-day old full-term ($\geq$ 37 weeks as determined by the Ballard exam) infants (28 boys, 22 girls) who resided in the normal newborn nursery at Montgomery Regional Hospital (n=28), a small hospital which serves a primarily white low- to moderate-socioeconomic class population in a predominantly rural area in Blacksburg, Virginia, or the full-term newborn nursery at Grady Memorial Hospital (n=22), a large inner city hospital serving a predominantly black, low socioeconomic class population in Atlanta, Georgia. Only infants who have been identified as healthy infants by their attending pediatrician after routine physical and neurological exams were selected. In addition, infants born to mothers who reported any illicit drug use were not included in the

study. Additional criteria for exclusion from the study included maternal psychosis, parental refusal, and a primary language other than English.

Maternal Characteristics. The general characteristics of the women recruited for this study are described in tables 5 and 6. The majority of the women recruited from Montgomery Regional Hospital (MRH) were white (89%), married (75%), and of low- to moderate-socioeconomic status as defined by the Hollingshead (1975) 4-factor index of social class. The average age was 24.4 years (SD=5.72) and only two women reported any use of alcohol during their pregnancy. In contrast, the majority of mothers recruited from Grady Memorial Hospital (GMH) were black (77%), unmarried (68%), and of low-socioeconomic status (82%). The average age of mothers in this population was 22.45 years (SD=4.73) and four women reported alcohol consumption during their pregnancy. Mothers at GMH and MRH did not differ in age at the time of delivery, $F(1,48)=1.7$, $p<.2$, the amount of weight gained during pregnancy, $F(1,48)=2.8$, $p<.1$, the average daily amount of caffeine, $F(1,48)=0.11$, $p<.74$, or alcohol, $F(1,48)=1.53$, $p<.22$, consumed during pregnancy or on the average number of cigarettes smoked per day, $F(1,48)=.23$, $p<0.63$, during pregnancy. In addition, the number of mothers who delivered via c-section, $X_2(1)=.001$, $p<.98$, smoked cigarettes, $X_2(1)=.001$, $p<.97$, or consumed alcohol, $X_2(1)=1.42$, $p<.23$, during their pregnancies did not differ between the two hospital populations. However, mothers at GMH had completed less years of school, $F(1,48)=11.69$, $p<.001$, were more likely to be from a low socioeconomic

background, $F(1,48)=14.64$, $p<.0004$, and were more likely to bottle-feed their infants, $F(1,48)=5.99$, $p<.02$, than mothers at MRH. Together, these two samples represent an heterogenous ethnic and SES sampling of mothers who did not differ on salient biomedical or risk indices.

Infant Characteristics. The general characteristics of the infants assessed for this study are described in Table 7. All infants observed in this study were healthy, full-term (Mean=39.5 weeks, SD=1.15) and full birthweight ($\geq$2500 gms) (Mean=3422.2 grams, SD=419.22) infants. Perinatal risk status as assessed by Apgar Scores at one, $F(1,48)=1.02$, $p<.32$, and five minutes, $F(1,48)=.57$, $p,.45$, did not distinguish between infants recruited at MRH and infants recruited at GMH, however, infants born at GMH did have significantly lower scores on the obstetrical complication scale, $F(1,48)=4.04$,$p<.05$, which indicates that infants from GMH had significantly more nonoptimal prenatal and perinatal obstetrical conditions than infants from MRH. This effect is frequently found among low-SES women because of the differences in lifestyle characteristics, such as marital status and reduced prenatal care, that are assessed by the OCS.

Infants from GMH were more likely to be African American than infants from MRH who were primarily Caucasian, $X_2(1)=35.95$, $p<.00001$. Infants recruited at the two hospitals also did not differ in anthropometric measures including birthweight, $F(1,48)=2.98$, $p<.09$, birthlength, $F(1,48)=1.77$, $p<.19$, head circumference, $F(1,48)=3.33$, $p<.06$, ponderal index, $F(1,48)=.05$, $p<.83$, or on measures of

dysmorphology as assessed by the Dysmorphia Checklist, $F(1,48)=.41$, $p<.53$.

Procedure

Mothers were approached on the day of testing and told that the relation between maternal diet during pregnancy on infant behavior was being studied. After being informed of all of the procedures, they were asked to participate in the study. If interest in participating was indicated, informed written consent was obtained (see Appendix A). When approached, four mothers declined to participate in the study. In addition, three infants began the procedure but were unable to finish due to concern about their health.

Maternal and infant medical records were screened in order to obtain information such as birthweight, head circumference, gestational age, maternal weight gain, maternal education, maternal age, number of previous spontaneous abortions, APGAR scores at both 1 and 5 minutes and to obtain information for the Obstetrics Complications Scale (OCS) (Littman, 1979). The ponderal index (PI) was calculated by dividing the infant's birthweight (gm) X 100 by the cube of the infant's birthlength (cm) (Miller & Hassanein, 1971). Based on this calculation, infants were classified as belonging to one of three categories of fetal growth: low-PI infants who are underweight-for-length, at or below the 10th percentile ($PI \leq 2.28$), average-PI infants who are average weight-for-length,and high-PI infants who are overweight-for-length, at or above the 90th percentile ($PI \geq 2.82$). These are the criteria used in previous studies of heart rate variability (Zeskind et al., 1991; Zeskind et al., 1992).

This method of assessing fetal growth patterns may be a more sensitive measure than the traditional use of birthweight for differentiating between healthy infants and infants who show signs of atypical fetal growth. The PI is a weight-for-length ratio that is believed to reflect a subtle condition of malnutrition which occurs late in gestation when weight is accumulated around the already established skeletal size or length of the fetus (Lester, 1979). In essence, the ponderal index identifies infants who are underweight- or overweight-for-length. The PI is even able to differentiate between healthy infants and infants who have an average birthweight but differ on other anthropometric measures such as birthlength. For example, while an infant may weigh in at an average weight of 2500 grams, a long infant may appear to be skinny at that weight. Conversely, a shorter infant may have accumulated to much mass for its length due to metabolic disturbances and, thus, appear to be chubby or overweight. These atypical patterns of fetal growth can be found among full term and full birthweight infants who are considered to be healthy by all routine pediatric measures (Zeskind, 1981; Zeskind & Lester, 1981).

Precise measures of physical dysmorphology may also be a sensitive indicator of the adverse physical effects of prenatal caffeine exposure. The effects of other prenatal teratogens, such as alcohol exposure, have been detected through the use of a standardized checklist in the neonatal identification of physical dysmorphology (Coles, Smith, Fernhoff, Platzman, Raskind-Hood, Brown, & Falek, in prep.). Because some work suggests that prenatal exposure to heavy doses of caffeine may also affect the

structural development of the infant (Battig, 1985; Mulvihill, 1973), this measure may detect more subtle effects on the physical morphology of the infant that may be associated with low to moderate amounts of maternal caffeine consumption during pregnancy. See Appendix B for copy of the Dysmorphia Checklist. This checklist assesses items such as birthweight, facial features, musculoskeletal measures and cutaneous features and has been found to be a valid and reliable measure of alcohol-related birth defects as well as a significant predictor of cognitive status at 7 years of age (Coles et al., in prep.). Although this checklist was developed to assess the presence of physical dysmorphology in infants prenatally exposed to alcohol, it was believed that it may also prove to reliably differentiate among infants prenatally exposed to varying doses of caffeine.

A compilation of two questionnaires previously used to measure the amount of caffeine consumed during pregnancy was administered to the mother by the examiner (see Appendix C). The questionnaire was designed to obtain detailed information concerning caffeine ingested through sources such as beverages (coffee, tea, colas, and hot chocolate), chocolate, and medications. A method for assessing variability in consumption patterns called the quantity-frequency-variability (QFV) interview, originally developed for use in alcohol studies (Mulford & Miller, 1960), has been modified for the assessment of caffeine intake (Barr, Streissguth, Martin, & Horst, 1981). This method effectively reduces information about caffeine intake to a continuous variable. This questionnaire also included questions about general nutrition

in order to disguise the true purpose of the interview. In addition, information about alcohol, drug use, and smoking habits during pregnancy were collected.

Although obtaining information about maternal caffeine consumption through an interview or questionnaire is not a direct measure of her caffeine consumption during pregnancy, this methodology has been effectively used in other studies examining the effects of prenatal exposure to caffeine on developmental outcomes. These studies have shown that questionnaires are sensitive to differences in neonatal behavior associated with prenatal exposure to caffeine. As detailed above, Hronsky and Emory (1987) found that differences in the amount of prenatal exposure to caffeine, as determined by a detailed questionnaire on the nutritional habits of mothers, were associated with variations in several measures of infant arousal. In addition, the QFV interview procedure which has been modified for use in the present study has been found to have a high test-retest reliability (r=.89-.95) over a one week period of time. It is also important to note that maternal reports of the average daily amount of caffeine consumed are strongly correlated with other methods of assessing caffeine consumption. Specifically, cord blood assays of caffeine (r=.49) and newborn salivary assays of caffeine (r=.53) were significantly correlated with maternal reports of caffeine consumption during pregnancy (Hronsky & Emory, 1987). Thus, the use of a questionnaire for assessing maternal caffeine consumption during pregnancy appears to have considerable scientific merit and clinical utility.

Based on this interview, the average daily amount of caffeine consumed during

pregnancy was calculated (see Appendices D & E). The total daily caffeine score was obtained by adding the mg/day of caffeine from each source of caffeine (see Appendix F). The caffeine content of the various sources was obtained from the most current studies on caffeine content in common foods and medications. Since individual caffeine intake is dependent on the size of the serving and method of preparation (e.g., instant coffee versus percolated) (Gilbert, Marshman, Schwieder, & Berg, 1976), questions concerning average serving size and method of coffee and tea preparation were included on the questionnaire.

Using a method presented by Barr, Streissguth, Martin and Horst (1981), individual caffeine scores for each food item were derived from the QFV questions (see Appendix E). The formula for the caffeine scores for beverages is caffeine content (C) multiplied by the frequency code (F) and number of servings (see Appendix D). To calculate the caffeine score for caffeine-containing medications, the frequency code (F) was multiplied by the number of tablets (Q) and the caffeine content per tablet (C). For chocolate candy, the caffeine score was obtained by multiplying the frequency code (F) by the caffeine per serving (QS). These subscores (e.g., caffeine in mg/day for coffee, tea, cola, cocoa, chocolate, and medications) were then summed to produce the total daily average caffeine score.

Behavioral Assessment. Infants were studied midway between scheduled feedings in a quiet, isolated area of the newborn nursery. Electrodes were attached to the infant's abdominal and pectoral regions and a Corometric Neonatal or Hewlett-

Packard Neonatal heart rate monitor displayed the infant's heart rate per minute with a moving average of 10 seconds. Heart rate was recorded every 30 seconds for 1 hour, which provided 120 time-series data points for each subject. In addition, the number of startles, defined as momentary abductions of the shoulders with extensions of the arms, elbows, wrists, and fingers, followed by a brief disturbance in respiration (Wolff, 1966), and tremors (observed quivering of extremities) that occured during each 30-second epoch were recorded.

Two observers who were blind to the amount of caffeine to which the infant was exposed recorded the infant's behavioral state every 30 seconds during the same one hour period that heart rate data was being collected. One research assistant was also responsible for using a stop watch to ensure that the measurements were recorded exactly every 30 seconds. The infant was carefully observed for tremors and startles during the initial 20 seconds of each epoch, as well. Following the procedure developed in previous studies (Zeskind et al., 1991; Zeskind et al., 1992), the behavioral state was determined by the consensus of the two observers who used behavioral characteristics present during the final ten seconds of each epoch as their criteria. At the end of the ten seconds, one observer mase a final decision as to the infant's current state. An 11-point nominal scale developed by Thoman (1975) was used as a sensitive assessment of individual differences in behavioral state among newborn infants (see Table 3 for a description of the 11 behavioral states). For purposes of comparison with other studies, behavioral state observations were

converted to the 6-point scale developed by Brazelton (1973; 1984) which includes 1) Quiet Sleep, 2) Active Sleep, 3) Drowse, 4) Alert, 5) Active Alert, and 6) Crying. The number of times that the infant was in each of the six behavioral states was then calculated. In addition, the number of state transitions were determined by simply counting the number of 30-second epochs that have a different behavioral state classification than the epoch occurring immediately prior to it. The observers were trained to criterion and remained blind to the exposure condition of the infant.

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insert Table 3 about here

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In summary, outcome measures included the total mean heart rate for the 120 observations of heart rate and the standard deviation of the heart rate as a measure of long-term heart rate variability. A $\log_{10}$ transform was conducted on the standard deviation of the heart rate which is a traditional method used to normalize the distribution of heart rate (Porges, 1976). A separate mean heart rate was then calculated for those 30-second episodes that infants spent in quiet sleep, active sleep, a drowsy state or a state of waking inactivity. The number of 30-second episodes spent in each behavioral state and the total number of state transitions was also calculated. In addition, the total number of startles and the total number of tremors were determined for each infant. Birthweight, the PI, the OCS, and the Pedscore were also included as outcome measures in all statistical analyses.

Hypotheses

Based on the findings of previous studies, it was hypothesized that infants who were prenatally exposed to caffeine would display disturbances in their ability to regulate their arousal. Specifically, it was hypothesized that a dose-related effect would be found such that infants exposed to higher amounts of caffeine during prenatal development would have a higher total heart rate mean and standard deviation, spend more time in alert and active alert behavioral states, have a higher number of state transitions, startles and tremors and have more nonoptimal Pedscores, OCS scores, and PI's, as well as a reduced birthweight.

It was hypothesized that infants who have been prenatally exposed to higher amounts of caffeine during pregnancy would:

1. have atypical patterns of fetal growth, as measured by the PI and their birthweight, birthlength, and head circumference.

2. have a higher Pedscore than infants who have been prenatally exposed to smaller amounts of caffeine.

3. have a lower OCS (less optimal) than infants who have been prenatally exposed to smaller amounts of caffeine.

4. have a higher total mean heart rate summed over the 120 observations and have a higher mean heart rate when they are in quiet sleep, active sleep, a drowsy state or a quiet alert state.

5. have lower heart rate variability as measured by the standard deviation of their total heart rate assessed in the 120 observations.

6. spend more time in alert and active alert behavioral states and, subsequently, less time in sleep states than infants who have been prenatally exposed to lower amounts of caffeine.

7. exhibit more startles and tremors than infants who have been prenatally exposed to smaller amounts of caffeine.

8. exhibit a higher number of state transitions than infants who have been prenatally exposed to smaller amounts of caffeine.

Results

Strategy of Analyses

A correlation matrix will first be constructed in order to examine general associations among all outcome measures and as a preliminary indication of the existence of possible multicollinearity among the predictors. Stepwise multiple linear regression analyses will then be used to explore the effects of prenatal exposure to caffeine on neonatal behavior and development. Data from the two hospital sets will be pooled for all regression analyses. Because alcohol and nicotine use during pregnancy have been found to be correlated to maternal caffeine consumption during pregnancy in past studies (Jacobson et al., 1984), they will both be included as independent variables in each regression analysis. Thus, each outcome measure, with the exception of ponderal index, will be assessed using a stepwise multiple linear regression analysis with alcohol, nicotine, and caffeine use during pregnancy as the independent variables. Because lifestyles embedded in different SES levels have been hypothesized to be an important influence on behavioral patterns in newborn infants (Birch & Gussow, 1970), it will also be included as an independent variable in the stepwise multiple linear regression. Specifically, the outcome measures will include time spent in each of the six behavioral states, number of state transitions, the mean

heart rate, mean heart rate during each of the four behavioral states, heart rate variability, number of startles, number of tremors, birthweight, the Pedscore, and the OCS.

A hierarchical multiple linear regression will then be conducted on all outcome measures that were found to have a significant predictor using the stepwise entry method. Because previous studies have suggested that caffeine is only one of several significant predictors of differences in regulatory abilities and, therefore, may not necessarily account for the most variance relative to other regressors, caffeine will be entered into the regression equation only after the other three regressors in order to determine the amount of additional variance that was accounted for by caffeine. Nicotine will be entered in Step 1 to determine if the average number of cigarettes smoked per day during pregnancy is related to outcomes, followed by alcohol which will be entered in Step 2. SES will then be entered into the regression equation on the third step, followed by maternal caffeine consumption during pregnancy as the last independent variable entered into the equation. Because the PI is a curvilinear variable where values at either end of the scale are considered to be nonoptimal, a polynomial regression will be conducted to look for the quadratic function.

Because the number of cigarettes smoked during pregnancy and the amount of alcohol consumed during pregnancy has been highly correlated with maternal caffeine consumption during pregnancy in previous studies, additional regressions were conducted on a subsample of the population using only subjects who reported no

alcohol consumption or cigarette smoking during pregnancy (n=37) on outcomes found to have caffeine use during pregnancy as a significant predictor.

To confirm that multicollinearity is not a problem among any of the regressors, a variance inflation factor (VIF) which measures the interrelationships among the predictors in the model will be examined in each of the regression analyses. VIF's which are greater than 10 will be used as indications of the presence of multicollinearity between two regressors and VIF's which are less than 5 will be considered an indication that multicollinearity is not present. VIF's which fall between 6 and 10 may indicate the presence of multicollinearity and will be carefully examined (Montgomery & Peck, 1982). Eigenvalues and tolerance values will also be examined in order to rule out the possibility of multicollinearity among the predictors.

Analyses

Correlation matrices were created to examine the association between various maternal characteristics and all anthropometric (see Table 8) and behavioral outcome measures (see Table 9). Maternal caffeine consumption during pregnancy was significantly correlated with average heart rate across all observed 120 30-second epochs, $r=.41$, $p<.003$, the average heart rate for observations only when the infant was in quiet sleep, $r=.45$, $p<.001$, or active sleep, $r=.37$, $p<.001$, but not for the heart rate when the infant was observed to be in a drowsy, $r=-.07$, $p<.71$, or quiet, alert state, $r=-.17$, $p<.41$. Maternal caffeine consumption during pregnancy was

also not found to be significant for the remaining behavioral (see Table 9) or anthropometric variables (see Table 8).

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insert Table 8 about here

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The number of cigarettes smoked during pregnancy was also signficantly correlated with the average heart rate across all observed 30-second epochs, $r = .41$, $p < .05$, average heart rate for all observations when the infant was in quiet sleep, $r = .3$, $p < .05$, but not for heart rate when the infant was in active sleep, $r = .26$, $p < .07$, drowsy, $r = .31$, $p < .12$, or in a quiet, alert state, $r = .20$, $p < .34$. Although the number of cigarettes smoked during pregnancy was not found to be correlated to any of the remaining behavioral outcomes (see Table 9), pedscore, $r = -.04$, $p < .77$, or anthropometric variables (see Table 8), it was correlated to infants' score on the OCS, $r = -.33$, $p < .02$, which assesses the number of nonoptimal prenatal, perinatal, and postnatal conditions experienced by the infant.

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Socioeconomic status was also significantly correlated with infants' average heart rate across all observations, $r = -.33$, $p < .02$, and with their heart rate during quiet sleep, $r = -.38$, $p < .007$, but not with their heart rate during active sleep, $r =$ -

.26, $p < .07$, or while they were drowsy, $r = -.07$, $p < .71$, or in a quiet, alert state, $r = -.17$, $p < .41$. In addition, SES was significantly correlated with scores on the OCS, $r = .39$, $p < .005$, but not with pedscore, $r = .01$, $p < .96$, or any of the anthropometric (see Table 8) or remaining behavioral outcomes (see Table 9).

Finally, the amount of alcohol consumed during pregnancy was significantly correlated with the total number of observed tremors across all observations, $r = .37$, $p < .01$, but not with any of the other behavioral outcomes (see Table 9). In addition, alcohol was significantly correlated to birthlength, $r = -.28$, $p < .05$, but was not significantly correlated to any of the other anthropometric or perinatal risk status outcomes (see Table 8).

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insert Table 10 about here

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Examination of the correlation matrices showed that the high correlations found among maternal caffeine consumption during pregnancy and the number of cigarettes smoked during pregnancy and among maternal caffeine consumption during pregnancy and SES were the only correlations that suggested possible multicollinearity and were, therefore, explored further using assessments of multicollinearity in regression analyses (see Table 10). These analyses showed no indication of multicollinearity among any of the predictor variables as evidenced by the variance inflation factors, tolerance values, and eigenvalues calculated in the regressions on anthropometric and

risk status outcomes (see Table 11) and on behavioral outcomes (see Table 15).

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Anthropometric and Perinatal Risk Status. Birthweight, birthlength, head circumference and PI were each included as criterion variables in separate stepwise multiple regressions to examine whether substance use during pregnancy served as predictors of various anthropometric outcomes. Predictor variables in the regressions included nicotine use during pregnancy, alcohol use during pregnancy, caffeine use during pregnancy, and socioeconomic status.

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Contrary to the first hypothesis, reported maternal caffeine consumption during pregnancy was not found to be a significant predictor of any of the anthropometric outcomes, including PI, birthweight, birthlength, and head circumference. However, the stepwise regression conducted on birthlength showed that alcohol contributed to a significant portion of the total variance (8%), $F(1,48)=4.05$, $p<.05$ (see Table 12). In general, infants who were prenatally exposed to higher amounts of alcohol were shorter than infants exposed to lesser amounts of alcohol (see Figure 4). Nicotine, SES and caffeine were not found to be significant predictors of birthlength outcomes

(all p's > .10). Results of the hierarchical multiple linear regression conducted on birthlength showed that only alcohol accounted for a significant increment in the total variance above the variance accounted for by predictor variables previously enterd into the regression. The stepwise regressions on birthweight and head circumference showed that none of the predictor variables were entered into the regression equation as significant (all p's > .10). Results of the quadratic regression conducted on ponderal index also showed that none of the predictor variables, including caffeine, were significant (all p's > .10).

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Stepwise multiple linear regressions were also conducted on the two perinatal risk status outcome variables, pedscore and OCS (see Table 12). The second hypothesis that prenatal exposure to higher amounts of caffeine would be related to an increased incidence of dysmorphology was not supported by these results. However, alcohol was found to be a significant predictor of dysmorphology, as measured by the pedscore, $F(1,48)=4.13$, $p<.05$, accounting for 8% of the total variance, while nicotine, SES, and caffeine were not entered into the regression equation (all p's > .10). Infants who were prenatally exposed to higher amounts of alcohol had significantly more dysmorphic features than infants who were not exposed to alcohol or who were exposed to lower amounts of alcohol during gestation (see Figure 5). A

subsequent hierarchical multiple linear regression conducted on pedscore found that caffeine use during pregnancy, $t(45)=1.16$, $p<.25$, was not found to contribute to significant portions of the total variance after the other predictors had been entered into the regression.

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insert Figure 5 about here

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Results of the stepwise multiple linear regression conducted on OCS showed that SES was the only significant predictor of the number of obstetrical complications, $F(1,48)=8.64$, $p<.005$, (see Table 12). As would be expected, infants from higher socioeconomic backgrounds, in general, had a more optimal score on the OCS than infants from lower socioeconomic backgrounds (see Figure 6). However, contrary to the hypothesis that prenatal exposure to higher amounts of caffeine would be related to lower scores on the OCS (see Hypothesis #3), caffeine use during pregnancy was not found to contribute to a significant portion of the total variance ($p>.10$). Nicotine and alcohol use during pregnancy were also not entered into the equation (all p's$>.10$). However, when a subsequent hierarchical multiple linear regression was conducted on OCS to determine how much variance caffeine use during pregnancy was able to account for beyond the contributions of the other predictor variables, caffeine, $t(45)=2.38$, $p<.02$, was found to account for a significant increment in the variance in addition to the variance already accounted for by previously entered

predictor variables (an additional 6%) (see Table 13). In general, infants who were exposed to higher amounts of caffeine during their prenatal development were more likely to have less optimal scores on the OCS than infants who were prenatally exposed to lower amounts of each of these substances. A stepwise multiple regression was then conducted on OCS using only reported nonsmokers and nondrinkers (n=37) in order to control for possible nicotine and alcohol effects. Results of this regression found only caffeine to be a significant predictor of scores on the OCS, $F(1,35)=4.8$, $p<.01$, accounting for 9% of the total variance (see Table 14). SES was not found to be linearly related to OCS scores.

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insert Figure 6 about here

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In summary, reported maternal alcohol use during pregnancy appears to be a strong predictor of differential anthropometric outcomes in exposed newborn infants. On the other hand, reported maternal caffeine and nicotine use during pregnancy and SES were not found to be related to differences among newborn infants in any of the anthropometric measures which were assessed.

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insert Table 13 about here

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Measures of Arousal

Total number of 30-second epochs spent in quiet sleep, active sleep, and states of drowsiness, quiet waking, active waking, and crying as well as average heart rate mean of infants while they were in quiet sleep, active sleep, a drowsy state or a state of quiet alertness were all used as criterion variables in separate stepwise multiple linear regressions. Average heart rate mean across all 120 observation epochs, the $\log_{10}$ transform of the standard deviation of that heart rate mean, the total number of state transitions, total number of observed startles and total number of observed tremors were also included as criterion variables in separate stepwise multiple linear regressions. Nicotine use, alcohol use, SES, and caffeine use were again entered as predictor variables into each regression.

Additionally, because the number of cigarettes smoked during pregnancy and the amount of alcohol consumed during pregnancy have been highly correlated with maternal caffeine consumption during pregnancy in previous studies, additional regressions were conducted using only subjects who reported no alcohol consumption or cigarette smoking during pregnancy (n=37) on outcomes found to have caffeine use during pregnancy as a significant predictor.

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insert Table 15 about here

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Heart Rate. Beginning with an analysis of the full sample (N=50), as hypothesized (Hypothesis #4), results of a stepwise multiple linear regression found that caffeine, $F(1,48)=9.71$, $p<.003$, was a significant predictor of the heart rate mean across all observations, accounting for 17% of the total variance (see Table 16). Infants who were prenatally exposed to greater amounts of caffeine had higher overall heart rates than infants exposed to smaller amounts of caffeine during gestation (see Figure 7). Nicotine and alcohol use during pregnancy, and SES were not entered into the regression equation (all p's $>.10$). A subsequent hierarchical multiple linear regression also found that caffeine was the only significant predictor of newborn infants' overall heart rates, $t(45)=1.84$, $p<.05$, accounting for an additional 6% of the variance beyond the 15% of the variance accounted for by nicotine and alcohol use during pregnancy and maternal SES (see Table 17). Results of a subsequent stepwise multiple linear regression conducted on average overall heart rate using only nonsmokers and nondrinkers also found that only caffeine use during pregnancy, $t(34)=3.36$, $p<.001$ was entered as a significant predictor and accounted for a significant portion of the total variance (24%) (see Table 14).

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The hypothesis that infants who were prenatally exposed to higher amounts of caffeine would have lower measures of heart rate variability (Hypothesis #5) was not

supported by these data. The regression conducted on the $\log_{10}$ transform of the standard deviation of the total heart rate mean found that none of the independent variables entered into the regression were significant predictors of this measure of heart rate variability (all p's > .10).

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As hypothesized (see Hypothesis #4), results of the stepwise regression on the heart rate mean of infants while they were in quiet sleep found that only maternal caffeine consumption during pregnancy, $F(1,48)=11.61$, $p<.001$, contributed to a significant portion of the total variance (20%) (see Table 16). Infants who were prenatally exposed to higher amounts of caffeine had higher heart rates during quiet sleep than infants who were exposed to lower amounts of caffeine (see Figure 8). Nicotine and alcohol use during pregnancy and SES were not entered into the stepwise regression as significant predictors (all p's > .10). Results of the hierarchical multiple linear regression showed that caffeine use during pregnancy, $t(45)=1.96$, $p<.05$, contributed to a significant portion of the total variance (7%) in addition to the portion of the variance accounted for by the predictor variables previously entered into the regression (see Table 17). In general, infants who were prenatally exposed to higher amounts of caffeine and who were from a lower socioeconomic background had higher heart rates during quiet sleep than infants who were exposed to smaller

amounts of caffeine during pregnancy and were from a higher socioeconomic background. Results of a subsequent stepwise multiple linear regression conducted on average heart rate of infants while they were in quiet sleep using only nonsmokers and nondrinkers found that both SES, $t(34)=-3.49$, $p<.001$ and caffeine use during pregnancy, $t(33)=2.79$, $p<.01$ were entered as significant predictors (see Table 14). Each of these independent variables accounted for a significant portion of the total variance (SES=26%, Caffeine=14%).

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insert Figure 8 about here

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A stepwise multiple linear regression conducted on the heart rate of infants while they are in active sleep found that caffeine accounted for a significant portion of the variance (14%), $F(1,48)=7.51$, $p<.01$, (see Table 16). As hypothesized (see Hypothesis #4), infants who were prenatally exposed to higher amounts of caffeine also had higher heart rates during active sleep than infants who were exposed to lower amounts of caffeine (see Figure 9). Nicotine and alcohol use during pregnancy and SES were not entered into the regression equation (all p's$>.10$). When a multiple hierarchical regression was conducted on the heart rate of infants while they were in quiet sleep, none of the independent variables were found to account for a significant portion of the total variance (see Table 17). Thus, while maternal caffeine use during pregnancy was found to be a significant predictor of average heart rate of newborns

while they were in quiet sleep in the stepwise multiple linear regression, it was not found to be a significant predictor when forcibly entered into the hierarchical multiple linear regression. However, results of a subsequent stepwise multiple linear regression conducted on average heart rate of infants while they were in quiet sleep using only nonsmokers and nondrinkers found that caffeine use during pregnancy, $t(35)=2.99$, $p<.005$ was entered as a significant predictor, accounting for a significant portion of the total variance (20%) (see Table 14).

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insert Table 17 about here

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Contrary to the hypothesis (see Hypothesis #4) that caffeine use during pregnancy would be related to higher heart rates while infants were in states of drowsiness or alert inactivity, stepwise multiple regressions conducted on the average heart rate of infants while they were in a drowsy state or a state of alert inactivity found that caffeine use during pregnancy did not account for a significant portion of the total variance. Nicotine and alcohol use during pregnancy, and SES were also not found to be significant predictors of the average heart rate of infants while they were in a drowsy state, or a state of alert inactivity when stepwise multiple linear regressions were conducted (all p's $>.10$).

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insert Figure 9 about here

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In order to determine the dose-response of caffeine on infants' average heart rate, the slopes and y-intercept obtained from the multiple linear regression conducted on average heart rates were used to determine the amount of increase in heart rate for exposure to various amounts of caffeine corresponding to the range of reported maternal caffeine consumption found in the present study (0.9-820.08 mg/day). When the equations from the stepwise regressions were solved, heart rate was found to increase at two beats per minute for every additional 100 mg/day than an infant had been exposed to prenatally. The dose-response of caffeine on heart rate in quiet and active sleep were also determined using the slopes and y-intercepts obtained from the stepwise multiple linear regressions. Heart rate during quiet sleep was found to increase by 2.4 beats per minute and heart rate during active sleep was found to increase by 2 beats per minute for every additional 100 mg/day than an infant had been prenatally exposed.

Behavioral State. As would be expected, infants were observed to spend the majority of their time in sleep states (Berg & Berg, 1987). Specifically, newborn infants were observed to spend the majority of their time in either quiet sleep (44.6%) or active sleep (39.6%). They spent a considerably less amount of time in a state of drowsiness (3.3%), quiet alertness (2.8%), waking activity (7.2%) or crying (1.8%)

(See Table 18).

The hypothesis that infants who were prenatally exposed to higher amounts of caffeine would spend significantly more time in alert and active alert states (see Hypothesis #6), was not supported by these data. The stepwise multiple linear regressions conducted on the number of 30-second epochs that infants were observed to be in each of the six behavioral states found that none of the four independent variables entered into the regression were significant predictors of the amount of time infants spent in any of the six behavioral states (all p's $> .10$). Thus, differences in heart rate were found even though no effects were found for the amount of time infants spent in different behavioral states.

Other Autonomic Activity. Results of the stepwise multiple linear regression conducted on the total number of observed tremors found that alcohol use during pregnancy was a significant predictor, $F(1,48)=7.73$, $p<.01$, contributing to 14% of the total variance (see Table 16). Infants who were prenatally exposed to larger amounts of alcohol were observed to have significantly more tremors (see Figure 10). Nicotine and caffeine use during pregnancy, and SES were not entered into the regression equation (all p's $> .10$). When a hierarchical multiple linear regression was conducted on the total number of observed tremors, results showed that caffeine use during pregnancy was not found to contribute to a significant increment in the variance over the variance accounted for by previously entered predictor variables. In general, infants who were prenatally exposed to greater amounts of alcohol had

significantly more tremors than infants who were exposed to smaller amounts of alcohol.

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insert Figure 10 about here

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The hypotheses that prenatal exposure to higher amounts of caffeine would be associated with an increased number of behavioral startles (see Hypothesis #8) and an increased number of state transitions (see Hypothesis #7) were not supported by these data. When stepwise regressions were conducted on the total number of times that infants changed behavioral state and on the total number of observed startles, none of the independent variables were entered into the regressions (all p's $> .10$).

Discussion

Caffeine is believed to be the drug most widely ingested by pregnant women (Gilbert, 1976) and, as such, has generated concern about is potential physical and behavioral teratogenicity. Although animal studies have consistently found both anthropometric and behavioral effects in rodents as a result of prenatal exposure to caffeine (e.g., Sinton et al., 1981; Sobotka, Spaid, & Brodie, 1979; West et al., 1986), the results of human studies are far less definitive. While some of the existing human studies have found little or no behavioral effects associated with caffeine (e.g., Barr & Streissguth, 1991), others suggest that prenatal exposure to caffeine may be associated with differential regulation of arousal in newborn infants (Hronsky &

Emory, 1987; Jacobson et al., 1984). In particular, previous studies have shown caffeine consumption during pregnancy to be associated with poorer orientation, greater irritability, a greater range of behavioral states (Jacobson et al., 1984) and an increase in behavioral startles (Hronsky & Emory, 1987). However, these studies explored the relation between prenatal exposure to caffeine and behavioral outcomes in newborn infants during periods of extensive visual, auditory, and tactile stimulation. To date, no studies have explored the relation between maternal caffeine consumption during pregnancy and spontaneously occurring patterns of behaviors in newborns. Since spontaneous neonatal behaviors associated with infants' physiological responses to endogenous stimulation have been conceptualized as being important factors in infant development (DeGangi, DiPietro, Greenspan, & Porges, 1991; Huntington, Zeskind, & Weiseman, 1985; Kessen, Haith, & Salapatek, 1970; Korner, 1969; Woodson, 1983), it is important to understand how various developmental experiences affect the ability of infants to maintain the homeostatic balance of their biobehavioral systems. The present study provides the first known evidence of the association of prenatal exposure to caffeine on newborn infants' autonomic functioning as a response to endogenous, rather than exogenous, stimulation.

As would be expected in a study of human subjects from a "real-world" population, close associations were found among a variety of behavioral, social and environmental factors. One such association is the positive correlation that was found between maternal caffeine consumption during pregnancy and maternal smoking

during pregnancy. The finding that caffeine consumption during pregnancy and cigarette smoking during pregnancy are highly correlated has consistently been found in previous studies (e.g., Barr & Streissguth, 1991). In particular, heavy caffeine users (>300 mg/day) are more likely to also be smokers (Barr & Streissguth, 1991) which is consistent with the present finding that infants exposed to higher amounts of caffeine were more likely to have mothers who smoked during pregnancy than infants exposed to lower amounts of caffeine. Because smoking and caffeine consumption during pregnancy are so consistently and highly correlated, it is possible that any of the behavioral effects associated with maternal caffeine use are actually a consequence of a synergistic or additive relationship between multiple drug use during pregnancy. However, when additional analyses were conducted only on subjects who reported no smoking during pregnancy (n=41), caffeine was still found to be a significant predictor of the infants' average heart rate and heart rate during sleep states. Even without the added influence of prenatal exposure to nicotine, prenatal exposure to relatively heavy amounts of caffeine may be a significant risk factor which compromises the development of the exposed infant.

Socioeconomic status was also found to be associated with the number of obstetrical complications experienced by the newborn infant. The finding that low socioeconomic status is associated with an increase in obstetrical complications and risk status among infants is a widely reported association. Poverty has been correlated with a myriad of risk factors among pregnant women including poorer health histories

among women prior to their pregnancy and a increased likelihood of inadequate prenatal care (Halpern, 1993). Pregnant women from lower socioeconomic backgrounds are also more likely to behave in ways which are potentially harmful to the developing fetus (Halpern, 1993). In fact, the present findings that mothers from lower socioeconomic backgrounds were more likely to consume heavier amounts of caffeine during pregnancy supports this widely documented association between SES and maternal substance use during pregnancy (e.g., Jacobson et al., 1984; Kuzma & Kissinger, 1981). Jacobson and colleagues also found that mothers from lower socioeconomic backgrounds were more likely to consume heavier amounts of caffeine during their pregnancy than mothers with a higher socioeconomic status. In addition, low SES mothers have also been found to smoke significantly more during their pregnancy than mother from higher socioeconomic backgrounds (Jacobson et al., 1984; Kuzma & Kissinger, 1981). It is a combination of these nonoptimal factors associated with lifestyles embedded in a low socioeconomic background that contributes to an increased number of obstetrical complications.

Results of this study also found significant associations between various prenatal teratogens and anthropometric and perinatal risk status outcomes. Although the hypothesis that infants who were prenatally exposed to higher amounts of caffeine during pregnancy would have more dysmorphic features (see Hypothesis #2), along with other altered anthropometric outcomes (see Hypothesis #1), was not supported in this study, maternal consumption of alcohol during pregnancy was found to be a

reliable predictor of both birthlength and dysmorphology in newborn infants. Infants who were exposed to higher amounts of alcohol had decreased birthlengths and more dysmorphic features than infants prenatally exposed to lower amounts of alcohol. This is particularly surprising since only 12% of the mothers in the study reported any alcohol consumption during their pregnancy. In addition, among those mothers that did report alcohol consumption, there were no heavy drinkers (typically considered >2 oz. of absolute alcohol per day) with only one mother reporting drinking as much as one alcoholic beverage per day. Although several of the infants who were prenatally exposed to alcohol did have scores that categorized them as possibly being "alcohol affected and dysmorphic" (Coles et al., in prep) (n=5), only one infant had a score high enough to indicate possible fetal alcohol effects (FAE) or fetal alcohol syndrome (FAS). These findings are consistent with the reports of minimal to moderate use among mothers who did drink during pregnancy since physical dysmorphology is typically found only in infants who have been prenatally exposed to higher amounts of alcohol.

Although alcohol was found to have strong effects on some aspects of morphological development despite the relatively small amounts reported by mothers in this study, results of the present study did not support the hypothesis (see Hypothesis #1) that caffeine would be associated with altered anthropometric measures among the full-term, full birthweight infants in this study. The finding of no association between maternal caffeine consumption during pregnancy and birthweight,

which has often been found to be lower in infants who were prenatally exposed to relatively high amounts of caffeine (e.g., Fortier, Marcoux, & Beaulac-Baillargeon, 1993; Martin & Bracken, 1987; Watkinson & Fried, 1985), is particularly noteworthy. The discrepancy in these findings may be explained by the significant difference in sample sizes between studies. For example, Martin and Bracken (1987) studied a total of 3,891 mothers and their newborns and another study examined the association between birthweight and caffeine consumption during pregnancy in 7,025 subjects (Fortier, Marcoux, & Beaulac-Baillargeon, 1993). The present sample size of 50 healthy subjects may not be large enough to detect any effect that caffeine may have on anthropometry.

Although maternal caffeine consumption during pregnancy was not found to be associated with differences in anthropometric outcomes among exposed newborn infants, as hypothesized (see Hypothesis #3), caffeine consumption during pregnancy and cigarette smoking during pregnancy were both found to be associated with scores on the Obstetrical Complication Scale which assesses a variety of prenatal, perinatal, and postnatal conditions. Mothers who consumed larger amounts of caffeine during pregnancy, smoked a greater number of cigarettes during pregnancy or who were from a lower socioeconomic background were more likely to have infants who experienced a greater number of obstetric complications. These findings are similar to previous studies which have also found that substance use by pregnant mothers was significantly associated with obstetrical complications in their infants (e.g., Coles et

al., 1992). Since smoking during pregnancy is consistently found to be associated with numerous nonoptimal outcomes assessed by the OCS, such as higher incidences of low birthweight (e.g., Bailey, 1970; Underwood, Kesler, O'Lane, & Callagan, 1967) and prematurity (Lowe, 1959; Underwood et al., 1967) and lower Apgar scores at one and five minutes after birth (Pagel, Smilkstein, Regen, & Montano, 1990), it is not surprising to find that smoking during pregnancy was related to a higher number of obstetrical complications in the present study.

As hypothesized, caffeine consumption during pregnancy was also related to the number of obstetrical complications as assessed by the OCS. It is not certain from these findings whether maternal caffeine consumption during pregnancy has any type of causative influence on risk factors assessed by the OCS or whether mothers who consume larger amounts of caffeine during their pregnancies are also more likely to have other characteristics associated with a less optimal score on the OCS. Regardless of the specific mechanism by which caffeine is related to obstetrical complications, it is clear from these results that caffeine consumption during pregnancy, along with cigarette smoking during pregnancy, can be considered a significant predictor of an infant's perinatal risk status. Thus, the finding that both maternal caffeine consumption and maternal smoking during pregnancy are related to less optimal scores on the OCS, as well as the finding that maternal alcohol consumption during pregnancy is a significant predictor of some physical outcomes, shows that these measures are sensitive to the assessment of a range of prenatal teratogens and not just

to the effects of prenatal exposure to caffeine.

Unlike the anthropometric outcomes which appear to be particularly sensitive to the teratogenic effects of alcohol, the behavioral outcomes assessed in this study appear to be predominantly influenced by the effects of caffeine. Specifically, the results of this study indicate that, as hypothesized (see Hypothesis #4), the average resting heart rate of a newborn infant may be particularly sensitive to the effects of prenatal exposure to caffeine. The higher the amount of caffeine that an infant had been exposed to prenatally, the higher was their overall heart rate. Careful analyses of this dose-response of caffeine on the heart rate of exposed infants found that heart rate increased by at least two beats per minute for every additional 100 mg/day of caffeine to which an infant had, on average, been exposed prenatally. This effect translates to a two beat increase in heart rate for approximately every additional cup of coffee per day consumed by the pregnant woman. In other words, within the range of gestational exposure to caffeine found among infants in a normal newborn nursery (0-820 mg/day), this translates to a potential increase in heart rate of 16 beats per minute.

The significance of this finding can be understood when neonatal heart rate is conceptualized as a measure of energy utilization (Woodson, Field, & Greenberg, 1983). Previous work has shown that there is a positive linear relation between energy utilization and heart rate (Chessex et al., 1981). Infants who have higher heart rates as a consequence of being prenatally exposed to caffeine may be expending

energy that is needed for growth and other developmental processes (Woodson et al., 1983). This positive linear relationship between heart rate and energy expenditure has been clearly demonstrated in neonates as well as among older children and adults (e.g., Bradfield, 1971; Spady, 1980). This could be particularly problematic if future work finds that the altered patterns of arousal found in the present study exist beyond the early postnatal period into childhood or beyond. At this point, however, the present study can not indicate whether higher energy utilization is just a transient perinatal phenomena.

Although infants who were prenatally exposed to higher amounts of caffeine differed from infants who were prenatally exposed to smaller amounts of caffeine in their mean resting heart rate, heart rate variability, as measured by the standard deviation of the 120 observations of heart rate, was not associated with maternal consumption of caffeine during pregnancy. This particular measure of long-term heart rate variability was chosen for study because it has been shown to differentiate among young infants who differ in other measures of autonomic functioning (Lester, 1979; Zeskind & Field, 1981; Zeskind, Marshall & Goff, 1991). Although this measure of heart rate variability did not prove to be a sensitive measure of regulation of arousal in infants who were prenatally exposed to caffeine, perhaps a more sensitive measure of regulatory difficulties could be through the spectral analysis of long-term heart rate variability (Zeskind et al., 1991; Zeskind, et al., 1992). Spectrum analysis of long-term heart rate variability would be able to detect phasic changes in heart rate over

time. Phasic measures of heart rate variability are not directly associated with the measure of standard deviation. Thus, future studies should explore the relation between prenatal exposure to caffeine and the rhythmic pattern of the variability of the infant's heart rate by spectrum analyzing time samples of heart rate over extended durations.

The scope of this study does not allow definitive conclusions to be drawn about the relative permanence of these altered heart rate patterns. It is possible that the behavioral outcomes observed in this study indicate a transient form of neonatal withdrawal from the stimulating effects of caffeine. However, it is also possible that, these findings may reflect subtle alterations in nervous system development among infants prenatally exposed to higher amounts of caffeine. Both heart rate and heart rate variability are the result of a complex interaction between the parasympathetic and sympathetic components of the autonomic nervous system (ANS) and are influenced by a wide range of endogenous and exogenous influences (Berg & Berg, 1987). The sympathetic nervous system responds to internal and external sources of stimulation by raising the infant's level of arousal which is reflected in an increased heart rate. In uncompromised nervous systems, the parasympathetic nervous system then reacts to this heightened arousal by inhibiting arousal and, consequently, decreasing the infant's heart rate (Glick & Braunwald, 1965). This continuous interplay between the two components of the efficiently operating autonomic nervous system results in a rhythmic pattern of oscillations between the sympathetic and parasympathetic nervous

system.

The findings in the present study of an increased heart rate in infants who have been prenatally exposed to relatively higher amounts of caffeine suggests a pattern of sympathetic dominance over their autonomic functioning. This conclusion is supported by the additional finding that heart rate variability, which is hypothesized to reflect parasympathetic activity (Porges, 1974; 1976), does not differentiate among infants prenatally exposed to various amounts of caffeine. The biological mechanism underlying this hypothesized sympathetic dominance may be an increased level of circulating catecholamines as a result of chronic and high prenatal exposure to caffeine. An increased level of circulating catecholamines has been found to affect autonomic functioning by producing uterine vasoconstriction. This, in turn, decreases the blood flow to the placenta which reduces the amount of nutrients and oxygen available to the fetus, creating the increased possibility of intrauterine hypoxia (Armitage, 1965).

Experiencing intrauterine hypoxia as a consequence of numerous prenatal conditions has previously been linked to a pattern of sympathetic dominance in infants as measured by differential patterns of heart rate (Downing, 1972). In addition to displaying increased sympathetic activity (Martin, Siassi, & Hon, 1974), these infants have a higher level of circulating catecholamines (Downing, 1972). Similarly, infants who are prenatally exposed to higher amounts of caffeine may experience intrauterine hypoxia as a consequence of an increased level of circulating

catecholamines. This condition may then manifest itself in a tendency toward sympathetic dominance in their autonomic functioning as assessed by an increased heart rate.

Experiencing intrauterine hypoxia as a result of prenatal exposure to caffeine is one possible explanation for why infants who were prenatally exposed to lower amounts of caffeine had a significantly lower average heart rate than infants exposed to higher amounts of caffeine when they were asleep but not when they were in a drowsy or quiet, alert state. This finding is similar to heart rate patterns observed in infants whose development has been compromised due to other prenatal and postnatal experiences. For example, cocaine-exposed infants display an elevated heart rate during quiet sleep relative to nonexposed infants (Woo et al., 1990). In addition, premature infants who are classified as being at risk for sudden infant death syndrome (SIDS) (Harper et al., 1982), as well as infants who later become victims of SIDS (Schectman et al., 1988) have also been shown to display elevated heart rates during the sleep states. It may be that caffeine has pharmacologic effects similar to those of cocaine or other risk conditions that result in hypoxia and, as a result, are manifested in increased heart rates, particularly during periods of sleep. Thus, these findings suggest that infants who are prenatally exposed to higher amounts of caffeine have behavioral patterns that are similar to those of infants who experience negative developmental trajectories.

In addition to patterns of higher heart rate, the number of observed tremors

was also found to be associated with maternal substance use during pregnancy. In general, infants who were exposed to higher amounts of alcohol were observed to have more tremors than infants exposed to smaller amounts of alcohol. These findings are consistent with previous work that has shown tremors to be signs of autonomic or central nervous system (CNS) instability and to be associated with a pattern of hyperarousal characteristic of neonatal withdrawal from a range of chemical substances (Harper, 1991), including alcohol (Coles et al., 1984; 1991) and cocaine (Chasnoff et al., 1987). In fact, increased tremoring is the one feature of Neonatal Withdrawal Syndrome (NWS) that is most consistently observed among substance-exposed neonates (e.g., Coles et al., 1984; Harper, 1991; Householder, Hatcher, Burns & Chasnoff, 1982; Robe, Gromisch & Losub, 1981). It is hypothesized that disturbances in motor control structures as a result of an increase in neurotransmittors and circulating catecholamine levels may be responsible for the tremors observed in newborn infants. Exposure to alcohol, nicotine, and caffeine have all been shown to increase the level of circulating catecholamines. Thus, it appears that caffeine, like other substances, including alcohol, nicotine, and cocaine, may alter important neurological structures and functions which are then manifested in excess neuromuscular activities such as tremors.

When the present findings of altered heart rate patterns and an increased number of tremors in infants prenatally exposed to higher amounts of caffeine are considered, it is evident that maternal caffeine consumption during pregnancy may be

one factor which can contribute to autonomic nervous system instability, at least, during the first days of postnatal life. In particular, all of the altered behaviors observed among infants prenatally exposed to higher amounts of caffeine have been linked to increases in the level of circulating catecholamines which impacts the sympathetic component of the autonomic nervous system. While it is possible that these observed behavioral effects may indicate permanent insults to the CNS which compromises continued development, all of the altered behavioral patterns found in the present study and discussed above were only evident during the first few days of postnatal life. Therefore, it is also possible that they represent a subtle, transient form of neonatal withdrawal from intrauterine exposure to the nervous system stimulant. In other words, once the infants have metabolized and excreted the final remnants of caffeine from their last prenatal exposure, the behavioral outcomes observed in this study may decrease in their intensity or cease to exist. The long-term developmental implications of prenatal exposure to caffeine, consequently, can only be speculated upon. Future research should clarify this issue by comparing the behaviors of newborns who differ in the amount of time that has passed since their last exposure to a caffeinated substance, as well as by testing and observing behavioral outcomes in prenatally exposed infants and children beyond the early postnatal period.

Whereas maternal caffeine consumption during pregnancy was associated with differential patterns of heart rate and an increased number of tremors, it was not found to significantly alter other regulatory measures, as hypothesized, such as the number

of observed startles (see Hypothesis #7) or the number of times infants changed behavioral states (see Hypothesis #8). In addition, contrary to the hypothesis that infants who were prenatally exposed to higher amounts of caffeine would spend more time in alert and active alert states (see Hypothesis #6), no association between maternal caffeine consumption during pregnancy and the amount of time infants spent in each behavioral state was found. However, even when there were no differences in the number of times infants changed behavioral state or in the amount of time infants spent in each behavioral state, there were important differences in heart rate. Since caffeine functions as a direct cardiac muscle stimulant in adult consumers (Howell et al., 1981), and readily crosses the placenta and enters the fetal circulatory system (Morris & Weinstein, 1981), it is not surprising to find evidence that caffeine also acts as a cardiac muscle stimulant in the fetus and newborn infant. Thus, even though there is a strong relationship between heart rate and behavioral state, these findings suggest that caffeine may have specific action on cardiac activity, perhaps independent of behavioral state.

As discussed above, behavioral states are descriptive categorizations of behavioral patterns that provide a convenient method of conceptualizing observable changes in infants' levels of arousal (Prechtl, 1974). However, in the process of creating such global categorizations of behavioral states, subtle, but informative shifts in arousal, such as changes in heart rate, may get subsumed. In other words, prenatal exposure to different amounts of caffeine may affect arousal at the level of heart rate

but may not alter the entire range of behaviors needed to move the infant into the qualitatively unique level of arousal which indicates a change in behavioral state.

One speculation is that an overall pattern of increased heart rates and lack of increased heart rate variability in infants who have been exposed to higher doses of caffeine may have important consequences for future perceptual and cognitive development, particularly if these altered behavioral outcomes are determined to be relatively permanent. Regulation of arousal, which is often measured by recording heart rate (Gardner & Karmel, 1983), is widely believed to be an essential factor in the modulation of sensory reactivity and attention (Als, Lester, Tronick, & Brazelton, 1982; Field, 1981; Sroufe, 1979). Associations between levels of arousal, as measured by heart rate, in infants and visual and auditory responsiveness to stimulation have been widely documented (see Gardner & Karmel, 1983 for a review). Too much or too little arousal in the infant negatively affects the infant's ability to orient and attend to stimulation. For example, several previous studies have found a relationship between resting heart rate variability and overall heart rates and an infant's ability to attend to perceptual stimulation (e.g., Porges, Stamps, & Walter, 1976). Preterm infants who display relatively unmodulated heart rates and had higher overall heart rates were less likely than full-term newborn infants to have a deceleration in their heart rate, which is associated with attentional processes, in response to the presentation of stimulation (Field et al., 1979).

In addition to affecting perceptual processes such as orienting and attending, an

infant's level of arousal also affects its visual and auditory preferences (Gardner & Karmel, 1983). In general, young infants (<2 months of age) who are highly aroused orient towards and prefer less intense stimuli (e.g., Field, 1981; Gardner, 1979). In particular, highly aroused infants avert from almost all exogenous stimulation, whereas sleeping infants respond only to relatively intense environmental stimulation (Gardner & Karmel, 1983). Consequently, infants who have heightened levels of arousal as a result of prenatal exposure to caffeine may systematically attend to less intense environmental stimulation than infants who do not have altered levels of arousal as a result of prenatal exposure to caffeine. If this preference for less intense stimulation reflects a relatively permanent change in structural or functional components of the infant's nervous system, the cognitive and perceptual developmental pathway of the infant may be changed (Gardner & Karmel, 1983). Of course, the duration of this preference depends on the duration of the effects found in the present study of newborn infants.

Previous studies have, though, shown that newborn infants who were prenatally exposed to high amounts of caffeine respond to stimulation differently than infants exposed to smaller amounts of caffeine in regulating their arousal in response to stimulation (Hronsky & Emory, 1987; Jacobson et al., 1984). For example, infants exposed to high amounts of caffeine during gestation were more difficult to console than infants exposed to lower amounts of caffeine (Hronsky & Emory, 1987). Infants prenatally exposed to higher amounts of caffeine in their study also had more

difficulties with visual-orienting and head-turning to a human face, which suggests that infants who have been prenatally exposed to higher amounts of caffeine may be compromised on their ability to attend and respond to stimulation, including social stimulation. The significance of these findings for long-term development is not clear since these infants were not followed up beyond the first few days of life. Thus, it is unclear how permanent these perceptual and attentional difficulties are among infants prenatally exposed to caffeine. If infants do, in fact, have more longlasting difficulties in responding to social stimulation, the caregiver-infant interactions which are vital to ensure optimal infant development may be negatively affected.

According to a transactional model of development (Sameroff & Chandler, 1975), infants who have altered levels of arousal, as measured by behavioral responses (i.e., heart rate) to endogenous or exogenous stimulation, as a consequence of prenatal exposure to chemical substances may have associated dispositional characteristics which affect the manner in which the caregiver responds to the infant (Zuckerman & Brown, 1993). For example, during infancy, caregivers typically provide stimulation to underaroused infants and reduce available stimulation when an infant becomes overaroused. An infant who has difficulty in regulating its arousal as a result of prenatal exposure to caffeine may not be able to effectively elicit appropriate caregiving responses. In addition, substance-using mothers have been shown to have difficulty in adjusting to their infants' altered behaviors at birth and through early infancy (see review by Freier et al., 1991) and perceive their infants more negatively

than mothers who did not use drugs during pregnancy (Coles et al., 1987). This creates the increased potential of beginning a cycle of inadequate interactive behaviors with the caregiver in which the infant is unable to elicit the optimal response from the caregiver who, in turn, may perceive the child as difficult or unpredictable. Consequently, an infant who is already at risk for nonoptimal development as a result of prenatal exposure to relatively heavy amounts of caffeine may also be more likely to experience inadequate or negative interactive behaviors with its caregiver which has been shown to have negative attachment and behavioral ramifications beyond infancy (Rodning, Beckworth, & Howard, 1990). Again, this speculation depends upon the duration of the effects of caffeine found only on newborn behavior.

The close relationship found between SES and the number of obstetrical complications experienced by the newborn infant may also have longlasting effects for the development of the infant. The multitude of risk factors typically experienced by the mother and infant from low socioeconomic backgrounds paired with the increased tendency of these mothers to engage in behaviors which are potentially harmful to the developing fetus account for the less optimal scores on the OCS typically found among these mother-infant dyads. Experiencing this higher number of obstetrical complications and risk factors increases the risk that an infant will be born biologically vulnerable and difficult to care for (Halpern, 1993). Since experiencing multiple risk factors may indicate the presence of CNS stress (Prechtl, 1968), the combination of nonoptimal obstetric complications that impact an infant born in poverty may have

important implications for long-term development. For example, Birch and Gussow (1970) found that these compromising developmental influences are associated with altered patterns of infant-caregiver interactions and affect the capacity of caregivers to respond to the infant.

This can be particularly problematic since risk status in infancy has been demonstrated to be associated with an interaction between biological insults and environmental insults resulting from low SES (Aylward, 1992; Coles & Platzman, 1993; Zeskind & Ramey, 1981). For example, Drillien et al. (1980) demonstrated that, among newborns exhibiting the same biological conditions, those from a lower socioeconomic background showed significant deficits by school age, while children from higher socioeconomic backgrounds demonstrated no observable effects. When heavier substance use is added to the already less than optimal environmental factors, the child is at even greater risk for nonoptimal development.

In many cases where the child has only suffered subtle insults to nervous system integrity during the prenatal period, a supportive, nurturing postnatal environment can overcome the negative effects of earlier substance exposure (Zeskind & Ramey, 1981). In fact, there is increasing evidence that infants who are considered at risk for nonoptimal development at birth often show no deficits later in development if the mother has adequate resources, such as social support and educational opportunities, available to her (Coles & Platzman, 1993). However, an abusive or neglectful environment can also potentiate the negative effects of teratologic insults

and is associated with a higher incidence of infants who fail to thrive (Bullard et al., 1986). Thus, the postnatal environment may play a significant role in their long-term developmental outcome. Despite the negative outlook that exposed infants face, infants who show altered behavioral patterns at birth associated with prenatal caffeine exposure may not necessarily be condemned to a negative developmental trajectory. Future research should explore this issue by more closely examining the interaction of SES and other social/environmental factors with biological insults related to prenatal exposure to caffeine. Additionally, it is important to explore the long-lasting effects that prenatal exposure to caffeine may have on behavioral and social development by assessing exposed infants beyond the first few days of postnatal life.

While the results of this study indicate that prenatal exposure to heavier amounts of caffeine may operate as a risk factor during prenatal development, there are methodological issues inherent in studies using human subjects which may limit the conclusions that can be drawn. One such issue is the association of maternal caffeine consumption during pregnancy with other life-style factors such as maternal smoking during pregnancy and socioeconomic background. Several researchers have suggested that observed behavioral effects in newborn infants may actually be the result of poly-drug exposure or life-style characteristics which are common among substance-users (Lutiger, Graham, Einarson, & Koren, 1991). Although this issue can be dealt with, in part, by eliminating infants whose mothers who report poly-drug use from the study or statistically controlling for other reported drug use, it is more

difficult to control for other potentially influential life-style issues such as maternal stress or depression.

Another methodological difficulty involves accurately assessing the complex pattern of timing and dosage of any type of substance use during pregnancy. In order to assess how timing of caffeine consumption during pregnancy affects developmental outcomes, it is important to know detailed information about caffeine exposure at various points during pregnancy. Unfortunately, this involves either extensive record keeping throughout pregnancy, the frequent use of biological measures such as blood and urine tests, or retrospective reports of caffeine consumption during pregnancy. All of these methods have potential methodological problems. For example, keeping detailed, accurate diaries of caffeine consumption during pregnancy requires the full cooperation of committed women who can be identified and recruited early in pregnancy. In addition to the time and expense involved, these criteria systematically exclude a large percentage of the population of interest. Biological measurements of caffeine consumption provide only limited information about the amount of caffeine currently in the woman's blood or urine rather than information about chronic exposure. On the other hand, retrospective measurement, which was the method of choice in this study, relies on self-reports of amount, frequency and variability of caffeine consumption over a relatively long period of time. Even among women who are reporting their consumption patterns as accurately as possible, their recall may be in error.

Yet another related difficulty involves the timing of exposure. Typically with substance use, pregnant women have variable patterns of use across the duration of pregnancy. For example, Coles (1994) reports that, among alcohol users, pregnant women typically drink heaviest around the period of conception and then reduce or discontinue their alcohol use once they realize that they are pregnant. Surprisingly, this was not the general finding with patterns of caffeine consumption during pregnancy reported by mothers in this study. Specifically, only seven women reported any significant reduction of caffeine consumption during their pregnancy, primarily by reducing their average daily amount of coffee consumption. The majority of women continued to consume caffeine in similar amounts throughout their pregnancy, although several women reported that they had reduced their caffeine consumption when they began to attempt to conceive. In addition, three women reported that they had increased their consumption of caffeinated sodas and coffee towards the end of their pregnancy. Unfortunately, the small number of these subjects did not permit any definitive statistical analyses to be conducted concerning the timing of prenatal exposure to caffeine. Perhaps future research can more closely examine the relationship between the timing of prenatal exposure to caffeine and behavioral outcomes in infants.

Finally, it is important to note that results of the present study are based on data collected from subjects recruited at two hospitals with populations who differed in several significant ways. This provided some interesting data on the differences between a small community hospital (MRH) in a primarily rural area and a large inner

city hospital (GMH). Perhaps the most noticeable difference concerned the SES differences between the two populations. Subjects at GMH were from a signficantly lower socioeconomic background than were subjects from MRH. Other differences noted between the two populations, such as a higher percentage of bottle-fed infants at GMH, higher incidence of married mothers at MRH, higher percentage of minority infants at GMH, and fewer years of formal schooling and prenatal visits among mothers at GMH, are all factors that are, most likely, functions of the sociocultural differences between GMH and MRH related to SES differences.

As discussed above, SES is an important risk factor during infancy and may be expected to significantly alter behavioral patterns in affected infants. This was, in fact, found to be the case in several of the regulatory measures (i.e., heart rate patterns) assessed in this study. Interestingly, however, there were no differences found in measures of heart rate between the two hospital populations despite the significant differences in SES. This supports the findings that other factors that do not differ between the populations at the two hospitals (i.e., caffeine and nicotine exposure) contribute important effects to the altered behavioral outcomes. Thus, although lower SES undeniably functions as a risk factor among newborn infants, other risk factors, including maternal caffeine consumption during pregnancy, contribute to nonoptimal developmental outcomes among affected infants in significant ways.

Although definitive conclusions about the causative influence that prenatal exposure to caffeine has on neonatal outcomes can not be drawn from the present

study, these findings indicate that prenatal exposure to heavier amounts of caffeine may operate as a risk factor during prenatal development. In combination with other known and suspected risk factors, prenatal exposure to heavier amounts of caffeine may place the already vulnerable infant at an even higher risk of nonoptimal development. Since prenatal exposure to caffeine may be related to behavioral patterns that have been shown to be associated with negative outcomes in perceptual abilities, attention, and social interactions, the possibility of long-term consequences of heavier maternal consumption of caffeine during pregnancy should not be discounted. The next step should be to explore the relationship between early exposure to caffeine, with and without the presence of other risk factors, and future cognitive and social functioning.

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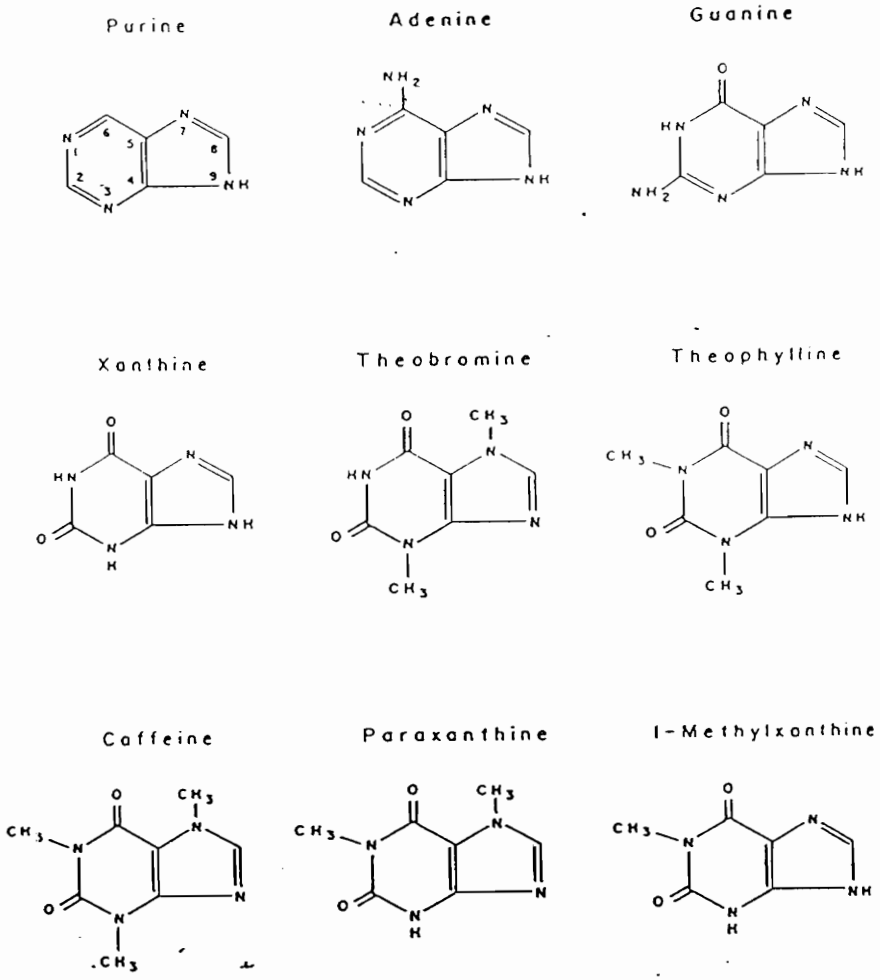


Figure 1. Structures of caffeine (1,3,7-trimethylxanthine), purine, xanthine and guanine.

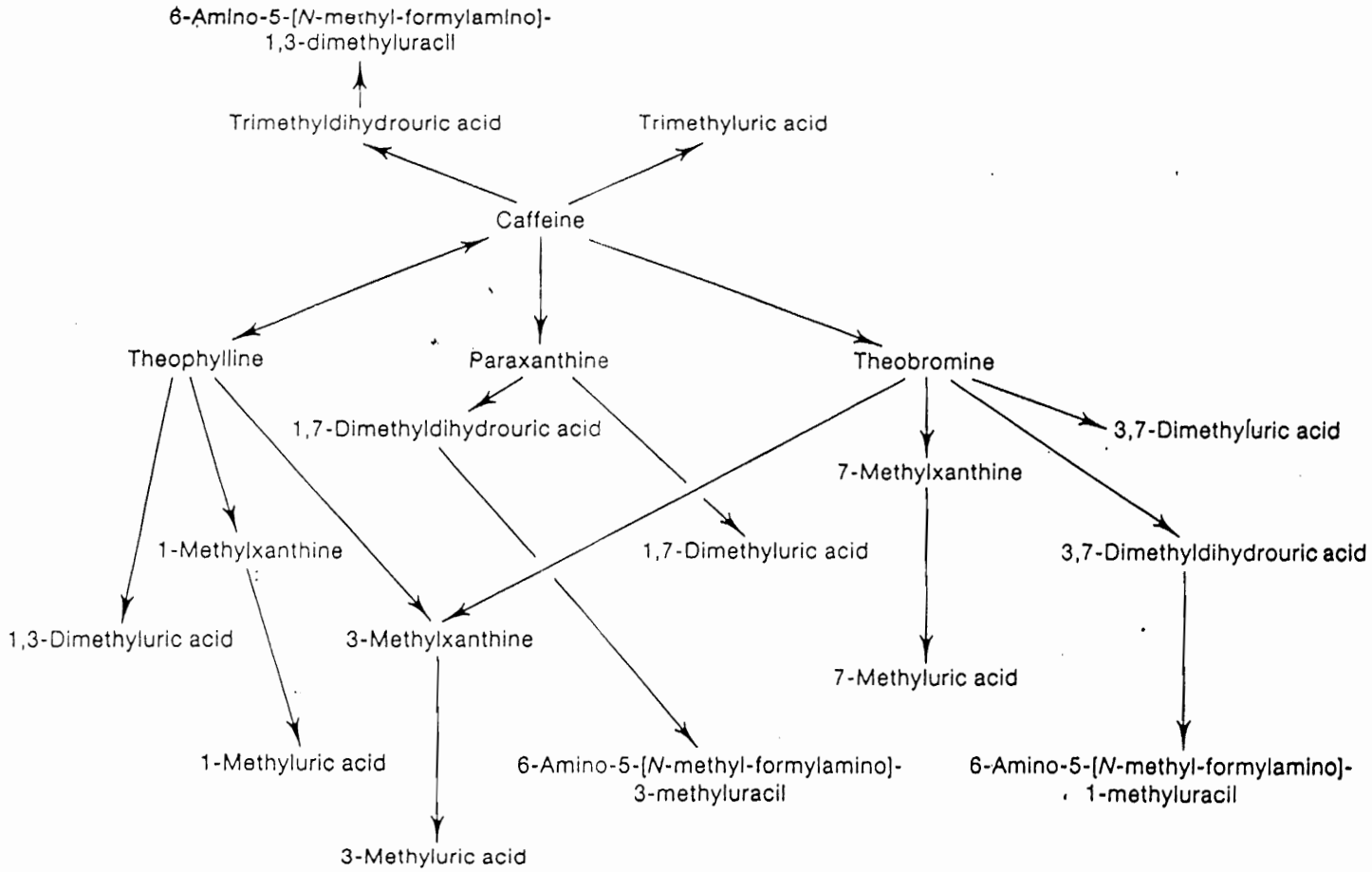


Figure 2. Metabolic pathways of caffeine. (Adapted from Tarka, 1982.)

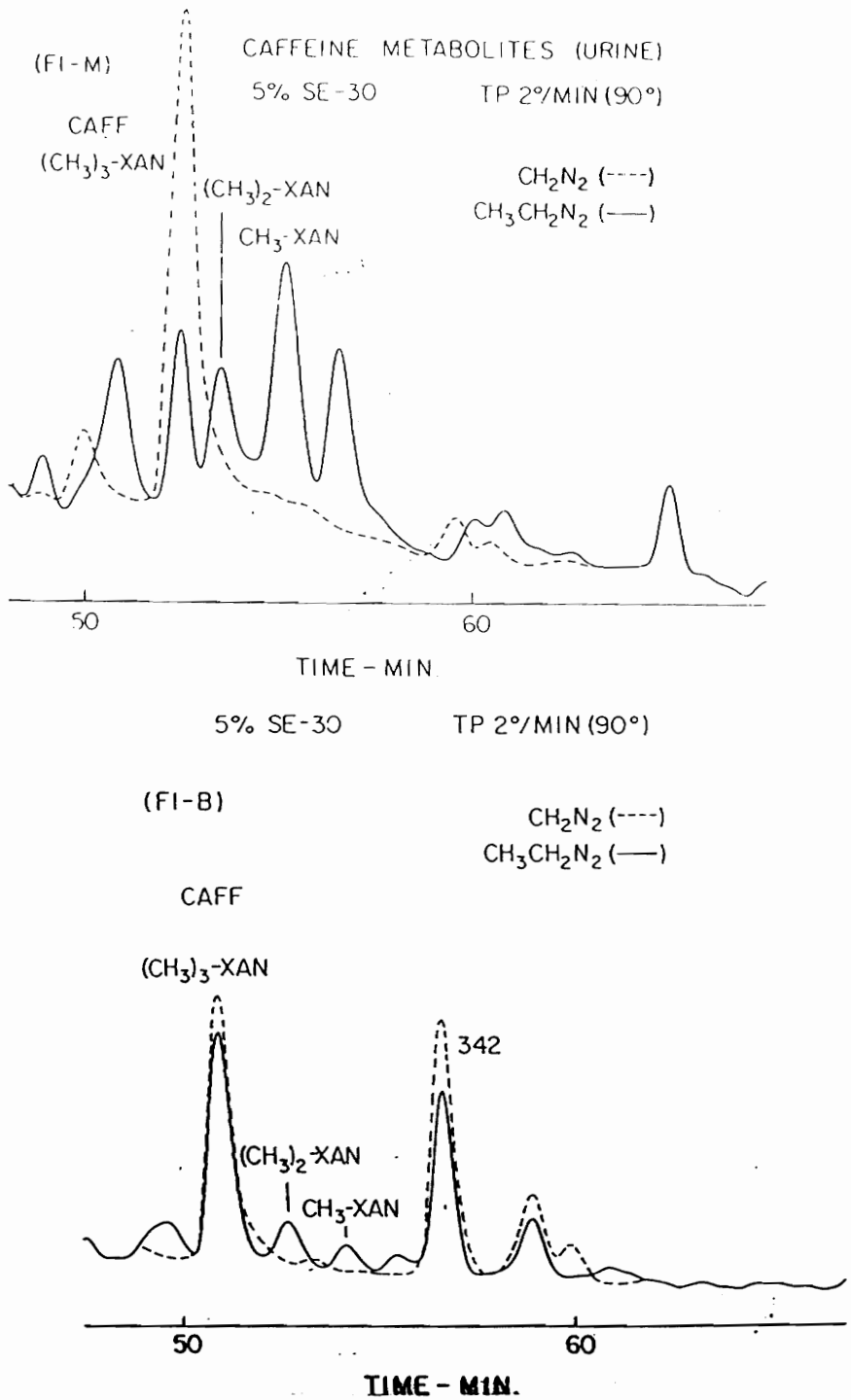


Figure 3. Gas chromatographic separation of caffeine and its metabolites in the urine of a mother (upper) and her newborn infant (lower). (Adapted from Horning, Stratton, Nowlin, Wilson, Horning & Hill, 1973).

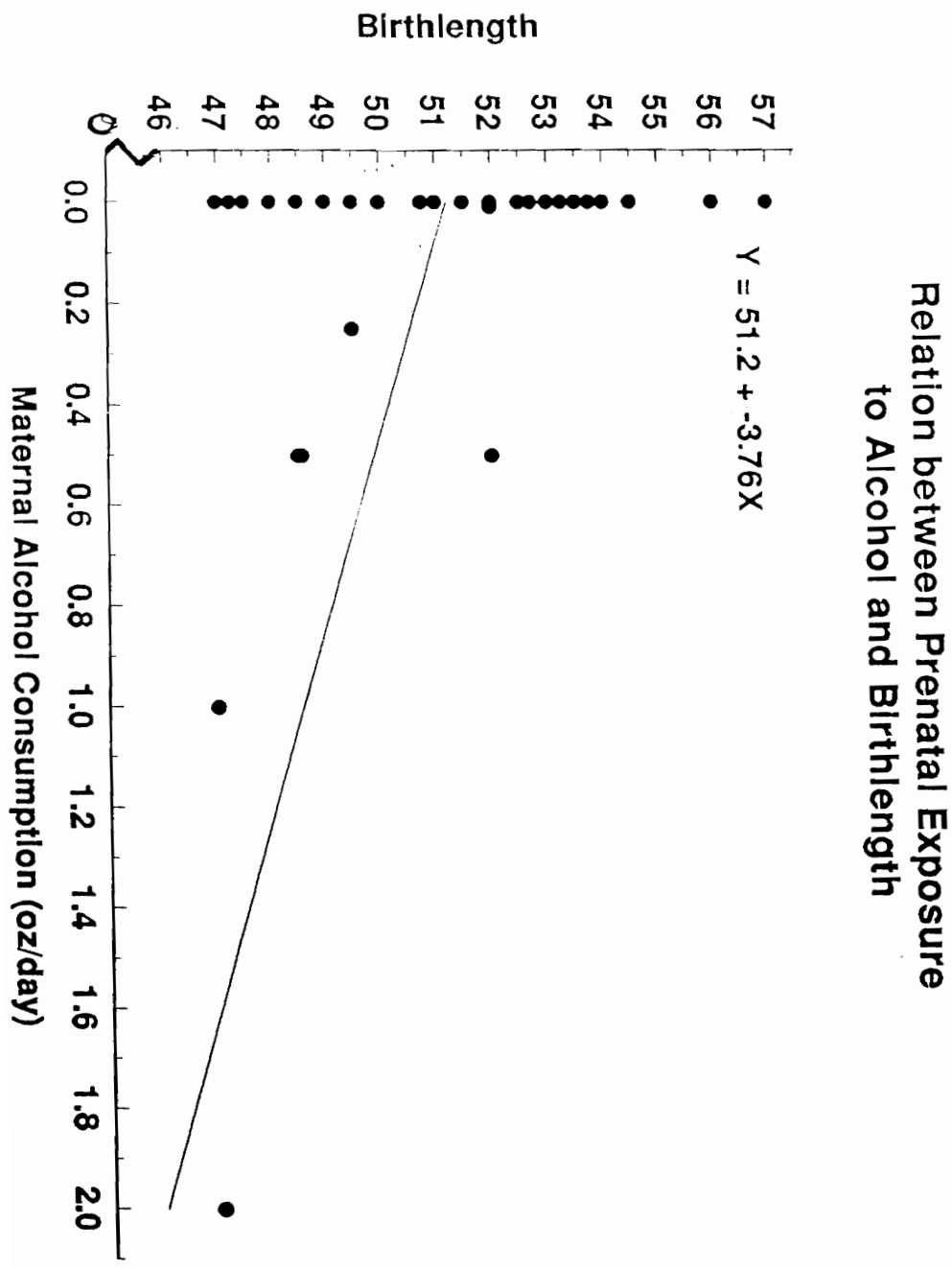


Figure 4. Relation between prenatal exposure to alcohol and birthlength.

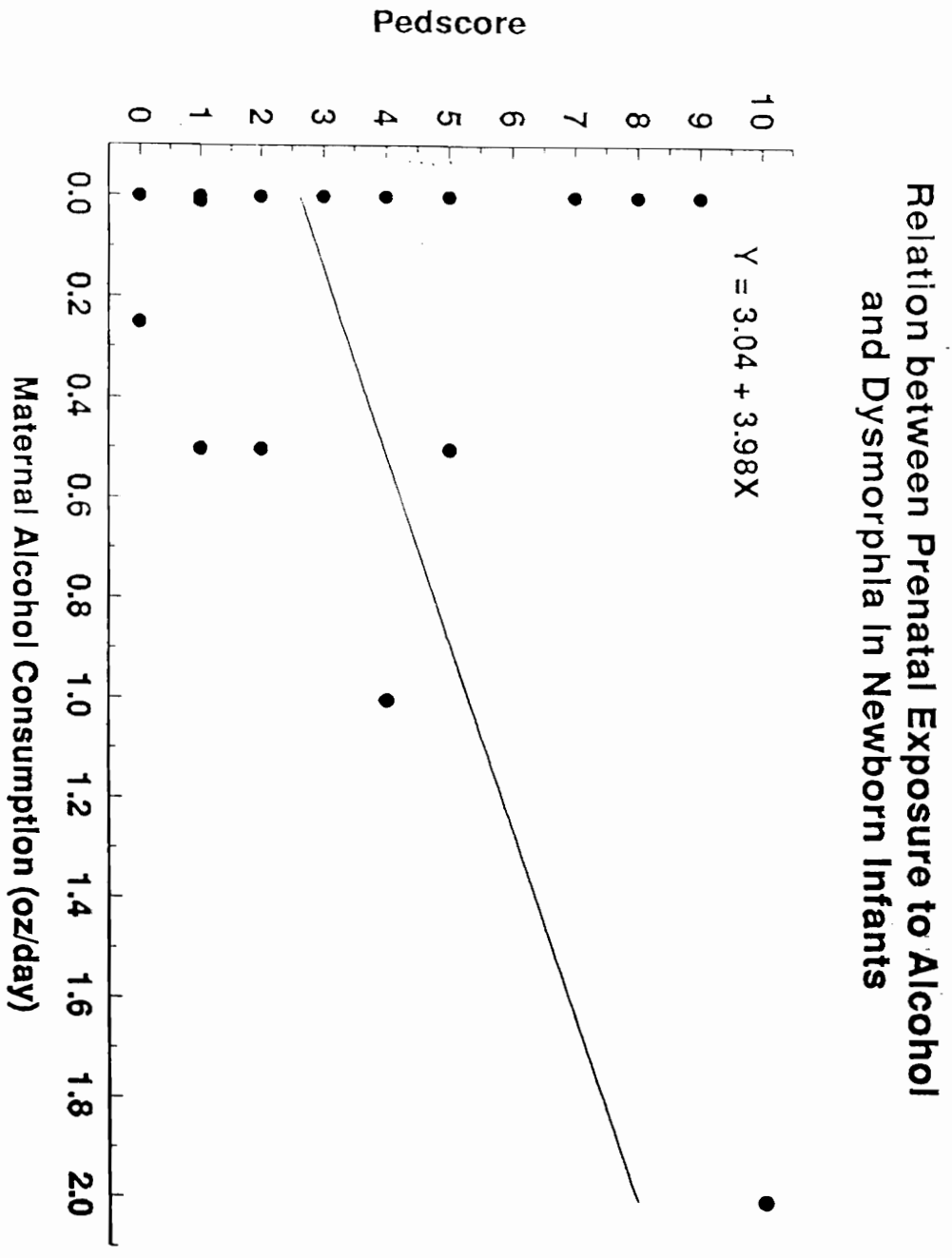


Figure 5. Relation between prenatal exposure to alcohol and dysmorphia in newborn infants.

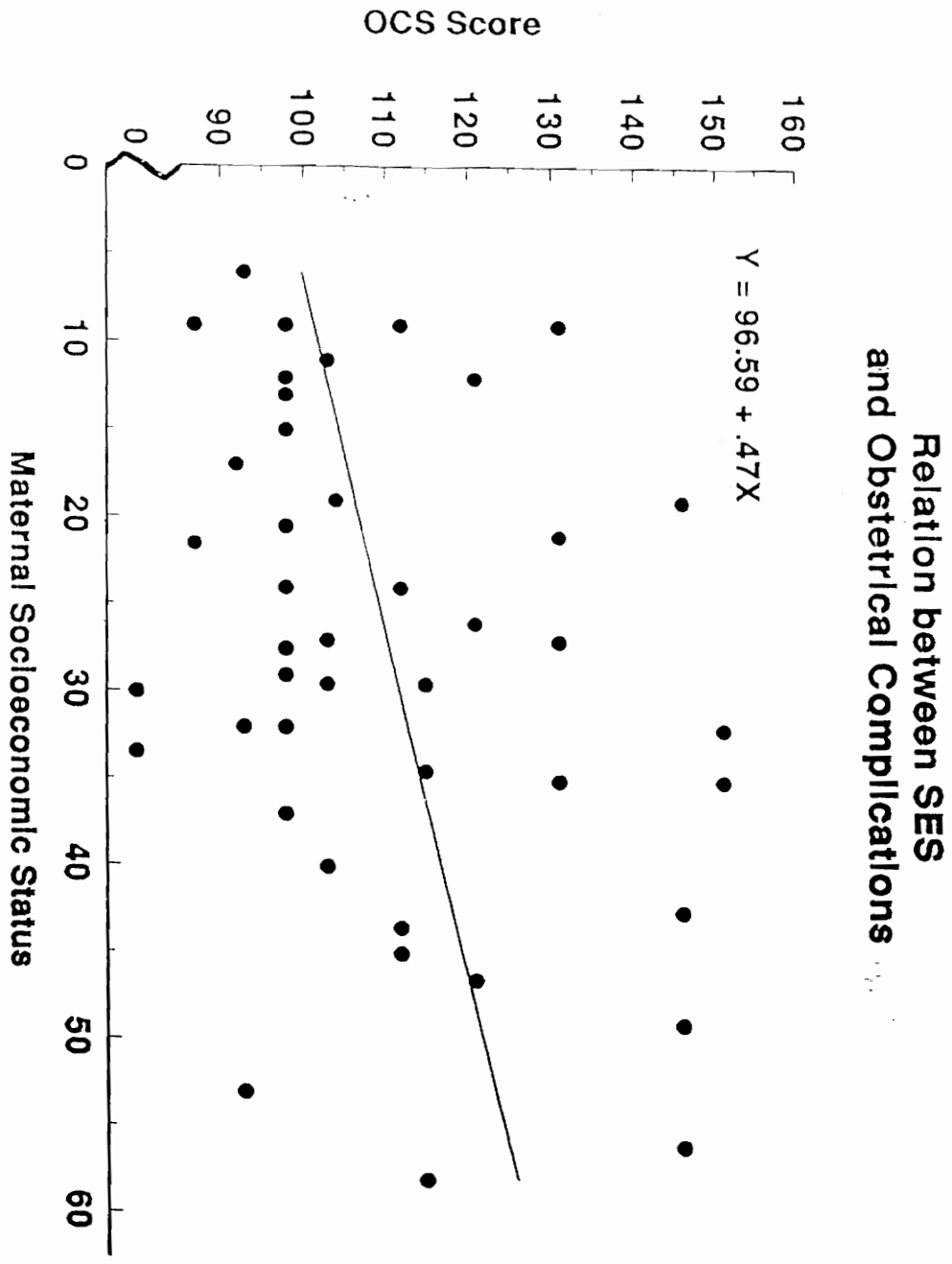


Figure 6. Relation between SES and obstetrical complications.

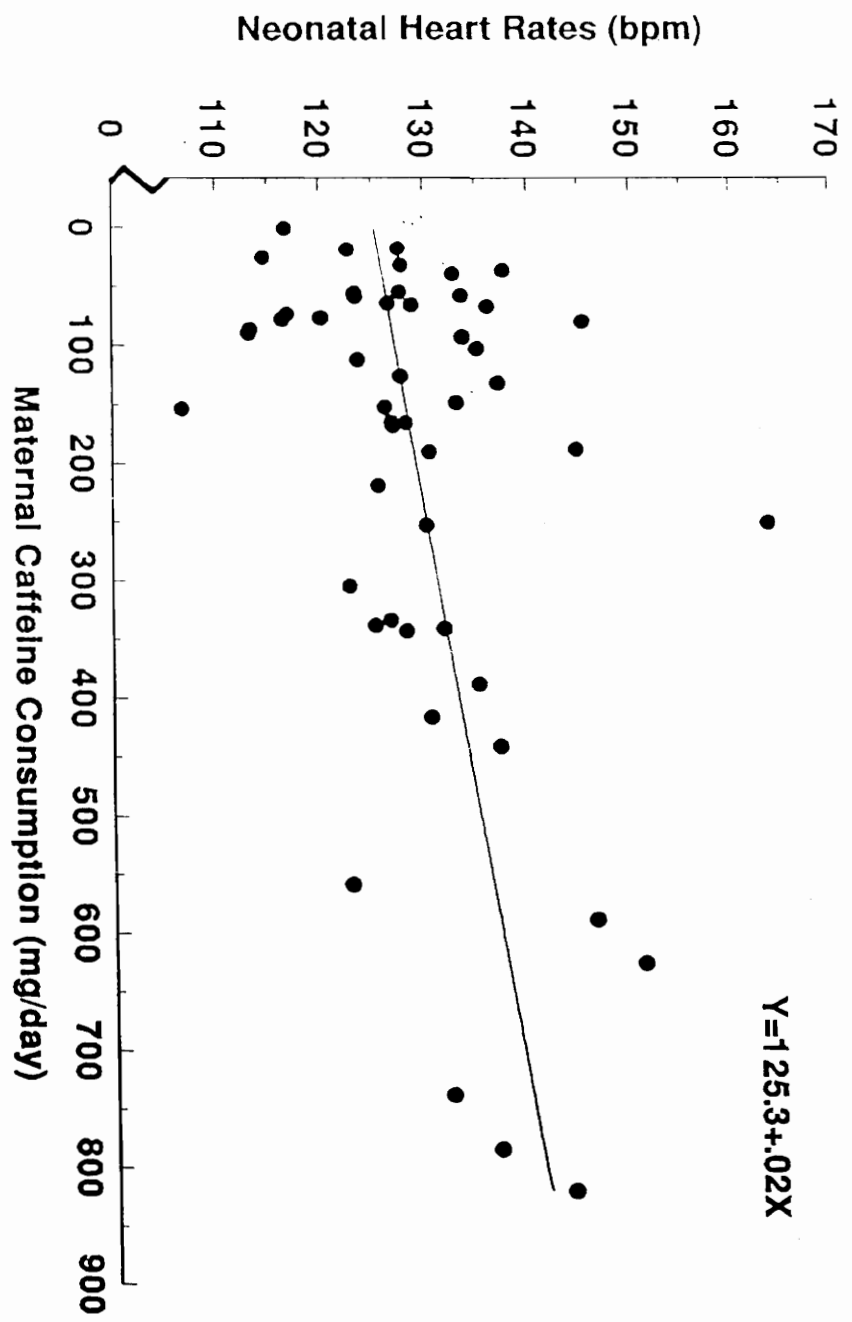


Figure 7. Relation between prenatal exposure to caffeine and neonatal heart rates.

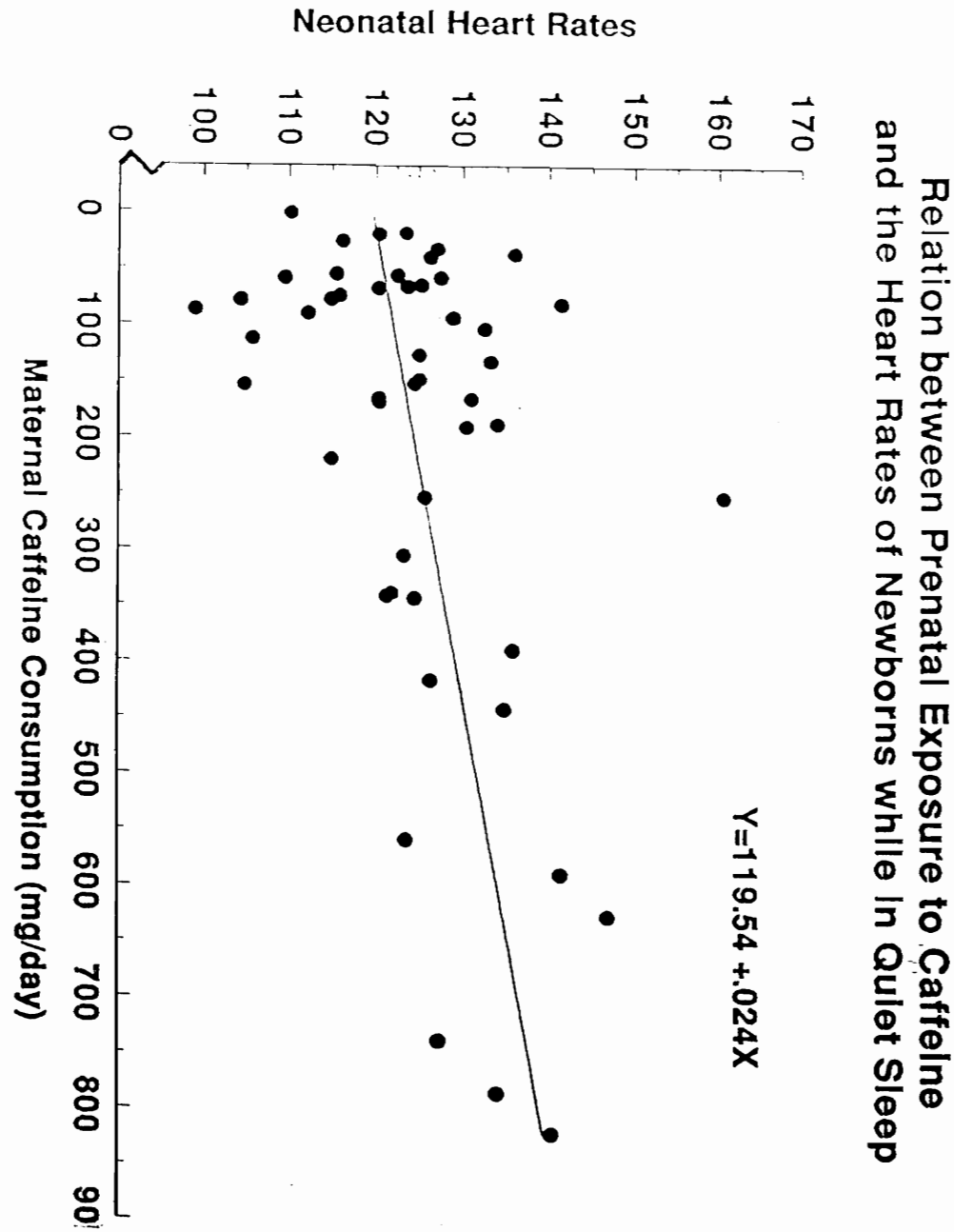


Figure 8. Relation between prenatal exposure to caffeine and the heart rates of newborns while in quiet sleep.

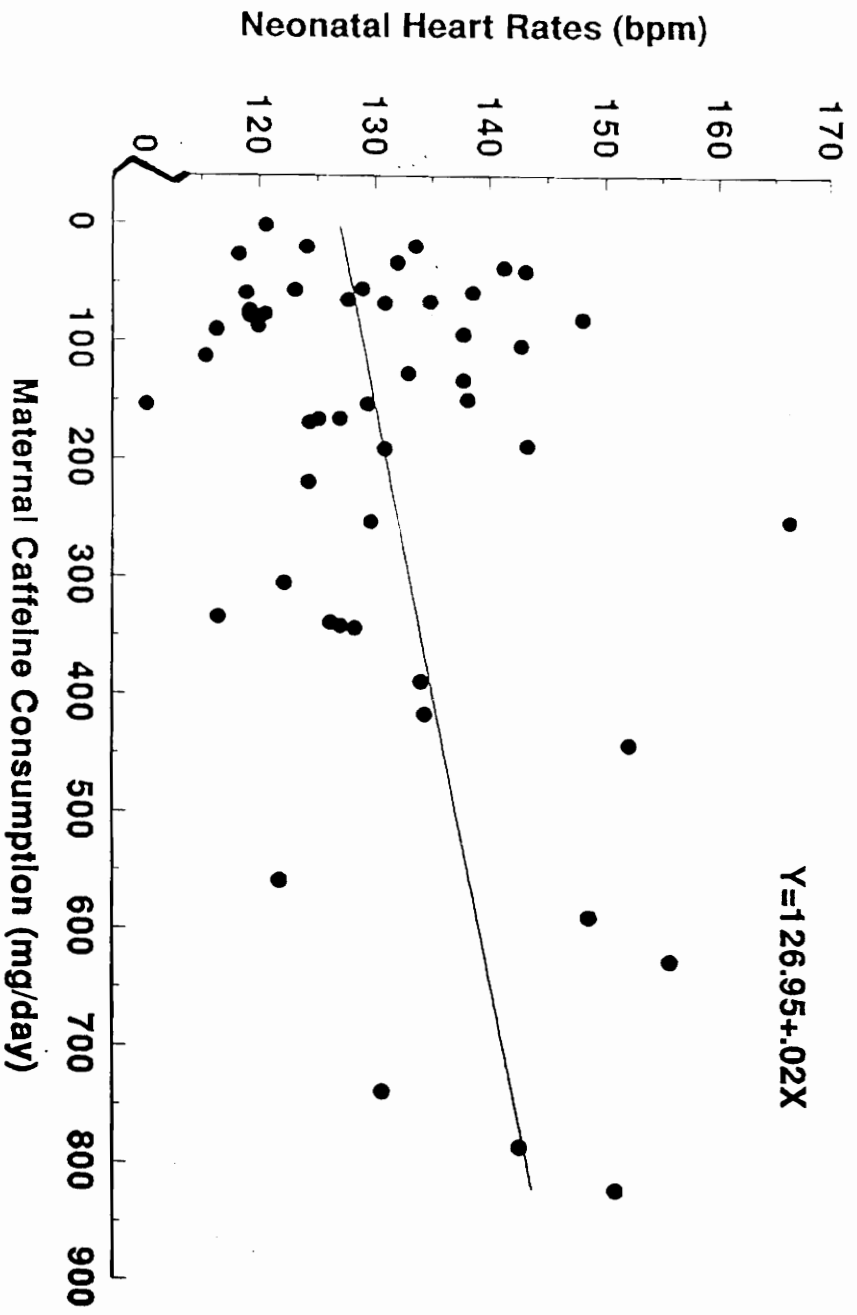


Figure 9. Relation between prenatal exposure to caffeine and the heart rates of newborns while in active sleep.

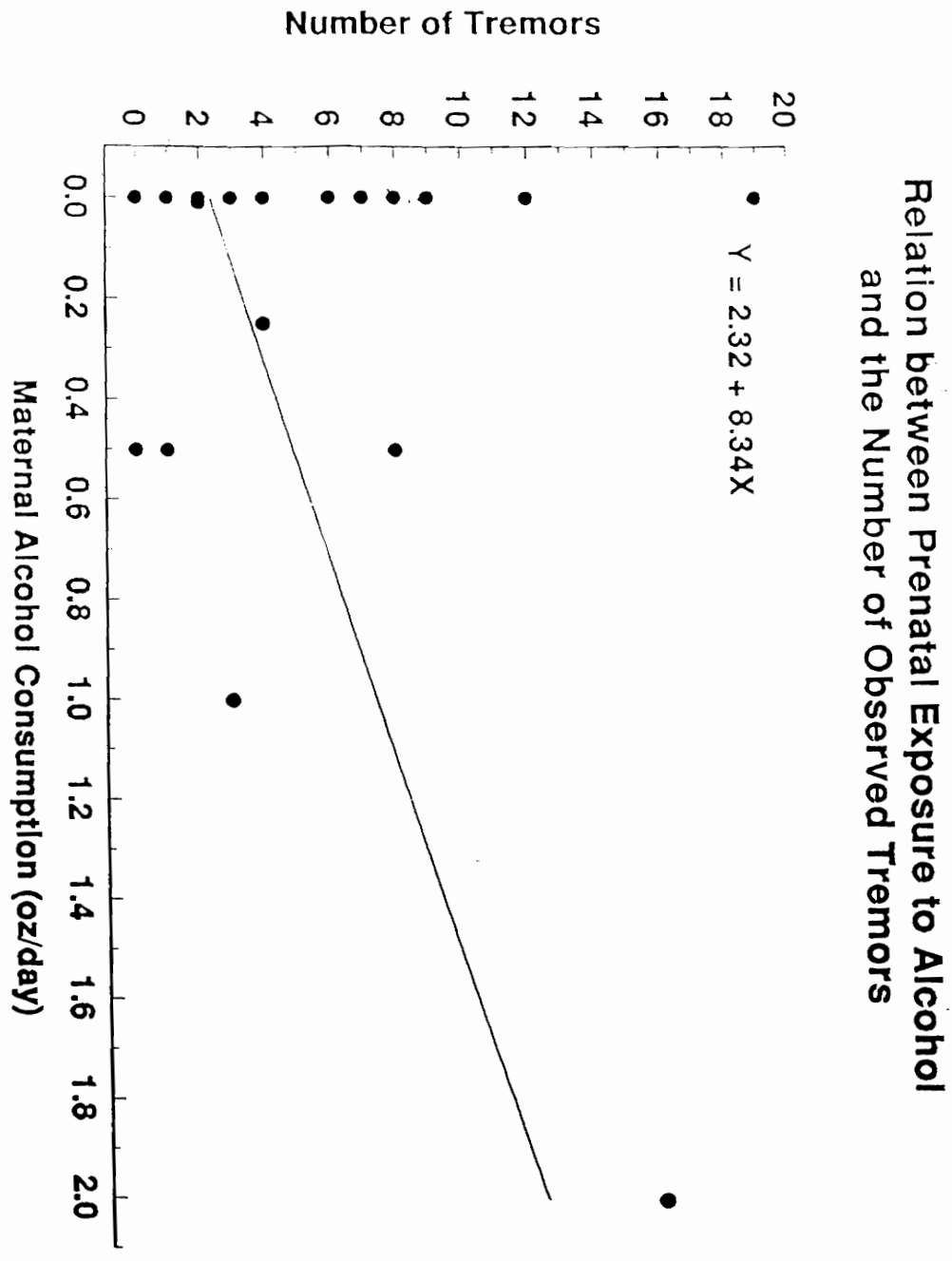


Figure 10. Relation between prenatal exposure to alcohol and the number of observed tremors.

Table 1

Various Indications of the Teratogenicity of a Drug

Observable Manifestation	Underlying Mechanism
Failure to ovulate	Endocrine or metabolic imbalance
Prevented fertilization	Reduction of the fertilizing capacity of the germ cells
Interference with migration	Interference with ovum or early embryo
Faulty/no implantation	Damaged blastocysts or improper uterine condition
Indirect damage to embryo or fetus	Altered placental function or maternal metabolism
Direct damage to embryo or fetus	Increased fetal mortality and morphological or behavioral anomalies

Adapted from Wilson (1973)

Table 2

Descriptions of Behavioral States on a 6-point Scale

State 1. Sleep with regular breathing, eyes closed, no spontaneous activity except startles or jerky movements at quite regular intervals. No eye movements.

State 2. Sleep with eyes closed; rapid eye movements can often by observed under closed lids; low activity level, with random movements and startles or startle equivalents; movements are likely to be smoother and more monitored than in state 1. Respiration is irregular, sucking movements occur off and on. Eye opening may occur briefly at intervals.

State 3. Drowsy or semi-dozing; eyes may be open but dull and heavy-lidded, or closed, eyelids fluttering; activity level variable, with interspersed, mild startles from time to time. Movements are usually smooth. Dazed look when the infants is not processing information. Some infants may also show fuss/cry vocalizations in this state. What distinguishes state 3 from state 5 when both are accompanied by fuss/cry vocalizations is the minimal movement in state 3 and considerable movement in state 5.

State 4. Alert, with bright look and appropriate changes in facial expression as stimulation is varied. Motor activity is at a minimum. There can be a glazed look which is easily broken through in this state.

State 5. Eyes open; considerable motor activity, with thrusting movements of the extremities, and even a few spontaneous startles or motor activity, but discrete reactions difficult to distinguish because of general activity level. Some infants may transition directly from lower states (1, 2, or 3) directly to state 5. These are often the cases described above in which fuss/cry vocalizations occur and states 5 and 3 are difficult to distinguish unless the differences in motor activity are taken into account.

State 6. Crying, characterized by intense, loud, rhythmic and sustained cry vocalizations which are difficult to break through with stimulation; motor activity is high. It is important to distinguish between crying as a state from the fuss/cry vocalizations that can occur in state 5 and even state 3. Some infants show repeated episodes of fuss/cry vocalizations in state 5 but may not reach state 6. This may also be a maturational issue as some preterm infants may not have the energy reserves to sustain state 6. In general, state 6 can be distinguished from state 5 by the intensity and sustained quality of the crying (at least 15 seconds) and unavailability of the infant in state 6. Examiners need to give the infant the opportunity to show state 6.

Table 3

Descriptions of Behavioral State on an 11-point Scale

1. *Quiet Sleep A.* The infant's eyes are firmly closed and still. Little or no motor activity, with the exception of occasional startles or rhythmic mouthing. Respiration is abdominal and relatively slow (average around 36 per minute), deep and regular.
2. *Quiet Sleep B.* Same as Quiet Sleep A except that respiration may be relatively fast (above 46/minute) and show some irregularities. Respiration is primarily abdominal in this state.
3. *Active Sleep without REM's.* The infant's eyes are closed, but slow, rolling movements may be apparent. Bodily activity can range from minor twitches to writhing and stretching. Respiration is irregular, and generally faster than that seen in Quiet Sleep. Facial movements may include frowns, grimaces, smiles, twitches, mouth movements, and sucking.
4. *Active Sleep with REM's.* Eyes are closed. Rem's occur during the ten-second epoch; respiration and movement characteristics are the same as in 3, except that facial activity is more likely to accompany REM's or to be interspersed between groups of REM's.
5. *Active Sleep with Dense REM.* Same as two categories of Active Sleep, except for the continuous occurrence of REM's throughout the ten second epoch. REM's in this category are often accompanied by raising of the eyebrows and by eye-opening.
6. *Drowsy State.* Eyes may open and close or be partially or fully open, but very still and dazed in appearance. There may be some generalized motor activity, and respiration is fairly regular, but faster and more shallow than that observed in Quiet Sleep.
7. *Indefinite State.* Infant's eyes may be closed, or opening and closing. Generalized motor activity, but no sufficient criteria by which infant's state can be classified as waking or sleeeping.
8. *Alert Inactivity.* Body and face are relatively quiet and inactive, and eyes are "bright and shining" in appearance (Wolff, 1967).
9. *Waking Activity.* Eyes are generally open, but may be closed. Generalized motor activity, accompanied by grimacing, grunting, or brief vocalization.
10. *Fussing.* Same as Waking Activity except for constant mild, agitated vocalization; or one cry burst may occur.
11. *Crying.* Same as Waking Activity except that generalized motor activity is more intense, and cry bursts are continuous.

Adapted from Thoman (1975; 1985).

Table 4

Means and standard deviations of time spent in each behavioral state for infants prenatally exposed to low, moderate, or high amounts of caffeine

	Groups					
	Low caffeine		Moderate caffeine		High caffeine	
Variables	M	SD	M	SD	M	SD
Deep Sleep	71.83	48.47	80.50	41.38	74.90	29.26
Active Sleep	93.33	47.87	113.60	47.67	133.10	29.26*
Drowsy	20.83	26.06	15.10	18.48	12.80	21.56
Alert	14.42	16.20	11.20	23.79	4.90	12.53*
Active Alert	29.08	45.85	13.05	22.65	7.80	19.81*
Crying	10.50	18.69	5.20	13.42	6.50	19.86

*=$p < .05$

Table 5

Characteristics of Women Consuming Caffeine during Gestation

Maternal Characteristics	Recruitment Sample					
	MRH (n=28)		GMH (n=22)		Total (n=50)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Maternal Age (years)	24.4	5.72	22.45	4.73	23.56	5.35
Mean Weight Gain during pregnancy (pounds)	34.57	14.99	25.08	23.97	30.73	19.47
Mean # of Prenatal Visits	11.04	4.1	7.81	4.41	9.65	4.49*
Mean Education (years)	13.0	1.83	11.18	1.92	12.2	2.1**
Daily Amount of Caffeine during pregnancy (mg/day)	223.02	238.99	202.56	174.25	214.0	211.2

*indicates $p < .01$
**indicates $p < .001$

Table 6

Characteristics of Women Consuming Caffeine during Gestation

Maternal Characteristics	Recruitment Sample		
	MRH (n=28)	GMH (n=22)	Total (n=50)
Ethnic Group (%)			**
Black	3.6	77.3	36.0
Caucasian	89.3	9.0	54.0
Other	7.2	13.6	10.0
Number of C-sections (%)	17.9	18.2	18.0
Regular Cigarette use during pregnancy (%)	17.9	18.2	18.0
Regular Alcohol use during pregnancy (%)	7.2	18.2	12.0

**indicates $p < .001$

Table 7

Perinatal Characteristics of Infants Exposed to Caffeine During Gestation

Infant Characteristics	Recruitment Samples					
	MRH (n=28)		GMH (n=22)		Total (n=50)	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
Mean Gestational Age (wk)	39.46	1.35	39.55	0.86	39.5	1.15
Mean Birthweight (gm)	3511.1	374.6	3309.1	453.6	3422.2	419.2
Mean Head Circ. (cm)	34.72	1.74	33.86	1.54	34.35	1.69
Mean Birthlength (gm)	51.36	2.34	50.43	2.62	50.95	2.48
Mean Apgar Score (1 min)	8.46	0.69	8.18	1.26	8.34	0.98
Mean Apgar Score (5 min)	9.11	0.50	9.73	4.32	9.38	2.87
Mean OCS	111.61	18.6	101.91	14.6	107.34	17.5*
Mean Age (hours)	27.14	11.31	31.93	15.71	29.25	13.49
Mean Pedscore	3.21	2.66	2.77	2.11	3.02	2.42
Mean Ponderal Index	2.6	0.29	2.58	0.28	2.59	0.28

*indicates $p < .05$

Table 8

Correlations of Predictor Variables with Anthropometric and Perinatal Risk Status Outcomes

Dependent Variables	Nicotine use	Alcohol use	SES	Caffeine Use
Birthweight	.08	-.24	.12	.05
Birthlength	-.04	-.28*	.13	-.10
Head circumference	.18	-.14	.13	.11
Ponderal Index	.17	.11	-.06	.19
OCS	-.33*	-.21	.39**	.01
Pedscore	-.04	.26	.01	.07

**$p < .01$
*$p < .05$

Table 9

Correlations of Predictor Variables with Behavioral Outcomes

Dependent Variables	Nicotine use in pregnancy	Alcohol use in pregnancy	SES	Caffeine use in pregnancy
Time in Quiet Sleep	.15	-.18	.19	.04
Time in Active Sleep	.07	.21	-.29*	.03
Time in a Drowsy State	-.23	-.07	.01	-.06
Time in a Waking, Alert State	-.27	-.19	.25	-.06
Time in an Active Alert State	-.10	.13	-.08	.02
Time spent Crying/Fussy	-.16	.15	.09	-.05
Overall Heart Rate	.29*	.02	-.33*	.41**
Heart Rate Variability	-.21	-.03	.26	-.18
Heart Rate in Quiet Sleep	.30*	-.02	-.38**	.45***
Heart Rate in Active Sleep	.26	-.03	-.26	.37**
Heart Rate in Drowsiness	.31	.10	-.07	.19
Heart Rate in Quiet, Alert State	.20	.06	-.17	.19
Number of State Transitions	-.24	-.21	.21	-.01
Number of Startles	-.08	-.05	.14	-.22
Number of Tremors	-.02	.37**	-.27	-.03

***$p < .001$
**$p < .01$
*$p < .05$

Table 10

Correlations among Predictor Variables

	Predictors			
Predictors	Nicotine use in pregnancy	Alcohol use in pregnancy	SES	Caffeine use in pregnancy
Caffeine use in pregnancy	.47***	-.00	-.36**	--
SES	-.21	-.09	--	
Alcohol use in pregnancy	.15	--		
Nicotine use in pregnancy	--			

***p < ..001
**p < .01

Table 11

Assessment of Multicollinearity among Regressors in Regressions conducted on Anthropometric and Perinatal Risk Status Outcomes with significant predictors

Outcome Variable	VIF	Tolerance	Eigenvalue
Birthlength			
Cigarettes	1.0	1.0	--
Alcohol	1.0	1.0	1.29
SES	1.01	.99	--
Caffeine	1.00	1.00	--
OCS			
Cigarettes	1.04	.95	--
Alcohol	1.01	.99	--
SES	1.0	1.0	1.88
Caffeine	1.15	.87	--
Pedscore			
Cigarettes	1.31	.76	--
Alcohol	1.03	.97	3.06
SES	1.16	.86	--
Caffeine	1.42	.70	--

Table 12

Summary of Stepwise Regressions of Predictors on Anthropometric and Perinatal Risk Status Outcomes

	Standardized Regression Coefficients		
Predictor Variables	OCS	Pedscore	Birthlength
SES	0.47	----	----
Alcohol	----	3.98	-3.76
Beta Weights	0.39	1.28	-0.28
Regression Constant	96.59	3.04	51.16
Multiple Correlation	0.39	0.28	0.28
Statistics	$F=8.64$ $p<.005$	$F=4.13$ $p<.05$	$F=4.05$ $p<.05$

Table 13
Summary of Hierarchical Multiple Regressions of Predictors on Anthropometric and Perinatal Risk Status Outcomes

	Standardized Regression Coefficients		
Predictor Variables	Birthlength	OCS	Pedscore
Nicotine Use	0.04	-1.31	-0.08
Statistics	t=.42 p<.68	t=-2.24 p<.03	t=-0.84 p<.4
Multiple Correlations	0.28	0.31	0.28
Beta Weights	0.07	-0.31	-0.14
Alcohol Use	-3.76	-22.62	3.98
Statistics	t=-1.94 p<.05	t=-1.76 p<.09	t=2.17 p<.05
Multiple Correlations	0.28	0.39	0.29
Beta Weights	-0.28	-0.24	0.31
SES	-0.23	0.34	-0.19
Statistics	t=-0.8 p<.43	t=2.2 p<.03	t=-0.69 p<.5
Multiple Correlations	0.31	0.48	0.29
Beta Weights	-0.12	0.29	-0.10
Caffeine Use	-0.001	0.03	0.002
Statistics	t=-0.54 p<.60	t=2.01 p<.05	t=1.16 p<.25
Multiple Correlations	0.32	0.54	0.34
Beta Weights	-0.09	0.3	0.19
Regression Constant	52.16	93.34	3.04

Table 14

Summary of Stepwise Regressions on Outcomes with reported nonsmokers and nondrinkers only

Predictor Variables	Standardized Regression Coefficients		
	Heart rate	Heart rate in quiet sleep	Heart rate in active sleep
SES	-0.29	-0.35	-0.26
Statistics	$t=-1.97$ $p<.06$	$t=-2.79$ $p<.01$	$t=-1.68$ $p<.10$
Multiple Correlation	----	0.51	----
Beta Weights	----	-0.39	----
Caffeine	0.02	0.02	0.02
Statistics	$t=3.36$ $p<.001$	$t=2.79$ $p<.01$	$t=2.99$ $p<.005$
Multiple Correlation	0.49	0.64	0.45
Beta Weights	0.49	0.39	0.45
Regression Constant	123.55	126.55	124.87

Table 15

Assessment of Multicollinearity among Significant Regressors in Regressions conducted on Regulatory Outcomes

Outcome Variable	VIF	Tolerance	Eigenvalue
Heart Rate			
Cigarettes	1.28	.78	--
Alcohol	1.0	1.0	--
SES	1.15	.87	--
Caffeine	1.0	1.0	1.72
Heart Rate in Quiet Sleep			
Cigarettes	1.28	.78	--
Alcohol	1.0	1.0	--
SES	1.15	.87	--
Caffeine	1.00	1.0	1.72
Heart Rate in Active Sleep			
Cigarettes	1.28	.78	--
Alcohol	1.00	1.0	--
SES	1.15	.87	--
Caffeine	1.0	1.0	1.72
Time in Active Sleep			
Cigarettes	1.15	.87	--
Alcohol	1.01	.99	--
SES	1.0	1.0	1.88
Caffeine	1.04	.96	--
Number of Tremors			
Cigarettes	1.02	.98	--
Alcohol	1.0	1.0	1.29
SES	1.01	.99	--
Caffeine	1.0	1.0	--

Table 16

Summary of Stepwise Regressions of Predictors on Regulatory Measures

	Standardized Regression Coefficients			
Predictor Variables	Heart rate	Heart rate in quiet sleep	Heart rate in active sleep	Tremors
Caffeine	0.02	0.024	0.02	----
Alcohol	----	----	----	8.34
Beta Weights	0.41	0.46	0.37	0.37
Regression Constant	125.3	119.54	126.95	2.32
Multiple Correlation	0.41	0.45	0.37	0.37
Statistics	$F=9.71$ $p<.003$	$F=11.61$ $p<.001$	$F=7.51$ $p<.009$	$F=7.73$ $p<.008$

Table 17

Summary of Hierarchical Multiple Regressions of Predictors on Regulatory Measures

Predictor Variables	Standardized regression coefficients			
	Heart rate	Heart rate in quiet sleep	Heart rate in active sleep	Tremors
Nicotine Use	0.29	0.32	0.34	-0.1
Statistics	t=0.75 p<.46	t=0.76 p<.45	t=0.77 p<.45	t=-0.62 p<.54
Multiple Correl.	0.02	0.02	0.03	0.37
Beta Weights	0.11	0.11	0.12	-0.09
Alcohol Use	-0.75	-3.4	-3.33	8.18
Statistics	t=-0.1 p<.92	t=-0.42 p<.68	t=-0.37 p<.71	t=2.7 p<.01
Multiple Correl.	0.29	0.30	0.27	0.38
Beta Weights	-0.01	-0.06	-0.05	0.36
SES	1.44	2.22	1.05	0.84
Statistics	t=1.27 p<.21	t=1.81 p<.08	t=0.79 p<.43	t=1.87 p<.07
Multiple Correl.	0.39	0.45	0.33	0.45
Beta Weights	0.18	0.25	0.12	0.27
Caffeine	0.01	0.02	0.02	-0.002
Statistics	t=1.85 p<.05	t=1.96 p<.05	t=1.66 p<.11	t=1.87 p<.63
Multiple Correl.	0.46	0.52	0.4	0.45
Beta Weights	0.29	0.3	0.27	-0.08
Regression Constant	120.85	112.75	123.88	-0.28

Table 18

Summary of Amount of Time spent in each of the Six Behavioral States

Behavioral State	% of time observed in that state	Mean number of epochs	S.D.
Quiet Sleep	44.6	53.56	24.18
Active Sleep	39.6	47.52	21.36
Drowsiness	3.3	3.98	5.8
Waking Inactivity	2.8	3.32	5.15
Waking Activity	7.2	8.6	15.52
Crying/fussiness	1.8	2.2	4.42

Appendix A

Informed Written Consent

INFORMED CONSENT FORM
SLEEPING AND HEART RATE IN NEWBORN INFANTS

Dear Mother,

Although newborn babies sleep most of the time, some babies sleep more than others and some sleep less. We think that differences among pregnancies and deliveries that mothers and babies experience may affect how much the baby sleeps. You are invited to participate in a study in which we will carefully examine how differences in pregnancy and delivery are related to the sleep patterns of newborn babies.

First, we are asking permission to record important facts about your pregnancy and delivery from the medical records here in the nursery. We will record only those events that are thought to be associated with how your baby sleeps that are found in your baby's chart and your prenatal records. Then we will attach your baby to a heart rate monitor in the nursery. We will simply watch and write down how your baby sleeps and what his/her heart rate and respiration rate is for one hour. At the end of this hour, the examiner will look at you baby's physical characteristics such as length, and the size of your baby's eyes and ears. After observing your baby, the examiner will ask you some questions about your diet and health during your pregnancy.

The results of this study will be strictly confidential. At no time will the researchers release the results to anyone without your written consent. The information you provide will have your name removed and only a subject number will identify you during analyses and any write-up of the research. There are no apparent risks to you or your baby from participation in this study. Because we are just learning what the baby's sleeping patterns mean, the results of this examination will not directly benefit you or your baby. However, by participating in this study, we may be able to help many parents and their babies in the future by knowing what their baby's sleeping pattern means about the baby's health. You will not receive anything for participating in this study and you are free to withdraw at any time without penalty.

The information from this research may be used for scientific or educational purposes. It may be presented at scientific meetings and/or published and reproduced in professional journals or books, or used for any other purpose that Virginia Tech's Department of Psychology considers proper in the interest of education, knowledge, or research. This research project has been approved by the Human Subjects Committee of the Department of Psychology, by the Institutional Review Board of Virginia Tech, and by representatives of the physicians, nurses, and administrators of Montgomery Regional Hospital.

I have read and understand the above description of the study. I have had an opportunity to ask questions and have had them all answered. I hereby acknowledge the above and give my voluntary consent for participation in this study. I further understand that if I participate, I may withdraw at any time without penalty. I understand that should I have any questions regarding this research and its conduct, I should contact any of the persons named below.

PRIMARY RESEARCHERS:	**DR. PHILIP S. ZESKIND**	**PHONE: 231-6598**
	MS. PAMELA SCHUETZE	**PHONE: 951-1431**
CHAIR, HSC:	**DR. ROBERT J. HARVEY**	**PHONE: 231-7030**
CHAIR, IRB:	**DR. ERNEST STOUT**	**PHONE: 231-9359**

Parent's Signature:_____ **Date:**_____

Mother's ID:_____

INFORMED CONSENT FORM

Emory University School of Medicine
1256 Briarcliff Rd., N.E. Room 323 W
Atlanta, Georgia 30309
(404) 894-8288

Research project Title: Sleeping and Heart Rate in Newborn Infants
Principle Investigator: Pamela Schuetze, M.S. Co-investigators: Claire Coles, Ph.D.
Philip S. Zeskind, Ph.D.

Dear Parent(s),

Although newborn babies sleep most of the time, some babies sleep more than others and some sleep less. We think that differences among pregnancies and deliveries that mothers and babies experience may affect how much the baby sleeps. You are invited to participate in a study in which we will carefully examine how differences in pregnancy and delivery are related to the sleep patterns of newborn babies.

First, we are asking permission to record important facts about your pregnancy and delivery from the medical records here in the nursery. We will record only those events that are thought to be associated with how your baby sleeps that are found in your baby's chart and your prenatal records. Then we will attach your baby to a heart rate monitor in the nursery. In order to monitor your baby's heart rate, we will place three physical sensors on his or her body. Two of these sensors will be placed on your baby's upper chest area and the third will be placed on the lower right rib cage. These sensors adhere to your baby's body much like a bandaid does and represents no potential harm to the infant. After your baby is connected to the heart rate monitor, we will simply watch and write down how you baby sleeps and what his or her heart rate and respiration rate is for one hour. At the end of this hour, the examiner will look at your baby's physical characteristics such as length, and the size of your baby's eyes and ears. After observing your baby, the examiner will ask you some questions about your diet and health during pregnancy.

The results of this study will be strictly confidential. At no time will the researchers release the results to anyone without your written consent. The information you provide will have your name removed and only a subject number will identify you during analyses and any write-up of the research. There are no apparent risks to you or your baby from participation in this study. Because we are just learning what the baby's sleeping patterns mean, the results of this examination will not directly benefit you or your baby. However, by participating in this study, we may be able to help many parents and their babies in the future by knowing what their baby's sleeping pattern means about the baby's health. You will not receive anything for paticipating in this study and you are free to withdraw at any time without penalty. If you decide not to paricipate in this study, this decision will have no effect on other services or benefits available to you. If you have any questions about the project, you may contact the investigators directly at the above address or telephone number for additional information.

Although the investigators will make arrangements for appropriate management and treatment for any physical injury resulting from this project, Emory University has made no provision for payment of costs associated with any physical injury resulting from participation in this study. By signing this consent form, you do not waive your legal rights nor release the institution from liability or negligence.

I have read and understand the above description of the study. I have had an opportunity to ask questions and have had them all answered. I hereby acknowledge the above and give my voluntary consent for participation in this study. I further understand that if I participate, I may withdraw at any time without penalty. I understand that should I have any questions regarding this research and its conduct, I should contact any of the persons named above.

Parent's Signature:_____ Date:_____
Mother's ID:_____

Appendix B

Dysmorphia Checklist

SIDE A

Version, 2.0. Revised 4/93

Infant's Name: _____ Mother's Name: _____

Birth Date: ___ / ___ / ___ Exam Date: ___ / ___ / ___ Examined by (Initials): _____

Estimate Age (Ballard): _____ wks. Sex: _____ Race: _____ White = 1 Asian = 3 Hispanic = 5 Black = 2 Native Am. = 4 Other = 6

	SCORE	WT.
General		
Light for gestational age		3
Short for gestational age		3
Postnatal growth failure		3
Head		
Microcephaly		3
Anterior fontanelle large		•
Eyes		
Short palpebral fissures		3
Micropthalmia		1
Ptosis		2
Epicanthal folds		3
Strabismus		2
Intraocular defects		2
Nose		
Low bridge		1
Anteverted nares		1
Ears		
Posterior rotation		1
Overfolding of superior helix		1
Mouth		
Hypoplastic philtrum		3
Thinned upper vermillion		3
Hypoplastic mandible		2
"Wide" mouth		1
Cleft lip or palate		1
Renogenital		
Hypoplastic labia		2
Renal anomalies		1

	SCORE	WT.
Cutaneous		
Hemangiomas		2
Hirsuitism		1
Musculoskeletal		
Abnormal palmar creases		2
a. Sharp distal bend to radial seg. of distal crease		•
b. Hypolasia or shortening of proximal crease		•
c. Marked thenar crease.		•
Limited joint movement		1
Overlapping of fingers		1
Clinodactyly		1
Hypoplastic nails		1
Pectus deformity		1
Other: _____		1
C.N.S.		
Poor suck		1
Irritability		3

To Be Completed By MSA Personnel Following Exam:

	SCORE	WT.
Cardiovascular		
Congenital heart disease		2
Single umbilical artery		1
Blood pressure elevated		•
Arrhythmia		•
Miscellaneous C.N.S.		
Neonatal Withdrawal Syndrome		•
Neonatal Complications		•

Other _____

_____

LEGEND:

0 = ABSENT

– = NOT DETERMINABLE

+ = PRESENT

PEDSCORE:

(ADD WT. COLUMN)

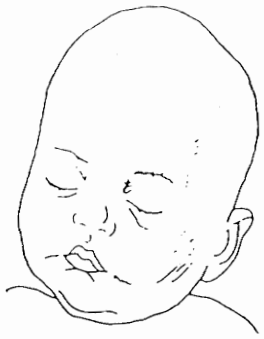
SCORER'S INITIALS

PLEASE COMPLETE SIDE B

Dysmorphia Checklist:

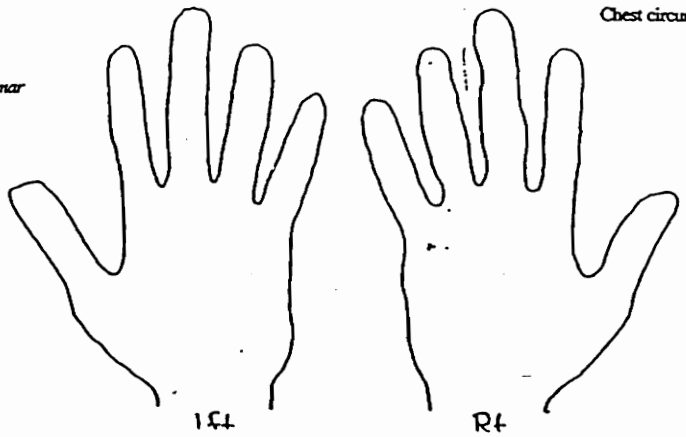
Measurements

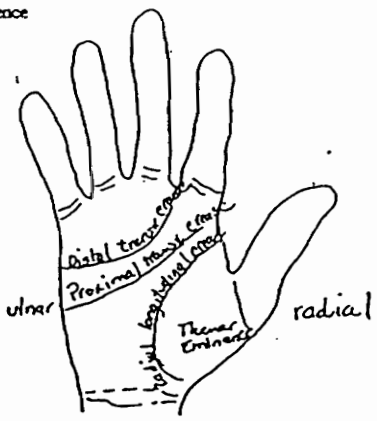
	Measurement	%Tile	
General			
Birth: Weight (gm)	____	____	
Length (cm)	____	____	
Current:: Weight (gm)	____	____	
Length (cm)	____	____	
Head			
Head circumference (cm)	____	____	
Ant. fontanelle (cm)	____ x ____	____	Draw fontanelle
Mean fontanelle (cm)	____	____	= width + length / 2
Eyes			
Palpebral Fissures, Right (cm)	____	____	
Palpebral Fissures, Left (cm)	____	____	
Inner Canthus (cm)	____	____	
Outer Canthus (cm)	____	____	
Interpupillary dist. (cm)	____	____	= 0.7 + 0.59 inner canthal distance + 0.41 outer-canthal distance
Ears			
Ear length, Right (cm)	____	____	
Ear length, Left (cm)	____	____	
Ear above eyeline, Right (cm)	____	____	
Ear above eyeline, Left (cm)	____	____	
Percent of ear above eyeline, Right (%)	____	____	= Ear above eyeline, R. / Ear Length, R.
Percent of ear above eyeline, Left (%)	____	____	= Ear above eyeline, L. / Ear Length, L.
Mouth			
Philtrum (cm)	____	____	
Mouth width (cm)	____	____	
Chest			
Circumference (cm)	____	____	
Intermipple distance (cm)	____	____	
Intermipple index (#)	____	____	= Intermipple distance x 100 / Chest circumference



LEGEND:
6–94%: 0
–2SD: 1
+2SD: 2

Hands
Draw palmar creases:





v.2.0
Revised
4/93

Appendix C

NUTRITION QUESTIONNAIRE

NAME_____ SUBNO_____

BIRTHDATE_____ GENDER_____

MATERNAL WEIGHT GAIN_____ MARITAL STATUS_____

1) Did you attend a prenatal class during this pregnancy?
Where_____ When_____

2) Did you receive any information/classes on nutrition during this pregnancy?_____

3) How would you describe your eating habits during this pregnancy?

Normal_____ Moderate_____ Irregular_____

4) How would you describe your appetite during this pregnancy?

Hearty_____ Average_____ Poor_____

5) Do you have any chronic medical problems (diabetes, high blood pressure, etc.)?_____

6) Do you regularly take any medications? If yes, what do you take and what is your dosage?_____

7) Are you currently taking them?_____

If yes, how frequently?_____

Did you take them throughout your pregnancy?_____

8) What medications do you take for headache? (check all that apply).

Bayer Aspirin_____ Bufferin_____ Anacin_____ Midol _____
Plain Aspirin _____ Tylenol _____ Other _____ None _____

9) Do you take over-the-counter cold medications?_____
If yes, which ones?_____
Did you take these during pregnancy?_____
How many tablets do you take each time?_____

10) Did you take any vitamin supplements during pregnancy?_____
If so, what kinds?_____

11) Were you on a special diet for medical reasons?_____
If yes, describe._____

12) Did you add or increase your intake of any particular foods or drinks during this pregnancy because you felt they were good for the baby?_____
_____
_____

13) Did you avoid or decrease any particular foods or drinks during this pregnancy because you felt they were bad for the baby?_____

When did you cut back on this food or drink?_____
How much did you cut back on this food or drink?_____

15) Did you smoke cigarettes during this pregnancy?_____
If yes, how many per day?_____

16) Did you drink alcoholic beverages during this pregnancy?_____
Wine_____ Beer_____ Liquor_____
On the average, how much did you drink?_____

17) How often have you been drinking coffee during this pregnancy?
3 or more times a day_____
2 times a day_____
about once a day_____
3-4 times/week_____
1-2 times/week_____
2-3 times/month_____
about once a month_____
less than once a month_____
not at all_____

How much coffee did you usually drink per day during
Your first trimester_____
Your second trimester_____
Your third trimester_____

18) When you did drink coffee, what kind was it?
Brand_____
Instant_____
Percolated_____
Drip_____
Decaffeinated_____

19) Think of all the times you've had coffee recently. When you do drink coffee, how often do you have 5 cups or more at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

20) When you do drink coffee, how often do you only have 3 or 4 cups at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

21) How often do you have only 1 or 2 cups at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

22) How often have you been drinking tea during this pregnancy?
3 or more times a day_____
2 times a day_____
about once a day_____
3-4 times/week_____
1-2 times/week_____
2-3 times/month_____
about once a month_____
less than once a month_____
not at all_____

How much tea did you drink per day during
Your first trimester_____
Your second trimester_____
Your third trimester_____

23) When you did drink tea, what kind was it?
Brand_____
Iced_____
Herbal_____

24) Think of all the times you've had tea recently. When you do drink tea, how often do you have 5 cups or more at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

25) When you do drink tea, how often do you have only 3 or 4 cups at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

26) How often do you have only 1 or 2 cups at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

27) How often have you been drinking sodas?
3 or more times a day_____
2 times a day_____
about once a day_____
3-4 times/week_____
1-2 times/week_____
2-3 times/month_____
about once a month_____
less than once a month_____
not at all_____

How many sodas did you drink per day during
Your first trimester_____
Your second trimester_____
Your third trimester_____

28) When you did drink soda, what kind was it?
Brand_____
Was it caffeine free?_____

29) Think of all the times you've had soda recently. When you do drink soda, how often do you have 5 cans (12 oz) or more at one sitting?

Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

30) When you do drink soda, how often do you only have 3 or 4 cans at one sitting?

Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

31) How often do you have only 1 or 2 cans at one sitting?

Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

32) How often have you been drinking cocoa?

3 or more times a day_____
2 times a day_____
about once a day_____
3-4 times/week_____
1-2 times/week_____
2-3 times/month_____
about once a month_____
less than once a month_____
not at all_____

How many cups of cocoa did you have per day during
Your first trimester_____
Your second trimester_____
Your third trimester_____

33) Think of all the times you've had cocoa recently. When you do drink cocoa, how often do you have 5 cups or more at one sitting?

Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

34) When you do drink cocoa, how often do you have only 3 or 4 cups at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

35) How often do you have only 1 or 2 cups at one sitting?
Nearly every time_____
More than half the time_____
Less than half the time_____
Once in awhile_____
Never_____

36) How often do you eat chocolate or chocolate candy?
3 or more times a day_____
2 times a day_____
About once a day_____
3-4 times/week_____
1-2 times/week_____
2-3 times/month_____
About once a month_____
Less than once a month_____
Not at all_____

How often did you eat chocolate per day during
Your first trimester_____
Your second trimester_____
Your third trimester_____

37) When you eat chocolate, how much do you usually eat at one sitting?
One or two small chocolates_____
3-6 small chocolates_____
More than 6 small chocolates_____
1 small chocolate bar_____
1 medium chocolate bar_____
1 large chocolate bar_____
More than 1 large chocolate bar_____
Does not apply_____

38) Do you work?_____What is your job?_____
39) What job does your baby's father have?_____
40) What is the last grade that you completed?_____
41) What is the last grade that your baby's father completed?_____

Appendix D
QUANTITY-FREQUENCY-VARIABILITY CALCULATIONS

For beverages, chocolate or medications:

Frequency Question	Frequency Code (F)
How often have you been drinking beverage (coffee)?	
3 or more times/ day	3.00
2 times/day	2.00
1 time/day	1.00
3-4 times/week	.50
1-2 times/week	.20
2-3 times/month	.10
1 time/month	.05
less than once a month	.01
not at all	0

For beverages only:

Quantity, Variability Question	Weighted Variability
Think of all the times you've had coffee recently. When you do drink coffee, how often do you have 5 cups or more?	
	($WV_{\geq 5}$)
nearly every time	(2)
more than half the time	(2)
less than half the time	(1)
once in awhile	(1)
never	(0)
When you do drink coffee, how often do you have 3 or 4 cups?	
	($WV_{\geq 3\text{-}4}$)
nearly every time	(2)
more than half the time	(2)
less than half the time	(1)
once in awhile	(1)
never	(0)
How often do you have only 1 or 2 cups?	
	($WV_{\geq 1\text{-}2}$)
nearly every time	(2)
more than half the time	(2)
less than half the time	(1)
once in awhile	(1)
never	(0)

Quantity-Frequency-Variability Calculations Continued

For chocolate candy only:

Quantity/Serving Question	Quantity Serving (QS)
When you eat chocolate, how much do you usually eat at a time?	
one or two small chocolates	2
3-6 small chocolates	6
more than 6 small chocolates	10
1 small chocolate bar	7
1 medium chocolate bar	20
1 large chocolate bar	40

For medications only:

Quantity Question	Quantity (Q)
How many tablets do you take each time?	
Record actual number	____

Appendix E

CALCULATIONS

For each beverage:

$$\text{caffeine (mg/day)} = C*F*\frac{(WV_{>5}*6 + WV_{3-4}*3.5 + WV_{1-2}*1.5)}{(WV_{\geq 5} + WV_{1-2} + WV_{1-2})}$$

For each medication:

caffeine (mg/day) = F*Q*C

For chocolate candy:

caffeine (mg/day) = F*QS

Appendix F

CAFFEINE CONTENT OF COMMON FOODS AND MEDICINES

Source	Serving	Caffeine (mg)
Coffee:		
Brewed	5 oz	125
Instant	5 oz	90
Percolated	200 ml	74
Decaffeinated	5 oz	4.5
Tea (leaf or bag)	5 oz	60
Cocoa, hot chocolate	5 oz	5
Cola drinks	12 oz	40
Chocolate	.44 oz (1 small)	2
	1.31 oz (3-6 small)	6
	1 3/8 oz (small bar)	7
	4 oz (med. bar)	20
	8 oz (large bar)	40
Aspirin :		
Excedrin	1 tablet	65
Other	1 tablet	32
Nodoz	1 tablet	100
Vivarin	1 tablet	200

Adapted from Gilbert, et al. (1976) and James & Crosbie (1987)

Appendix G
OBSTETRICS COMPLICATIONS SCALE

OCS Risk Index

Subno _____ Gender_____ Date_____

Name_____ APGAR1_____ OCS% Raw Score_____

Birthdate_____ APGAR2_____ CONVERTED OCS % Score____

GA_____ Age (hrs)____ PNF Raw Score_____

BW_____ WA_____ Converted PNF Score_____

BL_____ PI_____ HC_____

Number of prenatal visits_____ First visit_____ Mat. Wt. Gain_____

Circumcised_____ Ethnicity: B___W___A___H___O___

PRENATAL

1. Gestational Age	≥37 weeks_____	<37 weeks_____
2. Birth Weight	≥2500 grams_____	<2500 grams_____
3. Marital Status	Married_____	Other_____
4. Maternal Age	18-30_____	Other_____
5. Previous Abortions	2 or less_____	3 or more_____
6. Previous Premature Births	No_____	Yes_____
7. Previous Stillbirths	No_____	Yes_____
8. Prolonged Unwanted Sterility	No_____	Yes_____
9. Length of time since last pregnancy	≥12 months_____	<12 months_____
10. Parity	6 or less_____	7 or more_____
11. Pelvis (I)	No Disproportion___	Disproportion_____
12. Rh Antagonism or other Blood Group Incompatability	No_____	Yes_____
13. Bleeding During Pregnancy	No_____	Yes_____

14. Infections or other Acute Medical Problems during Pregnancy (e.g, Nutritional deficiencies, toxemia, etc.)	No	Yes
15. Drugs given to mother during Pregnancy	No	Yes
16. Maternal Chronic diseases (e.g., Diabetes, hypertension, thyroid problems)	No	Yes
17. Chronic Drug Abuse	No	Yes
18. Blood pressure During Pregnancy	≤140/90	>140/90
19. Albuminuria	No	Yes
20. Hyperemesis (I)	No	Yes
21. Hemoglobin Level at End of Pregnancy	10 or more	<10
22. Twins/multiple birth	No	Yes

OBSTETRIC

23. Membranes Ruptured Prior to Delivery	0-12 hours	>12 hours
24. Delivery	Spontaneous	Other
25. Forceps/vacumn	None or elective, low forceps	Other
26. Duration, First Stage	3-20 hours	<3 or >20 hours
27. Duration, Second Stage	10-120 min.	<10 or >120 mins.
28. Induced Labor (Pitocin)	No	Yes
29. Drugs During Labor/Delivery	No	Yes
30. Amniotic Fluid	Clear	Other
31. Fetal Presentation	Vertex	Other
32. Fetal Heart Rate During Labor	100-160/min.	<100 or >160/min.
33. Knotted Nuchal Cord	No	Yes
34. Cord Prolapse	No	Yes

35. Placental Infarction No_____ Yes_____

36. Placenta Previa/Abruptia No_____ Yes_____

NEONATAL

37. Onset of Stable Respiration Within 6 Minutes Yes_____ No_____

38. Resuscitation Required No_____ Yes_____

39. Prenatal Care During First Half of Pregnancy Yes_____ No_____

40. Apgar Score - 1 min 7-10_____ 0-6_____

41. Apgar Score - 5 min 7-10_____ 0-6_____

A. Total (Raw Score)_____

B. Number of Items Recorded_____

C. % Raw Score (A/B)_____

D. Converted % Raw Score_____

CONVERSION TABLE

100	160	82	89	73	71
99	146	81	87	72	66
98	146	80	87	71	63
97	135	79	81	70	63
96	131	78	80	69	60
95	131	77	78	68	57
94	122	76	76	67	54
93	121	75	74	66	54
92	115	74	73	65	50
91	**112**				
90	**112**				
89	**104**				
88	**130**				
87	**98**				
86	**98**				
85	**98**				
84	**93**				
83	**92**				

POSTNATAL FACTORS

ITEM		
1. Respiratory Distress	No_____	Yes_____
2. Positive or Suspected Infection	No_____	Yes_____
3. Ventilatory Assistance	No_____	Yes_____
4. Noninfectious Illness or Anomaly	No_____	Yes_____
5. Metabolic Disturbance	No_____	Yes_____
6. Convulsion	No_____	Yes_____
7. Hyperbilirubinemia or Exchange Transfusion	No_____	Yes_____
8. Temperature Disturbance	No_____	Yes_____
9. Feeding within 48 hours	Yes_____	No_____
10. Surgery	No_____	Yes_____

TOTAL
(Raw Score) _____

CONVERSION TABLE **Converted Score**_____

Raw Score	Converted Score
10	160
9	104
8	87
7	81
6	77
5	72
4	67
3	55
2	55
1	50
0	-

Curriculum Vita

Pamela Schuetze

PERSONAL INFORMATION

Born: November 6, 1969, Omaha, Nebraska

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EDUCATION

Ph.D Developmental Psychology, April, 1995
Virginia Polytechnic Institute and State University
Dissertation Title: Relation Between Maternal Caffeine Consumption During Pregnancy and Neonatal State and Heart Rate

M.S. Developmental Psychology, October, 1993
Virginia Polytechnic Institute and State University
Thesis Title: Detection by Adults of Differences in the Durations of Pauses in Infant Cries

B.M. Music Performance; Minor: Psychology, June, 1991
Wittenberg University
Graduated Magna Cum Laude

POSITIONS HELD AND RELEVANT WORK EXPERIENCE

Emory University, Department of Psychiatry, Atlanta, GA: Psychological Tester, Human and Behavioral Genetics Laboratory, January 1995 - Present.

Instruction

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Graduate Teaching Assistant, Psychology of Learning Course, Fall 1994.

Virginia Polytechnic Institute and State University, Graduate School, Blacksburg, VA: Workshop presenter at GTA Training Program Fall Workshop, Fall 1994.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Instructor for Advanced Developmental Psychology Lab, Spring 1994.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Graduate Teaching Assistant, Advanced Developmental Psychology, August 1992-December 1993.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Graduate Teaching Assistant, Introductory Psychology, August 1991-December 1993.

Research

Grady Memorial Hospital, Department of Neonatalogy, Atlanta, GA: Co-Investigator, Relation between Prenatal Substance Exposure and Neonatal Cardiac Output, 1995.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Principal Investigator, Relation Between Reported Maternal Caffeine Consumption During Pregnancy and Neonatal State and Heart Rate, Dissertation, supervised by Dr. Philip Sanford Zeskind, 1994-1995.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Co-Investigator, Detection by Adults of Differences in the Duration of Pauses in Infant Cries, Master's Thesis, supervised by Dr. Philip Sanford Zeskind, 1993.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Research Assistant, Effects of the Durations of Expirations and Pauses on the Perceptions of Infant Cries, supervised by Dr. Philip Sanford Zeskind, 1993.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Research Assistant, Prenatal Cocaine Exposure and Infant Cry Reactivity: A Longitudinal Analysis in the Newborn Period, supervised by Dr. Philip Sanford Zeskind, 1992.

Virginia Polytechnic Institute and State University, Department of Psychology, Blacksburg, VA: Research Assistant, Altered rhythms in motor and sucking activity in prenatally malnourished newborn infants, supervised by Dr. Philip Sanford Zeskind, 1991.

PROFESSIONAL ORGANIZATIONS AND ACTIVITIES

Membership in Professional Organizations

American Psychological Society; Student Member
American Psychological Association; Student Member
Society for Research in Child Development; Student Member
International Society for Infant Studies; Student Member
Alpha Lambda Delta, National Honor Society; Member
Omicron Delta Kappa, National Honor Society; Member

Editorial Activities

Professional Conference Presentations
Conference on Human Development - Infancy Subdivision

PAPERS PRESENTED

Zeskind, P. S., Saunders, H., and Schuetze, P. (1992). Altered rhythms in motor and sucking activity in prenatally malnourished newborn infants. Paper presented at the Conference on Human Development, Atlanta, GA.

Zeskind, P. S., Schuetze, P., Coles, C., & Platzman, K. (1993). Prenatal Cocaine Exposure and Infant Cry Reactivity: A Longitudinal Analysis on the Newborn Period. Paper presented to the biennial meeting of the Society for Research in Child Development, New Orleans, LA.

Schuetze, P. (1994). Effects of the durations of expirations and pauses on the perceptions of infant cries. Paper presented at the Conference on Human Development, Pittsburgh, PA.

Schuetze, P. (1994). Detection by adults of differences in the duration of pauses in infant cries. Paper presented at the Conference on Human Development, Pittsburgh, PA.

Zeskind, P. S., Schuetze, P., Coles, C., & Platzman, K. (1995). Cry analysis detects subclinical effects of prenatal alcohol exposure in newborn infants. Paper presented at the biennial meeting of the Society for Research in Child Development, Indianapolis, IN.

Schuetze, P., Zeskind, P. S., & Goff, D. M. (1995). Relation between prenatal exposure to caffeine and neonatal state and heart rate. Paper presented to the biennial meeting of the Society for Research in Child Development, Indianapolis, IN.

Schuetze, P., Zeskind, P. S., Coles, C., & Platzman, K. (1995). Cry analysis detects subclinical effects of prenatal alcohol exposure in newborn infants. Paper presented at the metting of the Society for Pediatric Research, Sand Diego, CA.

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