Perinatal infections
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Chairman's introduction

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For many years the Ciba Foundation has shown a great interest, through its symposia, in the health of the fetus and the newborn, and has examined the genesis of birth defects and other handicapping disorders. It is a great personal satisfaction that this interest continues, and it is very fitting that in the final weeks of the International Year of the Child we are meeting here to discuss perinatal infections.

In 1972 the symposium on Intrauterine infections (Ciba Foundation 1973) was held in this room at a time when we were looking forward to the prevention of congenital rubella and to the prospects for the prevention of congenital cytomegalovirus infection. At that stage the latter seemed just around the corner. Many conferences have been held elsewhere since then and some progress has been made, though perhaps not at the speed at which some people had hoped. Nevertheless this slower rate of progress may have been a better approach to the problem than progress at breakneck speed, and may prove to be the greater benefit in the long run.

In examining the programmes of many of those conferences in many different countries I find three things that seem to be relevant. First, the perinatal period has received inadequate attention. The 'classic' infections of toxoplasmosis, rubella, cytomegalovirus and herpes—TORCH, as André Nahmias put it, with an S added to include syphilis for some other countries—have been discussed in great detail. But other perinatal infections, if discussed at all at those meetings, were relegated to the end of the last session. Secondly, the placenta, if discussed at all, was also tacked on at the end of the meeting, sometimes appearing in the proceedings as the second last chapter. Finally, the amniotic fluid received scant attention.

At most of these conferences it was rare for all the appropriate disciplines to be gathered together to discuss the problems. It is at the time of birth that the
obstetrician, paediatrician, pathologist and microbiologist may be forced to meet, but quite often that is too late. At our meeting here the people responsible for the care of the mother and child have been gathered together, and the disciplines they represent were in Katherine Elliott’s mind when she designed the programme. But she didn’t stop at obstetricians, paediatricians, pathologists and microbiologists: she included epidemiologists and experts in comparative medicine, together with the vital component of geographical medicine, if that is the correct term to use.

There seems to be no formula for the organization of Ciba Foundation symposia. Perhaps it is just the genius of the people who work here and put together these programmes and the appropriate speakers. It is an art that I don’t think anybody could define.

The gathering together of these specialists ‘is surely guaranteed to deepen our understanding and stimulate our discussions’, as Professor June Lloyd (1976) said in chairing an earlier meeting here. For these three days we can focus our attention on perinatal infections without any distractions. I would like to show you this quotation which was taken from a facsimile of the second folio of *Hamlet*:

```
and now remains
That we finde out the cause of this effect,
Or rather say, the cause of this defect;
For this effect defectuie, comes by cause,

The Tragedie of Hamlet.
Actus Secundus. Scena Secunda.
```

I hope you will agree that one of the aims of our meeting is to discuss aspects of prevention. But before we can do that we must have firm answers on what the problems are and what their magnitude is. Dr Richard Naeye will start us along the first part of the road chosen for this conference.

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Ciba Foundation 1973 Intrauterine infections. Excerpta Medica, Amsterdam (Ciba Found Symp 10)
Lloyd JK 1976 In: Breast-feeding and the mother. Excerpta Medica, Amsterdam (Ciba Found Symp 45), p 3
Factors in the mother/infant dyad that influence the development of infections before and after birth

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Abstract A number of maternal factors strongly influence the development and outcome of fetal infections. Severely undernourished mothers produce neonates with evidence of an immunoincompetence that persists into later childhood. Mothers who fast during pregnancy develop metabolic acidosis much more rapidly than non-pregnant women. The metabolic acidosis leads to high fetal and neonatal death rates from a variety of pre-existing disorders, including infections. Such metabolic acidosis also appears responsible for the excessive fetal and neonatal deaths associated with maternal urinary tract infections. Finally, coitus during pregnancy markedly increases both the frequency of bacterial infections of amniotic fluid and the mortality due to them. The effects are greatest at mid-pregnancy and gradually decrease to term.

It is often assumed that the fetus is well protected from infectious agents but it is now known that this protection is breached with surprising frequency by both viruses and bacteria. The outcome of such exposures is determined by a variety of factors, including the route of infection, the nature of the infecting agent, its numbers, the stage of development of the embryo or fetus and the competency of maternal and fetal defence mechanisms. The maternal environment has a major influence on most of these factors. This paper focuses on maternal habits and disorders that influence fetal infections. Recognition of these risk factors in individual mothers offers the prospect that certain diseases in their offspring will be identified more easily. Most important, if some maternal habits are changed, it should be possible for some antenatal infections to be prevented.

THE ROLE OF NUTRITION

Several studies have shown that undernourished fetuses and neonates are more likely to die of infections than their better-nourished counterparts.
(Naeye & Dixon 1978, Naeye & Peters 1978). Ferguson et al in 1974 and Chandra in 1975 reported many signs of immunoincompetence in severely undernourished neonates. These included an impaired antibody response to some antigens, a subnormal number of T lymphocytes in peripheral blood, abnormally low plasma levels of opsonic activity and a severe defect in the bactericidal capacity of polymorphonuclear leucocytes. If Chandra's mothers were typical of other Indian women whose diets have been studied, they probably had diets that were deficient in calories, protein, vitamins and minerals during their pregnancies. It is not known which of these deficiencies might have been responsible for the immunological abnormalities that Chandra discovered. Ferguson's neonates were apparently undernourished as the result of uteroplacental underperfusion and placental insufficiency. Such newborns have spleens and thymuses that are more growth-retarded than their other organs (Naeye 1970). It has not been determined which nutrient deficiencies are responsible for their restricted growth.

In follow-up studies Chandra et al (1977) and Ferguson (1978) found that some features of the immunoincompetence they discovered in undernourished newborns persisted into later childhood. Children whose growth retardation persisted after birth continued to have a subnormal number of T lymphocytes in their peripheral blood and abnormal skin-test responses to various injected antigens. No surveys have been undertaken to determine how widespread these immune defects might be in children who were less severely undernourished or malnourished before birth, so the size of the public health problem is unknown.

Although uncommon in the industrial nations, inadequate maternal food intake during pregnancy occasionally impairs fetal growth. The prepregnancy nutritional stores of the mother can also affect fetal growth. Fig. 1 shows how mothers' prepregnancy body weights and weight gains in pregnancy influence the birth weights of their infants. In this figure, a mother's pregnancy weight gain minus the weight of her neonate and placenta is termed her net weight gain. Mothers' prepregnancy body weights and net weight gains in pregnancy had only a modest influence on birth weights when mothers weighed 43.6 kg or more at the start of pregnancy. When they weighed less, fetal growth retardation appeared abruptly at net pregnancy weight gains under 6 kg. This suggests that the efficiency of the fetus in competing for nutrients decreases markedly below a certain threshold. Many of Chandra's undernourished immunoincompetent neonates were probably below this threshold.

Other factors can also affect fetal nutrition in both the industrial and the third world nations. Several years ago, we found that successive neonates of undernourished mothers had increasing signs of antenatal growth retardation
in which the spleen and thymus were more affected than most other organs (Naeye et al 1973b). Hard physical work during pregnancy, with its attendant high calorie cost, can also lead to fetal undernutrition when maternal calorie intake and prepregnancy nutritional stores are low (Table 1). Again, we have no specific information on how these factors affect fetal and neonatal defence mechanisms against infection.

Maternal blood pressure and blood volume also influence fetal nutrition, presumably by affecting uteroplacental perfusion. We recently found that maternal diastolic blood pressures that are consistently under 60 mmHg (8 kPa) during pregnancy impair fetal growth. When prepregnancy body weights and maternal weight gains in pregnancy were held constant, birth weights were about 300 g less at term when mother's diastolic blood pressures did not rise above 60 mmHg than when such pressures were in the 65–80 mmHg (8.66–10.66 kPa) range throughout pregnancy. Hytten & Leitch showed some years ago (1971) that both fetal growth and the outcome of pregnancy are improved when normotensive gravidas develop oedema in their hands and faces. Recently such oedema has been found to correlate with a large blood volume in normotensive mothers. Holding a number of other fac-
TABLE 1  
Maternal characteristics affecting fetal nutrition

<table>
<thead>
<tr>
<th></th>
<th>Hard physical work during pregnancy</th>
<th>% of optimal</th>
<th>Light work only</th>
<th>% of optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>155.1 ± 5.4 (64)</td>
<td></td>
<td>158.3 ± 14.9(66)</td>
<td></td>
</tr>
<tr>
<td>Early pregnancy body weight (kg)</td>
<td>50.3 ± 6.1 (64)</td>
<td></td>
<td>54.3 ± 8.5(66)</td>
<td></td>
</tr>
<tr>
<td>Daily pregnancy dietary intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>1540 ± 488 (29)</td>
<td>64(64)</td>
<td>1641 ± 367(13)</td>
<td>68(13)</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>44.8 ± 13.7 (29)</td>
<td>75(64)</td>
<td>49.1 ± 12.9(13)</td>
<td>82(66)</td>
</tr>
<tr>
<td>Pregnancy weight gain at 38-40 weeks of gestation (g)</td>
<td>6494 ± 2802 (64)</td>
<td>52(64)</td>
<td>9214 ± 3722(66)</td>
<td>74(66)</td>
</tr>
<tr>
<td>Birth weight of offspring (g)</td>
<td>3068 ± 355 (64)</td>
<td>90(64)</td>
<td>3270 ± 386(66)</td>
<td>96(66)</td>
</tr>
</tbody>
</table>

Gravidas in the two categories of physical activity were similar with regard to dietary calorie and protein intake and height. Those who engaged in hard physical labour had lower body weights, lower pregnancy weight gains and lighter newborns than those who had lower levels of physical activity. The calorie and protein intakes in the table are the mean values for two dietary surveys conducted from 20 to 24 and 36 to 38 weeks of gestation.

All values ± 1 SD, no. of cases in parentheses. *"P >0.1 compared with hard physical work, \[P<0.01, 'P<0.001. Optimal weight gain at 38–40 weeks of gestation was considered to be 12.5 kg as cited by Hytten & Leitch (1971).

Not all the unfavourable effects of undernutrition on antenatal infections are exerted through the immunological systems of the fetus. We have recently discovered that maternal acetonuria is a marker for much of the excessive fetal and neonatal mortality associated with undernutrition (Table 2) (Naeye 1979a). This acetonuria is the presumed result of metabolic acidosis. When pregnant women fast, hyperketonaemia, acetonuria and other signs of metabolic acidosis develop within 24 hours whereas it takes two to four days for non-pregnant women to develop such acidosis (Felig & Lynch 1970). The exact mechanisms by which the metabolic acidosis increases infection-related perinatal mortality are not known but the answer may lie in changes in the
FACTORS INFLUENCING PERINATAL INFECTIONS

TABLE 2

Effects of maternal acetonuria during pregnancy on perinatal mortality rates in various categories of maternal pregnancy weight gain.

<table>
<thead>
<tr>
<th>Maternal pregnancy weight gain (% of optimal values)</th>
<th>Under 25</th>
<th>25-54</th>
<th>55-79</th>
<th>80-120</th>
<th>Over 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal acetonuria during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>117 (162)</td>
<td>46 (344)</td>
<td>36 (557)</td>
<td>23 (768)</td>
<td>70 (301)</td>
</tr>
<tr>
<td>Absent</td>
<td>65 (2372)</td>
<td>37 (2372)</td>
<td>34 (3791)</td>
<td>23 (5402)</td>
<td>31 (2261)</td>
</tr>
</tbody>
</table>

\(^aP<0.05\) compared with acetonuria present, \(^bP<0.005.\) No. of cases in parentheses. Pregnancies that lasted longer than 20 weeks are included in this table.

metabolic fuels supplied to the fetus. During metabolic acidosis, the supply of glucose to the fetus is reduced and the fetus presumably has to use fatty acids and ketone bodies as substitutes for both energy and growth. These substitute fuels may not be adequate for all fetal purposes. For example, not all areas of the brain may be able to use ketone bodies (Hawkins & Biebuyck 1979).

Several of the mechanisms just described seem responsible for the excessive number of fetal and neonatal deaths associated with urinary tract infections during pregnancy. Most of these excess deaths are due not to bacterial invasion of the fetus and placenta but rather to an increased death rate from pre-existing infections and other disorders. The fatal gestations are often marked by maternal acetonuria and hypertension (Naeye 1979d). Thus, metabolic acidosis and inadequate uteroplacental perfusion appear to be the main factors responsible for the excessive number of deaths. A temporary reduction in maternal food intake and a fever-induced increase in the metabolic rate are the probable causes of the metabolic acidosis.

Both monozygotic and dizygotic twins have rates of perinatal mortality due to bacterial infections of the amniotic fluid that are several times higher than the rates for single-born infants (Naeye et al 1978). All this excess mortality in twins is due to a higher death rate from pre-existing infections (Table 3). Since twins impose a greater load than single fetuses on maternal nutrients, it may be that immunoincompetence or some other nutritionally related impairment is responsible for the excess of infection-related deaths in the twins. We have discovered that the excess is not related to more frequent maternal acetonuria or hypertension.

In both Ethiopia and South Africa antimicrobial activity is usually absent or low in the amniotic fluid (Tafari et al 1977). This lack of antimicrobial activity leads to rates of amniotic fluid infections about double those found in
TABLE 3

Perinatal mortality rate due to amniotic fluid infections.

<table>
<thead>
<tr>
<th>Amniotic fluid infections</th>
<th>Single-born</th>
<th>Twins</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/1000 births</td>
<td>123 (3694)</td>
<td>113 (34)</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Deaths/100 cases</td>
<td>6.5 (240)</td>
<td>29.4 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perinatal mortality rate</td>
<td>8.0</td>
<td>33.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figures in parentheses denote number of cases. The perinatal mortality rate was greater in twins than in single-born infants due to a higher case fatality rate in the twins.

...the United States (Naeye et al 1977). Antimicrobial activity in the amniotic fluid is at least partially related to the presence of a polypeptide linked to zinc (Schlievert et al 1976). In Ethiopia and South Africa dietary deficiencies of zinc appear to be responsible for most of the deficiencies of antimicrobial activity in amniotic fluid. We have not discovered zinc deficiencies in blacks or whites in the USA but about 10% of their amniotic fluids lack antimicrobial activity at term. At present, we have no explanation for the abnormality in these fluids.

The influence of maternal dietary protein on the frequency and outcome of antenatal infections is uncertain. In fact, the role of this protein in other pregnancy disorders is unclear despite many investigations. It appears that mothers require from 20 to 30 g dietary protein per day during the last half of pregnancy if fetal needs are to be met without loss of maternal lean body mass. The fetus may be able to adjust to lower maternal intakes by preempting protein from the mother's stores: a study in New Guinea (Durnin 1980) has shown that mothers can eat less than 30 g of poor quality protein per day and still produce healthy neonates weighing 3100 or more grams. David Rush and his associates at the Columbia University School of Public Health have recently completed a study in which milk protein supplements given to mothers during pregnancy seemed to increase both the morbidity and mortality rates of their neonates. These disturbing findings may not have a simple nutritional explanation, as the rate of amniotic fluid bacterial infections in Rush's patients was several times higher than the rates that have been found in other studies in the USA.

THE ROLE OF COITUS

Many researchers have found that a large proportion of pregnant women
fear that coitus will damage their infants (Falicov 1973, Clark & Hale 1974). Such fears are discounted by most textbooks and by physicians who advise that coitus is safe until the last four to six weeks of pregnancy (Pugh & Fernandez 1953, Pritchard & MacDonald 1976). Such advice has been based on analyses of a relatively small number of cases, often late in gestation. Coital data have recently become available from the US Collaborative Perinatal Project, a large prospective study of pregnancy. More than 1000 pieces of clinical information were gathered on each case in this study. Placental and autopsy examinations were routinely made so it was possible to study the relationship of coitus to both the genesis and outcome of specific antenatal disorders. At each clinic visit for prenatal medical care, and usually at admission for delivery, mothers were asked a series of questions, including the number of coital acts, if any, since their last clinic visit. This information was then used to establish coital activity in the month before delivery.

Data included in the analyses were derived from the 26,886 singleton pregnancies in the study for which detailed placental examinations had been made. The frequency of amniotic fluid infections was 156/1000 births when mothers reported coitus once or more per week during the month before delivery, compared to 117/1000 when mothers reported no coitus (P < 0.001) (Naeye 1979c). Eleven per cent of infected infants died as fetuses or neonates when coitus was reported, compared to only 2.4% when there had been no coitus (P < 0.001). The frequencies of low Apgar scores, neonatal respiratory distress and hyperbilirubinaemia were about doubled when mothers reported recent coitus (Naeye 1979c). The coitus-associated effects were greatest at mid-gestation and gradually decreased to term.

Not all the noxious effects of coitus appear to be due to amniotic fluid infections. We have recently found that the frequency of abruptio placentae is increased with coitus in the absence of amniotic fluid infections. Perhaps the large amount of prostaglandin F2α in seminal fluid and the uterine contractions sometimes induced by coitus are the responsible factors (Goodlin et al 1971). Goodlin and his associates found that transient fetal bradycardia followed the uterine contractions induced by orgasm.

Coitus-related infections of the amniotic fluid have both short- and long-term influences on children’s neurosensory development. Neonates who have been exposed to amniotic fluid infections have about a 50% greater frequency of the following neurological abnormalities than neonates not so exposed: abnormal Moro reflex, abnormal muscle tone, myoclonus, abnormal suck and abnormal cry (Naeye 1978). These neurological abnormalities are increased about sixfold if the neonate develops hyperbilirubinaemia in conjunction with the amniotic fluid infection. The infection-related impairments are indepen-
dent of a large number of parental, pregnancy, intrapartum and other factors that influence neurosensory development (Naeye 1978). The frequencies of all these impairments increase with the severity of the infections. We found that the incidence of low IQ values was 68% greater in children who had antenatal amniotic fluid infections than in those not so infected. In most cases psychomotor defects were not severe. The affected children had mean IQ values about 10 points below the expected mean (Naeye 1978). Neonatal intraventricular and subarachnoid haemorrhages along with hypoxaemia no doubt explain some of the brain damage in the infants born before term, but these will not easily explain the infection-related impairments found in infants who were infected near term. Intracerebral haemorrhage is rare in these latter infants.

THE ROLES OF DRUGS AND TOBACCO

One of the most widely used drugs in pregnancy is alcohol. Heavy consumption correlates with the occasional appearance of a group of malformations termed the fetal alcohol syndrome. Mothers who are heavy drinkers have also been reported to have an increased frequency of spontaneous abortions and mid-term fetal and neonatal deaths. Both the congenital malformations and the spontaneous abortions are more frequent in mothers who have high rather than moderate or low alcohol consumption. It needs to be determined whether amniotic fluid or other types of infections are involved in this excessive mortality.

Heroin addicts have an excessive number of spontaneous abortions and fetal losses. In one study an excessive number of amniotic fluid infections was found in such mothers (Naeye et al 1973a). The infections are more likely to be related to the promiscuous sexual behaviour that many of the addicts adopt to raise money to purchase drugs, and to their poor nutrition during pregnancy, than to heroin itself.

No relationship has been found between the use of tobacco during pregnancy and antenatal infections. Cigarette smoking reduces uteroplacental perfusion, reduces oxygen transfer to the fetus, and appears to damage intrauterine blood vessels (Naeye 1979b). These effects predispose mothers to abruptio placentae, placenta praevia and large placental infarcts but seem to have no effect on the development or outcome of antenatal bacterial and viral infections.
THE ROLE OF MATERNAL AGE

In many studies fetal and neonatal deaths have been found to increase with the mother's age, particularly after age 39. In a recent study (Naeye 1980) we found that 82% of the increase over age 39 was due to a variety of seemingly unrelated disorders, including amniotic fluid infections (Table 4). The link between these disorders was an increase in case fatality rates, i.e. more frequent deaths from disorders already in progress. This may be due to decreases in uteroplacental perfusion, as decidual vascular markers for high perfusing pressures decreased progressively with age. It remains to be determined whether offspring of aged mothers show signs of immunoincompetence more often than children of younger mothers.

TABLE 4

Effects of maternal age and coitus on perinatal mortality due to amniotic fluid infections

| Mother's age     | Amniotic fluid infections |             |
|                 | No coitus       | Coitusa     |
|                 | Cases/1000 births | Deaths/100 cases | Perinatal mortality rate |
| 14-34 years     | 114 (2508)      | 9.3 (234)   | 10.7               |
|                 |                 |             |                    |
| 35-39 years     | 159c (206)      | 12.6 (26)   | 20.1d              |
|                 |                 |             |                    |
| Over 39 years   | 135 (47)        | 21.3c (10)  | 28.8d              |
|                 |                 |             |                    |

Perinatal mortality rates increased with maternal age, mainly due to increases in case fatality rates from the amniotic fluid infections. Perinatal mortality rates were also several times higher with than without coitus up to the time of delivery. Figures in parentheses denote no. of cases. aCoitus once or more per week in the month before delivery. bP<0.05 compared with figure in same coitus category, 14-34 years of age, cP<0.03, dP<0.005, eP<0.001.
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Discussion

*Chan:* How do you diagnose amniotic fluid infections, Dr Naeye?

*Naeye:* They were diagnosed when there was acute inflammation throughout the subchorionic plate of the placenta. We have found that neither meconium nor any of the common viruses that infect the placenta cause such inflammation. In experimental animals only bacteria have been able to produce this inflammatory process. Neither acidified gastric juice nor cellular debris nor meconium produce the inflammation. In human beings, fastidious anaerobic bacteria and mycoplasmas that are not routine-cultured cause many of the infections.

*Chan:* Did you also examine the placentas in instances where the fetus died?

*Naeye:* Yes.

*Mata:* In the developing nations we are not yet aware of the relationship between coitus and an increased risk of perinatal infection and neonatal mortality.

My experience in working with Dr Urrutia is that there is no clear-cut effect of diet during pregnancy and the outcome of pregnancy in the Indian village of Santa María Cauqué (Mata et al 1976). However, data from lowland Guatemalan villages and elsewhere indicate that there is such an effect, and I believe this is the position that WHO has taken recently. This worries me because most studies that I have seen do not prove conclusively that such an association really exists. In studies where dietary intake in pregnancy appeared to be associated with pregnancy outcome the statistics could have been faulty. For instance, the only valid way to analyse findings of this kind is to compare control villages with experimental ones (Lechtig et al 1972).

My other point is that most studies did not distinguish between fetal growth retardation and preterm delivery. The importance of your paper for developing countries is tremendous, Dr Naeye. We shall have to reanalyse stored information in the light of your observations, and future investigations should include the important variable of coitus and late infection during pregnancy.

*Banatvala:* How can you determine whether the results you have collected on the frequency of intercourse during pregnancy are accurate, Dr Naeye?

*Naeye:* The only way to confirm such information would be to examine vaginal specimens for acid phosphatase and spermatozoa. This was not done. However we think the information collected was probably correct because the proportions of women having coitus at the various stages of pregnancy were close to the findings in many previously published studies (Solberg et al 1973).
Malvern: Since the cervix in late pregnancy is usually more dilated and efaced in multigravid than in primigravid patients, were you able to correlate the incidence of infection with gravidity?

Naeye: Amniotic fluid infections are more often severe in multiparous than in primiparous women, with the result that the infections are more often fatal to the fetus and newborn of multiparous women. Older mothers have less coitus than younger mothers during pregnancy but this is balanced by the higher case fatality rates of amniotic fluid infections in older mothers.

J.M. Ross: In a personally conducted trial in the Harrow area I found that British women were very loath to divulge the frequency of intercourse. After a while I stopped asking this question because I realized that I wasn't getting a correct answer. Perhaps the American women are more outgoing.

Naeye: Most women in the USA seem to answer questions about coitus without hesitation. More important, we did not find that coitus three times per week during pregnancy had much more effect on amniotic fluid infections than coitus once per week. Thus the presence or absence of coitus, rather than its frequency, appears to be the important factor.

Blanc: Michael Reinhardt tells me that in the Ivory Coast a man is expected to serve his wife at least once a day. In the placentas Dr Reinhardt sent us there was a much lower incidence of amnionitis than in placentas from Harlem, where the incidence was very high. And may I say that some progress has been made since the Ciba Foundation symposium on Intrauterine infections when Dr Gamsu (1973) answered Dr McCarthy that coitus during pregnancy was a possible factor in infection but there was no evidence to incriminate it for certain.

Reinhardt: Cultural factors may influence the response of women to their doctors. We don't know a lot about this, even in very modern medicine. In the black American population, coitus during pregnancy is more frequent than among the white population, and incidence of perinatal deaths is higher. Do black women consider that coitus during pregnancy increases the stability of the union with the husband? What is the attitude among the white American population?

Naeye: Published studies in the US show that 50–75% of women have an underlying fear that coitus during pregnancy will damage their infants (Falicov 1973). This fear persists despite the advice given by most obstetricians that coitus is safe until the last few weeks of pregnancy. Our study (Naeye 1979a) has found that a higher proportion of blacks than of whites in the US have coitus during pregnancy. Orientals in the US had coitus less often than whites. The orientals had very few fetal and neonatal deaths due to amniotic fluid infections. There is excessive sexual pressure through television
and the cinema on young people in America, both black and white. All races probably expect frequent coitus.

_Urrutia_: Is there a relationship between coitus during pregnancy and urinary tract infections? Would this influence perinatal infections?

_Naeye_: We have studied these factors individually but to date have not looked at their interrelationship. In the non-pregnant state there is a strong association between coitus and urinary tract infections (Buckley et al 1978). Unlike coitus, urinary tract infections do not exert their main influence on pregnancy through amniotic fluid infections. Urinary tract infections appear to lead to mild episodes of metabolic acidosis in some women and it is the acidosis that appears to be responsible for the high perinatal mortality rates associated with the urinary tract infections (Naeye 1979b).

_Sosa_: Was the cause of perinatal death related to acute infections or to premature labour? Dr L. Gluck (personal communication) from San Diego mentioned recently that amniotic fluid infections might trigger prostaglandins and start premature labour.

_Naeye_: Most of the neonatal deaths were the consequence of premature labour. A high proportion of the fetal deaths appear to be due to sepsis.

_Klaus_: In trying to work out the mechanism by which coitus may initiate labour and result in infection, shouldn't you consider whether coitus is affecting the ejection of oxytocin from the pituitary? Large amounts of oxytocin would produce contractions of the uterus and possibly separation of the placenta. This might also be related to the increased rate of infection.

_Naeye_: It is quite possible that oxytocin released as the consequence of coitus could be responsible for some coitus-related placental abruptions. The large amounts of prostaglandin F2α in seminal fluid might also have some role in the abruptions.

_Hanson_: Dr D.M.V. Parrott (unpublished work) has suggested that transfer of lymphocytes to the intestine of the neonate is influenced by the blood flow. What you told us about the blood pressure of the mother might affect this defence factor, perhaps explaining the increased risk of infection.

My second point is about the antibacterial activity of amniotic fluid. Serum, for instance, kills many Gram-negative bacteria practically instantaneously, and many Gram-negative bacteria causing bacteraemia are sensitive to this antibacterial activity (Olling 1977). However, _in vivo_ the bacteria are taken up by granulocytes and survive in the blood because they are protected intracellularly. So I would question the importance of the antibacterial activity of amniotic fluid for host defence.

_Naeye_: There are large variations in the potency of the antimicrobial activi-
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...ty in amniotic fluid. These variations do not correlate very closely with the Gram-stain characteristics of the bacteria.

Taylor-Robinson: Are all the studies that you mentioned monitored bacteriologically? If so, how far are the methods standardized?

Naeye: The data were gathered between 1959 and 1966 when routine methods for isolating and identifying bacteria were inadequate to identify many of the agents that are now known to cause amniotic fluid infections. The bacteriological methods that were used were not standardized.

Taylor-Robinson: Are the methods sophisticated enough now to include chlamydiae?

Naeye: We have not studied Chlamydia.

Sterky: You showed a kind of threshold at about 6 kg weight gain in pregnancy in relation to birth weight. Could you advance a hypothesis to explain that threshold?

Naeye: I have no explanation for why the threshold appears at a net pregnancy weight gain of 6 kg. It appears to be a basic biological phenomenon because this threshold is the same in blacks and whites in the USA.

References