Papers and Originals

Neurological Sequelae of Prenatal and Perinatal Complications*

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In recent years several attempts have been made to assess the hazards of prenatal and perinatal complications. There is little doubt that obstetric complications carry an increased mortality (De Haas-Posthuma, 1962; Butler and Bonham, 1963). Moreover, where several obstetric complications are present in combination it would be expected, *a priori*, that the risks will be additive. While the exact causes of death in any case may be diverse, one major factor is fatal damage to the central nervous system. Post-mortem examination of the brains of babies who would have died after obstetric complications or unfavourable events during the neonatal period has clearly shown the possibility of these factors producing lesions in the nervous system (Debré *et al.*, 1955; Norman, 1956; Malamud, 1959; Clark and Anderson, 1961; Morf and Bretscher, 1966). Studies in monkeys (Ranck and Windle, 1959; Windle, 1960; Windle *et al.*, 1961) have provided evidence of the harmful consequences of experimentally induced perinatal complications.

While studies of mortality rate have a strict criterion available—death of the foetus within a given period of time—the assessment of damage to the surviving infant is much more difficult. Signs have to be found which indicate the baby's condition, and these signs must have both high interobserver reliability and long-term prognostic value. Apgar's technique has merits but is restricted to the first few minutes after birth and deliberately covers only general aspects of physiological status (Apgar, 1966; Drage and Berendes, 1966). A quite different approach has been used by Graham (1956), Graham *et al.* (1956), and Graham *et al.* (1957), who measured behaviour patterns of babies a few days old.

In my own department a detailed neurological examination has been developed for the assessment of babies (Prechtl and Beintema, 1964). This examination has good interobserver reliability and high prognostic value (Prechtl and Dijkstra, 1960; Prechtl, 1965). In a sample of 102 neonates without neurological signs 86% were found to be neurologically normal at follow-up between two and four years later. Of 150 neonates with abnormal neurological signs, 73% still showed abnormal signs at follow-up during a similar period.¹ Certain constellations of neonatal abnormal signs, which we designated hyperexcitable syndrome, apathetic syndrome, and hemisindrome respectively, were prognostic of continuing neurological abnormality in 67%, 59%, and 73% of cases respectively, when the latter were examined at 2-4 years (Prechtl, 1965). Preliminary findings from our follow-up studies at 8 years show a similar picture to that found at 2-4 years. This method of examination may thus be regarded as a highly sensitive indicator of long-term neurological functioning. The identification of

factors which contribute to neurological abnormality in the newborn is therefore a problem of crucial importance.

The aim of the present paper is to examine some inter-relationships between obstetric complications and the results of this examination. Our hypothesis is that obstetric complications carry a high risk of neurological damage to the surviving infant. The data on which the present study is based have been collected over a period of 12 years. This paper is restricted to presentation of a number of global findings. Full data will be published elsewhere.

Method

The Sample.—A neurological examination was carried out on 1,515 infants born in the Department of Obstetrics of the Groningen University Hospital. In the Netherlands about 70% of all infants are born at home. The 30% delivered in hospital are therefore primarily cases with a risk of obstetric complications, though a minority go to hospital for social reasons, such as poor housing. From this total the following were eliminated: (1) babies of women who did not regularly attend the outpatient unit of the obstetric department during pregnancy; (2) babies whose birth weight was less than 2,500 g.; (3) babies with gross malformations; (4) babies whose mothers were in a poor nutritional state, suffered from psychiatric disease, epilepsy, diabetes, or heart disease, or whose basal metabolism was low; and (5) babies whose mothers had suffered prolonged sterility. Both categories 4 and 5 occurred rarely in our material. Babies whose condition was poor or dangerous in the first week were not subjected to full neurological examination. The sample remaining after exclusion of the above cases consisted of 1,378 babies.

Neurological Examination.—The standard neurological examination technique has been previously described (Prechtl and Beintema, 1964). All infants were examined once, two to three hours after a feed. All examinations were carried out between the second and fourteenth days, 91% of them being between the third and tenth days. The babies were picked at random from the obstetric department and were examined without knowledge of the obstetric history.

Data Processing.—The obstetric and neurological data were entered on precoded forms and later transferred to IBM punched cards. Seventy-six items were related to the mother, the course of pregnancy and delivery, and the general aspects of the infant, and 142 items to the neurological examination. All computations were carried out on a general purpose computer (TR4) at the Computer Centre of the University.

Incidence of Obstetric Complications

An obstetric complication may be defined as any factor or group of factors in the prenatal or perinatal environment which

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¹ The correlation between neonatal findings and the presence or absence of abnormal neurological signs on follow-up gave a value of $\phi=0.583$ ($P<0.0001$).

increases the risk of foetal mortality. These will be symptoms of maternal disease during pregnancy, signs of foetal distress, and mechanical intervention in the delivery. Few of these factors are independent of each other and many are causally related. For example, maternal toxæmia may lead to perinatal foetal distress, which in turn will lead to instrumental extraction.

In order therefore to give a more precise meaning to the rather loosely used term "complication," the following procedure was adopted. For every case 42 variables of the obstetric history were analysed and a count was made of the number of variables which departed from optimal conditions, according to generally accepted criteria. The largest number of such non-optimal conditions was 15, while in 6.2% of our sample all 42 variables were in the optimal condition. Table I shows some of the most frequently occurring non-optimal conditions.

The data were next divided into six subgroups: those with 0, 1-2, 3-4, 5-6, 7-9, and 10 or more non-optimal conditions. The percentage of cases in each subgroup is given for boys and girls separately in Fig. 1.

FIG. 1.—Incidence of non-optimal conditions in boys and girls. FIG. 2.—Percentage of the non-toxaemic (—) and moderate and severe toxæmic cases (+) (N=370) in each subgroup of non-optimal conditions. The difference is significant.

FIG. 3.—Type of delivery and obstetric subgroup. Spontaneous delivery, elective caesarean sections C.S. I (N=33), non-elective C.S. II (N=85), and low forceps (N=133) are presented separately.

There were no statistically significant sex differences with respect to occurrence of non-optimal obstetric conditions. In the subsequent analysis the data for boys and girls are combined.

TABLE I

Condition	No.	%
Maternal age above 30 years	342	25.0
Moderate toxæmia	250	18.1
Severe toxæmia	108	8.5
Other than vertex presentations	235	17.2
Non-spontaneous delivery	427	31.0
Caesarean sections	81	5.9
Middle forceps	75	5.4
Low forceps	133	9.7
Prolonged labour ≥ 24 hours	170	12.3
Second stage longer than two hours	96	7.0
Tight cord around the neck	101	7.3
Foetal bradycardia < 100/min.	188	13.6
Post-partum apnoea > 1 min.	224	16.3

Interrelationships between Non-optimal Obstetric Conditions

It is of interest to examine which conditions occur in combination with others and which do not. This summary is confined to three examples only, illustrating complications of pregnancy, delivery, and foetal state respectively.

Toxaemia.—If all cases with moderate or severe toxæmia (characterized by blood pressure $\geq 140/95$ and by albuminuria and oedema respectively) are compared against the rest with respect to the distribution of non-optimal conditions it will be seen that there is a marked tendency for the toxæmia cases to occur in association with a large number of other non-optimal conditions (Fig. 2).

Delivery.—A similar picture emerges, as might be expected, for instrumental as compared with spontaneous deliveries (Fig. 3).

Foetal Heart Rate and Apnoea.—Signs of foetal distress, such as tachycardia or bradycardia during the second stage (Fig. 4) and post-partum apnoea longer than one minute (Fig. 5), behave similarly to the complications above.

Non-optimal Obstetric Conditions and Neurological Symptoms

Most of the items of the neurological examination are assessed on an ordinal scale with three or four points. For instance, the palmar grasp reflex is recorded as being absent (—), being weak or just discernible (+), giving a good sustained response for 10 seconds (++), or giving an exaggerated forceful grasp (+++). The rooting response is recorded as being absent (—), showing only a weak turn toward the stimulated side (+), giving a full turn and a grasp with the lips (++), and consisting of a very vigorous turn with grasping (+++). The intensity of the Moro reflex is recorded as low, middle, or high. In the case of the palmar grasp reflex and rooting response the ++ category may be regarded as the optimal response, whereas for the Moro reflex the optimal response would be that of intermediate intensity and threshold.

If we assume that for each item of the neurological examination there is an optimal response we may examine the frequency with which cases with varying numbers of obstetric complications fall into the optimal and non-optimal categories.

For the purpose of this analysis the data were divided on the

basis of the obstetric complications into three subgroups: (1) a "low risk" group (N=264; 19.2%) with no or only one non-optimal condition; (2) a "middle risk" group (N=943; 68.4%) with two to six non-optimal conditions; and (3) a "high risk" group (N=171; 12.4%) with seven or more non-optimal conditions. The word "risk" is used to denote a raised probability of mortality during the delivery and the first two weeks of life. It involves no assumptions about the possible outcome of the neurological examination.

FIG. 4.—Foetal heart rate and non-optimal conditions. The tachycardia group with a heart rate >160 /min. (N=59) and the two groups of bradycardia 100–80/min. (N=101) and <80 /min. (N=89) are all significantly different from the group with normal heart rate (160–100). FIG. 5.—Onset of respiration and incidence of non-optimal conditions. The longer the apnoea the more other non-optimal conditions are present. The difference is highly significant at 1–3 min. (N=187) and >3 min. (N=37).

FIG. 6.—Distributions of response intensities of the palmar grasp reflex in the low and high risk groups. The difference is significant ($\chi^2=60.9$; $P<0.001$). FIG. 7.—Distributions of response intensities of the rooting response in the low and high risk group. The difference is significant ($\chi^2=22.2$; $P=0.001$).

For illustration the distributions of response intensities of the palmar grasp reflex and the rooting response are shown for the low and high risk groups (Figs. 6 and 7).

Fifty-eight neurological items were selected which, as above, could be assigned a position on a four-point ordinal scale. Contingency tables were constructed showing the frequency with which patients from the three risk groups fell into different positions on each scale. In 42 of the tests the differences between expected and observed frequencies as measured by χ^2 tests were significant at least at the 1% level of confidence. The low risk group predominantly showed those responses described as "optimal," whereas the high risk group showed relatively few optimal responses. In all 42 items the middle risk group was intermediate between the other two with respect to the number of optimal responses. In other words, there is a highly significant association between the number of non-optimal obstetric conditions and neurological abnormalities in the newborn.

The relation between non-optimal obstetric conditions and neurological abnormality is seen even more clearly if we carry out the following transformation. For each ordinal item of the neurological examination a score of "1" was given if the baby's response was in the optimal category. It was thus possible to obtain a "neurological score"—the number of items of the neurological examination in which the baby gave an optimal response. For all babies on whom the full neurological examination was carried out (N=1,378) the neurological scores were plotted against the corresponding number of non-optimal conditions. It was found that the mean neurological score decreased as the number of obstetric complications increased.

The neurological scores were next separated into three main groups, taking the following cut-off points: scores equal to 47 or less, scores 48 to 52, and scores 53 to 58. The babies in each of these three groups were then allocated, on the basis of

TABLE II

Neurological Scores	Risk Group			Totals
	Low	Middle	High	
≤ 47	73 (101.7)	375 (363.4)	83 (65.9)	531
48–52	84 (87.9)	316 (314.1)	59 (57)	459
53–58	107 (74.3)	252 (265.5)	29 (48.1)	388
	264	943	171	1,378

Figures in parentheses are expected frequencies.

their mother's obstetric score, to the high, middle, and low risk groups. The relation between the neurological and obstetric findings is shown in Table II. There was a very highly significant difference between the observed and expected frequencies with which the three neurological subgroups were represented in the three risk groups ($\chi^2=38.5$, d.f.=4, $P<0.001$). It is clear, therefore, that there is a high association between obstetric complications as measured by the obstetric scores and the occurrence of neonatal neurological abnormalities.

Obstetric Risks and Neurological Syndromes

If a group of symptoms occur repeatedly in combination they may be said to constitute a syndrome. We have previously described a combination of low intensity of general motor activity and of sucking, rooting, hand- and foot-grasping, head-lifting in prone position, recoil of forearms, and the labyrinthine reflex—the *apathy syndrome* (Prechtl and Dijkstra, 1960). Similarly, babies showing lowered resistance to passive movements of the neck, trunk, shoulder, elbow, hand, hip, and knee and ankle joints have been described as hypo-

tonic. Significantly more babies showing the apathy syndrome and hypotonia were found in the high risk group than in either the middle or the low risk group. Babies with asymmetries of posture, tendon reflexes, and skin reflexes (which we have previously described as the *hemisindrome*) were equally distributed among the three risk groups. Interestingly, however, babies with the hemisindrome and those with facial palsies had a significantly raised incidence of occurrence after forceps delivery and version-extraction. Babies who are what we have called *hyperexcitable* were significantly overrepresented in the middle risk group. Hyperexcitability occurred significantly more among the boys.

Neurological Scores and Classical Neurological Signs

I have so far argued that there is a high positive correlation between non-optimal obstetric conditions and neurological abnormality as measured by our standardized procedure. Because neonatal abnormalities with this technique are predictive of continuing abnormality and future behavioural disturbance (Prechtl, 1965) we believe it is essential that full neurological examination is carried out on all babies who are obstetrically at higher risks. It might be argued, however, that since the full examination is a time-consuming and expensive procedure it is sufficient to record the presence of obvious neurological signs which any well-trained obstetrician or paediatrician could not fail to see. In fact, 25 of our babies showed one or more "obvious" neurological signs: facial palsies; bulging fontanelles; deviation of eye position; absence of sucking, Moro, or palmar grasp reflexes; severe floppiness; or marked asymmetry.

It is of interest to examine the distribution of the neurological scores of these babies relative to that of the remainder. No baby with an obvious neurologically abnormal condition ever obtains fewer than four non-optimal subtest items—that is, the baby is never misclassified as normal by our examination. On the other hand, a very large number of babies with no classical neurological signs obtain the same neurological scores as those with such classical signs. It is clear, therefore, that examination merely for gross pathological signs will result in the omission of a considerable amount of neurological abnormality which is prognostically ominous. Thus the presence of "classical neurological signs" is not exclusive evidence of neurological abnormality. Moreover, we have shown that neurological abnormality, as measured by the full standardized procedure, increases in relation to the number of non optimal obstetric conditions. It therefore follows that the urgency for full neurological examination of the newborn increases also as a function of the number of non-optimal obstetric conditions present.

Discussion

The identification of what constitute obstetric hazards remains still an urgent clinical problem. An approach to this question through studies of mortality rate has great merits, but the answers must remain incomplete, since the majority of infants survive obstetric complications. Among these babies, however, may be many who suffer major or minor impairment of brain function. The early recognition of nervous dysfunction is of great importance both with respect to the possibility of early treatment and in relation to handling difficulties arising during the development of the mother-infant relationship. Many studies seem to indicate that, besides handicaps such as cerebral palsy due to prenatal and perinatal brain damage, minor brain dysfunctions, undramatic from the clinical neurological point of view, may lead to severe problems in the life of children and their parents. Though well-controlled studies are still scarce the available data are alarming.

In the context of these aspects the need for early indicators of risks is evident. The attempt to design risk registers which would select those babies from the population who are at special risk of brain damage is a major task. If only for the purpose of practical management, criteria are needed which do not select for special attention half or even more of all newborn babies. In the light of our study, one possible approach is through the obstetric score. It will be remembered that obstetric scores were highly correlated with neurological findings which were themselves predictive of continuing abnormality. In practice this would mean filling in a check-list of non-optimal conditions that results in a risk score. This is obviously a more reliable strategy than to look only for the presence of particular dangerous obstetric conditions in the baby's history.

As a further result of our study new criteria are suggested for the interpretation of the quantitative results of our neurological test items. Though it was possible previously to indicate the optimal intensity of responses, it was still questionable, for many responses, at which points of the scale one should speak of an abnormal response, a fact we have indicated in our manual for the neurological examination of the full-term newborn infant (Prechtl and Beintema, 1964). Differences found between the neurological item scores of the obstetrically high risk group and those of the low risk group are very suggestive of a more valid demarcation of neurological abnormality. For example, with respect to the rooting response, the differences between the two risk groups are apparent in the scores — and +, but the incidence of +++ is no higher in the high risk group than in the low risk group. This offers a possible operational definition of "abnormal" as being the — and + responses only, in contrast to the normal responses ++ and ++++. In the case of the palmar grasp response, on the other hand, the ++++ response would still be regarded as abnormal.

This new information is valid for many test items of the neurological examination. There remain certain neurological signs which are undoubtedly abnormal, such as the absence of sucking or of the Moro response, persistent deviation of the eyes. Our study has shown, however, that application of these generally accepted criteria of abnormality alone would leave many neurologically abnormal babies unrecognized. The French technique as advocated by Dargassies (1962) uses only such qualitative signs. The quantitative assessment of neurological signs is not, however, a mere academic refinement of neurological examinations, but a clinical necessity.

Summary

A group of 1,378 full-term newborn infants born in the Obstetric Department of the University of Groningen were subjected to a standardized quantitative neurological examination in their first 10 days of life. Data on pregnancy, delivery, and condition of the infant at birth were available.

Since previous correlation analysis of neurological results with obstetric complications failed to give instructive results a new approach was carried out. Forty-two variables of the prenatal and perinatal history were analysed and counted if they deviated from optimal condition, giving an obstetric risk score for each baby. The distributions of response intensities of many neurological items were shown to be different in the low, middle, and high risk groups. This held true also for some syndromes. The number of optimal neurological responses was negatively correlated with the number of non-optimal obstetric conditions.

It was shown that non-optimal conditions tended to occur in association with each other. The more a condition deviated from the norm, the greater the number of other non-optimal conditions associated with it. A simple count of the number of such non-optimal conditions present offers promise as a means of identifying those babies at risk of neurological damage.

It is suggested that the criteria for assessing what is an abnormal neurological response may be refined by reference to the responses of our low and high risk groups.

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Concentration of Methoxyflurane for Obstetric Analgesia by Self-administered Intermittent Inhalation

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Methoxyflurane has been shown to possess advantages over trichloroethylene as an obstetric analgesic (Major, Rosen, and Mushin, 1966). In that initial study we varied the concentration of both vapours continuously, with the aim of giving each patient the best possible analgesia without undesirable side-effects. The design of the trial made it possible (by analysing the continuous recordings of the inhaled concentrations of methoxyflurane) to deduce that for intermittent use a single fixed concentration of the drug would prove adequate and that this would be 0.35%. The present trial tests the validity of these predictions.

Method

Two concentrations of methoxyflurane in air (0.35% and 0.25%) were compared. These were chosen because observations in our first trial indicated that patients tended to become unacceptably drowsy at concentrations higher than 0.35%. This decision has been confirmed by observations of some patients in this trial who were studied at a higher concentration (0.45%).

Methoxyflurane was given from identical Penlon P.D.V. vaporizers, as these were the most accurate "draw-over" vaporizers available to us for this drug. Each was modified so that only one predetermined concentration could be given. The vaporizers were calibrated by us with a katharometer, using a Beaver ventilator as a dummy patient, and the concentrations were checked frequently throughout the trial. Before being used by a patient each vaporizer was flushed with oxygen for at least three minutes to clear the "dead" space.

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The day on which each concentration was used was previously randomized. Though an anaesthetist was present as an assessor throughout the inhalation, the conduct of analgesia was left to the midwife, so that the conditions were as near "normal" as possible. Inhalation was therefore started at the midwife's discretion, usually towards the end of the first stage of labour. A record was kept of the dose and time of administration of other drugs given during labour; no direction or restriction was made regarding their use. Assessments were made separately by an anaesthetist, by the midwife, and by the mother.

The same anaesthetist was present for all cases and made continuous assessments. For the full details of the method of assessment readers are referred to our previous paper (Major *et al.*, 1966). In brief, assessments are made of the mother's response to contractions, her level of consciousness, and any restlessness between contractions. The anaesthetist's observations are plotted to show the proportion of time during the whole period of observation for which each of the three factors is deemed "satisfactory." The periods for which all factors are satisfactory are calculated and expressed as a percentage of the total duration of inhalation.

As in the previous trial, the midwife, for whom the trial was blind, gave her assessment just after delivery with respect to the degree of analgesia, the drowsiness of the patient, and the restlessness of the patient. The mother was questioned twice—15 minutes after delivery and then 36 to 48 hours later. The questions at 15 minutes were slightly modified in this trial. She was asked: "Do you consider that what you had to breathe helped you?" ; "Do you feel drowsy?" ; "Did you drift off at all?" ; and "Could you do what we asked?" At the second visit other questions were asked regarding nausea, vomiting, memory, and smell.