Studies on fetal motor behaviour in complicated pregnancies

Sival, Deborah Anita

D.A. Sival

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STUDIES ON FETAL MOTOR BEHAVIOUR IN COMPLICATED PREGNANCIES

Stellingen

1. In tegenstelling tot kwantitieve parameters, geeft de kwaliteit van prenatale bewegingen bruikbare informatie over het functioneren van het foetale zenuwstelsel in individuele gevallen.

2. Met betrekking tot foetale bewegingen geldt: "beter klein maar fijn dan groot en grof".

3. Foetale stuitligging heeft, motorisch gezien, een postnataal staartje.

4. Er is geen sluitende verklaring voor de discrepantie tussen pre- en postnatale motoriek bij spina bifida.

5. Bij "joy scanning" kan de "joy" korter duren dan de "scan".

6. Zien is weten.

7. Corruptio Optimi Pessima.
(ook toepasbaar op geavanceerde onderzoekstechnieken).

8. Werkdruk is geen nood aan de man (v/m), maar aan diens prioriteiten.

9. Het schaken als vrouwensport dient te worden afgeschaft.
Vrouwen moeten met mannen meedoen.
Jan Timman

10. Vanaf de top leiden alle wegen naar beneden (vanuit het dal omhoog).

11. Een kater ligt altijd op de loer, zelfs als het kat in 't bakkie is.

Stellingen behorend bij het proefschrift van D.A. Sival:

Studies on fetal motor behaviour in complicated pregnancies

Groningen, 7 april 1993

RIJKSUNIVERSITEIT GRONINGEN

STUDIES ON FETAL MOTOR BEHAVIOUR IN COMPLICATED PREGNANCIES

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aan de Rijksuniversiteit Groningen
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DEBORAH ANITA SIVAL

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Deborah

CHAPTER 1

INTRODUCTION AND AIM OF THE STUDY

Introduction and aim of the study.

A. General aspects of pre- and early postnatal motor behaviour:

The knowledge that spontaneous prenatal motor behaviour is a common feature in human fetuses dates back to more than a century ago (44, 54, 64). Although Preyer (44) was convinced that fetal movements are similar to those of the newborn infant, the impossibility to visualize the fetus non-invasively prevented detailed investigation. This problem was only partly overcome by Minkowsky (32), Hooker (for review see: 2) and Humphrey (24), who performed reflex studies in exteriorized fetuses. After the introduction of the ultrasound technique, Birnholz et al. (6) applied the results of these reflex studies by Hooker (22) for the assessment of fetal developmental milestones. However, later the application of reflex studies seemed less appropriate, as detailed investigations (59) indicated that fetal movements occur spontaneously, i.e. independent from external stimuli. These observations were supported by reports on nervous tissue- and monolayer cell- cultures (13, 53). In nervous tissue cultures, it was indicated that as soon as synapses and transmitters are formed, neuronal networks become active (13). In addition, monolayer cell cultures showed spontaneous generation of electrical activity in patterned sequences (53), implying formation of complex interneural functions independently from external stimulation.
Investigating the relationship between fetal motor behaviour and development of the central nervous system, general movements have proven to be of major interest due to their early emergence, frequent occurrence and complexity. According to the definition, general movements are motor patterns in which all parts of the body are involved and may last from a few seconds to a minute. The sequence of arm, leg, neck and trunk movements which follow each other within one general movement is variable (42). In the human fetus, the first general movements, can be observed between 8 and 10 weeks gestational age (59). The character of general movements remains essentially unchanged until the second month after birth at term, after which the form alters (23, 40) in concert with other transformations within the central nervous system (40). This considerable consistency in pattern is remarkable when the morphological and neurophysiological changes that occur during the pre- and early postnatal period are taken into account.

In the human embryo, the first primitive myoneural junctions (containing acetyl choline esterase) in the intercostal muscle are shown at 8.6 weeks and in the tibialis anterior muscle at 10 weeks, while adult synapses (consisting of junctional folds) appear at 19 weeks (27). From these data it might be concluded that primitive nerve endings, probably in absence of acetyl choline esterase, are already capable of generating organized motor patterns such as general movements. Data from animal experiments have shown that as soon as the first neuro-muscular contacts are formed, secondary neuronal cell death takes place (37). In the human spinal cord, secondary neuronal cell death (causing a reduction of about 35% of the amount of motoneurons) occurs until the 25th week gestational age (20). After the first primitive axons have made contact with myoblasts, myotubes develop in the 5th week g.a. (18). In the course of the next 20-25 weeks the motor units differentiate into the adult pattern of fast and slow twitch characteristics (14, 15, 17). Data from animal studies (data in the human fetus are lacking) strongly suggest that this proces is paralleled by a regression of poly-neuronal innervation (for review see: 5). Yet, despite the above mentioned morphological and neuro-anatomical changes, no

alterations in the movement patterns can be observed. The early presence as well as the consistency of fetal movement patterns raise the question about their neuro-biological significance.

As coordinator and conductor of many studies concerning fetal motor behaviour (for review see: 41), Prechtl has suggested on the significance of fetal movements for their pre-adaptive function (40): 1. Fetal movements are essential in preventing adhesions and local stasis of circulation in the fetal skin. 2. Fetal movements may influence certain neuro-physiological processes. In animal experiments it has been shown that enhanced motor activity accelerates motoneuronal cell death (10, 37) and regression from poly-neuronal innervation (9), whereas hindered motor activity has the opposite effect. 3. Fetal movements may also contribute to the epigenetic shaping of the muscles (26, 51), as well as proper formation of bones and joints (12, 16, 21, 33). 4. Fetal movements might be anticipatory for postnatal function (such as eye movements and fetal breathing movements). It can be added that the proprioceptive information generated by movements and posture may also affect the motor activity of the central nervous system (45). In infants born in breech position, Prechtl and Knol (39) have shown an effect of mechanical restriction of the legs on certain neonatal leg reflexes (withdrawal reflex and magnet response).

In addition to the lacunary knowledge on expression of neuro-physiologically developmental changes in fetal movements, also relatively little is known about the clinical significance of fetal movements for assessment of the integrity of the fetal central nervous system. For this purpose, studies on fetal motor behaviour during undisturbed, low risk pregnancies are helpful. Regarding these studies, fetal motor behaviour can be characterized by two different aspects: the quantity and quality of fetal movements.

The quantity of fetal movements in uncomplicated pregnancy:

Formerly, the quantity of fetal movements has been assessed either by means of maternal counts of sensitive perception, or by means of piezo-electric crystals placed upon the maternal abdomen receiving fetal movement related frequencies. However both methods lacked direct visual access and no distinction between the different movement patterns could be made. After introduction of the ultrasound technique, de Vries et al. (59) studied the quantity of fetal motor behaviour, discerning 15 different movement patterns, among which: general movements, stretches, breathing movements and hic-ups.

During the first half of pregnancy, the quantity of general movements and fetal breathing movements appeared to increase (59). The increase of fetal breathing movements was found to continue until the third trimester of pregnancy (49). With respect to trends of general movements during the third trimester, results of studies are conflicting: both a considerable (49) or small (62) decrease, as well as an absent decrease (the latter based on "fetal activity" rates (47)) have been reported.

Reports on the quantity of fetal general- and breathing- movements might differ due to several confounding factors: 1. Large intra- and inter- individual variability in the quantity of fetal movements have been reported (49, 60, 62). 2. Design of the study. From about the 20th week onward, fetal activity is occurring in activity cycles which are alternated by periods of relative inactivity (61). This feature creates the necessity to extend recording times over at least 1 hour. 3. Standardization of the study. During the third trimester variation in the quantity of movements has been reported to be related to certain environmental factors such as: fetal breathing

movements depending on the maternal blood glucose levels during the third trimester (34, 35, 38) and general movements depending on the time of the day (48, 58, 61). This latter consideration underlines standardization of such studies as of critical importance.

The quality of fetal movements in uncomplicated pregnancies:

In contrast to the quantity of fetal (general- and breathing-) movements, which shows large intra- and inter-individual variability, the quality of fetal general movements is consistent during normal growth and maturation of the fetal central nervous system (43). The quality of general movements can be assessed by means of visual gestalt perception. According to Prechtl (43): "Normal general movements are performed fluently and show a smooth waxing and waning of intensity, and vary in speed and force. The movements of arms and legs are complex, consisting of extensions, flexions and superimposed rotations, and show slight directional changes (pp.152-153)." These optimal characteristics, which can be scored according to the quality evaluation sheet by Ferrari et al. (19), are consistently found in absence of pathology of the fetal central nervous system.

B. Prenatal motor behaviour as expression of the fetal and neonatal neurological condition of the fetus and newborn infant.

As fetal motor behaviour is endogenously generated, abnormalities within the central nervous system may express themselves in abnormal spontaneous motor activity. In contrast to responses after applied stimuli (pathological reflexes), spontaneous motor activity indeed appears easily affected by compromising conditions of the nervous system (43). Until now, research on the assessment of the prenatal neurological condition during fetal abnormalities has been focused predominantly on clinical applicability of quantitative standards. However, large inter- and intra- individual variability in fetal movements in the normal fetus (49, 60, 62) prevents quantification of fetal movements to be used as reliable diagnostic tool.

In contrast to quantity of fetal motor behaviour as a diagnostic tool, research on the quality of motor behaviour seems more promising. In a study concerning preterm infants, assessment of the quality of general movements proved to be a sensitive method to discriminate low-risk infants from those developing brain lesions, which were objectivated by repetitive brain scans and neurological examinations (19). In human fetuses, the first studies upon the quality of motor behaviour have been focussed on major neurological defects. In a study on anencephalic fetuses, Visser et al. (57) showed that fetal movements persist in a considerable quantity, even despite a severely defective nervous system. However, the quality of fetal general movements was highly abnormal, as they consisted of a large amplitude and a forceful and jerky character. In fetuses with chromosomal abnormalities similar alterations in the quality of unspecified fetal movements were suggested (8, 25). From these studies the question comes up whether the assessment of the quality (and/or quantity) of fetal movements can be used as a clinical indicator for less obvious and more insidious alterations within the fetal nervous system, such as during intra-uterine growth retardation (IUGR).

Intra-uterine growth retardation, defined as fetal growth below the 5th percentile on the Kloosterman curves (29), can be caused by placental dysfunction

resulting in a diminished fetal supply of oxygen and nutrients. Doppler ultrasound studies have shown that during ongoing reduction of the fetal nutritional supply, the blood flow to the fetal body and placenta may be reduced, coinciding with a relative increase of the blood flow to the fetal central nervous system (64, 65). Arduini and Rizzo (1) hypothesized that the reduction of blood flow to the fetal body, measured as an increase in the pulsatility index of the abdominal aorta, is associated with a decrease in urine output (36, 63) and may lead to oligohydramnios. Despite this redistribution in blood flow from the fetal body to the brain (a brain sparing effect), research has indicated that the neonatal neurological condition may still be impaired (7, 28, 31). After a chronically reduced supply of nutrients, experiments in rats have shown histological alterations within the central nervous system consisting of a reduction in: dendritic arborization, number of synapses, and number of glial cells (2, 11, 52).

In order to avoid sub-optimal growth and maturation of the central nervous system during IUGR on the one hand, and complications related to prematurity on the other hand, the detection of the precise moment at which fetal deterioration starts is essential, so that clinical intervention (caesarean section) may take place.

Research on the assessment of the human fetal condition in IUGR:

Before the widespread application of the ultrasound technique, the quantity of fetal movements was often assessed by means of subjective maternal counts. Using this method, in growth retarded fetuses, Sadovsky et al. (50) reported a reduced amount of fetal movements to coincide with a maternal perception of weak and rolling fetal movements. However, due to absence of the ultrasound technique, these descriptions could not be objectivated. After the introduction of the ultrasound technique, Bekedam et al. (3) reported after a cross-sectional study that the quantity of fetal movements shows a large inter- and intra- individual variation during intra-uterine growth retardation. This phenomenon resulted in a large overlap between data from growth retarded and normal fetuses. Only in those growth retarded fetuses suspected of fetal hypoxaemia, fetal body movements tended to be reduced (4). In contrast to quantity, quality of fetal general movements was consistently altered in severely growth retarded fetuses. During this condition, fetal general movements were scored as invariably slow and small (3, 4).

Manning et al. (30) designed fetal biophysical profile scores: a semi-quantitative method to evaluate the fetal condition during IUGR. The fetal biophysical profile consists of four variables, each of which can be scored as either normal or abnormal: fetal heart rate pattern, amount of amniotic fluid, quantity of fetal movements and fetal tone. Studies using the biophysical profile score provided evidence that with deterioration of the fetal condition, changes in fetal heart rate pattern appear before alterations in quantity of fetal movements and fetal tone (46, 55, 56). However, fetal tone (presence of active fetal limb or trunk extension and their return to flexion, or opening and closing of the fetal hand) does not comprise all contributions as the quality of fetal general movements does.

During ongoing fetal deterioration in IUGR, the amount of amniotic fluid around the fetus reduces, which results eventually in a relative absence of amniotic fluid or oligohydramnios. Until now, it is unclear whether movement restriction, possibly mediated by oligohydramnios, affects spontaneous fetal motor behaviour. Within this perspective, some characteristics of fetal movements can be attributable to fetal environment, instead to the fetal neurological condition. In infants born after

breech position (intra-uterine movement restriction of the legs), Prechtl and Knol (39) showed that prenatal environment can affect the neonatal pattern of (exteroceptive) leg reflexes. This observation may implicate a modulating influence of fetal environment upon the development of motor functions. Unfortunately, at the time of the study, no prenatal ultrasound recordings could be made to assess the actual extent and duration of the prenatal restriction of leg movements, and no follow-up data upon the duration of the postnatal effects on the motor system were reported.

Aim of the study:

Within the perspective of the referred literature, the aim of the thesis is formulated by the following questions:

- What is the longitudinal effect of an insidiously reduced supply (of oxygen and nutrients) of the human fetus on the quality of its general movements?
- What is the relationship between the quality of general movements and other clinical variables of the fetal condition and neurological outcome during and after an insidiously reduced fetal supply?
- Does the relationship between the quality and quantity of fetal general movements give information about the pathophysiological mechanisms during an insidiously reduced fetal supply?
- How specific are alterations within the quantity of fetal breathing movements as indicators for related pathology?
- What is the effect of intra-uterine movement restriction on the quantity and quality of general movements?
- Does intra-uterine movement restriction have a carry-over effect on the motor functions of the central nervous system during the first year of life?

The above mentioned questions are approached in a clinical study, using three different patient groups in which a longitudinal follow-up is performed extending over the pre- and post-natal period. The three groups are characterized by:
1. Intra-uterine growth retardation
2. Prolonged premature rupture of the membranes
3. Uncomplicated breech position

Contents:

- Chapter two describes the effect of an insidiously reduced fetal supply of oxygen and nutrients on the quality of general movements during development and maturation of the fetal central nervous system. Intra-uterine growth retardation due to reduced utero-placental circulation was chosen as a model for this study, as it provided the opportunity to study the relationship between a deteriorating fetal condition and the quality of general movements in absence of primary pathology of the central nervous system. The contents of chapter two concern longitudinal data on the quality of general movements in relation to other clinical variables of the fetal condition and neurological outcome.

- Chapter three concerns the same intra-uterine growth retarded cases as described in chapter two, but focuses on the relationship between the quality and quantity of

prenatal movements during intra-uterine growth retardation. In order to reveal underlying patho-physiological mechanisms, the quantity of general- and breathing-movements were studied both cross-sectionally and longitudinally. The longitudinal study relates the quantitative variables to gestational age and neurological outcome. The cross-sectional study relates the quantitative variables to 1. the fetal clinical condition during intra-uterine growth retardation, 2. the quantitative variables obtained from normal control fetuses and 3. the quantitative variables obtained in fetuses during intra-uterine movement restriction (due to premature rupture of the membranes).

- In chapter four the question is raised whether quantitative assessment of fetal movements can be specific enough to predict related postnatal function. Within this perspective, the quantity of fetal breathing movements is studied in pregnancies with an increased risk for pulmonary hypoplasia (pregnancies complicated by oligohydramnios due to premature rupture of the membranes).

- The effect of intra-uterine movement restriction on the quality of pre- and postnatal motor behaviour is described in the fifth chapter of this thesis. As a model for intra-uterine movement restriction, pregnancies complicated by premature rupture of the membranes in absence of further complications were studied. This complication of pregnancy can lead to leakage of amniotic fluid and thus result in a reduction of the amount of amniotic fluid around the fetus. Chapter five provides data on the quality of general movements during and after intra-uterine movement restriction, as well as the results of the neonatal neurological examination in these infants.

- Chapter six deals with the question whether intra-uterine movement restriction can have a long lasting (postnatal) carry-over effect on the motor functions of the central nervous system after undisturbed pregnancy. As experimental model for this study, cases with intra-uterine movement restriction of the legs due to intra-uterine breech position were investigated. Before birth, intra-uterine movement restriction of the legs was objectivated by means of repetitive ultrasound scans of intra-uterine (leg) position. After birth, the responses to exteroceptive stimulation of the legs, the preference posture and the achievement of neuro-developmental milestones (up to walking without support) were compared to those observed in control infants born in vertex position.

- In chapter seven the previous studies are placed within general perspectives and their potential diagnostic value for early prediction of neurological morbidity are discussed.

- Chapter eight contains the summary and conclusions of the study.

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CHAPTER 2

THE EFFECT OF INTRA-UTERINE GROWTH RETARDATION ON THE QUALITY OF GENERAL MOVEMENTS IN THE HUMAN FETUS.

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The effect of intrauterine growth retardation on the quality of general movements in the human fetus

D.A. Sival[a], G.H.A. Visser[b] and H.F.R. Prechtl[a]

[a]Department of Developmental Neurology and [b]Department of Obstetrics and Gynaecology, University Hospital
Groningen (The Netherlands)

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Summary

The effect of severe intrauterine growth retardation on the quality of general movements was studied longitudinally in 17 human fetuses. During the prenatal and postnatal periods, fetal movements were recorded by means of weekly 1 h ultrasound and video registrations. Neurological examinations were performed at 1, 3, 6 and 12 months after birth. No clear effect of uncomplicated intrauterine growth retardation could be detected on the quality of general movements. General movements became slow and small in amplitude (4/5) in cases where there was a reduction in the amount of amniotic fluid. Parallel to the onset of abnormal fetal heart rate patterns, general movements became poor in repertoire (7/7), while they were hardly discernible after further deterioration of the fetal condition (5/7). With the exception of 3 infants with cerebral haemorrhages, the quality of general movements observed just before and after birth was identical (13/16). In these infants, the quality of general movements as well as the results of the standardized neurological examination tended to normalize at 3 months and 1 year, respectively. Uncomplicated IUGR had no marked effect on the quality of general movements or on the results of the neurological examination at the age of 1 year.

Key words: fetal movements; movement quality; intrauterine growth retardation; low birth weight; neurological condition

Introduction

Intrauterine growth retardation (IUGR) may affect the postnatal neurological condition [11,23,26] and the neuro-developmental outcome [18,21,25,31,32]; for review see Allen [1]. The type of IUGR being dealt with here arises from placental dysfunction, resulting in a reduced fetal supply of oxygen and/or nutrients [20]. In severe cases of IUGR, Doppler ultrasound studies have shown a relative decrease in the blood flow to the fetal body and placenta [10,35,41] in combination with a relative increase of blood flow to the fetal head [47,48]. Despite this redistribution of blood flow from the fetal body to the brain, both human and animal studies have indicated that growth and maturation of the fetal central nervous system can still be impaired as a result of a severe reduction in the nutritional supply [6,13,38].

Previous studies have shown that the quality of particular movement patterns is a marker of the functional integrity of the fetal central nervous system [34]. On this basis, Bekedam et al. [7] studied movements in a group of 10 growth retarded fetuses and reported slow general movements with a reduction in force and amplitude compared to controls.

The pathophysiological mechanism(s) for an altered fetal neurological condition is still unclear. Speculations exist that a chronically reduced supply of oxygen and/or nutrients can lead to structural changes in the central nervous system which in turn result in an impaired neural development [7].

Recently, we demonstrated in fetuses with premature rupture of the amniotic membranes that the speed and amplitude of general movements were highly correlated with the amount of amniotic fluid [37]. As a reduction in the amount of amniotic fluid is one of the complications of IUGR, a distinction should be made between the effects of IUGR itself on movement and those arising from complications related to IUGR. In the present longitudinal study, we investigated the relationship between the quality of general movements and several clinical variables indicative of the fetal condition (e.g. altered blood flow velocity waveforms, reduced amount of amniotic fluid and abnormal fetal heart rate patterns). In addition, we studied the relationship between the quality of prenatal and postnatal general movements as well as the early neonatal condition and subsequent neurological outcomes. These longitudinal data are of clinical relevance as they directly reflect the developmental course of central nervous system functioning in relation to fetal and neonatal clinical deterioration. Furthermore, such data might lead to more accurate predictions of neurological condition after birth.

Patients

Seventeen women with intrauterine growth retardation (IUGR) and singleton pregnancies volunteered to participate in this study and gave their informed consent. Selection criteria were placental dysfunction, suggested by an increased pulsatility index (PI) as measured in the umbilical artery (present from the first recording onwards); together with an estimated fetal growth $< P5$ (abdominal area, abdominal circumference). Cases have been kept in the research group only if their birth weight was $< P5$ according to the Dutch Kloosterman growth curves [24], corrected for

TABLE I

Clinical data.

Case	Maternal age	Parity	Other clinical complications	G.A. at delivery[a]	Birth weight		Apgar scores	Acidaemia[b]
					(g)	(%)		
1	32	0	—	28	400	<P2.3	†	†
2	34	0	PIH*[c]	29	870	<P5	1^1:2, 3^1:4	Yes
3	22	I	PIH*	29	785	<P5	1^1:3, 3^1:7	No
4	37	I	—	29	700	<P5	1^1:3, 3^1:6	No
5	27	II	PIH	29	740	<P2.3	1^1:1, 3^1:6	No
6	28	II	PIH*	30	505	<P2.3	1^1:2, 3^1:2	No
7	25	0	—	31	915	<P5	1^1:5, 3^1:8	Yes
8	25	0	—	31	890	<P2.3	1^1:3, 3^1:9	No
9	38	I	—	31	900	<P5	1^1:3, 3^1:5	No
10	33	0	PIH	31	900	<P5	1^1:6, 3^1:9	Yes
11	24	0	PIH	32	860	<P2.3	1^1:8, 3^1:9	No
12	25	0	PIH	33	1200	<P5	1^1:3, 3^1:5	No
13	26	I	Vaginal blood loss	34	1275	<P5	1^1:8, 3^1:9	No
14	26	I	—	34	1130	<P5	1^1:7, 3^1:9	No
15	23	0	PIH	34	1210	<P5	1^1:8, 3^1:8	No
16	27	0	PIH*	36	1530	<P5	1^1:9, 3^1:10	No
17	37	0	—	38	2285	<P5	1^1:9, 3^1:10	No

[a]G.A., Gestational age in weeks.
[b]pH_a < 7.15 and/or pH_v < 7.20.
[c]PIH, Pregnancy induced hypertension; PIH*, anti-hypertensive drugs used.
†Intrauterine death.

parity and sex. We excluded cases with: congenital malformations or chromosomal defects, alcohol or drug addiction, anti-epileptic medication, type I diabetes mellitus, and intrauterine infections.

All the women were admitted to the obstetric ward of the University Hospital Groningen. Eight had a pregnancy induced hypertension and one repetitive vaginal blood loss. Four women used antihypertensive drugs (Labetalol). No other medication was prescribed. Two women were delivered vaginally, one case (case 1) with an intrauterine death and the other (case 17) spontaneously. The latter was the only case with a normal antenatal and intrapartum fetal heart rate pattern. All other women were delivered by primary caesarean section because of abnormal antenatal fetal heart rate records (late decelerations and/or reduced heart rate variability). The clinical data are summarized in Table I.

Methods

Before birth, movements were recorded weekly on video-tape by means of continuous real-time ultrasound registrations of 60 min duration each (linear array; Acuson and Aloka, probe sizes 8.4 and 9.6 cm, respectively). In the case of fetal jeopardy, daily recordings were made. Weekly, an ultrasonographer who was not involved in the study, classified the amount of amniotic fluid independently. A reduction of the amount of amniotic fluid was diagnosed when the largest diameter of an amniotic fluid pocket measured < 2 cm. The fetal heart rate patterns were monitored for about 1 h, 1–3-times a day (Hewlett Packard 8040 A). Fetal heart rate patterns were analyzed by clinicians unaware of the results of the ongoing research on the movement quality. A normal reactive heart rate pattern was characterized by a basal heart frequency of 110–160, presence of accelerations and absence of decelerations. Fetal heart rate patterns were considered abnormal if they were outside this range [44]. The Doppler velocity waveforms were related to a reference curve from the Department of Obstetrics and Gynaecology, University Hospital Groningen [9]. An increase of the pulsatility index of the umbilical artery $\geq$ P97 was considered abnormal.

The quality of general movements was assessed by means of visual gestalt perception. According to Prechtl [34]: 'General movements are motor patterns in which all parts of the body are involved and may last from a few seconds to a minute. The sequence of arm, leg, neck and trunk movements which follow each other within one general movement is variable. Normal general movements are performed fluently and show a smooth waxing and waning of intensity, speed and force. They vary in speed and amplitude. The movements of the arms and legs are complex, consisting of extensions, flexions, and superimposed rotations, and often show slight directional changes.' (pp. 152–153).

Abnormal general movements lack one or more of these characteristics and have been described in fetuses and neonates with various pathologies [7,17,22,37,42]. Two observers assessed the quality of the general movements independently, one without any prior information on the clinical condition. Inter-observer agreement was, using kappa [19]: 0.90 ± 0.07. In order to evaluate the quality of the general movements, 3 general movements from each 1-h recording were chosen on the basis of the longest

duration and best expression and copied on a second video-tape. The new section was put on this tape, following the three general movements from the previous recording. In this way any bias on the basis of eventually abnormal quantity of GMs during 1 h was avoided for the second observer. In the case of inter-observer disagreement, the recording was discussed and re-scored during the replay of the tape.

In the neonatal period, the quality of general movements was studied in a similar way to that during the prenatally, by means of weekly, 1-hour video recordings. All the infants were in a supine or semi-lateral position and recorded under standardized conditions. Factors possibly affecting the infant's movements were carefully documented. None of the newborn infants (n = 16) received sedative drugs. In eleven cases artificial respiration was applied, and in all except two cases (cases 2 and 7) adequate blood gases and or transcutaneous Po_2 levels were obtained during all recordings. In the latter 2 cases a partial lung hypoplasia and a hyaline membrane disease (grade III–IV) were diagnosed, respectively. Both cases died within the first postnatal week with a severe respiratory insufficiency. Standardized neurological examinations were performed 1, 3, 6 and 12 months postpartum.

Results

Relationships between the quality of prenatal general movements and several clinical variables of the fetus

Individual trajectories of all the cases were obtained by (longitudinal) assessments of the quality of the general movements. Afterwards, this information was compared to that of (other) variables of the fetal condition (three examples are shown in Fig. 1). As clinical observations were sometimes made on other days than the registrations of fetal movement, differences in time between points of comparison could occur up to a maximum of 3 days (Fig. 1). Figure 2, in which the quality of general movements is shown in relation to specific clinical conditions, was obtained by combining all the individual trajectories (ignoring the delays of 1–3 days).

In cases with a relatively undisturbed fetal condition (no other signs than reduced growth and an increased pulsatility index) the quality of general movements was assessed as normal in 7 out of the 8 cases. In 5 out of 6 cases, a reduced amount of amniotic fluid coincided with slow general movements, which were additionally small in amplitude. After the onset of abnormal fetal heart rate patterns (fetal heart rate decelerations and/or reduced heart rate variability) a poor repertoire was scored in all the fetuses, while the relationship between speed, amplitude and amount of amniotic fluid remained. In 7 fetuses there was a further flattening of the heart rate trace with recurrent heart rate decelerations just prior to delivery, indicating a further deterioration of the fetal condition. In 5 of these fetuses general movements became so limited in speed and amplitude that they were hardly discernible.

Relationship between the quality of general movements and the perinatal clinical condition

Admission to the neonatal intensive care unit. All infants except one (case 17) were admitted to the neonatal intensive care unit. The quality of general movements was

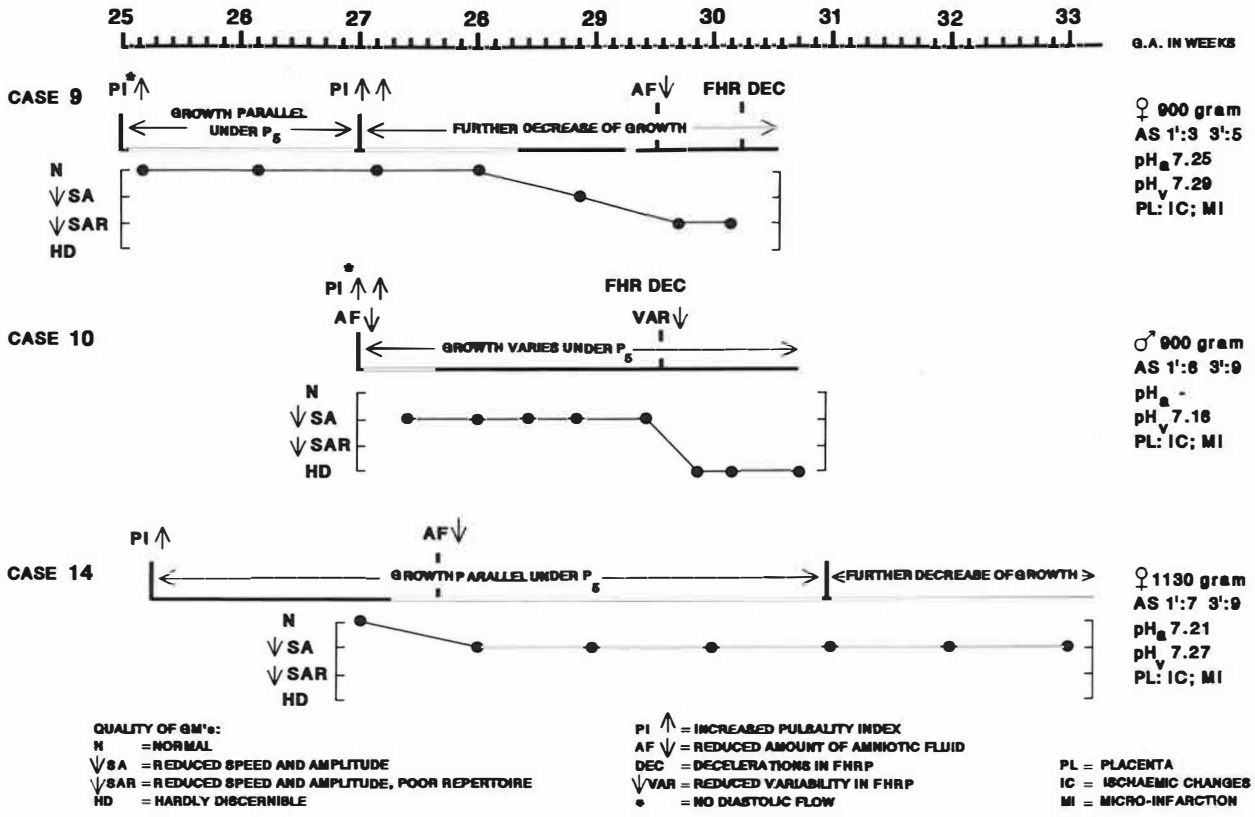

Fig. 1. Three different individual trajectories associated with IUGR. In case 14 fetal heart rate decelerations and immediate delivery occurred directly after the last movement recording.

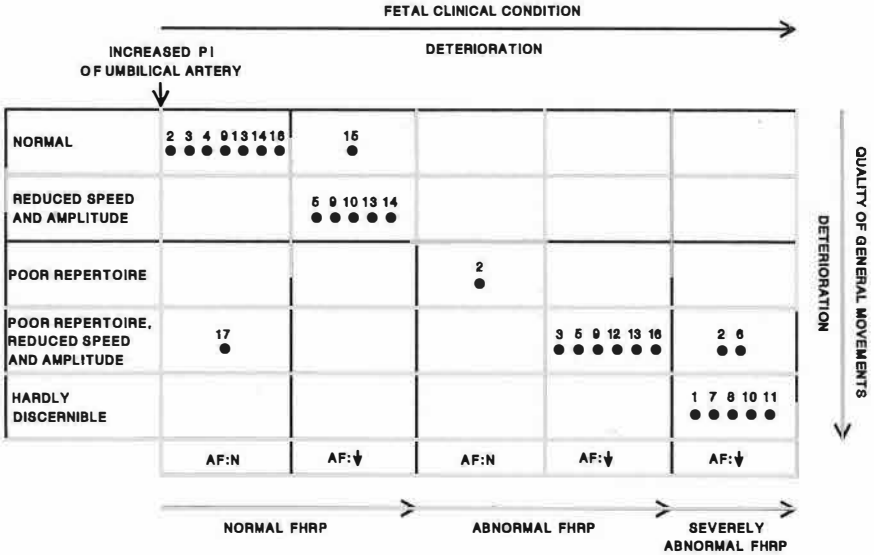

Fig. 2. Relationship between the quality of general movements and indices of fetal clinical condition. All the fetuses entered the study at a certain point on the horizontal axis indicating the fetal clinical condition and were followed longitudinally upon deterioration (indicated by the horizontal arrow from the left to the right). On the vertical axis the quality of general movements is indicated. Each combination of the quality of general movements and the clinical condition is represented by a dot. Case numbers are indicated above each dot.

not statistically significantly related to the duration of the admission to the neonatal intensive care unit.

Low Apgar scores and acidaemia at birth. Both the occurrence of low Apgar scores and the incidence of acidaemia were more evident in the newborns with the most disturbances in fetal movement (Table II), but these relationships were not statistically significant (Fisher's exact probability test).

Neonatal movement quality. In 13 of the 17 cases, the quality of general movements was identical before and after birth (Fig. 3). One intrauterine death occurred and in three other cases (cases 3, 4 and 8) postnatal general movements were scored as abrupt and synchronized. In these three neonates cerebral haemorrhage was diagnosed.

Later (postnatal) movement quality and neurological evaluations

The neonatal quality of general movements in relation to the quality at 10 weeks chronological age as well as the results of the neurological evaluations are shown in Table III. Although follow-up was not complete, a trend towards normalization was observed in both the quality of general movements (up to 10 weeks) and for the outcomes of the standardized neurological examinations (up to 1 year), excluding perinatal deaths and periventricular haemorrhages.

TABLE II

The quality of prenatal general movements and indices of perinatal clinical condition (N, normal GMs; ↓ SA, GMs with reduced speed and amplitude; ↓ SAR, GMs with reduced speed and amplitude, poor repertoire; HD, hardly discernible).

Prenatal general movements < 1 week before birth	Low Apgar scores $1^1 < 7$ and/or $3^1 < 7$	Acidaemia $pH_a < 7.15$, $pH_v < 7.20$
N (n = 2)	– (1)	– (2)
	+ (1)	
↓ SA (n = 1)	– (1)	– (1)
↓ SAR (n = 9)	– (3)	– (8)
	+ (6)	+ (1)
HD (n = 5)	– (1)	– (2)
	+ (3)	+ (2)
	† (1)	† (1)

–, absent; +, present.
†Intrauterine death.

Discussion

Prenatal relationship between the quality of general movements and other indices of fetal condition

In 7 out of 8 growth retarded fetuses, no abnormalities in the quality of general movements were observed before a reduction in the amount of amniotic fluid or the occurrence of abnormal fetal heart rate patterns. These results indicate that uncomplicated intrauterine growth retardation as such does not necessarily affect the quality of general movements. Furthermore, the presence of an increased PI of the umbilical artery in these fetuses clearly showed that this phenomenon precedes changes in the quality of movement. Under the condition of a reduced fetal supply of oxygen and/or nutrients, a decrease in the PI of the carotid artery is hypothesized to have an adaptive function, favouring blood supply to the fetal central nervous system [2,16]. In the light of our results, such a redistribution could indicate that an early reduction in the supply to the fetus has no influence on the quality of general movements, either due to the capacity of the central nervous system to adapt to such circumstances or due to a compensatory redistribution of blood flow from the fetal body to the central nervous system.

This study shows that with IUGR, the amount of amniotic fluid is related to a decrease in the speed and amplitude of general movements. Oligohydramnios together with intrauterine growth retardation is described as coinciding with an increase in the PI of the abdominal aorta [4] and with a reduced fetal urine output [29,46]. Arduini et al. [4] outlined a connection between the latter two events, in suggesting that a reduced renal blood flow (due to blood flow redistribution) can lead to a decrease in urine output and to the onset of oligohydramnios. Previously, we reported a close relationship between a reduction in the amount of amniotic fluid and general movements with reduced speed and amplitude in low risk pregnancies

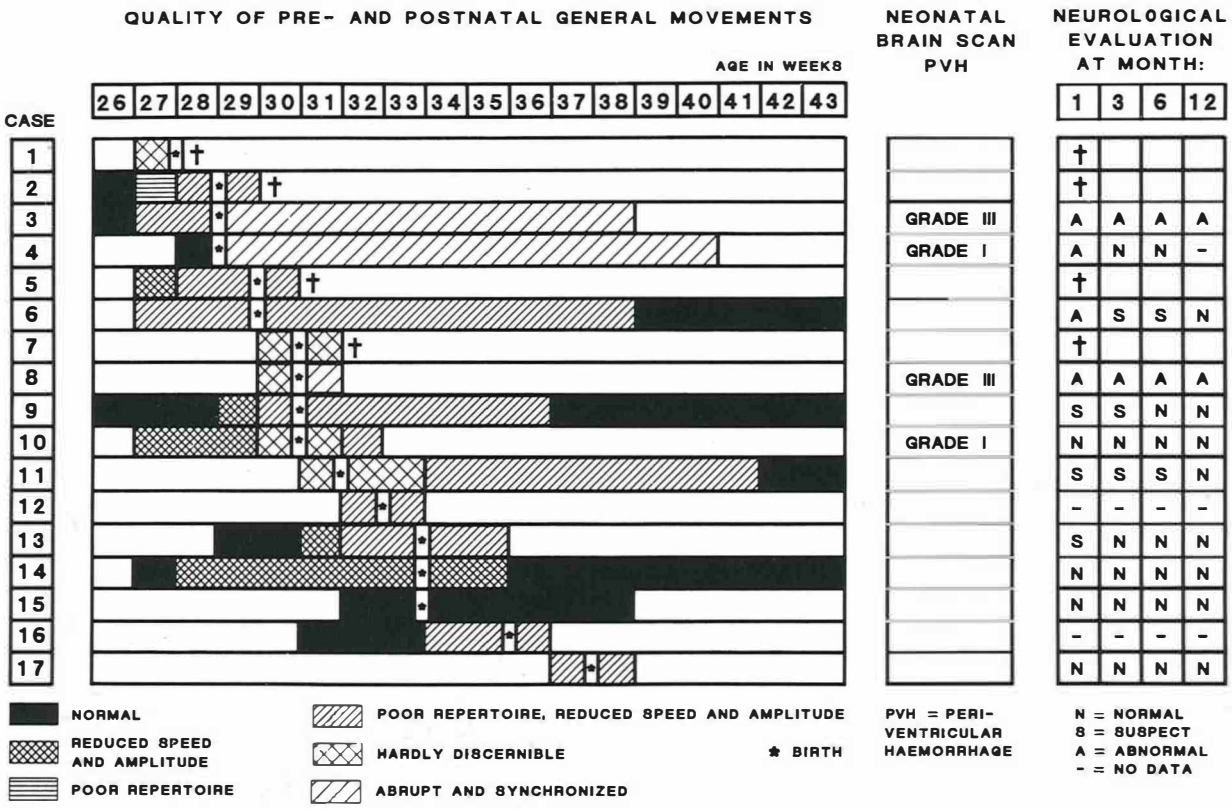

Fig. 3. The quality of general movements. neonatal brain scans and the outcomes of the standardized neurological evaluations.

TABLE III

The quality of postnatal general movements and the outcomes on a standardized neurological examination at 1 year (NR, normal repertoire; 1 SAR, GMs with reduced speed and amplitude, poor repertoire; HD, hardly discernible; A, abrupt and synchronized GMs).

Postnatal general movements 1 week after birth	Postnatal general movements at 10 weeks	Neurological examination at 1 year
NR (n = 2)	2 Normal	2 Normal
1 SAR (n = 8)	4 Not examined	2 Not examined
	2 Normal	4 Normal
	2 †	2 †
HD (n = 3)	1 Not examined	
	1 Normal	2 Normal
	1 †	1 †
A (n = 3)	1 Not examined	1 Not examined
	2 Abnormal	2 Abnormal

†Intrauterine death.

[37]. In the present study, the same characteristics of diminished speed and amplitude were found in intrauterine growth retardation. This suggests that a reduced amount of amniotic fluid directly affected the speed and amplitude of general movements. However, impairment of neurological development cannot be ruled out, since extensive blood flow redistribution is likely to be associated with a markedly reduced supply of nutrients. The same holds for the (strong) association that was found between the occurrence of abnormal fetal heart rate patterns and a poor repertoire of general movements. As the occurrence of abnormal fetal heart rate patterns coincides with fetal hypoxaemia [8,28,44], it is tempting to speculate that oxygen deprivation is at least partly responsible for the poor movement repertoire. However, recent cordocentesis data have shown that such fetuses suffer not only from hypoxaemia but also from chronic hypoglycemia and deprivation of essential amino acids [14,15]. The poor movement repertoire may, therefore, also be an expression of impaired neurological development. Support for this reasoning is rendered by the morphological findings in human growth retarded infants and in animal models where a smaller brain size, fewer neurones, deficits in synapse to neurone ratios and reduced dendritic growth have been found [6,13,38]. Moreover, even if the poor repertoire was due to hypoxaemia alone, restoration of movements would be expected to occur directly after birth when the oxygen supply is restored. However, the poor repertoire continued for some time after birth. It also has been found that neonatal neurological morbidity in growth retarded fetuses is largely restricted to those who antenatally showed signs of hypoxaemia (and malnutrition) [12,43].

Another aspect of neurological dysfunction in growth retarded fetuses is a delay in the development of behavioural states [45]. Van Vliet et al. [45] found a delay in the synchronization of state transitions. These observations have been confirmed by Arduini et al. [3] and extended by Rizzo et al. [36]. The normally occurring synchronization of coincidence around 36 weeks was delayed for several weeks. It should be mentioned that these observations relate to the near term growth retarded

fetus. However, Arduini [5] recently presented data indicating that also in preterm fetuses with late decelerations a relative increase in no coincidence precedes the occurrence of signs of fetal hypoxaemia. These data suggest that impairment of neurological development occurs before hypoxaemia becomes evident and thereby underline the effect of malnutrition on brain development. When comparing these data with our findings one may conclude that abnormalities in the development of behavioural states precede those in the quality of general movements.

Relationship between the quality of prenatal movement, Apgar scores and pH values at birth

Although no statistically significant difference could be detected, a trend in the relationship between pH values and movement quality seemed to be present. No acidaemia was found in the fetuses with normal general movements, whereas after the reduction in complexity the number of cases with acidaemia increased from 1 out of 9 fetuses to 2 out of 4 with hardly discernible general movements. Previously, we found in IUGR fetuses (of whom the majority was delivered by primary caesarean section) a significant relationship between pH at birth and neonatal neurological morbidity [12,43]. However, this significance stemed mainly from the fact that they were two study populations: one with antenatal fetal heart rate decelerations and one without. Morbidity was largely restricted to the former and within that subgroup no relationship between neurological morbidity and pH at birth was present. Signs of antenatal hypoxaemia (and of malnutrition) are, therefore, more important than the actual pH value at birth. In the light of these findings, it can be explained why no significant relationships were found between movement quality and pH in the present study, in which all but one of the fetuses had antenatal heart rate decelerations.

Comparison of the quality of prenatal and postnatal general movements with the results of the standardized neurological examinations

Excluding neonates with cerebral haemorrhages, the same characteristics in the quality of general movements were observed before and after birth (Fig. 3). This finding is in agreement with previous research on the relationship between prenatal and postnatal movements involving preterm infants [33]. All cases lacking a continuity in the quality of prenatal and postnatal general movements, suffered periventricular hemorrhages and/or leucomalacia, and in all the quality of postnatal general movements was abnormal. The same types of abnormal general movements have been described in infants with cerebral lesions [17].

In the cases studied, a normal quality of general movements by the third month was followed by a normal neurological examination at 1 year. However, although the neurological outcome at 1 year revealed no major deficits in the majority of cases, it is still possible that follow-up until early school age may reveal neurodevelopmental abnormalities [21,27,30,39,40].

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CHAPTER 3

THE RELATIONSHIP BETWEEN THE QUANTITY AND QUALITY OF PRENATAL MOVEMENTS IN PREGNANCIES COMPLICATED BY INTRA-UTERINE GROWTH RETARDATION AND PREMATURE RUPTURE OF THE MEMBRANES.

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The relationship between the quantity and quality of prenatal movements in pregnancies complicated by intra-uterine growth retardation and premature rupture of the membranes

D.A. Sival[a], G.H.A. Visser[b] and H.F.R. Prechtl[a]

[a]*Department of Developmental Neurology, University Hospital, Groningen and* [b]*Department of Obstetrics and Gynaecology, University Hospital, Groningen, (Netherlands)*

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Summary

In 17 fetuses with intrauterine growth retardation (IUGR), we studied the quantity of general movements and fetal breathing movements both cross-sectionally and longitudinally. In IUGR fetuses, cross-sectional comparisons were made between the quantity of fetal movements and (1) the fetal clinical condition and (2) the quality of general movements. In addition, the quantity of fetal movements in IUGR was compared with that in uncomplicated pregnancies and in pregnancies complicated by premature rupture of the amniotic membranes. In IUGR, the quantity of general movements declined from 25 weeks gestation onwards, whereas the quantity of fetal breathing movements increased. Longitudinal assessment of these parameters was obtained in four cases and showed a decline of general movements. No relationship between prenatal longitudinal data and neonatal outcome could be observed. Relating the quantity of general movements and breathing movements to the fetal condition, growth retarded fetuses were divided into three groups according to fetal deterioration. 1. Normal amount of amniotic fluid and normal fetal heart rate patterns. 2. Reduced amount of amniotic fluid. 3. Abnormal fetal heart rate patterns. The quantity of general movements as well as that of breathing movements was low in group 3, compared to group 1. In group 2 only the quantity of breathing movements and not of general movements was low. A similar pattern was found in the relation with the quality of general movements observed during fetal deterioration. Cross-sectional analysis of median values (28–31 weeks gestation) did not reveal differences in the quantity of general movements when IUGR, normal

pregnancies and premature rupture of the membranes (with or without oligohydramnios) were compared. The quantity of fetal breathing movements was significantly lower in pregnancies complicated by IUGR and by premature rupture of the membranes with oligohydramnios compared to those of normal pregnancies and premature rupture of the membranes without oligohydramnios. In uncomplicated IUGR, the quantity of general movements and breathing movements is in the same range as in normal uncomplicated pregnancies. Similar to the quality of general movements, the quantitative variables were related to the fetal condition. However, in contrast to the quality of general movements, the quantity of general movements and breathing movements showed a high inter- and intraindividual variation. Therefore, the results of this study discourage the use of quantitative aspects of general movements and breathing movements as reliable indicators of the neurological condition in the individual fetus.

Key words: intra-uterine growth retardation; fetal movements; movement quality; premature rupture of the membranes; fetal hypoxaemia

Introduction

Studies on the assessment of the fetal condition during intra-uterine growth retardation (IUGR) have shown that a chronically reduced supply of oxygen and nutrients can affect fetal behaviour [2,4,26,31]. These studies are of particular interest as they might help in the understanding of the patho-physiological mechanisms during IUGR and aid in the detection of the moment when deterioration of the fetal condition starts. With respect to the quantity of fetal movements, Bekedam et al. [4] showed that the incidence of movements during IUGR was low in comparison with controls. However, this cross-sectional study revealed a high inter-individual variability in the quantity of fetal movements as well as a considerable overlap between both groups. Therefore, no individual distinction between normal and growth-retarded fetuses on the basis of the quantity of fetal movements could be made.

The assessment of the quality of general movements (GMs) has been proven to be a valuable method of assessing the neurological condition in the infant [21]. In the growth-retarded fetus the quality of general movements can function as a marker for the fetal condition [26]. During uncomplicated IUGR, a normal quality of fetal general movements was found whereas general movements became small and slow after a reduction of the amount of amniotic fluid was diagnosed. The first abnormalities in the fetal heart rate patterns were related to a reduction in repertoire (i.e. reduction in complexity of GMs). During further deterioration of the fetal condition (indicated by fetal heart rate decelerations, reduced heart rate variability and a reduction of the amount of amniotic fluid), general movements became hardly discernable. It is still unknown how these changes of the quality relate to the quantity of general movements. In addition, it remains to be seen whether a distinction can be made between IUGR and control fetuses after relating the quantity of fetal movements to the different degrees of fetal deterioration during IUGR.

The aim of this study is to evaluate the clinical use of quantitative assessment of fetal motility during the various stages of IUGR. In this context the following questions arise: What are the differences in the quantity of GMs and fetal breathing movements (FBMs) comparing IUGR with control pregnancies and pregnancies complicated only by oligohydramnios? How does the quantity of GMs and FBMs in the growth-retarded fetus relate to changes in the qualitative assessment?

Patients

A. IUGR group

The IUGR group consisted of 17 cases in which 54 recordings were made. Maternal ages varied from 23 to 38 years. The same cases are described in a previous publication on the relationship between quality of GMs and fetal condition during IUGR [26]. All cases were admitted at the obstetrical ward of the University Hospital, Groningen, and were selected according to the following criteria: uteroplacental insufficiency, suggested by an increased pulsatility index (PI) in the umbilical artery (present from the first recording onwards); together with an estimated fetal growth $<$P5 (abdominal area, abdominal circumference, femur length; corrected for parity and sex [14]). We excluded cases with: congenital malformations or chromosomal defects, alcohol or drug addiction, anti-epileptic medication, type I diabetes mellitus and intra-uterine infections. Two cases were excluded after birth because their birth weight was $>$P5.

In eight pregnancies of the study group, a normal amount of amniotic fluid was found on admission. All but one of these cases (case 17) developed a reduction in the amount of amniotic fluid during the study period. The remaining nine cases presented a reduction of the amount of amniotic fluid at the first recording. Eight women of the study group had a pregnancy-induced hypertension and one had repeated vaginal blood loss. Four women used antihypertensive drugs (labetalol). No other medication was prescribed. Two women delivered vaginally, one case (case 1) induced after fetal death and the other (case 17) spontaneously. The latter was the only case with a normal antenatal and intrapartum fetal heart rate pattern. All other women were delivered by primary caesarean section after development of abnormal antenatal fetal heart rate records (late decelerations and/or reduced heart rate variability). In all but one case (case 2, one data point between 28 and 32 weeks) a reduction in the amount of amniotic fluid preceded the onset of abnormal fetal heart rate patterns. Additional clinical data are summarised in Table I.

B. Normal and PROM groups

Between 28 and 32 weeks gestation, cross-sectional comparisons were made between IUGR (13 cases; 31 recordings) and three control groups:

1. A normal control group (14 cases, 14 recordings): uncomplicated pregnancies with a normal amount of amniotic fluid
2. Premature rupture of the membranes (PROM, 6 cases, 10 recordings) with a normal amount of amniotic fluid
3. Premature rupture of the membranes (PROM, 9 cases, 19 recordings) with oligohydramnios.

TABLE I

Clinical data.

Case	Parity	Other clinical complications	GA at 1st recording	GA at delivery	Birth weight		Apgar scores	Acidaemia[a]
					g	%		
1	0	—	27	28	400	<P2.3	†	†
2	0	PIH[b]	26	29	870	<P5	1^1:2, 3:4	+
3	I	PIH[b]	26	29	785	<P5	1^1:3, 3^1:7	–
4	I	—	29	29	700	<P5	1^1:3, 3^1:6	–
5	II	PIH	27	29	740	<P2.3	1^1:1, 3^1:6	–
6	II	PIH[b]	27	30	505	<P2.3	1^1:2, 3^1:2	–
7	0	—	30	31	915	<P5	1^1:5, 3^1:8	+
8	0	—	29	31	890	<P2.3	1^1:3, 3^1:9	–
9	I	—	25	31	900	<P5	1^1:3, 3^1:5	–
10	0	PIH	27	32	900	<P5	1^1:6, 3^1:9	+
11	0	PIH	31	32	860	<P2.3	1^1:8, 3^1:9	–
12	0	PIH	32	33	1200	<P5	1^1:3, 3^1:5	–
13	I	Vaginal blood loss	29	34	1275	<P5	1^1:8, 3^1:9	–
14	I	—	30	34	1130	<P5	1^1:7, 3^1:9	–
15	0	PIH	33	34	1210	<P5	1^1:8, 3^1:8	–
16	0	PIH[b]	31	36	1530	<P5	1^1:9, 3^1:10	–
17	0	—	37	38	2285	<P5	1^1:9, 3^1:10	–

PIH, pregnancy induced hypertension; GA, gestational age in weeks.
[a]pH_a <7.15 and/or pH_v < 7.20.
[b]Anti-hypertensive drugs.
†Intrauterine death.

Excluded from the control groups were cases with clinical evidence of infection, fever (temperature >38°C), leucocytosis or the sudden appearance of immature forms of white cells, pregnancy induced hypertension, intrauterine growth retardation (based on fetal abdominal area measurements below the 10th percentile), congenital or chromosomal defects, use of sedative drugs, alcohol or drug addiction, and fetal distress (based on late decelerations or loss of heart rate variability).

Methods

In 17 growth-retarded fetuses, the quantity of fetal general movements (%GMs) and breathing movements (%FBMs) was studied both longitudinally and cross-sectionally. Cross-sectional comparisons were made between the quantity of fetal movements in IUGR and: (1) the quality of GMs (see Ref. 26) and other variables of the fetal condition in IUGR and (2) the quantity of fetal movements in three control groups (normal uncomplicated pregnancies, PROM without oligohydramnios and PROM with oligohydramnios). The quantity of GMs (%GMs) in IUGR was further explored by studying its relationship with the incidence (number/hour) and mean duration of GMs.

A. Recordings

Fetal motor behaviour was recorded weekly by means of continuous realtime ultrasound registrations of 60 min duration each (linear array; Acuson and Aloka, probe sizes 8.4 and 9.6 cm, respectively). All ultrasound registrations were recorded on videotape for off-line analysis of the quality of GMs and for the quantity of GMs and FBMs. If possible, recordings were standardised for the time of the day and maternal meals.

B. Assessment of fetal movements

Quantity of fetal movements. The quantity of general movements and breathing movements was scored by means of the keyboard of a personal computer which was synchronized with the videotape. Of each GM the time of on- and off-set was indicated. As only a part of the fetus could be visualized (due to the small size of the transducer compared to the body size of the fetus) and as succeeding GMs are separated by a pause, a moving window (of 10 s) was applied. This means that general movements were assigned to a single episode when they followed each other within 10 s. From these data the quantity (in % of time), incidence (in number/h and number/10 min) and median value of duration (in seconds) of GMs in each recording were obtained. Finally, we also obtained the quantity of GMs in IUGR after removal of the moving window and the results were compared. Breathing movements were assigned to a single bout (epoch) within a breath-to-breath interval of 6 s and were calculated in % of time. Cross-sectional comparisons were performed on median values derived from >4 cases obtained between 28–31 weeks gestation. Using median values, each case was given the same statistical weight, irrespective of the number of recordings performed in each case. For statistical evaluation, we used the Kruskal Wallis and Mann-Whitney rank-sum test.

Quality of general movements. The quality of GMs was assessed by means of visual Gestalt perception (for description see Ref. 21). In a previous publication [26] on the quality of general movements (GMs) in growth-retarded fetuses we described the existence of a strong relationship between the quality of GMs and other parameters of the fetal condition. The following qualitative criteria were distinguished which coincided with fetal deterioration during IUGR: (1) normal GMs, (2) GMs with reduced speed and amplitude, (3) GMs with reduced speed, amplitude and repertoire, and (4) hardly discernible GMs.

C. Fetal condition

In this study, the following criteria of fetal deterioration have been distinguished: (1) uncomplicated IUGR, (2) reduced amount of amniotic fluid, and (3) abnormal fetal heart rate patterns and a reduction of the amount of amniotic fluid. In contrast to the preceding study [26], the first signs of abnormalities of the fetal heart rate patterns were not taken as a separate category because of limited numbers. Therefore, fetal heart rate patterns were subdivided into two groups: normal or abnormal.

Fetal heart rate patterns were monitored two to three times per day lasting 1 h (Hewlett Packard 8040 A) and were analyzed by clinicians who were not involved in the study. According to Visser et al. [30], a normal reactive heart rate pattern was characterized by a basal heart rate of 110–160, presence of accelerations (≥ 10 beats/min) and absence of decelerations (late decelerations defined as ≥ 10 beats/min

or variable decelerations defined as ≥20 beats/min lasting more than ≥60 s). Fetal heart rate patterns were considered as abnormal if recurrent fetal heart rate decelerations and/or a constantly reduced heart rate variability were present.

The amount of amniotic fluid was estimated weekly by an ultrasonographer who was not involved in the study. The following criteria were applied: a normal amount of amniotic fluid (when the largest diameter of an amniotic fluid pocket was 2 cm or more); reduced amount of amniotic fluid (when the largest diameter of an amniotic fluid was between 1 and 2 cm); oligohydramnios (when the largest diameter of an amniotic fluid pocket was smaller than 1 cm).

The Doppler velocity waveforms were related to a reference curve from the Department of Obstetrics and Gynaecology, University Hospital, Groningen [7]. An increase of the pulsatility index of the umbilical artery above the P97 was considered as abnormal.

Results

1. Cross-sectional and longitudinal data of the quantity of general movements and breathing movements in 17 growth retarded fetuses

From the 25th week of gestational age onwards, the quantitative aspects of general movements (%GMs, number GMs/h and mean duration of GMs), declined with gestational age (Figs 1a and 2), whereas the quantity of fetal breathing movements (% FBMs) increased with gestational age (Fig. 1b). These trends were confirmed after relating the %GMs and %FBMs to gestational age in IUGR during a relatively uncomplicated condition (before signs of reduction of the amount of amniotic fluid

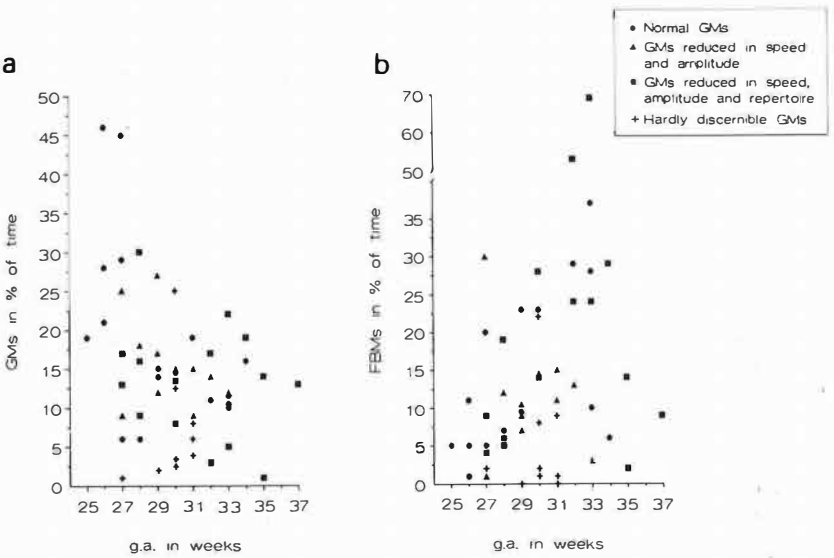

Fig. 1. Relationship between %GMs and gestational age (a) and between %FBMs and gestational age (b) according to the four different qualitative movement categories.

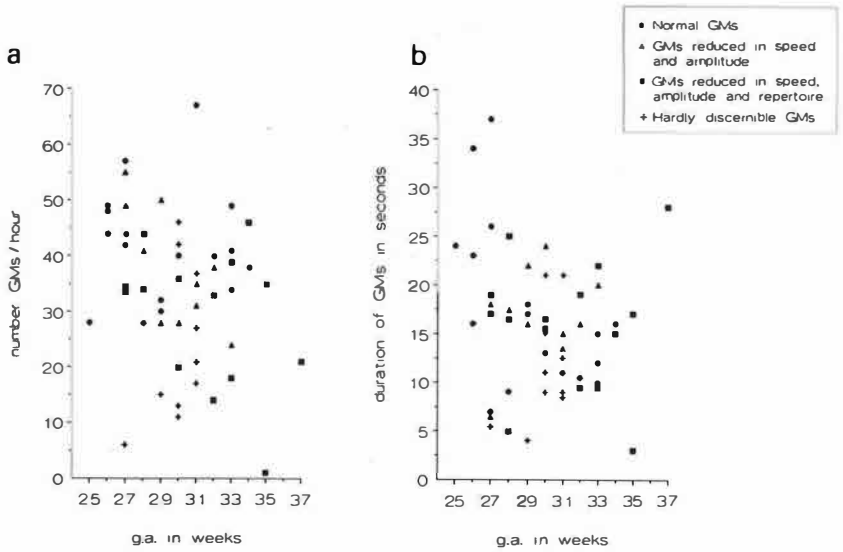

Fig. 2. Relationship between incidence of GMs (number/h) and gestational age (a) and between duration of GMs and gestational age (b) according to the four different qualitative movement categories.

or the onset of abnormal fetal heart rate patterns). Furthermore, a wide scatter of the percentages (of GMs as well as FBMs) could be observed, even after subdividing the recordings according to the quality of GMs (that is strongly related to the fetal condition [26]).

As the large scatters of the cross-sectional data could reflect both inter- as well as intraindividual variation, we separated them by calculating the regression lines of individual cases. Regression lines of all cases were calculated, however, large intraindividual variability was found and prohibited detection of trends in cases with only a few recordings. Therefore, we studied trends in longitudinal data which were recorded over a longer period of time (≥ 5 recordings over ≥ 5 weeks). Only four cases (cases 9, 10, 13 and 16) fulfilled this requirement. The longitudinal data of these four cases represented 50% of all cross-sectional data points. The averaged regression line was derived by calculating the mean value of intercept and slope from all four regression lines. That of %GM was defined by $\%GM = (82.31 \pm 9.02) - (2.23 \pm 0.30) \times GA$ and that of %FBM by: $\%FBM = (-24.14 \pm 121.68) + (1.82 \pm 4.66) \times GA$ (values depicted as ± S.E.M.). All four cases showed a negative slope between %GMs and gestational age (caused by a decline in the number GMs/h as well as in the mean duration of GMs; Figs 3a and 4). For % FBM the results were more inconsistent (Fig. 3b): the relation with gestational age was positive in two cases (case 9 and 13) and negative in two cases (case 10, 16). No significant differences were found by relating the quantity of fetal movements (of GMs as well as of FBMs) of the last recording prior to delivery as well as by relating the characteristics of the regression lines (of GMs as well as of FBMs) to the neonatal

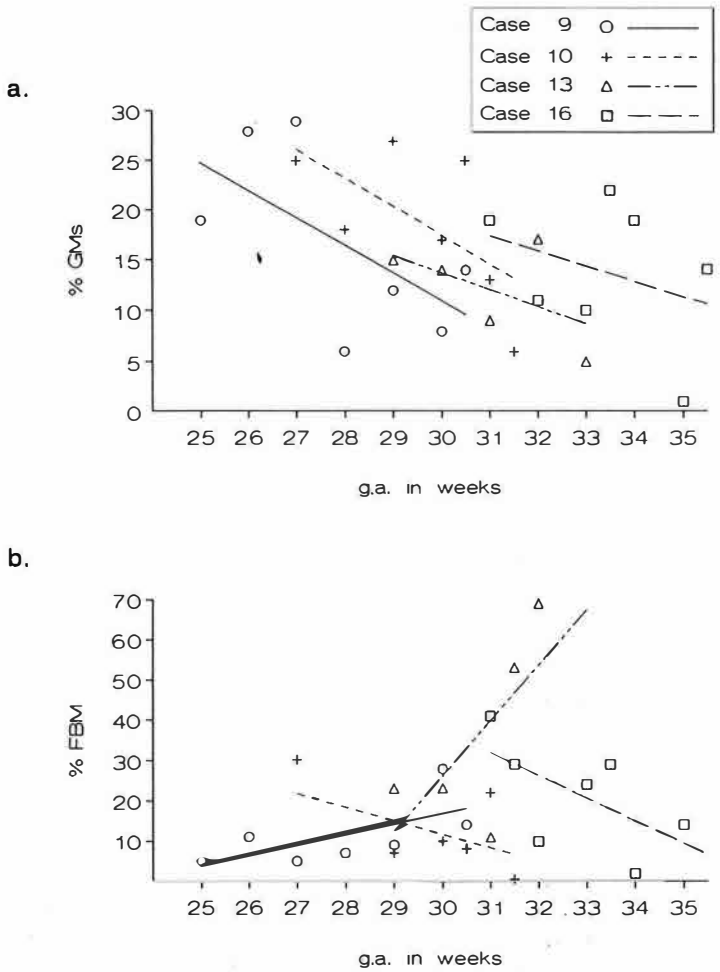

Fig. 3. Longitudinal values of %GMs and %FBMs in four individual cases (a and b).

outcome (Apgar scores, blood gases or neonatal neurological examinations; data not shown).

II. The quantity of fetal movements in IUGR, PROM and control pregnancies and its relationship with deterioration of the fetal condition during IUGR

(a) Median values of GMs and FBMs in normal pregnancy, in IUGR and in PROM. During 28–31 weeks gestation, the median value of %GMs in normal fetuses (17%) did not apparently differ from fetuses with IUGR or PROM, irrespective of the amount of amniotic fluid (Fig. 5a). Statistical evaluation (Kruskal-Wallis) concern-

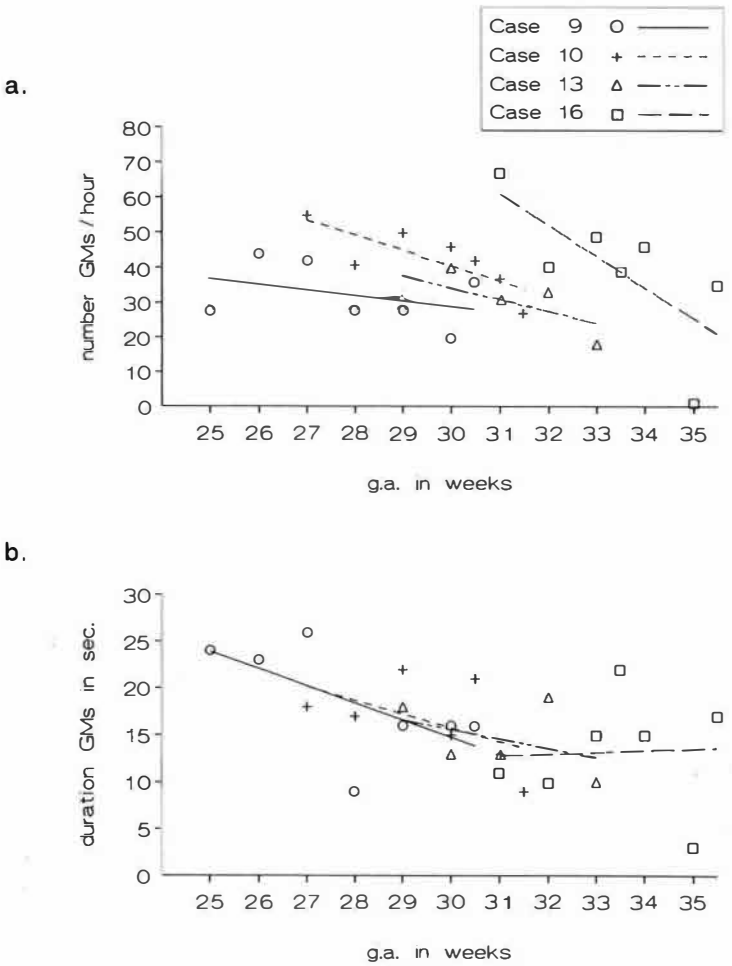

Fig. 4. Longitudinal values of the incidence of GMs (in number/h) and median value of duration in four individual cases (a and b).

ing all recordings revealed no significant differences in the distribution of the %GMs between these groups.

With respect to the median values of the %FBMs, differences between groups were more pronounced (Fig. 5c): normal controls 23%; IUGR 11%, PROM/without oligohydramnios 19% and PROM/oligohydramnios 2%. Statistical evaluation (Kruskal-Wallis) showed a significant difference ($P < 0.005$) in the distribution of the %FBMs between the four groups. Comparison between the control group and the (total) IUGR group alone, also revealed a statistical significant difference (Mann-Whitney rank-sum test, $P < 0.01$).

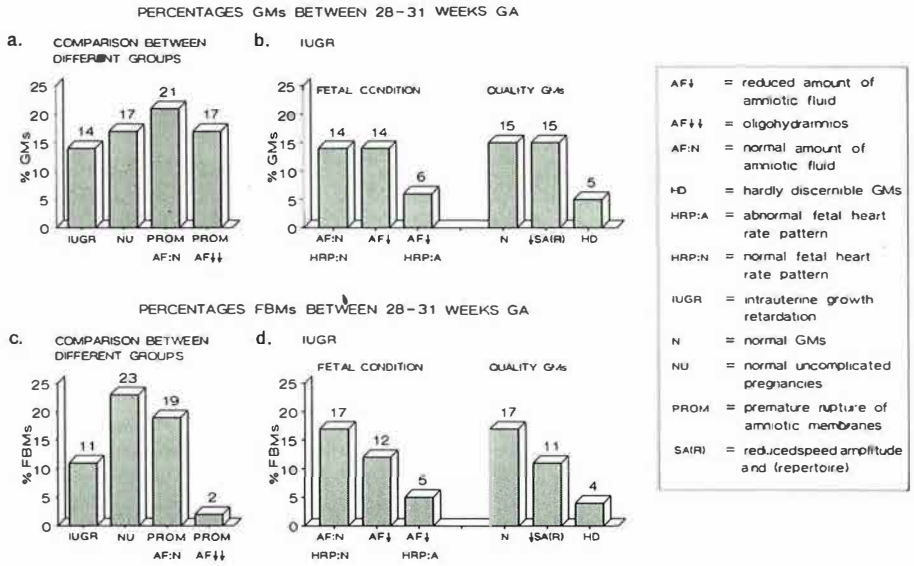

Fig. 5. Comparison of the median values of GMs and FBMs during normal and complicated pregnancies (a and c). Comparison of the median values of GMs and FBMs during the various stages of the fetal condition and qualitative movement categories (b and d).

(b) Median values of %GMs and %FBMs related to fetal condition and quality of GMs in IUGR at 28–31 weeks gestation. During a relatively undisturbed fetal condition (no other signs than reduced growth and an increased pulsatility index) the median value of %GMs (14%) was similar to that during a reduction in the amount of amniotic fluid (14%), whereas during a further deterioration of the fetal condition (indicated by recurrent fetal heart rate decelerations and/or a constantly reduced heart rate variability as well as a reduced amount of amniotic fluid) the lowest median value of %GM (6%) was found (Fig. 5b). During an uncomplicated fetal condition the median value of %FBM was 17%, compared to 12% during a reduction in the amount of amniotic fluid and 5% after further deterioration of the fetal condition (Fig. 5d).

At 28–31 weeks gestational age, cross-sectional comparison of the median values of %GMs and %FBMs with the qualitative categories of fetal movements showed similar trends as during deterioration of the fetal condition (Fig. 5b and d).

Although median values of %GMs and %FBMs declined during deterioration of the fetal condition and during alterations in the quality of GMs, no statistically significant differences (Kruskal-Wallis) could be shown in the distribution of the percentages of individual recordings over the four qualitative categories of GMs.

(c) Relationship between percentage, number and duration of GMs at 28–31 weeks gestation. At 28–31 weeks gestational age, comparison of IUGR and control groups (normal controls, PROM with a normal amount of amniotic fluid and with

TABLE II

Median values of GMs at 28–31 weeks gestation.

Group	%	No./h	No./10 min	Duration in s
Normal controls	17	32	5.3	17
PROM/AF:N	21	39	6.5	15
PROM/Oligo	17	37	6.2	18
IUGR (cross-sectional)	14	34	5.6	15

No., number; PROM, premature rupture of membranes; AF:N, normal amount of amniotic fluid; Oligo, oligohydramnios; IUGR, intrauterine growth retardation.

oligohydramnios, respectively) revealed similar median values of the quantity of GMs (%GMs), incidence of GMs (number/hour) and mean duration of GMs (Table II). Furthermore, we related the median value of the incidence of GMs (number/h) to the duration of GMs after subdividing IUGR according to the quality of GMs (Fig. 6). The mean duration of GMs was very similar in all four qualitative movement categories. Interestingly, however, the incidence of GMs (number/h) was low in the category representing hardly discernible GMs in comparison with the other three categories. Longitudinal data within the hardly discernible category itself,

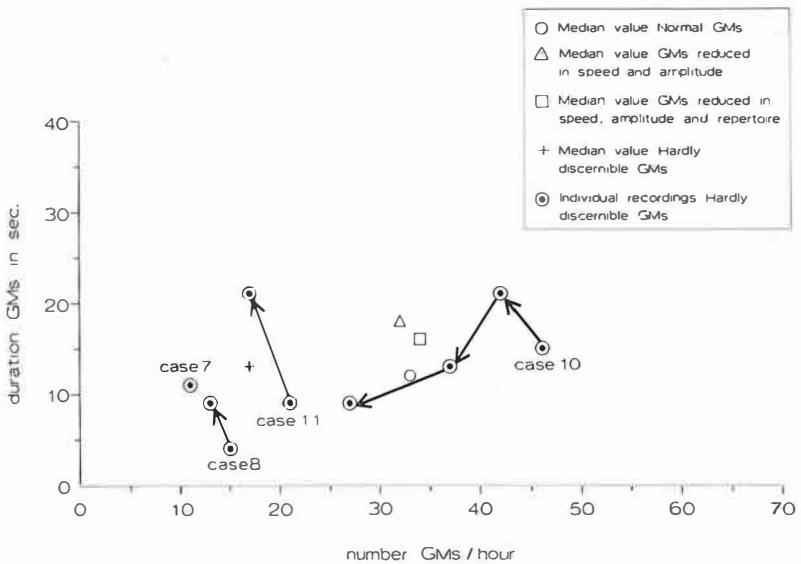

Fig. 6. Median values of the incidence of GMs (in number/h) and duration of GMs in IUGR according to the four qualitative movement categories at 27–31 weeks gestational age. Individual registrations from cases with hardly discernible GMs are encircled and shown in chronological order by the direction of the arrow.

revealed a decrease in the incidence of GMs in contrast to the duration of GMs (in cases 8, 10 and 11).

(d) The effect of the moving window technique on the %GMs in IUGR between 28–31 weeks gestation. Between 28–31 weeks gestation, application of the 10 s moving window (as we did in our study) caused a mean increase in the percentage of GMs of factor 1.16 (S.D. 0.20) or 16% point percentage (i.e. percentage from the %GM). If subdivided according to the fetal condition, the factors of increase were: 1.06 (S.D. 0.07) during a relatively undisturbed fetal condition; 1.19 (S.D. 0.16) during reduction of the amount of amniotic fluid, and 1.24 (S.D. 0.32) during further deterioration of the fetal condition.

Discussion

During the 3rd trimester of pregnancy in IUGR, the incidence of GMs decreased and the incidence of FBMs increased with gestational age. In a comparable study, E. Roodenburg et al. [23] reported similar trends with gestational age in control fetuses, whereas others [22] reported no decrease of trunk movements with gestational age (during 30 min recordings). These contradictory results might be explained by the different procedures followed.

Near term, the decrease of the %GMs has been related to reduced intrauterine space and/or to the maturation of the fetal central nervous system. With respect to a reduced intrauterine space as a cause for the reduction in the %GMs, results of studies in low risk preterm infants (lacking movement restriction) are conflicting. During the postnatal period, one study in preterm infants revealed the same reduction in the quantity of general movements as during the prenatal period [20], whereas a replicating study did not [10]. These conflicting results were explained by limitations in the recording-time of the replication study.

It is suggestive that other factors than intrauterine space restriction near term are regulating the decrease in %GMs. In our study in IUGR as well as in the study of E. Roodenburg et al. [23] in normal fetuses the decrease in %GMs could already be observed at the beginning of the 3rd trimester (after the 25th and 28th week's gestation, respectively). Furthermore, between 28–31 weeks gestational age, our cross-sectional data on fetuses complicated by PROM with and without oligohydramnios revealed similar quantitative data of GMs (median values of: %GMs, number GMs/h and duration of GMs; Table II). Finally, between 28–31 weeks gestation, in five low risk preterm infants (lacking movement restriction) similar median values of number GMs (4.2/10 min) and mean duration of GMs (18 seconds) were reported [10] as we did in our IUGR normal and PROM groups (Table II).

Beside the relationship of gestational age with the quantity of GMs and FBMs, a reduced fetal supply of oxygen and nutrients has also been reported to affect the quantity of fetal movements [4,6,15,25]. To exclude for the earlier reported inter-individual variability of the quantitative data [4], we obtained longitudinal quantitative data of four cases during IUGR. In contrast to the trends of GMs, which showed a decrease in all four cases, those of FBMs showed an increase (in two cases) as well as a decrease (in two cases). The latter might be explained by an opposing effect of increasing gestational age (causing a rise in FBMs) and deterioration of the

fetal condition (causing a decline in FBMs) on fetal breathing movements. However, characteristics of the regression lines were not related to the neonatal outcome, probably due to the earlier reported high intraindividual differences (Fig. 3). This illustrates why the longitudinal quantitative data in individual cases are of limited clinical use. In contrast to individual data, comparison of median values between different groups did enable us to reveal trends and differences.

Median values of %GM and %FBM in IUGR and control groups at 28–31 weeks gestational age

The effect of uteroplacental insufficiency on the quantity of GMs and FBMs without a confounding effect of gestational age, was studied by making cross-sectional comparisons between growth-retarded and normal control fetuses at 28–31 weeks gestation. In the control group, the median values of GMs and FBMs (17 and 23%) were in the same range as those reported by Roodenburg et al. [23] (16 and 29%, respectively), whereas in IUGR the median values of GMs and FBMs (14 and 11%) were higher than those reported by Bekedam et al. [4] (4 and 6%, respectively). However, their cross-sectional study in growth-retarded fetuses was performed at older gestational ages (between 29–35 weeks gestation) and, more importantly, in these cases fetal compromise was already suspected as all recordings were performed within one week before delivery (median value between recording and delivery was 24 h).

Comparison of the cross-sectional values of %GMs and %FBMs in fetuses with IUGR, uncomplicated pregnancies and in fetuses complicated by PROM with and without oligohydramnios revealed relatively similar median values of %GMs (Fig. 5a), whereas statistical evaluation of the median values of %FBMs revealed a significant difference between these four groups (Fig. 5b). Although the median value of %FBM in IUGR was significantly lower than that of the control group, a larger reduction in the median value of %FBM was found coinciding with oligohydramnios.

The cause for the extreme low median value of %FBM during severe oligohydramnios after PROM remains unclear. Regarding the possible effect of (impending) infections on fetal breathing movements, no effect of chorio-amnionitis on the %FBM could previously be shown in the absence of clinical signs of prenatal and early postnatal infection [27]. Beside the existence of a direct relationship between oligohydramnios and reduced fetal breathing activity, it is suggested that elevated prostaglandin levels might affect fetal breathing activity [29]. These preliminary data await further investigation.

Our results in IUGR and PROM indicate that a reduced amount of amniotic fluid might be related, at least partly, to a reduction of the %FBMs. With respect to IUGR, experiments in human fetuses [5] revealed a relationship between hypoxaemia and %FBMs as well as between hypoxaemia and fetal urine production [12,17]. Animal experiments indicated that decreased urine production can be caused by hypoxaemia leading to blood flow redistribution resulting in a decreased renal perfusion [19,24] as well as by an increase in antidiuretic hormone levels [28]. Relating these findings to our present data in IUGR, it is tempting to speculate that hypoxaemia plays a role either directly or indirectly, in the reduction of the amount of amniotic fluid and the reduction of %FBM.

Cross-sectional comparison of %GMs and %FBMs with the fetal condition and the quality of GMs in growth-retarded fetuses at 28–32 weeks gestational age

In uncomplicated IUGR (with an increased pulsatility index of the umbilical artery) no effect was found on the quantity of GMs and FBMs as the median values differed only slightly from those in control fetuses (Fig. 5a and b). This indicates that alterations in the quantity of fetal GMs and FBMs are no early signs of IUGR. During IUGR, only in the group representing the most deteriorated fetal condition (fetal heart rate decelerations, reduced heart rate variability and a reduction of the amount of amniotic fluid), was a low median value of the %GMs found (6%). This percentage is in agreement with the low movement incidence in IUGR fetuses suspected of fetal compromise [4]. In IUGR complicated by fetal heart rate decelerations Bekedam et al. [6] also reported a reduction in the quantity of GMs. This reduction in GMs as well as a reduction in fetal heart rate variability was strongly related to the onset of hypoxaemia, while a relationship with acidaemia remained absent. Further evidence on the relationship between fetal oxygen tension and the quantity of fetal body movements was provided after an experiment on maternal hyperoxygenation resulting in a significant increase of body movements in the growth-retarded fetus [8].

In contrast to the GMs, lower median values of %FBMs were already found during the presence of a reduced amount of amniotic fluid. Similar to the GMs, the lowest median value of %FBMs was found in the group representing the most deteriorated fetal condition. This same effect of a synchronized inhibition of FBMs and limb movements during pronounced hypoxia has also been reported after experiments in fetal sheep [9,16] and has been explained by central inhibition due to hypoxia [11,13]. Our findings indicate that mild hypoxaemia may be (indirectly) related to a decline in the %FBMs alone, whereas more pronounced hypoxaemia may affect both the quantity of GMs and FBMs (probably mediated by central inhibition).

From these results it can be concluded that during uncomplicated IUGR, no alterations in the quantity or quality of fetal movements could be substantiated. Thus, at least before the onset of fetal heart rate decelerations, we could not demonstrate alterations in fetal movements. These data are in agreement with Amiel-Tison [1] who reported that uncomplicated growth retardation does not impair, but may even accelerate, the maturation of neurological variables (measured by means of brainstem conduction times). During deterioration of the fetal condition, only in the last stage a low median value of %GMs was found. As the %GMs also declined during progressing gestation in control fetuses, it could theoretically be possible that the low value of %GMs during a deteriorated fetal condition in IUGR reflects an accelerated maturation. However, in control fetuses a rise in FBMs has been reported during increasing gestational age, whereas we observed in IUGR a decrease in FBMs during ongoing fetal deterioration.

Furthermore, in contrast to progressing gestation which goes together with a reduction in the number as well as duration of GMs (Fig. 2), fetal deterioration caused only a reduction in the number of GMs/h, leaving the mean duration relatively unaltered (Fig. 6). For the latter finding no clear explanation can be given as during a deteriorated fetal condition GMs appear short in duration and small in amplitude,

resulting in the term hardly discernible [26]. This qualitative description is in agreement with a previous study by Bekedam et al. [4] who reported a shorter duration of GMs in more or less compromised growth-retarded fetuses. However, in the latter study no moving window was applied, whereas we used a 10-s moving window. Although the use of this technique hardly affected the absolute values of the %GMs (mean increase with factor 1.16), the factor increased with deterioration of the fetal condition (from 1.06 to 1.24). On the one hand, these data could indicate that during ongoing deterioration (in an already compromised fetus) GMs continue to decrease in number and become fragmented by pauses, which are smoothed by the moving window. On the other hand, this could indicate that the moving window lumped separate small GMs which follow each other within 10 s. As both mechanisms would lead to a reduction in the number of GMs leaving the duration relatively unaltered, no explanation can be provided.

Another possible explanation for the reduction of fetal movements during the most deteriorated stage of fetal condition in IUGR, could be a relative increase of state variables 1F compared to 2F as has been described during normal progressing gestation in control fetuses [18]. However, an acceleration of the normal development of behavioural state variables is not likely as in IUGR the development of behavioural states is delayed for several weeks [31]. On the other hand, an increase of no coincidence of behavioural state variables described in preterm growth-retarded fetuses [3] could explain the reduction of the quantity of GMs. However, these alterations in the state variables are not related in time to alterations in the quantity of GMs, as an increase of no coincidence of behavioural state variables is described as an early sign of fetal deterioration (before the onset of hypoxaemia), whereas the reduction in the quantity of GMs occurred as a late sign of fetal deterioration. Therefore, no evidence is provided that the concomitant decrease in the quantity of both GMs and FBMs in the hardly discernible group, is due to accelerated maturation of the central nervous system or due to disturbances of the fetal behavioural states.

This study indicates that in uncomplicated IUGR the quantity of GMs and FBMs were in the same range as those found in control fetuses and in PROM without oligohydramnios. In IUGR, during the different degrees of fetal deterioration, alterations in the quality of GMs were accompanied by considerable decreases in the quantity of FBMs and GMs. However, in contrast to the quality of GMs, the quantity of GMs and FBMs showed a high inter- and intraindividual variation. Therefore, the results of this study discourage the use of quantitative aspects of GMs and FBMs as reliable indicators of the neurological condition in the individual fetus, unless the fetus is in a very serious condition.

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CHAPTER 4

FETAL BREATHING MOVEMENTS ARE NOT A GOOD INDICATOR OF LUNG DEVELOPMENT AFTER PREMATURE RUPTURE OF THE MEMBRANES AND OLIGOHYDRAMNIOS - A PRELIMINARY STUDY.

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Fetal breathing movements are not a good indicator of lung development after premature rupture of membranes and oligohydramnios — a preliminary study

D.A. Sival[a], G.H.A. Visser[b] and H.F.R. Prechtl[a]

[a]Department of Developmental Neurology and [b]Department of Obstetrics and Gynaecology, University Hospital, Groningen (The Netherlands)

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Summary

The effect of severe oligohydramnios (due to prolonged premature rupture of the membranes (PROM)) on breathing movements and lung development was studied longitudinally in 11 human fetuses. Prenatally, fetal breathing movements (FBM) were scored off-line from weekly, 1 h during ultrasound recordings (n = 47). In each recording, the incidence of FBM was scored according to 4 different methods. Postnatally, the cases were retrospectively assigned to a group with normal (n = 4), partially hypoplastic (n = 3), or hypoplastic (n = 4) lungs. Compared to control fetuses, the percentage of time spent breathing (%FBM) was low (2–5%) and did not increase with gestational age. Large inter-individual and intra-individual variations in the %FBM were found in all 3 diagnostic groups. Evaluation of the %FBM according to the 4 different methods revealed no significant differences between the 3 groups. We conclude that lung development is, at least partly, independent of the incidence of FBM. Furthermore, the analysis of FBM cannot reliably predict lung development in fetuses with oligohydramnios due to PROM.

Key words: fetal breathing movements; lung development; premature rupture of the amniotic membranes; oligohydramnios

Introduction

Prolonged premature rupture of the membranes (PROM) associated with oligo-

hydramnios is a risk factor for pulmonary hypoplasia [10]. The pathogenesis of this relationship is unclear. Adzik et al. [1] suggested a reduced space for fetal breathing movements (FBM) and lung growth, due to compression of the fetal chest and abdomen. Animal studies have shown that abolition of FBM leads to pulmonary hypoplasia [1,7,16]. In human fetuses, the effect of FBM on lung development is still unclear. Blott et al. [2, 3] described a strong relationship between FBM and lung growth in the presence of oligohydramnios, whereas Moessinger [8] reported complete independence of these variables. Although this discrepancy in results has been explained by the application of different criteria for the presence of FBM [4], conclusive evidence is absent. Therefore, we studied the relationship between oligohydramnios and the %FBM both cross-sectionally and longitudinally. After birth, all the cases were retrospectively allocated to 3 different diagnostic groups according to their lung development. The %FBM were compared between the 3 groups. Furthermore, the predictive value of FBM for lung development was compared by employing 4 different criteria for FBM (including those of Moessinger and Blott) to our data.

Patients

Eleven patients with spontaneous premature rupture of the amniotic membranes and severe oligohydramnios were selected for this study and gave informed consent. Rupture of the membranes had occurred between the 19th and 29th week of pregnancy as calculated from the first day of the last menstrual period or on the basis of first trimester ultrasonographic measurements. The diagnosis of PROM was based on the leakage of amniotic fluid which continued throughout the observation period. Only cases with severe oligohydramnios were included in this study. Severe oligohydramnios was defined as the absence of an amniotic fluid pocket of larger than 1 cm on the ultrasound scan.

Criteria for exclusion on admission were: (1) delivery within 48 h after the rupture; (2) clinical evidence of infection: fever, ($T > 38°C$), leucocytosis or the sudden appearance of immature white cells; (3) pregnancy induced hypertension; (4) intrauterine growth retardation, based on fetal abdominal measurements below the 10th percentile; (5) congenital abnormalities or chromosomal defects; (6) pregnancy induced or juvenile onset diabetes mellitus; (7) use of sedative drugs; (8) intoxication due to alcohol or drug addiction; and (9) antenatal signs of fetal distress, based on abnormal fetal heart rate recordings. All the patients were screened daily for infection or fetal distress, so that, if necessary, immediate delivery could take place. If any signs of infection were detected ($n = 2$), the last recording prior to detection was not taken into account.

Methods

Weekly, one hour ultrasound recordings of the fetal thorax were made using a linear array scanner (Acuson, Model 128, probe size 8.4 cm or Aloka, Model 256, probe size 9.6 cm) and recorded on videotape for off-line analysis. All the recordings ($n = 47$) were standardized for the time of the day (between 19:00 and 22:00 h). One

hour before the registrations, the mothers had a standard hospital meal containing a relatively high carbohydrate intake (fruit and bread). During replay of the videotape, FBM were scored off-line using a keyboard of a personal computer, which was synchronized with the videorecorder. After applying 4 different criteria for the presence of FBM to these data, the prognostic value of FBM for lung development was evaluated.

Diagnostic groups

After birth, all the data records of FBM were divided retrospectively into 3 groups according to the lung development of the infants: (1) normal size and development of the lungs (diagnosed by a radiologist, based on X-ray in combination with clinical data); (2) partial lung hypoplasia (diagnosed by a radiologist, based on X-ray in combination with clinical data and if necessary, on additional arterio-graphs and/or broncho-graphs); (3) lung hypoplasia (postmortem diagnosis by a pathologist based on the weight of the lungs after fixation in formalin $<$ 10th percentile).

Quantification criteria for FBM

Four different quantification criteria for FBM known from the literature [2,8,9], were applied (for a summary see Table I). According to all the methods, a bout of continuous breathing is present if the breath-to-breath interval is ≤ 6 s. In one method, no restrictions are applied (method 1), in two of the methods, there is a restriction regarding the minimum number of breaths required during an epoch (methods 2 and 3), whereas in one method, there is a restriction regarding the minimum duration of a bout of breaths (method 4).

The results after applying the criteria of methods 1, 2 and 3 are expressed as the 'sum bout %' (% of time during which epochs of FBM were present). The results according to the criteria of method 4, described by Blott et al. [3], are presented for each individual recording: a '+' sign was given whenever an epoch of breathing movements of 1 min or longer was present and a '−' sign when absent. Negative recordings were repeated within the same week.

TABLE I

Four different methods for quantifying fetal breathing movements. According to all the methods, a bout of continuous breathing is present if the breath-to-breath (Br-Br) interval is ≤ 6 s. In method 4, there is a restriction as to the minimum duration of a bout, whereas in methods 2 and 3, there is a restriction as to the minimum number of breaths required during a bout.

Method	Br-Br interval(s)	Minimum bout duration (s)	Minimum No. breaths/bout
1	≤ 6 s	—	—
2	≤ 6 s	—	≥ 3
3	≤ 6 s	—	≥ 6
4	≤ 6 s	≥ 60	—

Statistical analysis

We applied the Fischer exact probability test on the latency time between the gestational age of PROM and birth. Due to the variable latency between the rupture of the membranes and birth, as well as between PROM and admission to hospital, the number of recordings differed per case (from 1 to 8; Table IV). Therefore, statistical analysis was performed on the median values of methods 1, 2 and 3 by means of the Kruskal-Wallis test. For method 4 (based on individual recordings) we applied the Chi-square test over the distribution of positive recordings between the 3 diagnostic groups.

Control values

The median values of %FBM at 20, 24, 28 and 32 weeks gestational age were obtained cross-sectionally (according to method 1) in a control group of 11 fetuses with a normal amount of amniotic fluid and uncomplicated pregnancies.

Results

In the pregnancies complicated by PROM and oligohydramnios, all cases except one (case 10) developed neonatal pulmonary complications and required artificial respiration (Table II). Relating to lung development four out of the eleven infants

TABLE II

Clinical data and outcome of the 11 pregnancies complicated by PROM and oligohydramnios. (A, atelectasis; AR, artificial respiration; BPD, broncho-pulmonary dysplasia; H, lung hypoplasia; HMD, hyaline membrane disease; P, pulmonary hypertension; PH, partial lung hypoplasia; N, normal; PN, pneumothorax; T, tocolytic drugs.)

Case	Gestational age in (weeks) at		Medication	Chorio-amnionitis	Lung development	Pulmonary complications
	PROM	Delivery				
1	23	27	T at 26	–	H	†
2	24	30	—	–	H	†
3	22	29	—	+	H	†
4	25	29	—	–	H	†
5	18	27	—	+	PH	AR, A, BPD
6	23	31	—	+	PH	AR, BPD
7	28	32	T at 29 weeks	–	PH	AR, HMD, A
8	22	33	—	+	N	AR, HMD, A
9	26	29	T at 27 weeks	+	N	AR
10	28	30	T at 28 weeks	–	N	NONE
11	29	30	T at 29 weeks	–	N	AR, HMD, PN, P†

†Death due to pulmonary complications.

TABLE III

Median gestational age at premature rupture of the membranes (PROM) and delivery in fetuses with normal lung development and in fetuses with (partial) lung hypoplasia.

Lung development	*n*	Gestational age in weeks at	
		PROM	Delivery
Hypoplasia (partial)	7	23	29
Normal	4	27	30

developed lung hypoplasia (H),three infants developed partial hypoplasia (PH) and four infants had normal lung development (N). Of the cases with (partial) hypoplasia (n = 7), PROM occurred before the 26th week in 6 out of 7 fetuses and the latency between rupture and birth was four weeks or more in 7 out of 7 fetuses. Of the cases with normal lung development (n = 4), PROM occurred after the 26th week in 3 out of 4 fetuses, with a latency of less than four weeks in 3 out of 4 fetuses. Statistical analysis (Fischer exact probability test) showed a significant difference ($P < .025$) between the H, PH and N groups for the latency time of four weeks or more. Additional clinical data and outcome are summarized in Tables II and III.

In the cases with oligohydramnios, the median values of FBM varied from about 2% to 5%. No rise in the %FBM was seen with increasing gestational age (from 19 to 32 weeks g.a., according to method 1, Fig. 1). In the control group, the %FBM

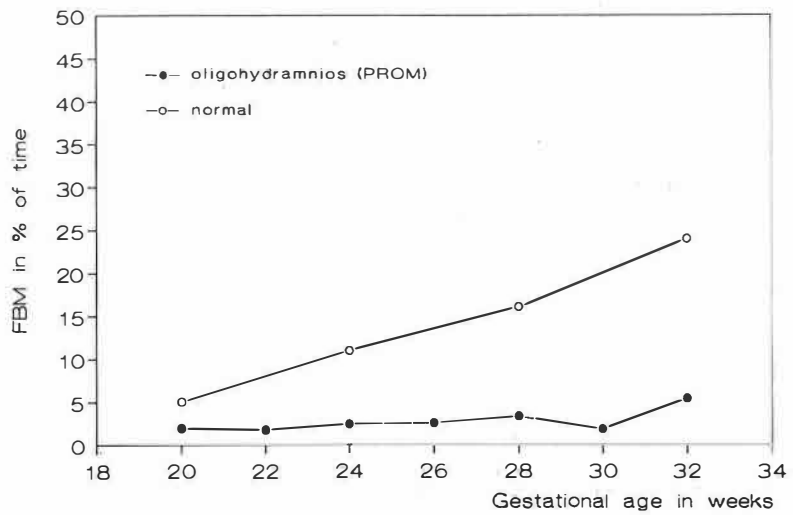

Fig. 1. Median values of %FBM in uncomplicated pregnancies (n = 11) and in pregnancies complicated by oligohydramnios due to PROM (n = 11).

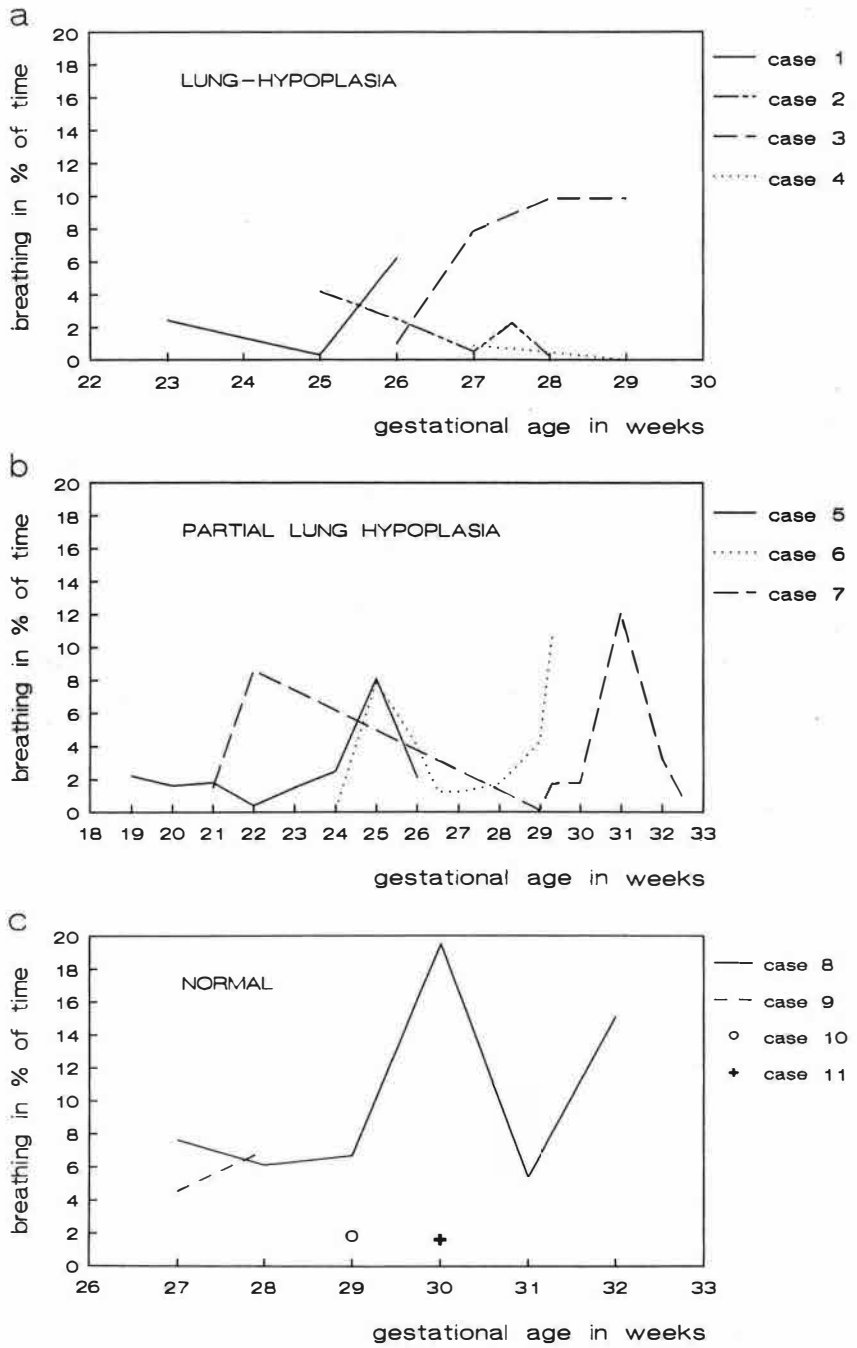

Fig. 2. %FBM (according to method 1) in fetuses with oligohydramnios due to PROM (a, b and c).

increased from about 5% to 25% (from 20 to 32 weeks g.a., according to method 1, Fig. 1). Longitudinal data on FBM (according to method 1) showed wide inter-individual and intra-individual variations in the % of time spent breathing. There were no clear differences between the 3 diagnostic groups. Intra-individual variation in the H group ranged from 1% to 9.9%, in the PH group from 0.2% to 12.2% and in the N group from 5.4% to 19.5% (Fig. 2 a, b and c). Inter-individual variation in the H-group ranged from 0 to 9.9%, in the PH group from 0.1% to 12.2% and in the N group from 1.6% to 19.5%.

Comparison of the results obtained by the methods 1, 2 and 3 demonstrated remarkably similar results. The %FBM (according to method 1) showed only a moderate decline (ranging from 0.2% to 2.6%) after the application of the restrictions of method 2 and 3 (Table IV). According to method 4, positive recordings were present in 5 cases (Table IV). These 5 cases were divided over all 3 diagnostic groups (H, PH and N). However, no bouts of 60 s or longer were present in any of them during all the individual registrations; thus all cases with positive recordings belonged to the intermediate group (defined by Blott et al. [3]), in which no prediction of lung development can be made; The ratio of positive to negative recordings in these fetuses varied from 1:8 to 1:2. The presence of positive recordings was not age-related: the median age at which positive recordings occurred was 28.5 weeks and that of the negative recordings 27 weeks. Comparison of the individual data obtained by method 1 and by method 4 showed that only cases with a FBM incidence of higher than 6% (according to method 1) had positive recordings (according to method 4). Actually, 60% of the recordings with a FBM incidence higher than 6% reached a positive score (according to method 4).

TABLE IV

Incidence of fetal breathing movements (in % of time) according to three different methods for quantifying these movements and according to a method that quantifies breathing as present (positive) or absent. For a summary of these methods see Table I.

Case	Number of recordings	Pulmonary outcome[a]	Gestational age median	Method 1 median sum bout (%)	Method 2 median sum bout (%)	Method 3 median sum bout (%)	Method 4 number of positive recordings
1	3	H	25	2.4	2.2	1.7	1
2	5	H	27	2.3	1.9	0.8	0
3	4	H	27.5	8.9	8.4	6.3	2
4	2	H	28	0.5	0.5	0	0
5	8	PH	22.5	2.0	1.6	0.8	1
6	8	PH	27	2.8	2.6	1.6	1
7	7	PH	30	1.8	1.7	1.6	0
8	6	N	29.5	7.2	6.6	5.7	3
9	2	N	27.5	5.8	5.5	4.4	0
10	1	N	29	1.8	1.8	1.0	0
11	1	N	29	1.6	1.6	0.6	0

[a]H, hypoplasia; PH, partial hypoplasia; N, normal.

Statistical analysis of the %FBM as quantified according to methods 1, 2 and 3 (Kruskal-Wallis test) and method 4 (Chi-square test) did not provide any significant difference between the H, PH, and N groups. In addition, analysis of the median values of rate/hour, bouts/hour, mean rate/bout and longest duration/bout, as quantified according to method 1, did not yield any statistical difference (Kruskal-Wallis).

Discussion

The effect of oligohydramnios on FBM

In control fetuses, we found a FBM incidence of about 5% at 22 weeks (according to method 1). At this point, our data are in agreement with those reported in the literature [9,12]. From 22 weeks onwards, the %FBM increased gradually to 25% at 32 weeks g.a. This rise in the %FBM confirms the data of Roodenburg et al. [12] who reported an increase in the %FBM in the same range. In pregnancies complicated by oligohydramnios, however, the median values of FBM were constantly low and did not show a positive correlation with gestational age (see Fig. 1).

Recently, Roberts et al. [11] reported a low %FBM for the first 2 weeks after PROM and an increase thereafter. In our study, the %FBM remained low after the 2nd week. Possibly, the shorter period of a low %FBM reported by Roberts et al., can be explained by different selection criteria. In their study, all the cases of PROM were included irrespective of the amount of amniotic fluid, whereas in our study we only accepted cases with severe oligohydramnios.

The cause of the low % FBM during oligohydramnios after PROM remains unclear. Experiments on fetal sheep have shown that oligohydramnios might result in compression of the abdominal contents leading to an upwards displacement of the diaphragm, favouring loss of lung liquid [5]. However, this phenomenon would lead to reduced lung expansion rather than to a reduced incidence of FBM. Tas et al. [13] reported that the exertion of active pressure on the fetal thorax during breathing can cause an immediate cessation of FBM (due to the intercostal-to-phrenic inhibitory reflex). In our cases, this phenomenon would have led to a relative decrease in the large bouts compared with the small bouts. However, comparison of the results of methods 1 and 2 (small bouts included) to those obtained with method 3 (small bouts excluded) showed remarkably similar %FBM. Another explanation for the low % of FBM could be an impending infection [15]. Although chorio-amnionitis was diagnosed in 5 cases (Table II), these 5 fetuses did not show a lower %FBM than the fetuses without chorio-amnionitis. Furthermore, all the bacteriological cultures (blood, throat and urine) performed after birth were negative. In a preliminary study, Thompson et al. [14] recently reported elevated maternal and fetal levels of prostaglandins (Biocyclo PGEM) during PROM. As these authors also found a reduced incidence of FBM in these cases, a direct relationship between elevated prostaglandin levels and a reduced fetal breathing activity was suggested. These data await further investigation. So far, no clear aetiology for the low breathing incidence can be provided.

The relationship between FBM and lung development

The contradiction existing in the literature concerning the relationship between

FBM and lung development in cases with PROM has been ascribed to the application of different criteria for FBM [4]. According to methods 2, 3 and 4, bouts are subject to restrictions with respect to the number of breaths per bout or to the bout duration. These restrictions, which increase from methods 2 to 4, were applied to eliminate the risk of mistakenly counting gasps or abnormal fetal breathing movements.

Based on method 4, Blott et al. [3] reported a predictive value of 100% for normal lung development if each recording of a fetus contained epochs of FBM of 60 s or longer (positive group). They also found a predictive value of 100% for lung hypoplasia if each recording of a case did not contain an epoch of FBM of 60 s or longer (negative group). The outcome varied if both positive as well as negative recordings were present in one case (intermediate group). However, these authors did not indicate how many recordings in succession had to be positive or negative before a case could be assigned to a certain group. In our data, we found positive recordings even after 6 or 7 negative recordings. This finding illustrates, to our opinion, that Blott's criteria for assignment of a case to the positive or negative group are hard to apply for prognostic purposes in clinical practise. The data on additional recordings may frequently result in the assignment of a case to the intermediate group. Although bouts of longer than 60 s were present in the fetuses in all 3 of our diagnostic groups, none of them showed bouts of longer than 60 s in all the individual recordings. This implies that all the fetuses with positive recordings (H, PH and N cases) would have belonged to the group which Blott et al. reported as having an uncertain outcome.Furthermore, statistical analysis (Chi square) did not show any difference in the distribution of positive recordings over the cases with hypoplastic, partially hypoplastic or normal lungs. Moessinger et al. [8] considered only bouts of 6 breaths or more within a 6 s window. They defined the start of an epoch when at least 3 breaths were detected and the end of an epoch when less than 3 breaths were present. Our results on the median values of bout %, confirmed the findings of these authors that no prediction of lung development can be made on the basis of FBM quantified according to this method. In method 2, bouts consisted of at least 3 breaths, thus ruling out 2 consecutive, more or less isolated breaths. This method is of relevance with regard to the observation that active pressure exerted on the fetal thorax could immediately induce fetal apnoea by means of the intercostal-phrenic-inhibitory reflex [13]. Therefore, we studied whether there were more isolated FBM or pairs of breaths in the (partial) lung hypoplasia groups than in the normal group. Statistical analysis did not show any significance in the distribution of these small bouts over the 3 groups. This finding does not support the hypothesis that (partial) lung hypoplasia could be caused by the inhibition of longer bouts, as a result of the intercostal-phrenic-inhibitory reflex.

We report that the incidence of FBM, at least according to the 4 definition criteria used, does not predict lung development in cases with severe oligohydramnios due to PROM. In contrast to the %FBM, the gestational age at which rupture of the membranes occurs and the latency between PROM and delivery seem to be more important indicators of lung development (Table III). On this point, our data are in agreement with those reported in the literature [10]. According to morphological studies, oligohydramnios impairs the lung growth most readily during the canalicular stage (in the human fetus before the 25th week gestational age; for review

see Ref. 17). Concerning the % FBM, one may hypothesize that an early onset of reduced FBM (before 26 weeks g.a.) together with a prolonged duration of this reduction (≥ 4 weeks) may have a negative effect on lung development. Interestingly, the effects of additional influencing factors seem likely as two of our cases had a normal outcome despite early onset and prolonged duration.

With respect to lung maturation, Higuchi et al. [6] reported (from 102 pregnancies with a diversity of pathologies, among them 50% PROM) a total absence of respiratory distress syndrome (RDS) in cases within a bout duration of 30 s or more. Although our study design did not focus on the postnatal development of RDS (hyaline membrane disease) one case with RDS (case 8, see Tables II and IV) was observed with bouts of FBM up to 60 s, indicating that RDS can occur despite long periods of FBM.

This study shows that severe oligohydramnios after PROM is associated with a low % of FBM after 26 weeks of gestation. In fetuses with severe oligohydramnios due to PROM, no individual prediction of lung development or maturation can be made by evaluating the incidence of FBM.

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CHAPTER 5

DOES REDUCTION OF AMNIOTIC FLUID AFFECT FETAL MOVEMENTS?

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Does reduction of amniotic fluid affect fetal movements?

D.A. Sival[a], G.H.A. Visser[b] and H.F.R. Prechtl[a]

[a]Department of Developmental Neurology, and [b]Department of Obstetrics, University Hospital, 9713 EZ Groningen (The Netherlands)

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Summary

The effect of the amount of amniotic fluid on the form of fetal general movements was studied longitudinally in 19 pregnancies complicated by premature rupture of the amniotic membranes (PROM). Before birth, general movements were studied weekly by means of 1-h ultrasound observations, performed under standardized conditions. In the early postnatal period, 11 of these infants were followed with video recordings of their spontaneous movements.

In the fetus, speed and amplitude of general movements were directly related to the reduction in amniotic fluid. A moderate reduction of amniotic fluid was associated with a decrease in amplitude, while a more severe reduction of amniotic fluid caused a decrease in speed as well. Postnatally, the small amplitude and low speed showed a marked tendency to normalize between 1 and 5 weeks. These results are important for the qualitative assessment of motor behaviour in pregnancies with obstetrical complications that are associated with oligohydramnios (such as PROM or intra-uterine growth retardation).

fetal movements; movement quality; premature rupture of the membranes; oligohydramnios.

Introduction

Several unfavourable conditions in pregnancy lead to a reduction of amniotic fluid. Only spontaneously broken membranes represent a situation which may be without prior compromise of the fetus. The study of fetal motility in such cases is of special interest for two reasons. Firstly, it may help in detecting possible effects of oligohydramnios itself on the movements of the fetus. This question is clinically highly relevant because of the new possibility of assessing the functional condition

TABLE I

Clinical data.

Case	Maternal age	Maternal illness	Parity	Obstetrical complications	Drugs	Gestational age at the time of rupture	Anniotic fluid class	Intra-uterine position	Gestational age at delivery	Delivery	Placenta	Apgar at birth	Acedaemia[a]
1	38	—	II	—	—	15	I	variable	38	S	N	1'9 3'9	—
2	46	—	0	—	—	18	V	vertex	27	S	CA	1'2 5'3	+
3	34	—	IV	placenta praevia	T	21	I	CIF-vertex-CIF	30	CS	N	1'9 3'8	—
4	27	—	I	—	—	22	V	CIF	29	CS	CA	1'3 5'5	—
5	38	—	II	—	—	22	V	CIF	33	CS	CA	1'3 3'5	+
6	29	—	III	—	—	23	IV	vertex	30	CS	CA	1'6 3'8	—
7	35	—	II	—	—	24	V	CIF	29	CS	N	1'1 5'6	—
8	31	D.M.	II	—	—	25	III	vertex	30	S	N	1'8 3'7	—
9	28	—	I	—	—	25	III—II	CIF	31	S	N	1'2 3'7	—
						i.m.	I	transverse	31	S	N	1'8 3'9	
10	29	—	II	vaginal blood loss	T	26	IV	CIF	33	CS	N	1'8 3'9	—
11	35	P.H.	I	—	AH	26	III	CIF	34	CS	N	1'3 5'7	—
12	33	—	0	—	T	26	IV	vertex	29	S	CA	1'5 5'8	—
13	27	—	II	—	T	27	III	CIF	30	CS	N	1'5 5'6	+
14	29	—	II	—	T	28	IV	CIF	32	CS	N	1'6 3'8	—
15	33	—	II	placenta praevia marginalis	T	28	IV	vertex	30	CS	N	unknown	—
16	26	—	I	—	T	29	V	CIF	31	S	CA	1'4 3'8	—
17	35	—	II	vaginal blood loss	—	29	III	transverse	32	CS	CA	1'4 5'9	—
18	25	—	II	—	T	29	IV	CIF	30	CS	IC	1'1 3'1	—
19	36	P.H.	0	D.M. grav.	AH	29	III	vertex	30	CS	CA	1'1 5'5	—

[a]Acidaemia ($pH_a < 7.15$, $pH_v < 7.2$.

[b]Twin pregnancy.

Abbreviations: AH, anti-hypertensive drugs; CA, chorio-amnionitis; CIF, caput in fundo (breech); CS, caesarean section; D.M., diabetes mellitus (type 1); I, ischemic changes; i.m., intact membranes; N, normal; P.M., pre-existing hypertension; S, spontaneous vaginal; T, tocolytic drugs.

of the fetal nervous system by analysis of the quality of fetal movements (see Prechtl, Ref. 15). This technique is similar to that proposed for the preterm infant [17] and recently substantiated in preterms with brain lesions [7]. In the fetus the situation is more complicated since the mechanical restriction of the fetus can vary with the amount of amniotic fluid, a factor which is not relevant for the preterm infant in the incubator. Hence, if the mechanical restriction of the fetus could affect the movement quality, such a factor must be taken into account when movement assessment is applied in the compromised fetus for diagnostic purposes.

The second aspect of interest in cases of reduced amniotic fluid concerns a more fundamental problem. If fetal movements are hampered by external mechanical restriction for a period of days or weeks, an effect on the developing peripheral and central motor system is theoretically not impossible. In fact, such a relationship between fetal motor activity and the proper development of joints, bones and muscles has been documented in animal experiments and has been conjectured for the human (for review, see Moessinger, Ref. 12). The extent to which neural functions may become impaired by external restriction of the execution of fetal movements is even less understood.

The aim of the present study is the investigation of possible effects of various degrees of oligohydramnios on the form of general movements in the human fetus. Ultrasound observations of the fetus will provide evidence of immediate effects while follow-up observations during the early postnatal period may indicate longer lasting influences.

Patients

A total of 19 women with spontaneous premature rupture of the membranes (PROM) volunteered for this study and gave informed consent. Rupture of the membranes occurred between the 15th and 29th week of pregnancy calculated from the first day of the last menstrual period or estimated on the basis of first trimester ultrasonographic measurements. All patients, except one (case 9) had singleton pregnancies. The twin pregnancy consisted of one fetus with ruptured membranes and the other fetus with intact membranes. For further clinical data see Table I.

The diagnosis of PROM was based on leakage of amniotic fluid which continued throughout the observation period or on an alpha-1 foetoprotein determination in case of doubt. In order to eliminate possible confounding factors on fetal motor behaviour we excluded cases with the following criteria on the admission:

1 delivery within 48 h after rupture
2 clinical evidence of infection: fever ($T > 38\,^{\circ}C$), leucocytosis or the sudden appearance of immature forms of white cells
3 pregnancy-induced hypertension
4 intra-uterine growth retardation, based on fetal abdominal area mesurements below the 10th percentile
5 congenital abnormalities or chromosomal defects
6 use of sedative drugs

7 intoxication due to alcohol or drug addiction
8 fetal distress, based on late decelerations or loss of heart rate variability

All patients were screened daily for infection or fetal distress, so that, if necessary, immediate delivery could take place.

Methods

Before birth, motor behaviour was studied by means of continuous real time ultrasound observations of 60 min duration each, repeated at weekly intervals. Observations were made with linear array scanners (Acuson, Model 128, probe size 8.4 cm and Aloka model 256, probe size 9.6 cm) and recorded on video-tape. Due to the limited display field of the transducer the fetus could not be visualized completely. Therefore, we recorded only the caudal part of the head, the trunk and a part of the upper and lower extremities. In a few instances we combined the images of two scanners with a split screen on one monitor, one scanner recorded the head, thorax and upper extremities and the other scanner the abdominal part and lower extremities. The twin pregnancy (case 9) was the only case where two scanners and a split screen were always used, in order to compare the motor behaviour of the oligohydramniotic fetus with that of the normohydramniotic fetus. Normally we worked with one scanner only.

All recordings were performed between 19.00 and 22.00 h. During the ultrasound examinations, all women were lying in a comfortable semi-recumbent position and were asked to lie as quietly as possible. If the fetus changed position, the transducer adjustment was kept to a minimum and performed as smoothly as possible. In spite of these precautions, it was sometimes necessary to interrupt the recordings. These interruptions, which never lasted longer than 5 min, were noted and accounted for in the off-line analysis of movements.

The volume of amniotic fluid was assessed on the basis of the sizes of amniotic fluid pockets, measured by ultrasound. Pockets containing loops of umbilical cord were excluded. On the basis of these measurements we distinguished 5 groups: Group I, largest diameter of pocket measured more than 3 cm; Group II, largest diameter of pocket measured between 2 to 3 cm; Group III, largest diameter of pocket measured between 1 to 2 cm; Group IV, largest diameter of pocket measured 1 cm or less and a layer of amniotic fluid was present around the fetus; Group V, largest diameter of pocket measured 1 cm or less and no layer of amniotic fluid present around the fetus.

After birth, histological analysis of the membranes and placenta was performed. Chorioamnionitis was diagnosed on the basis of the presence of an inflammatory response consisting of polymorphonuclear leucocytes appearing in the chorion spreading to the amnion.

During the early neonatal period, 1-h video recordings were repeated again at weekly intervals. All infants were in a supine or semi-lateral position. Possible confounding factors on the infant's motor behaviour were carefully noted on a screening list.

The quality of fetal and postnatal behaviour was judged by means of global visual gestalt perception. Gestalt perception is an important method for assessing the quality of human fetal motor behaviour and thus provides essential information on the functional integrity of the central nervous system (see Prechtl, Ref. 15).

General movements are motor patterns in which all parts of the body are involved and may last from a few seconds to a minute. The sequence of arm, leg, neck and trunk movements which follow each other within one general movement is variable [14]. Normal general movements are performed fluently and show a smooth waxing and waning of intensity. They vary also in speed and amplitude.

After the global judgement had been carried out, in a second replay of the videotape, we analysed semi-quantitatively specific details such as size of the amplitude and speed. Two observers judged the quality of general movements independently, one observer (H.F.R.P.) judged without having any prior knowledge of the clinical history. Studies on the agreement between different observers have shown the high inter-scorer reliability of this method, namely 89% agreement [1]. A neurological examination was performed at 1, 3 and 6 months.

Results

I. Quality of prenatal motor behaviour

In all but one case general movements were performed fluently throughout gestation. In addition to the analysis of general movements the appearance of other movement types such as startles, twitches and hiccups was systematically observed. No alteration of form and other properties of these movements could be found.

In the above mentioned exceptional case (case 3) the normal fluent character of general movements was completely lacking. The on- and offset of the general movements was abrupt and speed was predominantly slow with only minimal fluctuations. Furthermore, head retroflexions with a jerky character could be observed. As the amount of amniotic fluid was normal (category I), the abrupt character of these general movements could not be related to the ruptured membranes. In fact, during the first postnatal week, this neonate turned out to suffer from a non-cystic periventricular leucomalacia of prenatal origin. At 6 months a diplegia with hydrocephalus had developed.

Semi-quantitative aspects related to the amount of amniotic fluid. When premature rupture of the amniotic membranes was associated with a moderate to severe lack of amniotic fluid, general movements were modified (Fig. 1). Moderate reduction of amniotic fluid was associated with a decrease in the amplitude of general movements only. A more severe decrease of amniotic fluid also caused a reduction of the speed of general movements. Whenever speed was slow, the amplitude decreased. This is illustrated in Fig. 1. In amniotic fluid categories I and II, general movements were performed with a normal amplitude and speed. In amniotic fluid category III, in 3 out of 6 cases the amplitude was small and in one of these 3 cases speed was also reduced. In amniotic fluid category IV in all 6 fetuses general movements were performed with a small amplitude, of which in 4 fetuses a reduced speed could also be observed. In amniotic fluid category V all general movements were

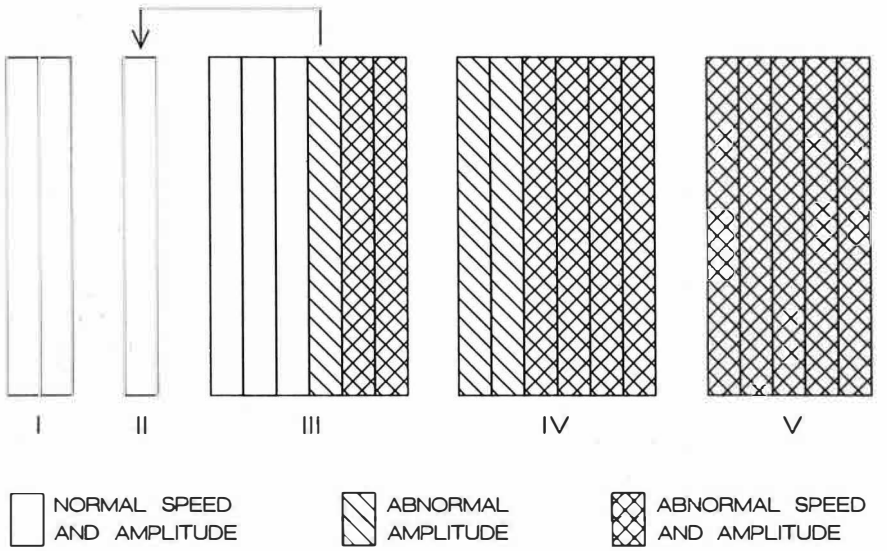

Fig. 1. Relationship between the semi-quantitative aspects of general movements and the amount of amniotic fluid. In one case, the amount of amniotic fluid increased from group III to II and is indicated by the arrow. Classes I to V are the categories of amount of amniotic fluid varying from normal to severe oligohydramnios.

performed at slow speed and with small amplitude. During repeated measurements in almost all cases the same quality of general movements was observed. Only in case 9 (twin pregnancy) did the amount of amniotic fluid increase, changing from category III to II, with a normalization of amplitude, speed remaining normal as before.

Relationship with the duration of movement restriction. The form of prenatal general movements seemed not to be influenced by the duration of movement restriction. However, we did not have enough cases to test this impression.

Relationship with breech position. Ten fetuses (55%) remained in a stable breech position after the spontaneous rupture of membranes. Figure 2 demonstrates that breech presentations were associated with the more severe categories of oligohydramnios. In almost all fetuses with breech position the amplitude of general movements was invariably small. Only one fetus with a constant breech position showed motor patterns with variable amplitudes compared with 5 fetuses in vertex or variable position.

Confounding factors. We screened carefully for the absence of possible confounding factors like intra-uterine infections. After birth, histological analysis of the membranes and placenta was done to screen for chorioamnionitis or villitis. In 8 out of 19 cases chorioamnionitis was diagnosed. However, normal as well as altered general movements could be found in fetuses with chorioamnionitis. Furthermore, all neonates had been screened carefully for the presence of infections. This yielded one case with a positive blood culture (case 4).

No relationship could be found between the administration of tocolytic drugs and abnormal general movements. All fetuses had been carefully monitored for the emergence of prenatal distress and caesarean section was performed as soon as it occurred. Four infants were born with acidaemia and/or low Apgar Scores (see Patients and Methods, Table I). As in three of them consistently normal antenatal FHR patterns had been recorded, we could more or less rule out pre-existent fetal distress in these cases. In only one case (case 18) chronic hypoxia before birth was present (ischaemic changes in the placenta; one severe bradycardia on CTG; low Apgar scores and acidaemia). In this case slow general movements with small amplitudes were observed.

Neonatal brain scans revealed a germinal layer bleeding (grade I) in cases 5, 6 and 10. In these cases however, repeated brain scans showed quick resorption. In cases 3 and 18 repeated brain scans revealed leucomalacia.

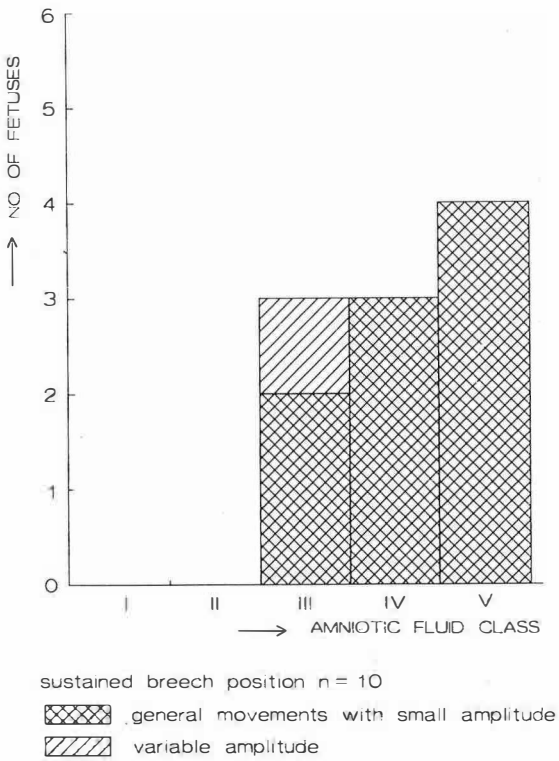

Fig. 2. Breech position and PROM. All fetuses in a sustained breech position belonged to the groups with a severely to moderately reduced amount of amniotic fluid. The amplitude of general movements was variable in only one case.

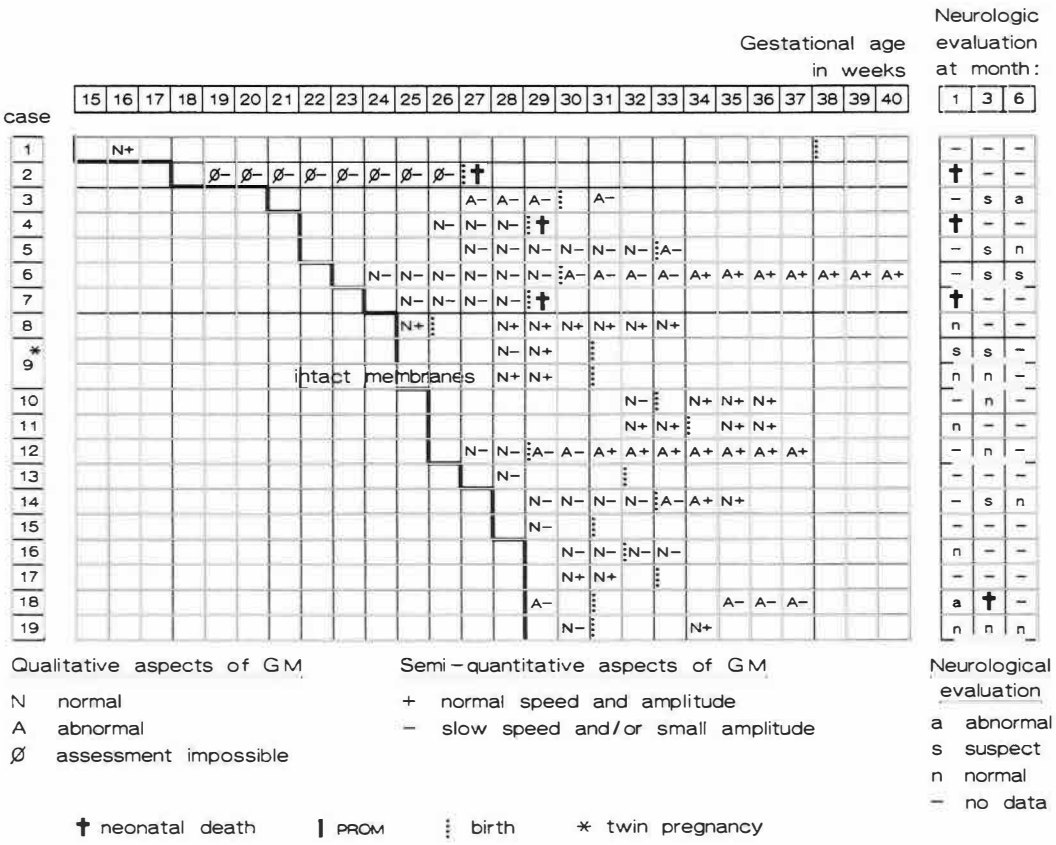

Fig. 3. Results of the neurological evaluation, qualitative and semiquantitative analysis.

II. Quality of postnatal general movements

General movements could be studied in only 11 infants. In these cases a standard neurological examination [13] was performed. In the other 8 cases perinatal death, critical clinical condition of the infant or transfer to another hospital prevented further investigation. Four neonatal deaths occurred (Fig. 3). In cases 2, 4 and 7 this was due to lung hypoplasia and in case 18 due to severe broncho-pulmonary dysplasia.

The results of the neurological evaluation in combination with the results of qualitative and semi-quantitative analysis are shown in Fig. 3. In six infants an abnormal quality of postnatal general movements was found. Two of these infants (cases 3 and 18) developed leucomalacia. In case 3 abnormal motor behaviour was already observed before birth. This infant turned out to suffer from leucomalacia of prenatal origin. In the other 4 infants neonatal complications that arose after birth should be held responsible (partial lunghypoplasia, broncho-pulmonary dysplasia, atelec-

TABLE II

Semi-quantitative aspects of general movements per case (upper) and clustered acccording to similar results (lower). In the left columns the semi-quantitative aspects of general movements during the prenatal period are given; in the right columns the changes of these aspects during the postnatal period, the number of days between brackets.

Case	GM prenatal period	GM postnatal period (at day)	Changes (at day)	Last postnatal recording (at day)
3	AaAs	AaAs (3)		AsAs (14)
5	AaAs	AaAs (7)		AsAs (7)
6	AaAs	AaNs (11)	NaNs (28—35)	NaNs (80)
8	NaNs	NaNs (14)		NaNs (55)
10	AaNs	NaNs (7)		NaNs (30)
11	NaNs	NaNs (2)		NaNs (16)
12	AaAs	AaAs (1)	AaNs (7—14); NaNs (14—21)	NaNs (58)
14	AaNs	NaNs (15)		NaNs (15)
16	AaAs	AaAs (1)		AaAs (7)
18	AaAs	AaAs (35)		AaAs (49)
19	AaAs	NaNs (24)		NaNs (24)

Summarised: clustered according to similar results

Total number of cases	GM prenatal period	Postnatal recording (at day)
2	NaNs	NaNs (14,2)
2	AaNs	NaNs (7,15)
3	AaAs	NaNs (28,14,24)
4	AaAs	AaAs (14,7,7,35)

Na, normal amplitude; Aa, abnormal amplitude; Ns, normal speed; As, abnormal speed.

tasis, germinal layer bleedings and icterus neonatorum). As these complications come to expression after birth, it is not surprising that prenatal motor behaviour had been normal in these cases. Figure 3 shows that the quality of postnatal motor behaviour is very well correlated with the results of the neurological evaluation.

Semi-quantitative aspects of postnatal general movements. When we compare the semi-quantitative aspects of general movements before and after birth, it becomes evident that during the postnatal period the amplitude and speed remained altered or became normal (Table II). Furthermore, it could be noted that the speed normalized earlier than the amplitude. In cases 10, 14 and 19 the amplitude became normal between 1 and 4 weeks after birth. In cases 6 and 12 we collected enough postnatal recordings to study the development of the motor behaviour over a longer period of time. In both cases the speed regained its fast components between 1 and 2 weeks after birth, while the amplitude became variable between 4 and 5 weeks. In case 18 we could not verify the same tendency as this infant was in a poor clinical condition and in addition his head was fixed in a headholder for artificial respiration and the limbs were restricted by bandages.

Discussion

Relationship between the quality of prenatal motor behaviour and the amount of amniotic fluid

Mechanical restriction of the fetus causes an alteration of general movements consisting of low speed and small amplitude. The quality of general movements is directly related to the amount of amniotic fluid and thus to the degree of movement restriction. When the amount of amniotic fluid is reduced, the amplitude becomes small and after a further reduction, general movements become slow. Presumably the observed speed diminishes when the amplitude is small. The hypothesis that this 'slow motion' characteristic is not due to a structural or functional abnormality in the fetus itself was confirmed by the observation that movement patterns with fast accelerations (startles, twitches and hiccups) remained present in all fetuses. This was also corroborated by the accidental observation of a fetus with severe oligohydramnios that was rehydrated for diagnostic purposes. We recorded fetal motor behaviour before and after rehydration. Before the rehydration, we observed slow movements with small amplitude. Immediately after rehydration, the amplitude increased and fast components were present again.

Not only fetal movements but also fetal heart rate patterns may be associated with the amount of amniotic fluid [8,11]. If so, abnormal fetal heart rate patterns could be associated with abnormal motor behaviour. Gabbe et al. [8] observed variable decelerations (periodic fetal heart rate changes) after amniotomy in the rhesus monkey. They related these changes to the lack of amniotic space around the fetus by which the umbilical cord was compressed. After restoration of the amniotic fluid volume by infusion of a saline preparation, a marked reduction of these decelerations could be noted. The association between rehydration and the disappearance of variable decelerations in humans has also been demonstrated by Miyazaki et al. [11]. In the present investigation heart rate monitoring was performed daily. Fetal heart

rate decelerations were noted in cases 3 and 18. Case 3 had prenatal brain damage and case 18 ischemic changes of the placenta. As Visser [21] pointed out, impaired neurological function is often found following antenatal late heart rate decelerations. As in all other cases, no fetal heart rate decelerations were recorded, the altered fetal general movements cannot be ascribed to the occurrence of decelerations caused by compression of the umbilical cord. Because a direct relationship exists between the amount of amniotic fluid and the observed motor behaviour, mechanical restriction of the movements through a lack of amniotic space is the most likely explanation.

Relationship with intra-uterine growth retardation (IUGR)

Growth retarded fetuses show abnormal general movements of monotonous, slow character with reduced force and amplitude [1]. These movements share certain similarities with those of fetuses after PROM. In both groups, general movements are performed slowly and with a small amplitude. However, in contrast to fetuses with IUGR, the general movements after PROM remain distinctly powerful, which is confirmed by the mothers who felt the strong and forceful fetal movements. In addition fast movements such as startles and twitches are not reduced in PROM cases. Because IUGR is often associated with oligohydramnios, caution should be taken before accepting slow general movements with a small amplitude as evidence of neural dysfunction. It is the forcefulness of the motility and the presence of fast components which distinguishes motor behaviour in severe oligohydramnios from that of the growth retarded fetuses.

Relationship with breech position

It is suggested that oligohydramnios is one of the main causes of breech position [3,10,19]. In our study, 10 out of 19 fetuses were lying in a stable breech position after PROM (see Table I). The breech positions occurred predominantly in the more severe cases of oligohydramnios (70% in categories IV and V). In 90% of these cases general movements were displayed with a small amplitude and a low velocity. We suggest that a quick release of amniotic fluid after the rupture rapidly fixates the fetus in its environment. Because the rupture took place at the median age of 26 weeks, the chance that the fetus was in a breech position at the time of the rupture could be estimated at about 50%. After the rupture, movement restriction probably prevents the fetus from turning from a breech into a vertex position.

Confounding factors

In 8 cases chorioamnionitis occurred. There was a predominant association of chorioamniontis with the more severe cases of oligohydramnios (Table I). Gonink et al. [9] demonstrated that a marked reduction of amniotic fluid after PROM increased the risk of amnionitis threefold. This might be explained by the fact that high volume leaks are associated with a more adequate amniotic volume and are more likely to close again. Vintzileos et al. [20] ascribed the higher percentage of the more severe oligohydramnios in the chorioamnionitis group to the bacteriostatic

effect of the amniotic fluid. In our opinion, it is not the chorioamnionitis itself but the severity of oligohydramnios that causes the altered motor behaviour.

This assumption is supported by the fact that already during the first days after the rupture altered motor behaviour can be observed while chorioamnionitis is not likely to have developed yet. Furthermore, normal as well as altered motor behaviour could be observed in cases of chorioamnionitis; and, as soon as clinical symptoms of infection occurred, caesarean section was performed. Last but not least, the altered characteristics of general movements of the oligohydramnios-chorioamnionitis group were exactly the same as the oligohydramnios non-chorioamnionitis group.

We applied Apgar scores and neonatal acid-base values in order to screen for acute asphyxia at birth, although previous studies (e.g. Touwen and Huisjes [18]) pointed out that the relationship between these values and neonatal neurological morbidity is rather poor. Furthermore, it was concluded by Dijxhoorn [5] that the neonatal neurological dysfunction is probably more dependent on the obstetrical complications themselves (such as IUGR) than on the acute asphyxia at birth that may be caused by these complications. Thus, the antepartum incidence of heart rate decelerations (indicative of chronic hypoxaemia) or of other abnormal heart rate patterns may be a better indicator of the neurological outcome than signs for acute asphyxia at birth [4,5]. Table I shows the Apgar scores and acid-base values of our group. Only in cases 2 and 18 could the severe clinical prognosis be correlated with the presence of low Apgar scores or acidaemia. In case 18, however, the ischaemic changes of the placenta and the presence of fetal bradycardia pointed towards a chronic prenatal hypoxaemia.

Quality of postnatal motor behaviour

After birth, the motor behaviour of 11 children was studied. Unfortunately, the neonatal data of the other infants could not be collected due to clinical circumstances. Postnatally, a tendency could be found for the general movements to keep the same characteristics regarding speed and amplitude as before birth and to normalize between 1 and 5 weeks. This same tendency was found by Bekedam [2], who performed a follow up study in two growth retarded infants and found the same abnormal motor patterns before and after birth. Our results are the more striking as the neurological examination did not show any change in resistance to passive movements, muscle power or severe limitation in ranges of the joints. Only in the cases of breech position small limitations in the flexion of the hips were present. One of the possible causes of the 1—5 week delay in the normalization of speed and amplitude might be an altered proprioceptive feedback before birth causing longer lasting changes in the motor output.

Other research on the influence of prenatal movement restriction on postnatal motor behaviour in the human infant was done by Prechtl and Knol [16]. Postnatal posture and reflex patterns of the legs were studied in healthy neonates after a period of breech position that caused intra-uterine movement restriction of the legs. A correlation was found between the duration of the intra-uterine breech position and the postnatal posture of the legs, the withdrawal response and magnet response. After a

period of intra-uterine breech position with knees extended and hips flexed, the neonates showed predominantly a spontaneous posture with extension of the knees and slight flexion of the hips (see Prechtl [13], Fig. 32). Furthermore, in contrast to the response of babies born in a vertex position, paradoxical extension of the legs could be observed after eliciting the withdrawal response, while an increased intensity of the extension of the knees was seen after eliciting the magnet response. The authors suggested that the altered proprioceptive input from the legs could be held responsible for the observed changes of the reflexes.

Concluding, our results indicate that mechanical movement restriction can affect motor behaviour in certain ways, both before and after birth. Before birth, direct mechanical factors can be held responsible for the change in motor behaviour. However, these changes continue after birth when the restriction has been ended. This indicates a short lasting carry-over effect on the functional properties of the motor system.

Acknowledgement

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CHAPTER 6

THE EFFECT OF INTRA-UTERINE BREECH POSITION ON POSTNATAL MOTOR FUNCTIONS OF THE LOWER LIMBS.

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The effect of intra-uterine breech position on postnatal motor functions of the lower limbs

D.A. Sival, H.F.R. Prechtl, G.H.A. Sonder and B.C.L. Touwen

Department of Developmental Neurology, University Hospital Groningen (Netherlands)

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Summary

The effect of intra-uterine movement restriction on the development of motor functions was studied longitudinally by comparing infants born after uncomplicated breech position (n = 13) with control infants (vertex position, n = 5). Before birth, fetal leg posture was studied at regular intervals by means of real time ultrasound observations, and classified as complete (n = 1), inconsistent (n = 6), or incomplete (n = 6) breech position. Limited extension of the hips, preference posture and joint position in percentage of time (each until 12 weeks), withdrawal reflex and magnete response (until 26 weeks) and posture while sitting, standing and walking without support (up to 12–18 months) were assessed longitudinally. The results showed statistically significant, positive relationships between intra-uterine breech position and neonatal limited extension of the hip-joint, between limited extension of the hip-joint and the percentage of time that the hips are in flexion during the first 12 weeks, between this flexion of the hips (in percentage of time) and an abnormally 'flexed' walking pattern at 12–18 months, and finally, between a positive magnete response at 6 months and an abnormal walking pattern at 12–18 months. These findings suggest that intra-uterine movement restriction of the legs can cause long term alterations in (development of) motor functions (leg posture, reflexes and posture while walking), possibly mediated by alterations in proprioceptive feedback mechanisms.

Correspondence to: H.F.R. Prechtl, Department of Developmental Neurology, University Hospital Groningen, Oostersingel 59, 9713 EZ Groningen, Netherlands.

Introduction

For a long time reflexes have been looked upon as genetically programmed, and stereotyped responses to a specified stimulus. However, in low-risk infants born in breech position Prechtl and Knol [13] reported that intra-uterine environment (causing fetal movement restriction of the legs) can alter neonatal leg reflexes (flexion reflex and magnet response). After distinction of complete — (both hips and knees flexed, feet presenting as first part during vaginal delivery) and incomplete — (i.e. both hips flexed and knees extended, buttock presenting as first part during vaginal delivery) breech position, the following modifications of reflexes were found: (1) in neonates born after complete breech position the flexion reflex consisted of an exaggerated flexion of the legs, whereas in neonates born in incomplete breech position the flexion reflex was either weak or absent and consisted of leg extension; (2) after eliciting the magnet response in neonates born after complete breech position, leg extension was either absent or weak; whereas in neonates born after incomplete breech position leg extension was more pronounced. As the selection criteria included normal pregnancies in the absence of any neonatal neurological morbidity, the authors suggested a prolonged aberrant proprioceptive feedback (due to intrauterine movement restriction of the legs) as underlying mechanism for these findings.

Due to the impossibility of visualizing the fetus at the time of this study, assessment of fetal motor behaviour and accurate estimation of fetal leg psition was impossible. Nowadays, due to the development of ultrasound technology, more detailed assessment of fetal positions and movements can be made. In addition, a longitudinal study of the effects of fetal movement restriction on the postnatal postures, development of leg reflexes and achievement of neuro-developmental milestones (such as sitting and walking) can provide information about the modulating role fetal environment may play in the development of motor functions.

The aim of the study is to investigate the short- and long-term effects of intrauterine movement restriction caused by breech position on: development of posture (until 12 weeks) — withdrawal reflex, magnet response, and limited extension of the hips (until 26 weeks) — appearance of neuro-developmental milestones (until 12–18 months).

Patients

Study group

Thirteen pregnant women volunteered for this study and gave informed consent. Selection criteria were: breech position at 36 weeks of gestational age, and absence of polyhydramnios, multiple pregnancy, grande multiparitas, fetal abnormalities, pre- or postnatal complications, or neonatal neurological abnormalities. All fullterm neonates except one (case 4) had birth weights at the 50th percentile (according to

TABLE I

Case	Maternal age	Parity	Amount amniotic fluid	GA 1st discovery breech in weeks	GA delivery in weeks	Delivery	Birthweight in grams	1′ and 3′ Apgar scores
1	31	1	N	32	39	V	3220	10/10
2	29	0	N	31	37	V	3040	—
3	26	0	M	32	39	V	3120	7/10
4	24	0	M	31	39	V	2610	8/9
5	31	0	M	31	40	CS	3600	9/10
6	39	1	N	34	40	V	3030	5/10
7	28	0	N	32	41	V	3770	9/10
8	24	0	R	33	39	CS	3405	—
9	31	1	M	32	42	V	3560	8/9
10	27	0	M	37	42	CS	3540	8/10
11	29	1	M	36	41	V	3530	10/10
12	23	0	M	37	39	CS	2950	9/10
13	28	0	N	35	39	CS	4650	8/9

N, normal; M, moderately reduced; R, reduced; GA, gestational age; CS, caesarean section; V, vaginal.

Kloosterman [9]). Case 4 had a birthweight around the 10th percentile, but Doppler data and cardiotocograms revealed no abnormalities. This particular case was not diagnosed as IUGR (according to Goodlin [4]), as fetal measurements were in proportion with the small body lengths of both parents, and obstetrical data based on prenatal ultrasound measurements revealed small fetal measurements parallel to the 10th percentile early in gestation. Clinical data are summarized in Table I.

Control groups

Neonatal foot-sole reflexes in breech born infants were compared to those of a group of 10 low-risk fullterm infants born after consistent vertex position during the third trimester. Longitudinal data on the development of spontaneous posture and on the posture during sitting, standing or walking without support were processed from two other (unpublished) studies performed in our department, yielding, respectively five and 10 low-risk control infants born at fullterm age in vertex presentation.

Methods

Before birth, at regular intervals (if possible weekly) real-time ultrasound observations were made of fetal position and leg movements. The total number of ultrasound recordings depended on the length of the period between entering the study and the date of delivery (varying from 1 to 7 observations (Table II)). All cases were categorized according to intra-uterine position and way of delivery. We distinguished three categories according to the following criteria: (1) complete breech position: both hips and knees flexed during all recordings and feet delivered first, (2) incomplete breech position: both hips flexed and both knees extended (feet near the head) during all recordings and buttock delivered first, (3) inconsistent breech presentation: both hips flexed together with one knee flexed and one knee extended and/or any (inter- or intra-recording) alteration from complete to incomplete breech position (or reversely) diagnosed by means of repeated ultrasound recordings.

In order to detect the influence of oligohydramnios [18] on type of breech position, the amount of amniotic fluid was estimated in each case at regular intervals (Table I). The following criteria were applied: a normal amount of amniotic fluid (largest diameter of an amniotic fluid pocket 2 cm or more), moderately reduced amount of amniotic fluid (largest diameter of an amniotic fluid pocket between 1 and 2 cm and presence of a layer of amniotic fluid around the fetus, or largest diameter of an amniotic fluid pocket 2 cm or more and absence of a layer of amniotic fluid around the fetus), reduced amount of amniotic fluid (largest diameter of an amniotic fluid pocket between 1 and 2 cm and absence of a layer of amniotic fluid around the fetus), oligohydramnios (largest diameter of an amniotic fluid pocket smaller than 1 cm).

Passive limitation of the hip joint was estimated by extension of the hips with the infant in supine position on the examination table [15] and expressed in ranges of 10 degrees (<10, 10, 20, 30, 40, etc.). In calculations of mean values, the smallest limitation (0–10 degrees) was counted as 5 degrees.

During the first postnatal week, neurological condition was assessed according to the standardized neurological examination by Prechtl [15]. At 1 year of age a

TABLE II

Case	Number of ultrasound obserations			position at delivery	Categorized as	Duration breech position after 1st observation
	Complete	Variable	Incomplete			
1			3	Incomplete	Incomplete	7 weeks
2	1			Complete	Complete	6 weeks
3			7	Incomplete	Incomplete	7 weeks
4			6	Incomplete	Incomplete	8 weeks
5			3	Caesarean section	Incomplete	9 weeks
6	1	1	3	Left leg Incomplete Right leg: Complete	Inconsistent	6 weeks
7		2	2	Incomplete	Inconsistent	9 weeks
8		2	1	Caesarean section	Inconsistent	6 weeks
9		2	1	Incomplete	Inconsistent	10 weeks
10			5	Caesarean section	Incomplete	5 weeks
11			1	Complete	Inconsistent	5 weeks
12			3	Caesarean	Incomplete	2 weeks
13			1	Caesarean section	Inconsistent	4 weeks

neurological examination was repeated [20].

At 1 week and at 1, 2 and 3 months postnatal age, video-recordings of spontaneous motor behaviour were made with the infant in supine position, approximately 1 h postprandially. The duration of the recordings was between 30 and 60 min and contained at least 10 min of spontaneous motor behaviour during state 3 or 4 (for definition of state criteria see Ref. 14). After all recordings were made, hip and knee positions were scored off-line during state 3 and 4. The following classification for hip and knee position was used [15]: (1) flexion: angle between hips and examination table >90 degrees; (2) semi-flexion: angle between hips and examination table between 90–45 degrees; (3) extension: angle between hips and examination table <45 degrees.

Statistical evaluation between intra-uterine posture and postnatal hip- and knee-position was made by means of Student *t*-test. Values of both legs were accounted as independent values (accounting the values of both legs as being dependent revealed similar differences). Significant differences between the inconsistent and incomplete breech groups as well as between the flexed and normal walkers, were also determined by a non-parametric test (Mann-Whitney rank-sum test). The same significant differences were found as with the student *t*-test, except for one parameter (hip flexion at 3 months, flexed compared to normal walkers).

Withdrawal reflex and magnet response

At 1 week, 1, 2, 3 and 6 months the withdrawal reflex and magnet response were elicited (1 h postprandially) and recorded on videotape. In accordance with Prechtl [15], the withdrawal reflex was elicited by scratching the soles of the feet during state 3 with the legs in a semi-flexed position. The magnet response was elicited after the withdrawal reflex by a light pressure on the foot-soles during state 4 and with the legs in a semi-flexed position. Two observers (D.A.S. and B.C.L.T.) judged the responses independently off-line. The withdrawal reaction was labelled positive (present) in case it elicited an immediate response of either flexion, flexion followed by extension or solely extension of the legs. Flexion followed by extension or solely extension after the flexion reflex were noted separately. The magnet response was regarded as either present when it elicited extension of the legs or as absent when no extension could be elicited. The results of the breech infants were compared to those from the control group consisting of 10 neonates.

Developmental milestones

Parents were asked to document the age at which specific neuro-developmental milestones were achieved, such as rolling from back to belly and the reverse, sitting, standing and walking without support.

Sitting with and without support was recorded on videotape at, respectively, 6 and 12 months and judged according to balance and posture.

At 1 year standing and walking, depending on the development of the motor functions, with or without support, was recorded and judged off-line according to the posture during standing and walking. In case of walking without support was not performed at 1 year, an extra recording was made at the time when walking occurred (at 18 months). Data on the posture during walking were compared to 10 control

cases.

Results

Prenatal data

During the subsequent ultrasound observations a shift from complete to incomplete (or the reverse) could be observed in five fetuses. In one fetus the prenatal position was recorded as incomplete, followed by delivery in complete breech position 4 weeks later. Hence, in six out of the 13 fetuses breech position was defined as inconsistent (Table II), implicating that movement restriction was merely confined to flexion of the hips whereas flexion and extension of the knees remained present.

Relating the three types of complete, inconsistent and incomplete breech positions to the number of ultrasound recordings, complete breech position was diagnosed in only one case with one ultrasound recording, incomplete in six cases with a median value of four ultrasound recordings and inconsistent in six cases with a median value of three ultrasound recordings (Table II). In cases with a normal amount of amniotic fluid, inconsistent breech was diagnosed in three out of five cases, whereas in cases with a reduced or moderate reduction of amniotic fluid, inconsistent breech position was diagnosed in three out of eight cases. Although this trend suggests a relationship between the amount of amniotic fluid and the type of breech position, differences were not statistically significant.

Postnatal data

Limited extension of the hips, withdrawal reflex and magnet response related to gestational age. All infants born in breech position (n = 13) had a limited extension of the hips at birth. The median value of limited extension of the hips decreased from 20 degrees at birth to zero at 12 weeks postnatal age (Fig. 1). The percentage of breech infants with a positive magnet response decreased from 100% at birth to about 60% at 26 weeks and appeared positively correlated with the limited extension of the hips (Fig. 2). The regression line was characterized by: %MR = 58.8 + (1.93)LE, r = 0.99 (%MR is percentage positive magnet response; LE is limited extension of the hips). A similar correlation was found between the percentage of breech infants with a withdrawal reflex accompanied by extension and limited extension of the hips. This regression line was characterized by: %(WR+E) = 23.1 + (3.84)LE, r = 0.88 (%(WR+E) is percentage withdrawal reflex accompanied by extension; LE is limited extension of the hips). However, at 26 weeks, both the limited extension of the hips and the withdrawal reflex accompanied by extension approached zero, whereas still 60% of the breech infants had a positive magnet response (see for individual data Table III). Only one out of 10 infants from the control group had a small limited extension of the hips at birth (< 10 degrees). In the latter infant, also a withdrawal reflex accompanied by extension was present at birth. At later postnatal ages, these parameters were absent in all control infants. In none of the cases from the breech- or control-group, a limited extension of the knees did exist.

Longitudinal data of leg postures (in percentage of time) in breech born infants and

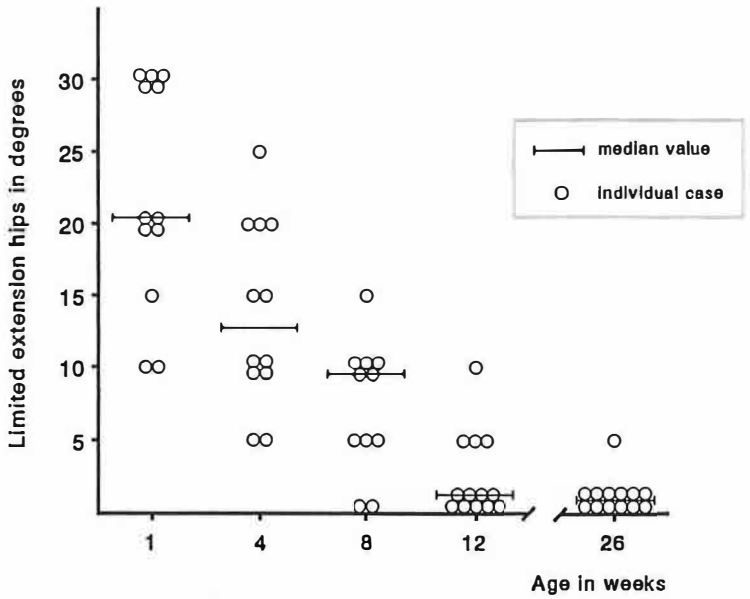

Fig. 1. Relationship between limited extension of the hips in degrees and postnatal age in weeks in infants born in breech position. Data from the control group are not indicated, as the mean values were 0 degrees at all ages (S.E.M. at 1 week < 1; S.E.M. at 4–26 weeks: 0).

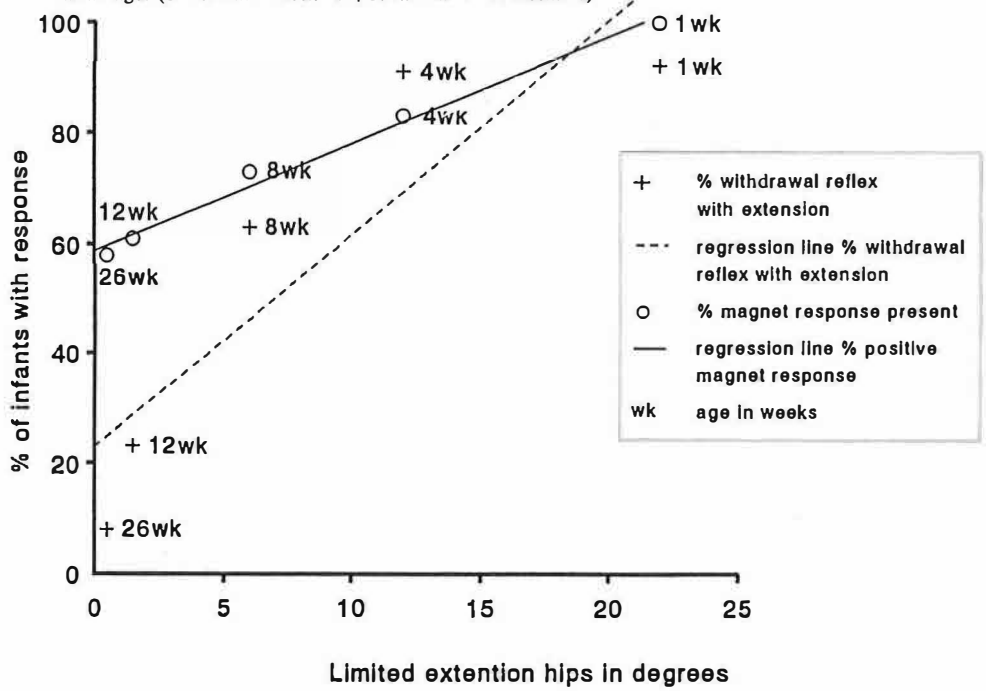

Fig. 2. Relationship between limited extension of the hips and presence of positive magnet response (continuous line) and with withdrawal reflex followed by extension of the legs (broken line). Postnatal ages at which mean values were derived are indicated near each value.

TABLE III

Case	Limited extension of hips in degrees						Withdrawal reflex with fast extension					Magnet response					After 1 year unsupported walking
	Birth	1 mth.	2 mth.	3 moth.	6 mth.	1 yr.	Birth	1 mth.	2 mth.	3 mth.	6 mth.	Birth	1 mth.	2 mth.	3 mth.	6 mth.	
1	20	ND	ND	0	0	0	+	ND	ND	—	—	+	ND	ND	+	+	FH
2	30	20	10	< 10	< 10	0	+	+	+	+	+	+	+	+	—	—	N
3	30	10	< 10	0	0	0	+	+	+	—	—	+	+	+	+	—	N
4	30	15	0	0	0	0	+	+	+	+	—	+	+	+	+	+	FH
5	30	15	0	0	0	0	+	+	—	—	ND	+	+	(+)	(+)	ND	FH
6	10	10	10	0	0	0	+	(+)	(+)	(+)	—	+	+	+	+	+	FH
7	20	10	< 10	0	0	0	+	(+)	—	—	—	+	+	+	+	—	N
8	15	< 10	10	0	0	0	+	+	+	+	—	+	+	+	+	—	FH
9	30	25	10	0	0	0	+	+	+	—	—	+	+	(+)	(+)	(+)	N
10	ND	20	15	10	0	0	ND	+	—	—	—	ND	+	(+)	(+)	—	N
11	10	< 10	< 10	< 10	0	0	—	+	+	—	—	+	+	+	+	—	N
12	20	20	ND	0	0	0	+	+	ND	+	—	+	+	ND	+	+	FH
13	20	10	10	< 10	0	0	+	(+)	+	+	—	+	+	+	+	+	FH

ND, no data; +, present; —, absent; (+), dubious; FH, flexed hips; N, normal; Mth., months(s); Yr., year.

controls until 3 months. In order to study the influence of breech position on postnatal posture of the legs in detail, the percentages of time spent in flexion, semi-flexion or extension were compared between breech and control infants. Regarding the variable knee posture in the breech group according to its three defined subgroups, only hip postures were taken into account comparing breech and control infants. Comparing the three (breech) subgroups with each other, differences in posture of both hips and knees were studied.

Comparison of flexion, semi-flexion and extension of the hips (in % of time) between the breech- and control-group. At all ages studied, the mean percentage of time during which the hips were flexed was significantly higher in the breech group than in the controls (Fig. 3a). In contrast to the control group, in the breech group hip-flexion (in % of time) declined with increasing age. No major differences between the two groups were observed regarding semi-flexion of the hips (in % of time). However, regarding hip-extension (in % of time) comparison between both groups did reveal significantly lower values in the breech group at all ages studied (Fig. 3b,c). In the breech group, the hip flexion (observed posture in % of time) showed positive correlation with the limited extension of the hips (in degrees): $HF = 1.25 \times (LE) + 43.03$, $r = 0.98$ (HF, percentage of time hips in flexion; LE, degrees of limited extension of the hips; Fig. 4), whereas hip extension (observed posture in % of time) was not related to the limited extension of the hips (in degrees).

Comparison of hip- and knee-postures (in % of time) between complete, inconsistent and incomplete breech positions. We compared the results of hip- and knee-postures (in % of time) between the three categories of breech position (complete, inconsistent and incomplete), in order to explore the influence of renatal movement restriction on postnatal leg posture. As complete breech position was found in only one infant, statistical comparison was made between incomplete (six infants) and inconsistent breech position (six infants).

Until 8 weeks, inconsistent and incomplete breech position revealed similar percentages of time during which the hips were flexed (Fig. 5a). In contrast to the incomplete breech position, in the inconsistent breech group the percentage of time during which the hips were flexed decreased at 12 weeks, yielding a significant difference between both groups ($P < 0.05$). Semi-flexion of hips in complete breech position showed the same trend as in inconsistent breech position. At 12 weeks, the incomplete breech group spent significantly more time with hips flexed, whereas the inconsistent group spent more time with hips semi-flexed ($P < 0.02$, data not shown).

At 1 week, the group of incomplete breech position revealed a significantly lower percentage of flexion in the knees together with significantly higher percentage of knee extension, compared to the group of inconsistent breech position ($P < 0.001$, Fig. 5b,c). This difference disappeared in the next 3 months.

Developmental milestones: sitting, standing, walking without support

Comparing breech and control infants, no differences appeared in the age at which developmental milestones were reached. These developmental milestones included rolling from back to belly and reverse, sitting, standing and walking. At 6 months, differences in balance while sitting, and posture while standing (with and without

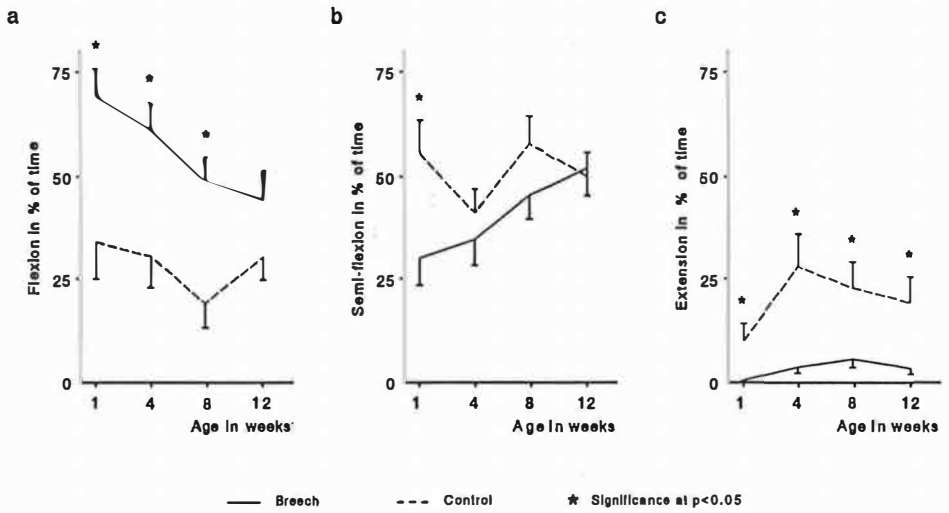

Fig. 3. Relationship between hip postures in infants born in breech position (interrupted line) and control infants born in vertex position (continuous line) with gestational age. Hip postures are expressed as flexion (a), semi-flexion (b) and extension (c) in percentage of time. significant differences are indicated with an astrix (Student's *t*-test, $P < 0.05$). Bars indicate S.E.M. values.

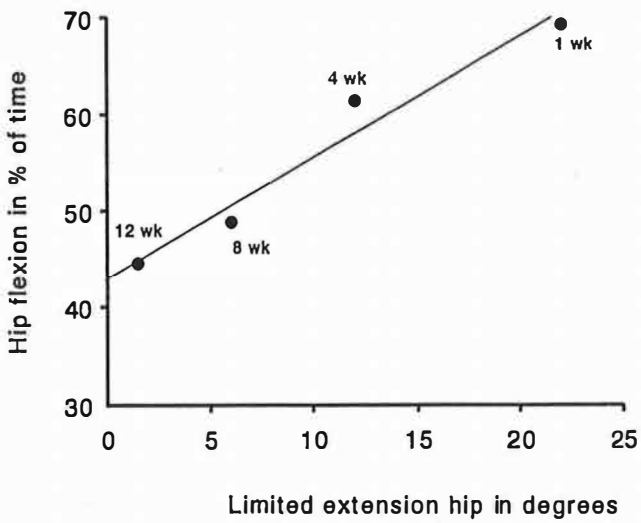

Fig. 4. Relation between hip flexion (in percentage of time) and limited extension of the hips in breech infants at 1, 4, 8 and 12 weeks postnatal age.

BREECH POSITION

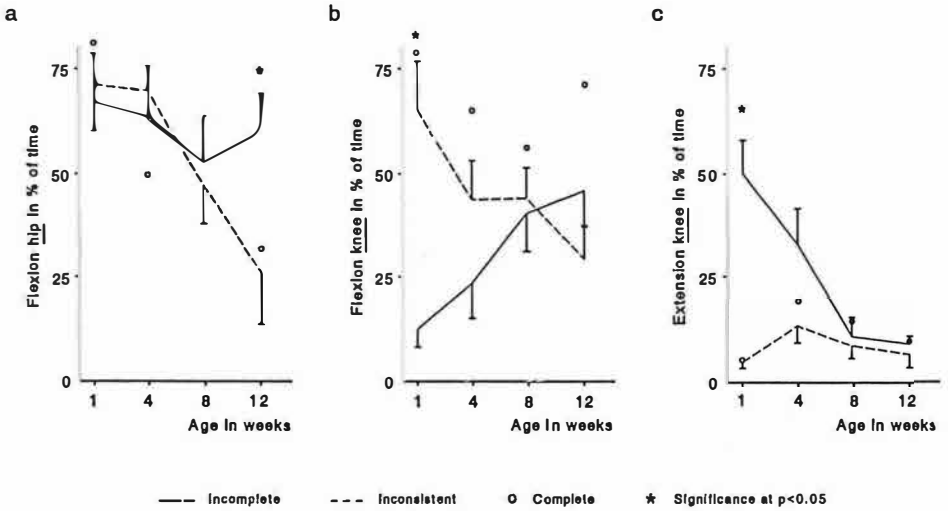

Fig. 5. Relationship between postnatal age and hip flexion (a), knee flexion (b) or knee extension (c) according to the type of breech position: (i.e. incomplete (continuous line), inconsistent (broken line) and complete (single data points)) of breech position. Significant differences between incomplete and inconsistent breech position are indicated with an asterisk (Student's t-test, $P < 0.05$). Bars indicate S.E.M. values.

WALKING POSTURE

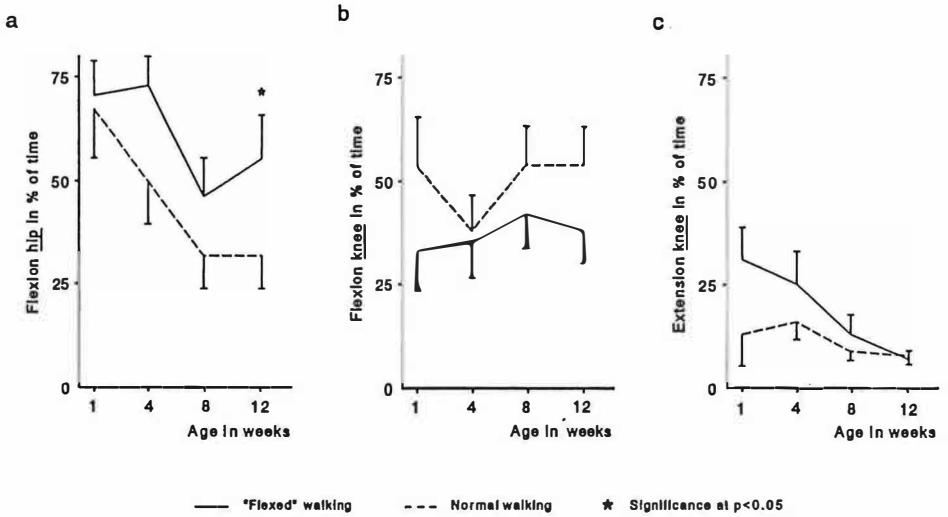

Fig. 6. Relationship between postnatal age and hip flexion (a), knee flexion (b) or knee extension (c) according to the type of walking: (i.e. 'flexed' (continuous line) or normal (broken line)). Significant differences between incomplete and inconsistent breech position are indicated with an astrix (Student's t test, $P < 0.05$). Bars indicate S.E.M. values.

support), were studied. These observations revealed no substantial differences between infants born in breech position and controls.

In addition, posture while walking without support was studied. Seven out of 12 infants from the breech group walked with a small flexion in the hips resulting in a forward bending of the trunk. These 'flexed' walkers consisted of three infants in inconsistent and four infants in incomplete breech position, compared to the normal walkers that consisted of three infants in inconsistent, two in incomplete and one infant in complete breech position (Table III). Interestingly, in six out of seven 'flexed' walkers, a positive magnet response at 6 months was found. No significant relation was observed between 'flexed' walking and extension limitation of the hip joint, nor between 'flexed' walking and the category of breech position (tested at 1 week, 3 and 6 months).

In order to explore differences in postures between normal and 'flexed' walkers at earlier ages, the longitudinal data of the first 3 months were retrospectively compared. During the first 3 months, infants that were later diagnosed as 'flexed' walkers (after the first year of life) had shown significantly more hip flexion than 'normal' walkers at 12 weeks ($P < 0.05$; Fig. 6a).

Neurological examination after the first year

Neurological examinations at 1 week and at 1 year demonstrated no abnormalities. In particular, abnormal muscle resistance to passive movements appeared absent.

Discussion

Prolonged movement restriction of the human fetus, caused by oligohydramnios, can affect the normal development of bones and joints [2,12]. Recently, we have shown that fetal movements (in particular, the quality of general movements) are also altered by a reduced amount of amniotic fluid in pregnancies complicated by oligohydramnios [18]. These alterations persist until the first week after birth. This could indicate an influence of movement restriction of the fetus on the postnatal development of motor functions. However, long term effects of prenatal movement restriction on the postnatal development of motor functions (such as reflexes, preference posture of the legs and developmental milestones) have not been systematically investigated. The present study indicates a long term effect of intrauterine movement restriction on the postnatal development of motor functions.

Neurological morbidity

Certain fetal abnormalities have been associated with an increased incidence of intra-uterine breech position [7,8,10]. Although we excluded pregnancy-related complications and retrospectively, abnormal neurological conditions at birth, it might theoretically be possible that neurological deficits causing an altered motor output of the central nervous system led to intra-uterine breech position and to the consecutive alterations in exteroceptive leg reflexes and postures. However, the quality of fetal general movements in our study was normal, which suggests absence of neurological abnormalities [16]. Regarding the quantity of fetal movements between

33 and 34 weeks gestational age, Luterkort and Maršál [11] did not reveal differences between fetuses in breech and in vertex position [11]. Furthermore, until 18 months postnatal age we could not substantiate neurological deficits in the infants of the present study. These data are in agreement with those of Faber-Nijholt [3], who reported the absence of a relationship between fetal breech position and increased neurological morbidity after excluding pregnancy and/or delivery related complications, fetal chromosomal abnormalities and congenital defects. Thus, it might be assumed that our observed alterations of the postnatal motor functions after breech position cannot be explained by a pathological condition of the developing central nervous system.

Classification of breech position

Surprisingly, the usual classification in incomplete or complete breech position did not give full account of fetal leg position(s) during the prenatal period. Our present data indicate that the type of breech position is often variable in time. In the group of inconsistent breech positions which accounted for almost 50% of all cases, we also found combinations of one flexed and one extended knee. This variability should be considered regarding the etent of intra-uterine movement restriction of the legs. Tompkins [19] described a low incidence of complete, compared to incomplete breech positions during delivery. Our prenatal data were in line with this observation; six incomplete breech positions versus one complete breech position. To underline this difference even more, the case representing the complete breech position was classified on basis of just one ultrasound recording. Therefore, it cannotbe excluded that an additional ultrasound registration would have resulted in assigning this particular case to the group of inconsistent breech position. The same reasoning holds true for the six cases which were assigned to the incomplete breech group. However, in the latter group the chance of incorrect assignment was much smaller due to the higher number of repeated recordings. Altogether, prenatal movement restriction of the hips was a common factor in all three subgroups, what was reflected by the orthopaedic finding of limited extension of all hips. This limited extension has been ascribed to abnormal growth of the fetal acetabulum due to relative fixation of the hips in flexed position [13].

Withdrawal reflex and magnet response

Our neonatal data regarding the influence of intra-uterine movement restriction on the flexion reflex and magnet response confirm the findings of Prechtl and Knol [13], who reported alterations in the neonatal withdrawal reflex and magnet response after breech position. The first detailed descriptions of exteroceptive skin reflexes stem from neuro-physiological experiments in decerebrated or spinal animals at the beginning of the century [17]. In vertebrates, the flexion reflex (caused by stimulation of the footsole resulting in contraction of the hip- and knee-flexors and in reciprocal inhibition of the extensor muscles) was found to be present. By stimulation of exteriorized human fetuses (i.e. dying fetuses just after abortion), Hooker [5] and Humphrey [6] showed the early presence of exteroceptive skin reflexes (at 11.5 weeks) as well as their persistence after abortion. The above characteristics have led to the hypothesis that neonatal exteroceptive reflexes could

be regarded as primitive and genetically programmed and stereotyped responses which disappear during ongoing maturation of the central nervous system, only to reappear during extreme pathological conditions of the adult central nervous system [1]. However, behavioural state dependency of neonatal exteroceptive reflexes [14,15] and the modification of the responses by aforementioned environmental factors such as early movement restriction suggest that these responses are subjected to epigenetic processes.

Longitudinal follow-up of the presence of the magnet response showed a decrease with age. At birth, all infants from the breech and the control group showed a positive response. However, at 26 weeks, in controls a positive magnet response was found to be almost absent [20], whereas in 60% of the breech group it was still present (Fig. 2). These results, combined with almost complete absence of limited extension of the hips at 26 weeks, indicate that the magnete response is not directly (or not completely) related to the limited extension of the hips. Although this finding does not provide direct evidence, it supports the hypothesis that altered proprioceptive input into the central nervous system is mediating.

Leg posture in breech infants and controls

At all ages studied, posture in breech infants consisted mainly of flexion in the hips. similarly to reflexes described above, the flexion of the hips showed a strong correlation with the limited extension of the hip joint (Fig. 3). Along with this limited extension a shorter (tendon length of the) iliopsoas muscle could be expected. Therefore, an inability to extend the hip could theoretically explain the frequently occurring hip flexion. However, a position of hip extension was defined as an angle between leg and trunk of more than 135 degrees, whereas the maximal (mean) limitation still allowed extension up to 160 degrees. Furthermore, spontaneous extension of the legs was found at all postnatal ages. Comparison of the longitudinal data between normal and 'flexed' walkers showed a significantly higher percentage of hip flexion at 12 weeks in the latter group. This relationship suggests an effect of increased flexion in the hips (at 12 weeks) on later locomotion.

The present study indicates a long-term effect of intra-uterine movement restriction on the development of posture (at least until the 12th postnatal week), withdrawal reflex and magnet response (up to 26 weeks), and posture of the hips during walking without support (12–18 months). Another carry-over effect of intrauterine movement restriction on postnatal motor behaviour has been previously described in pregnancies with oligohydramnios due to premature rupture of the amniotic membranes [18]. This type of movement restriction ends immediately after birth and has only short lasting postnatal effects. In the breech group, effects of movement restriction on the motor output were observed during a longer period of time. The longer lasting effect can be explained by the presence of a limited extension of the hip joint during the first 3 postnatal months in the breech group. This limited extension of the hip joint might also mediate the proprioceptive feedback during the postnatal period.

Acknowledgements

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CHAPTER 7

GENERAL DISCUSSION.
STUDIES ON MOTOR BEHAVIOUR IN COMPLICATED PREGNANCIES.

Early Human Development, 1993 (in press)

GENERAL DISCUSSION.

This thesis deals with the impact of human fetal environment and of blood supply to the fetus on the development of pre- and postnatal motor behaviour. Preexisting abnormalities within the fetal central nervous system itself were excluded from the study groups. By the recent opportunity to observe pre- and postnatal motor behaviour non invasively, studies on the value of certain deviations within fetal motor behaviour for the prognosis of the integrity of the neonatal nervous system came within reach (18). For these studies, the necessity arose to discriminate alterations within motor behaviour due to primary abnormalities within the fetal central nervous system from those due to environmental factors (which may cause secondary alterations within the central nervous system).

In the Introduction section, it is indicated that major pathology of the fetal and neonatal central nervous system leads to a quality of general movements which is essentially different from that during normal, physiological development. Instead of fluency and variability in amplitude, speed and direction, characteristics of general movements during normal pregnancies (18), general movements become monotonously abrupt during major deficits of the central nervous system (such as anencephaly (22) and chromosomal defects (8)). Also during the postnatal period, quality of general movements is discriminative between normal infants and those who develop brain lesions (cerebral hemorrhages and leucomalacia). In the latter group, signs for poor prognosis consist of an abnormal character of general movements, consequent synchronization of the limb movements, and absence of superimposed rotations of the limbs (10).

Thus, it can be concluded that major neurological deficits are related to severe abnormalities in quality of fetal general movements. In contrast to the relationship between abnormal quality of general movements and adverse neurological outcome, the relationship between abnormal quality of general movements and type of brain lesion (localisation, extent and nature) is still unclear. An unspecific effect of brain lesions upon motor function has been reported by Ferrari et al. (10). These authors hypothesized that many subsystems converge on to the central pattern generator for general movements, whereby lesion within one of the subsystems might alter the output signal of the central pattern generator. In addition, it is remarkable that unilateral lesions within the developing central nervous system do not express themselves as "hemi-defects", but as abnormalities in all four limbs (10).

In order to gain more insight in the relationship between fetal abnormalities and their expression in the quality of motor behaviour, research on fetal motor behaviour during less severe and/or more insidious alterations of the fetal brain could be helpful. Furthermore, correlating data of fetal motor behaviour with other clinical variables might help to understand the patho-physiology of related mechanisms. Therefore, fetal general movements were explored during ongoing fetal deterioration in intra-uterine growth retarded fetuses due to reduced fetal blood supply (chapter 2). Under these circumstances, a relative shift of blood flow from the fetal body to its central nervous system has been reported (24). Despite this apparent "brain sparing effect", neurological outcome may still be aversively affected (6, 13, 15). During ongoing intra-uterine growth retardation, four different stages of alteration within the quality of general movements were distinguished. These alterations in the quality of general movements appeared to be strongly related to other clinical variables of the fetal clinical condition. As indicated in the order of deteriorating clinical condition:

- No clear effect of uncomplicated intra-uterine growth retardation could be detected on the quality of general movements.
- During a reduced amount of amniotic fluid, general movements were invariably small in amplitude and slow in speed.
- At the onset of abnormal fetal heart rate patterns (i.e. fetal heart rate decelerations or reduced heart rate variability) general movements became additionally reduced in complexity (i.e. reduction in rotational components, and shifts in fetal position predominantly in one plane).
- After further deterioration of the fetal clinical condition (reduction in amount of amniotic fluid coinciding with repetitive fetal heart rate decelerations and reduction in heart rate variability) general movements became hardly discernible.

Thus it was concluded that the quality of general movements could serve as an indicator, at least in combination with other clinical variables, for the assessment of fetal clinical condition. In order to explore the value of the quality of general movements as a clinical tool during intra-uterine growth retardation, the inter-observer agreement was tested after correction for the extent of agreement expected by chance alone. Using kappa (11), the inter-observer agreement in the assessment of the quality of general movements between two trained observers appeared to be high (kappa = 0.90 ± 0.07). In this study, highest agreement was achieved with respect to normal or hardly discernible general movements (kappa > 0.90), whereas slightly lower agreements were observed regarding reduced speed, amplitude and additional complexity (0.80 < kappa < 0.85). In the present study the inter-observer agreement between two trained observers was similar to the value reported by Prechtl (18), who found an agreement of 90% in the distinction between normal and abnormal motor behaviour after consulting ten observers with varying experience (neonatologists, neuro-paediatricians and developmental neurologists).

In order to reveal possible underlying patho-physiological mechanisms during intra-uterine growth retardation, the quantitative variables of fetal general- and breathing- movements were assessed (chapter 3) and compared with the qualitative assessments and clinical variables (chapter 2). In order to correct for longitudinal effects of gestational age on the quantity of fetal movements, cross-sectional comparisons between 28-31 weeks gestational age were made. Statistical comparisons on the quantity of fetal general- and breathing- movements during three different levels of fetal conditions could be made: (1) uncomplicated intra-uterine growth retardation. (2) intra-uterine growth retardation and reduced amount of amniotic fluid. (3) intra-uterine growth retardation and abnormal fetal heart rate patterns as well as a reduced amount of amniotic fluid.

In contrast to quality of general movements, quantity of fetal (general- and breathing-) movements did not indicate statistically significant differences between the 3 levels of fetal condition. Thus, regarding the individual fetus, it was concluded that the quantitative assessment correlates to a lesser extent with the clinical condition than the qualitative assessment. Nevertheless, in the cross-sectional group between 28-31 weeks gestational age, the quantity (in median value in % of time) of both general- and breathing- movements was clearly diminished at deteriorated fetal condition.

The quantity of fetal breathing movements was found to decrease at an earlier stage of fetal deterioration than the quantity of general movements. Already during a reduction in the amount of amniotic fluid, the quantity of fetal breathing movements was found to decrease with 30 point %. It has been speculated that a diminished renal perfusion due to hypoxaemia could be an underlying mechanism for a reduced

amount of amniotic fluid (2). Therefore, it is tempting to speculate that the reduction in amount of amniotic fluid and the reduction in fetal breathing movements are both related to onset of hypoxaemia. Both in human and sheep fetuses breathing movements are temporarily reduced following acute hypoxemic events (4, 16). However, in sheep these movements return to normal values in case of chronic hypoxemia (14) and decrease only significantly with the onset of acidaemia (19). Therefore, the lower incidence of breathing movements observed in the present study, may be independent from hypoxaemia (what usually coincides with fetal heart rate abnormalities (23). After diagnosis of a reduced amount of amniotic fluid and onset of abnormal fetal heart rate patterns, a reduction of 60 point percentage of both general movements as well as of breathing movements was observed. These data on reduction of breathing and general movements in human fetuses following the onset of abnormal heart rate patterns are in line with previous observations (5, 20). Also in fetal sheep, a synchronized reduction of breathing- and limb- movements during hypoxaemia has been reported (7, 16). This phenomenon has been implied in the inhibiting influence of hypoxia on the central nervous system (9, 12). Determination of the quantity of general movements during clinical deterioration showed a reduction in the number of general movements per hour, whereas their mean duration remained relatively unaltered. Provided that the use of a 10 seconds moving window during data acquisition is negligible, the length of individual general movements appears more conserved than their frequency. This finding may be interpreted as an ongoing central inhibition during lasting hypoxaemia.

The early reduction in fetal breathing movements was hypothesized to be related to a reduced amount of amniotic fluid, which was possibly mediated by hypoxaemia. It was found that factors other than hypoxaemia also can affect the incidence of fetal breathing movements (chapter 3). Between 28-31 weeks gestational age, median values of fetal breathing movements were compared in two groups of pregnancies complicated by premature rupture of the amniotic membranes, in absence of other pathology: one group consisted of fetuses with a normal amount of amniotic fluid and the other group of fetuses with oligohydramnios. Statistical comparison clearly showed a significant reduction in the median value of the quantity of fetal breathing movements in fetuses with premature rupture of amniotic membranes and oligohydramnios compared to a normal amount of amniotic fluid (median values, chapter 3). Additionally, comparison of fetal breathing movements in pregnancies complicated by premature rupture of the membranes with those in control pregnancies showed that the percentage of fetal breathing movements in the first group did not increase with gestational age, in contrast to the situation in the latter group (chapter 4). For these observations, no conclusive explanations can be provided (yet). Beside the possibility of a direct relationship between oligohydramnios and fetal breathing activity, preliminary data suggest that elevated prostaglandin levels may play a mediating role (21).

Not only a reduction in the incidence of fetal breathing movements, but also pulmonary hypoplasia is frequently observed in pregnancies complicated by premature rupture of the amniotic membranes (1). Adzik et al. (1) suggested that compression of the fetal chest and abdomen was one of the underlying mechanisms for both reduction in fetal breathing movements and development of lung hypoplasia. In chapter 4, the relationship was studied between the incidence of fetal breathing movements and lung development in pregnancies complicated by premature rupture of the amniotic membranes and oligohydramnios. Analysis of longitudinal and cross-sectional data of fetal breathing movements showed large inter- and intra-individual

variability in incidence of fetal breathing movements. Furthermore, although fetal breathing movements tended to be lower in cases developing lung hypoplasia, no statistically significant relationship could be shown between low incidence of fetal breathing movements and lung development. These observations indicate that assessment of fetal breathing movements for prediction of postnatal lung development in individual fetuses is not reliable as a prognostic tool. In addition, the same conclusion can be drawn with respect to assessment of fetal breathing movements for an early prediction of hypoxaemia in the individual growth retarded fetus. Absence of prognostic validity of quantity of fetal breathing movements for either pulmonary hypoplasia or hypoxaemia, can be ascribed to the complex regulation of the fetal breathing incidence and to the large intra- and inter- individual variability (3).

In contrast to the quantity of fetal breathing movements, the quantity of fetal general movements was not influenced by the amount of amniotic fluid in pregnancies complicated by premature rupture of the membranes (chapter 3). However, assessments of quantity of general movements also revealed large inter- and intra-individual variability, which was shown to extinct potentially statistical differences between growth retarded fetuses at respectively low and high risk for the development of hypoxaemia, and to reduce the clinical applicability as prognostic parameter. In contrast, it was indicated that during reduction in amount of amniotic fluid, quality of general movements altered and became characterized by a reduced speed and amplitude (chapter 2). Furthermore, it was hypothesized that the reduction in amount of amniotic fluid and early quantitative reduction in fetal breathing movements could both (in)directly be related to hypoxaemia (chapter 3). This raised the question whether qualitative alterations of general movements were mediated by a reduced amount of amniotic fluid, causing movement restriction, or alternatively, reflected early, primary impairments within the central nervous system. In order to discriminate between these two possibilities, quality of general movements during a reduced amount of amniotic fluid was studied in absence of hypoxaemia (chapter 5).

As a model for this study, pregnancies complicated by premature rupture of the amniotic membranes, but in absence of other pathology, were considered. During this pregnancy-related complication, the relationship between reduction in amount of amniotic fluid and quality of general movements can be studied under a condition without indications for impaired integrity of the central nervous system. In this model, a relationship between a (severely to moderately) reduced amount of amniotic fluid and small and slow general movements was observed (chapter 4). This indicates that early alterations in the quality of general movements are closely associated with intra-uterine movement restriction and do not aversively affect the prognosis concerning the integrity of the central nervous system. Interestingly, during the first postnatal weeks, i.e. after suspension of intra-uterine movement restriction, the slow speed and small amplitude of general movements were still observed, suggesting a carry-over effect from the pre- to the postnatal period.

Another condition during which a similar pre- to postnatal carry-over effect on motor functions has been reported, involves fetuses (presenting) in breech position. Breech position can be regarded as intra-uterine movement restriction of the legs. In these infants, type and intensity of the exteroceptive leg response after stimulation of the footsole was found to relate to intra-uterine leg position (17). In order to explore the extent of this carry-over effect on motor functions during the neonatal period, fetuses in breech position were regularly recorded for intra-uterine position and for presence of movement restriction of the legs. Postnatally, the infants were repetitively screened for motor functions and neurological development up to the

developmental stage of walking without support (chapter 6). It appeared that the effects of intra-uterine movement restriction due to breech position on motor function may even outlast the first postnatal year. Although direct evidence could not be provided, exclusion of other potentially related factors (such as limited extension within the hip joint) led to the hypothesis that altered proprioceptive input into the central nervous system could be modifying.

It can be concluded from these studies that, in contrast to quantity of fetal movements, quality of general movements, in combination with other clinical variables, can serve as a reliable diagnostic tool for prediction of the fetal condition and for assessment of the integrity of the fetal central nervous system. However, in order to explore the validity of the quality of general movements as a diagnostic tool in more detail, alterations in the quality of general movements due to an impaired integrity of the fetal central nervous system should be discriminated from those caused by impaired environmental or physiological conditions. As the latter conditions might even cause longer lasting effects upon the motor function itself, follow-up research should be performed on quality of general movements in carefully defined study groups.

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CHAPTER 8

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS.

The recent possibility of non-invasive observation of fetal motor behaviour by means of ultrasound technique, has initiated research on the significance of fetal movements for assessing the prenatal neurological condition. For this purpose, longitudinal investigations on fetal movements in normal pregnancies indicated the importance of one particular movement pattern: the "general movement". In normal fetuses, general movements are complex and fluent motor patterns, which involve all parts of the fetal body in variable sequence, speed and amplitude. In undisturbed pregnancy, the characteristic appearance (the "quality") of general movements remains essentially similar from their emergence (at about 8 weeks gestational age) until 3 months after birth. During major pathology of the developing central nervous system, these optimal characteristics are consistently altered. In fetuses and newborn infants, the quality of general movements has proven to be highly discriminative between normal and severely abnormal neurological conditions. This observation suggested that assessment of the quality of general movements provides a new diagnostic tool for early detection of brain lesions.

Within this perspective, the question was raised whether the assessment of quality of general movements allows diagnosis of a more insidious or mild onset of fetal deterioration. Such information, related to other clinical variables (such as fetal heart rate patterns and amount of amniotic fluid), may reflect pathophysiological mechanisms impairing the integrity of the fetal central nervous system during ongoing deterioration. Furthermore, as this information could lead to early detection of imminent fetal jeopardy, optimalization of therapeutic intervention may come into reach.

This thesis deals with the impact of human fetal environment on pre- and postnatal motor behaviour, in order to assess the fetal and neonatal neurological condition. Pre-existing abnormalities within the fetal central nervous system were excluded from the study groups. Two approaches were chosen to study fetal motor behaviour: 1. assessment of quality of general movements, and 2. assessment of quantity of general- and breathing movements per 1 hour recording.

In chapter 1, the historical background and aims of the study are described.

Chapter 2 deals with a prospective study on intra-uterine growth retarded fetuses, containing longitudinal data on the quality of general movements in relation with other clinical variables of the fetal condition and the neurological outcome. During ongoing fetal deterioration in intra-uterine growth retardation, 4 different stages of alteration within the quality of general movements could be distinguished. These alterations in quality of general movements appeared strongly related to other clinical variables of the fetal clinical condition in growth retarded fetuses: 1. Normal quality of general movements was related to uncomplicated intra-uterine growth retardation. 2. Slow and small general movements were related to a reduced amount of amniotic fluid. 3. A poor repertoire of general movements occurred simultaneously with the onset of abnormal fetal heart rate patterns. 4. Hardly discernible general movements were observed after further deterioration of the fetal condition. From these results, it was concluded that the quality of general movements could serve as an indicator, at least in combination with other clinical variables, for the assessment

of the fetal neurological condition. Furthermore, the study indicated that in absence of additional complications, results of the standardized neurological examination tended to normalize between 3 months and 1 year.

The same intra-uterine growth retarded pregnancies as described in Chapter 2, were also analysed with regard to the relationship between the quality of general movements and the quantity of general- and breathing movements (chapter 3). Similar to quality, quantitative variables appeared related to fetal condition. In contrast to the quality, however, the quantitative variables showed a high inter- and intra-individual variation. Therefore, the quantity of general movements were indicated as unreliable indicators of the neurological condition in the individual fetus.

Furthermore, the question was addressed whether fetal breathing movements could predict neonatal prognosis, in particular with respect to pulmonary function (chapter 4). In pregnancies at high risk for pulmonary hypoplasia (oligohydramnios due to premature rupture of the membranes), the quantity of fetal breathing movements has been analysed in relation to postnatal lung development. The incidence of fetal breathing movements showed large inter- and intra-individual variability, and no statistically significant relationship between incidence of fetal breathing movements and lung development was observed. Thus, in the individual fetus, no predictive value could be derived from the quantitative assessment of fetal breathing movements for prognosis of postnatal lung development.

Chapter 5 describes the effect of intra-uterine movement restriction on the quality of pre- and postnatal motor behaviour in pregnancies complicated by oligohydramnios due to premature rupture of the membranes. In these cases, a positive correlation was observed between a (severely to moderately) reduced amount of amniotic fluid on the one hand, and small and slow general movements on the other hand. The first few weeks after birth, the slow speed and small amplitude of general movements continued to be present, despite the suspension of movement restriction at birth. These results suggested a carry-over effect of mechanical intra-uterine movement restriction on the postnatal period.

The extent and duration of the carry-over effect by intra-uterine movement restriction on postnatal motor functions was studied in more detail in infants born after intra-uterine breech position (chapter 6). A significant relationship was found between breech position and alterations in neonatal motor functions, such as preference posture of the legs, patterns of exteroceptive leg reflexes, and posture while walking without support. It was concluded that the fetal environment could exert a long-term modulating influence on the development of motor functions, extending even up to 12-18 months postnatal age.

Chapter 7 describes the interrelationhip between the various experimental results and possible underlying patho-physiological mechanisms. Furthermore, clinical implications of quantitative and qualitative variables for diagnostic purposes are discussed.

It is concluded that:
- during a chronically reduced fetal supply of oxygen and/or nutrients, alterations in quality of general movements are strongly related to variables of fetal clinical condition.
- similar to quality, also quantitative variables (of fetal breathing- and general movements) are related to the fetal condition. However, due to large inter- and intra-individual variability, quantity of general movements appears unreliable as indicator of the neurological condition in the individual fetuses.

- the unreliability of quantity of fetal breathing movements as clinical indicator is underlined, as it did not only prevent detection of fetal condition but also of prediction of neonatal pulmonary outcome.
- fetal movement restriction can alter pre- and even (long- lasting) postnatal motor functions, in absence of pathology of the central nervous system. With respect to quality of general movements, these changes concern their speed and amplitude, while complexity, fluency and superimposed rotations of the extremities remain unaltered.

The above mentioned findings may indicate that, in contrast to the quantity, the quality of general movements can be used as a non-invasive approach, in combination with other clinical variables, to assess insidious onset of mild fetal clinical deterioration. Future studies on the quality of general movements in well-defined study groups are needed to elucidate underlying structure-function relationships as well as influences exerted by fetal environment.

CHAPTER 9

SAMENVATTING

SAMENVATTING.

Tegenwoordig kan men, met behulp van ultrageluid, op een onschadelijke wijze menselijke foetale bewegingen observeren. Aangezien bewegingen informatie geven over het functioneren van het centrale zenuwstelsel, ontstond de vraag of men aan de hand van foetale gedragsobservaties een voorspelling kon doen omtrent de neurologische ontwikkeling. Om deze vraag te kunnen beantwoorden werden allereerst foetale gedragsobservaties uitgevoerd bij normale zwangerschappen met een ongestoorde ontwikkeling van het foetale zenuwstelsel. Uit deze observaties bleek dat al vanaf de vijftiende zwangerschapsweek een groot aantal bewegingspatronen aanwezig is, zoals bijvoorbeeld adembewegingen, hikken, gapen, zuigen, slikken, geïsoleerde bewegingen van hoofd, armen en benen, en zogenaamde "algemene lichaamsbewegingen" (ook wel genoemd "gegeneraliseerde bewegingen", dit zijn gecoördineerde bewegingen waaraan het gehele foetale lichaam deelneemt). Vooral dit laatste bewegingspatroon gaf op een eenvoudige wijze informatie omtrent de conditie van het zich ontwikkelende zenuwstelsel. Deze relatief frequent voorkomende "algemene lichaamsbewegingen" zijn bij de gezonde foetus vloeiend en worden verder gekenmerkt door variabiliteit in snelheid, amplitude, en volgorde waarin de verschillende lichaamsdelen aan de beweging deelnemen. Bij de ongestoorde zwangerschap blijven deze karakteristieken, ofwel de "kwaliteit" van bewegen, in essentie onveranderd vanaf het moment van ontstaan (ongeveer 8 weken zwangerschapsduur) tot aan drie maanden na de geboorte. Deze kwaliteit van bewegen bij de normale zwangerschap staat in schril kontrast met die tijdens een ernstig gestoorde ontwikkeling van het foetale centrale zenuwstelsel. Hierdoor kan men aan de hand van de kwaliteit van bewegen een onderscheid maken tussen foetussen (en pasgeborenen) met een normale of met een sterk afwijkende neurologische ontwikkeling. Dit suggereert dat het beoordelen van de kwaliteit van bewegen een hulpmiddel zou kunnen zijn om foetale hersenschade te ontdekken.

In dit verband werd onderzocht of de kwaliteit van bewegen ook bij een langzaam toenemende verslechtering van de foetale conditie als diagnostisch hulpmiddel zou kunnen dienen. Deze onderzoeksgegevens zouden in relatie met andere variabelen van de foetale conditie (zoals foetale hartritme patronen en hoeveelheid vruchtwater) kunnen verduidelijken wat de onderliggende oorzaken en mechanismen zijn van een verslechterd functioneren van het foetale centrale zenuwstelsel. Bovendien kan het, met het oog op eventuele therapeutische interventie, gunstig zijn om dreigende foetale verslechtering in een vroeg stadium te kunnen onderkennen.

Dit proefschrift gaat over de invloed van de intra-uteriene (betekent letterlijk "binnen-baarmoederlijke") omgeving op de bewegingen van het kind voor en na de geboorte en op de neurologische bevindingen. Alleen zwangerschappen zonder reeds vastgestelde neurologische afwijkingen werden in dit onderzoek betrokken. Er werden twee methodes toegepast bij het bestuderen van foetale bewegingen: 1. de beoordeling van de kwaliteit van de algemene lichaamsbewegingen en 2. de beoordeling van het aantal bewegingen (van zowel algemene lichaamsbewegingen als van adembewegingen): de zogenaamde kwantiteit van bewegen.

In hoofdstuk 1 wordt, naast bovengenoemde achtergronden, het doel van deze studie beschreven.

Hoofdstuk 2 beschrijft de bevindingen van wekelijkse gedragsobservaties die

bij intra-uteriene groei-vertraagde foetussen werden verricht. Bij intra-uteriene groeivertraging ontstaat een te kleine lichaamsgrootte van de foetus door een ontoereikende bloedtoevoer (van zuurstof en bouwstoffen) naar het ongeboren kind. Aanvankelijk ontstaat bij een verminderde bloedtoevoer alleen een achterblijvende groei van het foetale lichaam, maar bij voortdurende en langzaam toenemende tekorten zal uiteindelijk ook het centrale zenuwstelsel worden aangedaan. Bij in groei vertraagde foetussen werd iedere week de kwaliteit van bewegen vervolgd vanaf het moment dat de groeivertraging ontdekt werd tot enkele weken na de geboorte. Deze kwaliteit van bewegen werd vergeleken met de resultaten van andere methoden om de foetale conditie vast te stellen, en na de geboorte gerelateerd aan de uitkomsten van het neurologische onderzoek. Tijdens intra-uteriene groeivertraging werden bij toenemende verslechtering van de foetale conditie vier overgangen in de kwaliteit van bewegen waargenomen. Deze veranderingen in de kwaliteit van bewegen vinden tegelijkertijd plaats met een verslechtering van andere maatstaven voor de foetale conditie: 1. Een normale kwaliteit van bewegen wordt gevonden tijdens ongecompliceerde intra-uteriene groeivertraging 2. Langzame gegeneraliseerde bewegingen met een kleine amplitude zijn gerelateerd aan een vermindering van de hoeveelheid vruchtwater. 3. Een verminderde complexiteit van generaliseerde bewegingen wordt tezamen met afwijkingen in foetale hartritme-patronen gevonden. 4. Gegeneraliseerde bewegingen worden nauwelijks herkenbaar na nog verdere foetale verslechtering.

Hieruit werd geconcludeerd dat de kwaliteit van bewegingen, in combinatie met andere klinische variabelen, een hulpmiddel kan zijn bij het vaststellen van de foetale klinische conditie. Na de geboorte, in afwezigheid van bijkomende (neurologische) complicaties, lijkt de kwaliteit zich binnen een tijdsbestek van ongeveer drie maanden te normaliseren. Deze ontwikkeling wordt gereflecteerd door de bevindingen bij het neurologische onderzoek, welke zich tussen 3 maanden en 1 jaar normaliseren, mits er zich geen nieuwe neurologische complicaties voordoen.

Bij dezelfde groei-vertraagde foetussen als beschreven in hoofdstuk 2 werd ook de hoeveelheid adem- en algemene lichaamsbewegingen per uur bepaald, de zogenaamde kwantiteit. Deze kwantitatieve gegevens werden vervolgens gerelateerd aan de reeds hierboven beschreven kwalitatieve gegevens (hoofdstuk 3). In overeenstemming met de kwaliteit van algemene bewegingen, bleek ook de kwantiteit van bewegingen verband te houden met de klinische conditie van de foetus. Echter, in tegenstelling tot de kwaliteit van bewegen vertoonde de kwantiteit grote schommelingen bij verschillende registraties verricht tijdens dezelfde foetale conditie. Door deze grote variabiliteit in de kwantiteit van zowel adem- als algemene lichaamsbewegingen bleek de voorspellende waarde van de kwantiteit van bewegen voor de klinische conditie van de foetus laag. Op grond hiervan werd geconcludeerd dat de kwantiteit van adem- en algemene lichaamsbewegingen van een enkele registratie niet betrouwbaar is als hulpmiddel voor het inschatten van de foetale conditie.

Bij proefdieronderzoek was geconstateerd dat de longen zich niet goed kunnen ontwikkelen bij afwezigheid van foetale adembewegingen. Op grond hiervan werd de kwantiteit van foetale adembewegingen in de mens gerelateerd aan de ontwikkeling van de longen (hoofdstuk 4). Het was reeds bekend dat zwangerschappen met te weinig vruchtwater geassocieerd zijn met een verhoogd risico op onderontwikkelde longen bij de foetus. Als model voor deze studie werden zwangerschappen gekozen met te weinig vruchtwater ten gevolge van vroegtijdig gebroken vliezen. Binnen deze groep werd de kwantiteit van de adembewegingen wekelijks bepaald. Na de geboorte

werd de kwantiteit van adembewegingen gerelateerd aan de ontwikkeling van de longen. Net zoals bij intra-uteriene groei-vertraagde foetus vertoont de kwantiteit van adembewegingen bij zwangerschappen met voortijdig gebroken vliezen een grote variabiliteit. Mede hierdoor bleek de kwantiteit van adembewegingen geen voorspellende waarde ten aanzien van de long-ontwikkeling te hebben.

Hoofdstuk 5 behandelt de invloed van intra-uteriene bewegingsruimte-beperking op de kwaliteit van algemene lichaamsbewegingen van de foetus en pasgeborene. Als model voor intra-uteriene bewegingsruimte-beperking werd gekozen voor zwangerschappen met te weinig vruchtwater ten gevolge van voortijdig gebroken vliezen. In deze zwangerschappen houdt een vermindering van de hoeveelheid vruchtwater verband met langzame algemene lichaamsbewegingen met een kleine amplitude. Opvallend is in dit verband dat zeer vergelijkbare langzame lichaamsbewegingen met een kleine amplitude ook na de geboorte worden gevonden, terwijl er dan geen sprake meer is van bewegingsruimte-beperking. Dit suggereert dat de effecten van bewegingsruimte-beperking op de bewegingen zijn overgedragen van voor tot na de geboorte.

De mate en duur van het effect van intra-uteriene bewegingsruimte-beperking op bewegingen na de geboorte werd in meer detail bestudeerd in kinderen die geboren waren na een intra-uteriene stuitligging (hoofdstuk 6). In deze onderzoeksgroep bestaat er een relatie tussen de stuitligging voor de geboorte en verschillende bewegingsfuncties na de geboorte, zoals voorkeurshouding van de benen, beenbewegingen na prikkelen van de voetzool en houding tijdens lopen zonder steun. Hieruit volgt de conclusie dat de foetale omgeving invloed kan uitoefenen op de ontwikkeling van bewegingsfuncties, zelfs tot op een leeftijd van 12-18 maanden.

In hoofdstuk 7 worden de bovengenoemde onderzoeksresultaten met elkaar in verband gebracht en worden mogelijk oorzakelijke mechanismen besproken. Tenslotte wordt aandacht besteed aan de klinische relevantie van de kwaliteit en kwantiteit van bewegen met betrekking tot diagnostische doeleinden.

Conclusies uit het in dit proefschrift beschreven onderzoek:

- gedurende een chronisch ontoereikende foetale toevoer van zuurstof en/of bouwstoffen (intra-uteriene groeivertraging), vinden er veranderingen plaats in de kwaliteit van algemene lichaamsbewegingen. Deze veranderingen zijn sterk gerelateerd aan andere maatstaven voor de foetale conditie.
- onder deze omstandigheden verandert, evenals de kwaliteit, ook de kwantiteit van de foetale bewegingen. Echter, deze kan niet als betrouwbaar hulpmiddel ter vaststelling van de neurologische conditie dienen in verband met een forse variabiliteit.
- de grote spreiding in de hoeveelheid adembewegingen is er mede-verantwoordelijk voor dat deze waarde geen betrouwbare, individueel-voorspellende waarde heeft met betrekking tot long-ontwikkeling en -rijping.
- foetale bewegingsruimte-beperking kan niet alleen voor, maar ook tot (lang) na de geboorte aanleiding geven tot veranderingen in bewegingsfuncties, zonder dat er afwijkingen gevonden worden bij het algemeen neurologische onderzoek.

Uit de bovengenoemde bevindingen kan worden geconcludeerd dat de kwaliteit van bewegen gebruikt kan worden als betrouwbare, niet-invasieve maatstaf om een langzaam toenemende verslechtering van de foetale klinische conditie op te sporen en te vervolgen. Toekomstig onderzoek bij nauwkeurig omschreven studiegroepen is nodig om de verantwoordelijke, onderliggende relaties tussen structuren van het zenuwstelsel en hun functies nader op te helderen.

CURRICULUM VITAE

Deborah Anita Sival
geboren te Utrecht op 28 augustus 1960

1972 - 1978	Gymnasium ß
1978 - 1979	Propaedeuse studie Geneeskunde Rijksuniversiteit te Gent (België)
1980	Begin studie Geneeskunde Erasmus Universiteit Rotterdam
1987	Artsexamen, Erasmus Universiteit Rotterdam
1987 - 1992	Promotie onderzoek, Instituut voor Ontwikkelingsneurologie, Rijksuniversiteit/Academisch Ziekenhuis Groningen (hoofd: prof.dr. H.F.R. Prechtl)
1992 - heden	Opleiding tot neuroloog, Academisch Ziekenhuis Groningen (hoofd: prof.dr. J.M. Minderhoud, opleider:prof.dr. H.J.G.H. Oosterhuis)

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