THE RELATIONSHIP BETWEEN SMOKING DURING PREGNANCY AND THE DEVELOPMENT OF PHYSIOLOGICAL JAUNDICE IN THE INFANT

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BY

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Dedicated to

Jack R. Vizuete

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I. INTRODUCTION

The question of exactly which infants are at risk for development of physiological jaundice remains unanswered, yet reports indicate that the occurrence of this type of jaundice is on the rise (1,2). Research attempting to demonstrate cause and effect has been focused on behaviors which have shown an increase in practice at the same time that the incidence of physiological jaundice has risen. Cigarette consumption among women of child bearing age is increasingly practiced, and there is evidence to suggest that smoking may play a role in the development of hyperbilirubinemia. The purpose of this paper is to research the association between neonatal jaundice and maternal smoking.

Physiological neonatal jaundice is the term applied when a newborn exhibits a minimum rise in serum bilirubin of 2 mg/100 ml serum, often causing the child's skin to take on a yellowish appearance. The serum bilirubin rises to an average of 5 mg/100 ml serum (normal = 1 mg/100 ml), an occurrence thought to be the result of liver immaturity. To understand the involvement of the liver requires an explanation of bilirubin and its excretory path. Bilirubin, a breakdown product of hemolysis, binds to albumin and

travels through the blood to the liver. In the liver, it is conjugated via the glucuronic transferase system and excreted.

Normally, there is sufficient albumin to bind up to 20 mg/100 ml bilirubin. However, any change such as altered albumin concentration, abnormal production of bilirubin, or inadequate hepatic clearance contributes to the release of unbound bilirubin, even if total serum bilirubin remains low. Theoretically, the unbound portion is free to cross the barrier between the blood and the brain of the infant and deposit in brain tissue. Infants with jaundice of known etiology, such as hemolytic jaundice of Rh and ABO incompatibilities are at medical risk because of the excessive liberation of bilirubin (>18-20 mg/100ml) and the chance for bilirubin deposition in the brain. The deposition can result in neurological damage, impaired motor performance, and ultimately death if treatment is not initiated.

On the other hand, jaundice that is termed "physiological" is usually considered to be transient and harmless; however, research indicates that 13 to 20 per cent of newborns develop bilirubin levels greater than 12 mg/100 ml serum (3,4). These figures have serious clinical significance because it has been demonstrated that neuromuscular impairment of children may occur with

bilirubin levels as low as 12 and 13 mg/100 ml (5).

Hyperbilirubinemia may influence the post-natal period in a variety of ways. Characteristically, the affected infants may appear yellow, feed sluggishly, and may be febrile. With fever, the infant's calorie requirements may be expected to increase, yet the disinterest in food complicates feeding. As a general rule, serum bilirubin measurements are not taken unless the infant exibits clinical evidence of the condition. Once jaundice has developed, however, serum bilirubin levels in the newborn are closely monitored. The child then must endure frequent heel pricks and an extended hospital stay.

Treatment with phototherapy is usually initiated when unconjugated bilirubin reaches 10 mg/100 ml serum (6). Light therapy to the skin degrades bilirubin to water soluble pigments which may be excreted without hepatic conjugation. Though serum bilirubin levels are indeed lowered with this method, treatment potentially generates a host of other clinical problems. Under supplemental light, peripheral blood flow is increased, thereby increasing skin temperature, heart rate, and calorie requirements. Secondly, phototherapy produces increased insensible water loss and loose stools, compounding a problem of fluid and electrolyte maintenance (7). Thirdly, Lucey (8) reports decreased serum riboflavin levels and an increased excretion

of urinary tryptophan metabolites resulting from phototherapy. Vitamin status and available amino acids essential in protein anabolism are thus altered.

In view of these reports, it seems essential that early diagnosis and treatment of the condition be provided. Moreover, so that headway is made toward disease prevention, infants whose health may be at risk must be identified.

There has been an increase in the practices of using oral contraceptives, of breastfeeding, and of using oxytocin for induction and acceleration of labor. Each has been reviewed regarding its possible relationship to the development of jaundice. The results have been inconclusive.

Both premature and low birthweight infants are at risk for the development of jaundice due to anatomical immaturities. Smoking mothers tend to produce low birthweight and premature infants. Though the mechanism is not clearly defined, these effects appear to be dose related and operate independently of other factors influencing birthweight (9). In addition, acidosis, hypoxia, and hypoalbuminemia can contribute to hyperbilirubinemia. Smoking, since it relates to each of these conditions, may itself relate to hyperbilirubinemia. Therefore, there is need for delineation of the association between smoking during pregnancy and the development of neonatal jaundice.

The research should omit infants predisposed to hyperbilirubinemia and offer scientific control for jaundice of hemolytic origin.

CHAPTER II. PROBLEM STATEMENT

The purpose of this study was to explore the following questions:

1. Is there a significant association between smoking during pregnancy and the development of physiological jaundice in neonates?

2. Is there a significant association between the degree of neonatal bilirubinemia and volume of smoking?

The following literature review reflects current research on the development of physiological jaundice and underscores the role that smoking during pregnancy may play in the development of this condition.

CHAPTER III. HISTORICAL PERSPECTIVE

Many advances in medicine have been made by scientific investigations of apparent coincidences. The development of phototherapy itself was initiated after a chance observation by a pediatric nurse that the jaundice of newborns resolved somewhat after exposure to sunlight (10). It has been observed that an increasing incidence of hyperbilirubinemia has coincided with changes in: 1) contraceptive use prior to conception, 2) nourishment of the newborn, and 3) medical management of the delivery. Each has been researched to determine if significant relationships truly exist. Results have been included in this text for review.

Background

In 1971, Wood and Wong (11) reported a 35.4% increase in jaundice among breastfed infants whose mothers had taken "the pill" as opposed to breastfed infants whose mothers had previously used other forms of contraception (11). The evidence appeared to confirm that the use of oral contraceptive agents (OCA) corresponded to the development of hyperbilirubinemia. Research at Birmingham Maternity Hospital, however, found no significant relationship in the incidence of jaundice between breastfed infants whose mothers had taken OCA's and those who had not (n=690). The

authors attributed the discrepancy between the two reports to be due to lower estrogen levels in OCA's in 1979 versus 1971 (4).

Omitting the influence of OCA's and comparing breastfeeding alone with artificial feeding, Wood and others found that the incidence of jaundice was significantly higher ($p=0.001$) in the breastfed infants. The authors rationalized that the variance was due to differences in weight recovery between the infants on the two types of feeds, but concluded that the breastmilk itself perhaps contained some icterogenic factor accounting for the jaundice (4).

The hypothesis that breastfeeding is associated with hyperbilirubinemia also was supported by Jeffares (12), who conducted a multifactorial survey of 981 newborns in a British military hospital. The research controlled for gestational immaturity as well as hemolytic jaundice and found a significant relationship between the incidence of jaundice in breastfed infants as compared with artificially fed infants. On the other hand, Campbell (1) failed to find the same difference in the incidence of jaundice when infants with hyperbilirubinemia receiving only breastmilk ($n=13$) and only artificial nourishment ($n=118$) were compared to controls by chi square.

In addition to OCA's and breastfeeding, the use of

oxytocin in the management of labor has received serious attention for its possible role in the development of jaundice, a theory first noted in 1971 (13). Since that time, Campbell found that an increased incidence of jaundice, from 8 per cent in 1971 to 15.4 per cent in 1973, corresponded to an increased use of oxytocin. However, statistically, the increase could not be attributed to oxytocin usage, even with consideration for dose and use for induction of labor as opposed to acceleration of labor. Instead, Campbell found that the percentage of mothers who had received oxytocin and produced jaundiced infants did not differ significantly from those who had received oxytocin and did not produce jaundiced infants. Note should be made though, that in the control group of this retrospective study, oxytocin was used to induce labor in "post-mature" deliveries, while in the jaundiced study group the drug was used primarily for induction prior to 40 week gestation. Thus, the use of oxytocin may relate to the increased frequency by promoting "the jaundice of prematurity" (1).

Sims and Neligan (2) also examined whether oxytocin was used primarily to induce labor or secondarily to accelerate labor. There was a significant relationship between the development of jaundice and the use of oxytocin to induce labor (n=46 index group, n=92 matched controls). When dosage was considered, it appeared that the larger the dose

of oxytocin used to induce labor, the greater the mean serum value of bilirubin.

Research by Chalmers (14) from review of 10,951 birth records, identified a definite association between the use of oxytocin and the development of jaundice with dosage considered. Chalmers supported the idea that by precluding the priming of fetal enzyme systems, oxytocin contributed to hyperbilirubinemia. Contradicting the Chalmers report, further research by Wood and Culley (4) found that the use of oxytocin was not associated with the increased frequency of jaundice on observation of 407 samples. Probing deeper into this study, records indicated that the dose used for most deliveries was very low, suggesting that results may have been different if dosage had been manipulated.

In summary, then, there remains no clear correlation between physiological jaundice and the use of OCA's, breastfeeding, or oxytocin use. However, the lack of fetal enzyme priming by labor induction with oxytocin spans the literature as an explanation for the observed effects of the drug (15).

Effect of Smoking

Reflecting other behavioral change coinciding with the increased incidence of jaundice has been the increased practice of cigarette smoking among women. Despite intense publicity about the detrimental effects of smoking during

pregnancy on newborn birthweight, consumption has not decreased (16). The proposed mechanism for altered birthweight is that pregnant women who smoke have increased serum levels of nicotine and carboxyhemoglobin, resulting in poor oxygen perfusion to the fetus (9, 16, 17). Oxygenation of tissues also may be expected to be poor in high altitudes. Studies on Sherpa natives (18) at high altitudes have shown that increases in hemoglobin and hematocrit occur. Results were thought to be due to the increased development of deoxyhemoglobin as a compensatory mechanism to increase tissue saturation. These facts reflect the importance of environment on on fetal development. Smoking may relate to an increased release of abnormal amounts of unconjugated bilirubin when elevated hemoglobin is degraded after birth.

As far back as 1968, Younoszai and Hayworth (19) demonstrated that the infants of smoking mothers have mild metabolic acidosis and a higher mean capillary blood hematocrit when compared to non-smokers. The selection criteria for 16 sample mothers in this study included smoking twenty or more cigarettes each day throughout the pregnancy. No mention was made of the infants being jaundiced, though the small sample size may have limited that factor. The birthweight, length of gestation, and Apgar score did not differ significantly between the study

group and control group of non-smokers.

In a controlled retrospective study from data of the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke, 48 hour hemoglobin and hematocrit values were found to be elevated in the infants of smokers regardless of socioeconomic background. The study also demonstrated a direct relationship between amount of cigarette consumption and increase in red cell volume (20). Note should be made that infants normally have an excess of hemoglobin after birth which is broken down and contributes to unconjugated bilirubin. If the rate of erythropoiesis increases beyond the usual elevated amount in the progeny of smokers due to oxygen deprivation in utero, an increase in the release of extraordinary amounts of unconjugated bilirubin might also be expected.

Supporting the idea that increased hemolysis could contribute to hyperbilirubinemia was the research conducted by Necheles (21) who measured cord and third day blood levels of carboxyhemoglobin (COHb) in 250 normal, term newborns. During the conversion of heme to bilirubin, carbon monoxide is released and transported as COHb. The authors, therefore, determined that COHb was a sensitive index of hemolysis. Necheles found that cord and third day values for COHb were significantly related to serum

bilirubin levels. Results also demonstrated that maternal smoking dramatically increased cord, but not third day, COHb levels in the blood.

Additionally, smoking mothers contact amniotic fluid infections more often than non-smoking mothers as confirmed by Naeye (22) in his research involving microscopic examination of placentas from 53,518 pregnancies. The affected infants may be at risk for hyperbilirubinemia by virtue of the hemolytic activity of bacteria in the blood adding to the serum bilirubin pool.

The preceding variables are associated with the release of excessive amounts of bilirubin which could contribute to hyperbilirubinemia. However, there are other aspects associated with smoking during pregnancy which lead to inadequate clearance of circulating bilirubin. Smoking can produce amniotic fluid infections which could result in early labor and preclude fetal enzyme priming. Maternal smoking may result in a slightly acidotic neonate with lowered albumin capacity to bind with bilirubin. And finally, nicotine induces fetal tachycardia and/or hypoxia and can produce a small-for-date infant at risk for having an immature hepatic system, and that the same fetal tachycardia increases demand for metabolic oxygen which could decrease glucose available for glucuronyl transferase essential in the excretory system for bilirubin.

First, it has been demonstrated that amniotic fluid infections in smokers occur most often during the last three weeks of pregnancy and that labor usually begins three to five days later (23). The current theory on labor onset is that induction of enzymes from the fetus itself "primes" the system for delivery. The enzymes would also prepare the liver for conjugation of bilirubin. Researchers rationalize that oxytocin may produce hyperbilirubinemia because chemical induction of labor precludes fetal enzyme priming. If this is true, then the mechanism should be similar in the labor induced by infection.

Secondly, bilirubin normally is transported in the blood bound to albumin; however, binding capacity decreases as pH decreases. Younoszai and Hayworth (19) observed that the offspring of smokers showed a mild metabolic acidosis when compared with offspring of non-smokers. This finding was substantiated by Suzuki in studies with cardiovascular catheterization of 43 monkeys. After constant infusion of nicotine to the mother, the more mature fetus became acidotic and developed tachycardia. Of importance, however, was that the results appeared to have been due to both decreased placental perfusion and the pharmacologic action of nicotine on the cardiovascular system of the subject (24). Results may be similar on human fetuses, especially if the mother smoked during the last trimester of pregnancy.

Hypoxia, induced from the carbon monoxide affinity for hemoglobin, deprives growing tissues of vital oxygen (9, 16, 24). Offspring of smokers, therefore, could be expected to be small-for-date with grossly immature liver systems, depending on the time of greatest oxygen deprivation. In conjunction with hypoxia, the cardiovascular effects of nicotine produce a shift to the left of the oxygen dissociation curve (25), resulting in increased utilization of metabolic oxygen. Therefore, the suggestion is made that excess glucose as substrate for glucuronyl transferase is not readily available to the newborn whose mother smoked cigarettes during pregnancy. This enzyme is necessary for the system of conjugation and excretion of bilirubin.

Although the proposed association between smoking during pregnancy and the development of jaundice appears to be supported by the literature, controversy still exists. Nymand (26) demonstrated that serum bilirubin was actually higher in infants of non-smokers (n=1459) when compared with infants of smokers (n=1024). Nymand did not, however, control for hemolytic jaundice, gestation length, or other factors known to influence neonatal bilirubin. Hardy and Mellits (27) observed similar results by measuring bilirubin from infants of 143 mothers who smoked 10 or more cigarettes each day. These values were compared to a matched set of non-smoking controls and were found to be significantly

higher among the progeny of non-smokers. However, as in the Nymand report, the apparent relationship lacks reliability due to lack of control on the population sample regarding hemolytic jaundice.

On the other hand, Calder (15) failed to find that smoking lowered bilirubin levels in research where data on smoking habits was measured incidently. Though results were not significantly different, this author reported that the mean serum bilirubin of infants from smokers (n=33) averaged 8.5 mg/100 ml with a standard deviation of 4.7, while mean bilirubin levels from infants of non-smokers (n=87) was 8.2 mg/100 ml with a standard deviation of 4.4.

Highlighting important considerations in justifying analysis for an association between smoking during pregnancy and neonatal jaundice recalls that 1) the effect of nicotine may decrease oxygen availability, resulting in excessive red blood cell production with excessive hemoglobin in the neonate. This extra hemoglobin when hemolyzed could produce a higher bilirubin load on the liver; 2) smoking may produce amniotic fluid infections which may increase bilirubin because of bacterial hemolysis; 3) smoking may produce amniotic fluid infections which could result in early labor and preclude fetal enzyme priming; 4) maternal smoking may result in a slightly acidotic neonate and lowered albumin capacity to bind with

bilirubin; 5) nicotine induces fetal tachycardia and/or hypoxia and can produce a small for date infant at risk for having an immature hepatic system; 6) finally, the same fetal tachycardia and/or hypoxia increases demand for metabolic oxygen, which could decrease glucose available for glucuronyl transferase which is essential in the excretory system for bilirubin.

CHAPTER IV. HYPOTHESES

The literature thus suggests an association between smoking during pregnancy and the development of neonatal physiological jaundice. The hypotheses which were tested are:

1. There is no significant association between smoking during pregnancy and the development of physiological jaundice in the newborn.

2. There is no significant association between the degree of neonatal bilirubinemia and volume of maternal smoking.

CHAPTER V. METHODS AND PROCEDURES

As illustrated by the current literature, it is reasonable to suggest that there may be a relationship between smoking and physiological jaundice and between smoking and the exacerbation of jaundice. In an effort to approach this theory scientifically, a group of 45 mother/infant pairs was randomly identified from a population of newborns referred for serum bilirubin evaluation by physicians at a major metropolitan hospital. To control for jaundice of known hemolytic etiology, pairs with Rh incompatibilities and ABO blood group incompatibilities were excluded. Also excluded were cases of multiple birth and maternal ages less than 20 years and greater than 30 years to control for high risk in pregnancy. Further, gestation lengths less than 37 weeks and greater than 41 weeks were excluded in an effort to control for the effects of obvious liver and fetal enzyme immaturity (APPENDIX A). Subject selection information was obtained from the infant's medical record, the mother's room number was identified, and informed consent was obtained.

Instruments and Study Design

Information regarding parental smoking habits was systematically collected and recorded during a personal

interview with the mother. Data included type and number of cigarettes smoked. If the mother or the father of the infant smoked, she was shown a drawing representing cigarettes smoked to varying degrees. The mother was then asked to identify the drawing which best represented the percentage of each cigarette she and/or the husband smoked during her pregnancy (APPENDIX B). The data were then used to determine total amount of cigarette consumption. A description of paternal smoking habits was collected in order to ascertain environmental effects on the pregnancy. "Husband" was defined as the male associate of the mother whose smoking may influence the fetus. Mothers were also questioned about previous OCA usage prior to pregnancy and a simple analysis of variance was calculated between the groups (OCA's vs No OCA's) using the corresponding peak serum bilirubin values.

The mother's medical record was used as a source for demographic data, oxytocin usage, and method of infant feeding. The infant's medical record was then used as a source for peak level of serum bilirubin, birthweight, hemoglobin and hematocrit values, use of phototherapy, and other demographic data.

Concurrently with the study described above, 45 subjects from the general population of live births at the same major metropolitan hospital who were not referred for

serum bilirubin evaluation were randomly selected. The mothers were questioned whether they smoked cigarettes during their pregnancy, and baseline smoking habits of the sample population at this hospital were determined.

Analysis

The association between the incidence of maternal smoking and jaundice was analyzed by utilizing the chi square statistical test of homogeneity. This test is useful for determining if two populations are similar with respect to a particular criterion variable, which in this case was smoking. The results were submitted to the test in two different groupings: 1) only the number of mothers who smoked the duration of the pregnancy and 2) the total number of mothers out of 45 who smoked during any part of the pregnancy regardless of the fact that they may have quit or reduced smoking with knowledge of their pregnancy.

Additionally, analysis of the association between incidence of maternal smoking and neonatal jaundice was made on the study group with known serum bilirubin values using the point-biserial correlation coefficient. This statistical procedure is a measure of linear relationship.

Further testing was done to determine the association between volume of smoking and degree of hyperbilirubinemia. Accordingly, 21 infants with known serum bilirubin levels were categorized into 3 groups: 24 non-smoking cases, 11

cases where mother and/or father smoked 0-15 cigarettes per day, and 10 cases where mother and/or father smoked 16 or more cigarettes per day. Analysis of variance between the mean peak bilirubin scores of each of the groups was calculated. Though the F test is commonly used to determine differences in population variances, the statistic was utilized as a prerequisite to further testing for degree of association. An analysis of variance between peak bilirubin scores of breastfed infants and formula fed infants was made and F determined. As well, analysis of variance between peak bilirubin scores of infants whose mothers had not used OCA's prior to pregnancy and those infant's whose mothers used OCA's was calculated.

All statistics were hand calculated using Downie and Starry's Descriptive and Inferential Statistics(28) as a reference and verified on the TWU DEC-20 computer using the Statistical Package for the Social Sciences. In every test, significance was tested at the 95% confidence interval ($p<0.05$). Only total peak serum bilirubin was used for analysis.

CHAPTER IV. RESULTS AND DISCUSSION

The purpose of this paper was to investigate the association between smoking during pregnancy and the development of neonatal jaundice. Data obtained from the sample population most importantly included an analysis of the smoking characteristics of respective mothers and the bilirubin score of infants with hyperbilirubinemia. Results were consistent with the following description:

Demography

Of the 45 mothers of non-jaundiced infants interviewed, only five of the 45 (11%) smoked cigarettes. Of the 45 mothers of jaundiced infants interviewed, 14 of the 45 (31%) admitted to smoking cigarettes. However, within this group, there were those who described their smoking habits as "occasionally," "two to three," or "once a month," having substantially decreased smoking since pregnancy. Three of these 14 claimed to have quit smoking entirely when the pregnancy was verified. This evidence may suggest that greater public awareness of the hazards of smoking during pregnancy has effectively limited or at least decreased cigarette smoking among pregnant women. In addition, among the sample set who met the criteria for selection were women who would not consent to participate in the study. Perhaps

fear of criticism or guilt for smoking precluded their participation.

Of the fourteen mothers who smoked, 13 of the husbands also smoked. A total of 21 of the fathers of 45 infants smoked. In this sample, if the wife of the couple smoked, it was most likely that the husband smoked also.

Although the total amount of cigarettes that the mothers reported to smoke was small, combined parental smoking may have had an effect on the birthweight of the newborn. As predicted by Harvey and Mellits, (27) the birthweights of infants of the smoking mothers in this sample averaged 227 gms (~8 oz.) less than infants from non-smokers. The mean birthweight of infants from smokers was 7.02 lbs, while the mean birthweight of non-smokers was 7.57 lbs. These figures represent approximately an 8 per cent reduction in body weight, although the difference was not statistically significant. The affected infants could have been predisposed to jaundice because of immature organ systems.

Results also demonstrated that there was a total of 25 infants in the jaundiced group who required treatment with phototherapy. Sixteen of these were infants from mothers who did not smoke, representing 50% of the total of non-smokers, while 9 were offspring of smokers, representing 66% of the infants from smokers. The data presented here,

if representative, indicates the need for larger sampling. Longo and others have suggested that phototherapy results in increased insensible water loss, increased heart rate, and altered vitamin and amino acid status. Data, if representative of a larger sample, indicates that the already compensated small-for-date infant expected from smokers may be unusually taxed by treatment with phototherapy.

However, as illustrated by Table I, the population sampling of jaundiced infants was homogenous by various other criteria, including race, maternal age, lenth of gestation, number of previous pregnancies, and sex of the child. Similar results were found by Jeffares in his survey of neonatal jaundice. According to Naeye, early partruition can be expected to result from amniotic fluid infections and these infections are more prevalent among smokers than non-smokers. Differences between gestation lengths of smokers and non-smokers were incrementally different (.5 weeks) and there was no evidence of amniotic fluid infections. Therefore, neither increased hemolysis or lack of fetal liver enzyme priming contributed to hyperbilirubinemia.

Research Questions

The Chi square statistic was applied to the populations of jaundiced infants and non-jaundiced infants to determine

TABLE I

Comparison of perinatal factors between jaundiced infants and corresponding mothers who smoked throughout pregnancy with those of jaundiced offspring and corresponding mothers who did not smoke the duration of pregnancy

Variable	Smokers (n=11)	Non-smokers (n=34)
Race		
# White	2	12
# Black	4	5
# Mexican	4	14
# Other	1	3
Maternal Age (yrs)		
(Mean)	23.7	24.3
(Mode)	22	22
Gestation (wks) Duration		
(Mean)	39.5	39
(Mode)	40	40
Previous Pregnancies		
(Mode)	0	1
Sex of Child		
# Male	4	18
# Female	7	16
Birthweight (lbs.)		
(Mean)	7.02 SD=0.87	7.57 SD=1.03

the association between smoking during pregnancy and neonatal jaundice (Table II). For the purpose of this statistic, all 14 mothers who smoked during any part of the pregnancy were included. Results were significant at the $p<0.01$ level. Therefore, the hypothesis that there is no significant association between smoking during pregnancy and the development of jaundice was rejected.

Further testing with chi square using only those mothers who continued to smoke for the duration of the pregnancy (N=11) yielded insignificant results. Assuming that the responses to questions in the interview with the mothers were honest, an association between maternal smoking and neonatal hyperbilirubinemia was not demonstrated by this study. Although the intent was not to show cause and effect, the rationale provided by the literature suggests an association between smoking and hyperbilirubinemia because of the pharmacologic effects of the nicotine, carbonmonoxide, and changes in blood chemistry of the infant as a consequence of smoking. This rationale is negated if smoking did not continue throughout pregnancy.

The conflict in these results emphasizes the need for further research with larger sample numbers. The possibility of lasting biochemical changes in the fetus reulting from smoking early in pregnancy must not be rejected. Perhaps the fetus could not detoxify the

Table II. Chi square analysis of the effect of smoking on neonatal jaundice

	no smoking	smoking
no jaundice	40	5
jaundice	31	14 *

Chi square = 8.08
$p<0.01$, significant
* n=smoked during any part of pregnancy

	no smoking	smoking
no jaundice	40	5
jaundice	34	11 *

chi square = 2.80
$p>0.10$, insignificant
* n=smoked the duration of pregnancy

chemicals introduced into the system, and therefore, would still suffer from the effects of maternal smoking even if the mother quit during the pregnancy.

The point-biserial statistical procedure, including all 14 smokers, failed to show a significant difference between maternal smoking and neonatal jaundice hypothesis. The data also failed to confirm the findings of Hardy and Mellits, who determined that serum bilirubin levels were significantly higher among infants of non-smokers (27). The research presented here found no correlation, positive or negative. It should be noted, however, that the present study controlled for hemolytic jaundice while the former study did not.

The Nymand research, which also reported lowered neonatal bilirubin with maternal smoking, postulated that the by-products of cigarette smoking which are detoxified by the liver perhaps stimulated the glucuronyl transferase system, resulting in increased conjugation of bilirubin in the liver. Without controlling for jaundice of hemolytic origin, Nymand substantiated the idea that smoking during pregnancy may have actually lowered neonatal bilirubinemia. Again, this theory was not confirmed by the current study.

The question remains whether there is an association between the degree of smoking and degree of

hyperbilirubinemia. Three categories, defined as non-smokers, those who smoked 0 to 15 per day, and those who smoked >16 cigarettes per day each were compared by analysis of the mean serum bilirubin scores. The mean serum bilirubin score of infants from non-smoking parents was 9.89 mg/100 ml, while the mean serum bilirubin for infants from parents who alone or together smoked the equivalent of 0 to 15 whole cigarettes per day was 8.78 mg/100 ml. Furthermore, mean serum bilirubin for infants from parents who either combined or alone smoked >15 cigarettes per day was slightly higher at 10.37 ml/100 ml (Table III). When variance of the three subsets was calculated and F determined, there was no significant difference between the populations. The effect of varying degrees or increased volume of cigarette consumption apparently did not affect or potentiate hyperbilirubinemia.

Other Factors

Since current research has also investigated the effect of oral contraceptives prior to pregnancy on hyperbilirubinemia, this data was collected and variances analyzed to determine effects other than smoking. There was no significant difference in the mean peak serum bilirubin of infants whose mothers who had taken OCA's (N=24) and those who had not (N=21). This evidence is consistent with the conclusion of Wood and others in 1979 (4) who also found

TABLE III.

ANALYSIS OF NEONATAL BILIRUBIN SCORES

AND AMOUNT OF PARENTAL CIGARETTE CONSUMPTION

Cigarettes per day	Serum Bilirubin (mean)	Standard Deviation
Non-smokers (N=24)	9.89	2.64
0 to 15 (N=11)	8.87	2.17
> 16 (N=10)	10.37	3.71

$p > 0.05$

no relationship between OCA use and neonatal bilirubinemia.

Regarding the possibility of an "icteric" substance in breastmilk, the data in this sample demonstrated that breastfeeding had no effect on the development of hyperbilirubinemia, as determined by analysis of variance. The mean peak serum bilirubin of infants who were breastfed was 9.88 mg/100 ml while the mean peak bilirubin of those who were not breastfed was 9.51 mg/100 ml. The insignificant difference may well have been predicted from the Campbell study of 1975 (7).

The third major theory reported as the cause of physiological jaundice postulated that the use of oxytocin for induction or acceleration of labor leads to an increase in serum bilirubin. In this sampling, oxytocin was not used for either induction or acceleration of labor; therefore, no effect could be measured.

CHAPTER V. SUMMARY, CONCLUSIONS AND IMPLICATIONS FOR FURTHER RESEARCH

The present study was undertaken to determine if smoking during pregnancy influences the development of neonatal hyperbilirubinemia. Sample selection included identification of a group of jaundiced infants and from that, investigation of the smoking habits of the mothers. This method limited the study and corresponding statistical analyses because of the small number of mothers who actually smoked during pregnancy. Because there were few mothers who smoked for the duration, others who decreased their consumption, and still others who quit smoking, it is suggested the increased public awareness of the hazards of smoking during pregnancy has effectively limited maternal smoking.

The mean birthweight of neonates from smoking mothers was 227 gms less than infants of non-smokers, although the difference was not statistically significant. As expected, the smokers produced small-for-date infants, in spite of the fact that actual reported cigarette intake was not excessive.

Data including all samples who reported having smoked at all during pregnancy demonstrate a significant

association between smoking during pregnancy and the development of hyperbilirubinemia. Further analysis of the sample characteristics with respect to smoking habit was done using only those subjects who reported having smoked the duration of the pregnancy. The resulting analysis demonstrated no significant difference in the incidence of hyperbilirubinemia in offspring of non-smokers as compared to smokers.

The correlation procedure revealed no significant association between smoking during pregnancy and the development of jaundice. However, there was no negative correlation found between maternal smoking and hyperbilirubinemia as reported by other research.

When total volume consumption was compared with level of serum bilirubin, it was determined that the volume of ciarettes smoked had no effect on the resulting bilirubin scores. Therefore, as volume of smoking increased, a direct proportional increase in bilirubin value was not demonstrated.

There was no effect on hyperbilirubinemia demonstrated by the use of oral contraceptives. Mean serum bilirubin in infants from OCA users and in infants of non-OCA users did not vary significantly. Though this data was not the focus of the current study, in future research the number of OCA users in the population of non-jaundiced infants would be

interesting to compare to the number of OCA users among mothers of the jaundiced infants.

Breastfeeding demonstrated no effect on mean peak serum bilirubin scores. Oxytocin was not used to induce or accelerate labor in any of the samples identified in this study and therefore would have had no effect on the offspring.

Further investigation into the same research question should be made on a larger sample of mothers who smoked during pregnancy. With regard to this, the suggestion is made that the smoking mother be identified during the early course of her pregnancy. Rapport should be established between the researcher and the subject so that data collected about smoking habit is reliable and measured serially. Medical science would profit from the knowledge of the biochemical effects that maternal smoking has on the neonate. Research should include measurements of bilirubin in all infants, measures of serum albumin, pH, hemoglobin, and glucose.

APPENDIX A

SCREENING CRITERIA

	YES	NO
Multiple birth	___	___
Rh incompatibility	___	___
Coomb's Positive	___	___
ABO blood group incompatibility	___	___
Mother <20 years	___	___
>30 years	___	___
Gestation <37 weeks	___	___
>42 weeks	___	___

APPENDIX B

A. 

B. 

C. 

D. 

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