Fetal Behavior in High-risk Pregnancies Assessed by Two-Dimensional (2D) and Three-Dimensional/Four-Dimensional (3D)/(4D) Ultrasound: A Review

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Abstract: Direct assessment of functional development of the fetal central nervous system is not possible, but the assessment of fetal behavior may provide the possibility to distinct between normal and abnormal brain development. Since the ultrasonographic technique allowed the investigation of spontaneous fetal motor activity *in utero* first studies of spontaneous prenatal movements and fetal behavior were performed and published. 2D ultrasound was considered somewhat subjective method because information needs observer interpretation. The latest development of three-dimensional (3D) and four dimensional (4D) sonography that overcame some of the limitations of 2D methods enable precise study of fetal and even embryonic activity and behavior. In the following text we reviewed the literature on the behavior in the high-risk pregnancies for cerebral palsy assessed by the ultrasonographic techniques.

Keywords: Fetal behavior, high-risk pregnancies, cerebral palsy, behavior in fetus with congenital disorders, antenatal behavior screening.

INTRODUCTION

Fetal behavior could be described as any fetal action or reaction on stimuli that could be observed by the mother or other more objective method as ultrasonography. Through history, maternal registration of fetal movements and obstetrician auscultation of fetal heartbeats in the previous century were the only methods of the follow up of fetal well being *in utero.* A turning point in the assessment of fetal behavior was the development of real time two-dimensional (2D) ultrasound that enabled the direct visualization of fetal anatomy and activity. Investigators started to analyze the dynamics of fetal behavior in comparison with morphological studies which led to the conclusion that fetal behavioral patterns directly reflect developmental and maturational processes of fetal central nervous system. Therefore, it was suggested that the assessment of fetal behavior in different periods of gestation may provide the possibility to distinct between normal and abnormal brain development, as well as early diagnose of various structural or functional abnormalities.[1] However, 2D ultrasound was considered somewhat subjective method because information needs observer interpretation. The latest development of three-dimensional (3D) and four dimensional (4D) sonography that overcame some of the limitations of 2D methods enable precise study of fetal and even embryonic activity and behavior. The use of new technologies showed that fetal activity occurs as early as the late embryonic period, which is far earlier that a mother can sense it and from that time we can say that fetal behavior can be defined as any fetal activity observed or recorded with ultrasonographic equipment.

Although more than 100 years of curiosity in fetal behavior and almost three decades of sustained awareness and research, the study of fetal behavior has achieved widespread acceptance in perinatal medicine. As it is not yet possible to assess functional development of the CNS directly, it was the window for the investigators to analyze fetal behavior as a measure of neurological maturation including properties of fetal hemodynamics and the muscular system, as well.[2] Since this technique allowed the investigation of spontaneous fetal motor activity *in utero* first studies of spontaneous prenatal movements and fetal behavior were performed and published.

In the following text we reviewed the literature on the behavior in the high-risk pregnancies for cerebral palsy that were defined according to our previous study.[3,4] Although we were aware that major prenatal pathologies associated with CP are prematurity, antepartum hemorrhage, complications of multiple pregnancy, genetic disorders, intrauterine infection, intrauterine growth restriction, maternal coagulopathies, multiple congenital anomalies, maternal diseases (hypothyroidism, diabetes, drug abuse, severe pre-eclampsia, viral illness) placental pathology, tight nuchal cord, fetal hemorrhage and fetal rhesus disease, we also included prenatal history of

neuromuscular disease which can adversely affect fetal movements and their inadequate interpretation.[5]

Fetal Behavior in Pregnancies Complicated by Maternal Diabetes Mellitus Type 1

Among previously mentioned risk states for disturbed fetal behavior and motility one of the most investigated is maternal diabetes mellitus, mostly type-1. Those pregnancies were shown to be often complicated by early fetal growth delay and congenital malformations that frequently involve the nervous system. Both abnormal embryogenesis and early growth restriction are suggested to shear the common mechanism. One of the first study on that matter was performed in order to determine whether there is a specific delay in the emergence of specific fetal movement patterns, as an expression of the functional motor development of the nervous system in embryos and fetuses of ten women with type-1 diabetes.[6] All women had tight metabolic control achieved with continuous subcutaneous insulin infusion which in half patients started before conception. The results showed that there is a delay of 1-2 weeks in almost all but one of the movement patterns emerging in the first 12 weeks of gestation. Only fetal breathing movements (FBM) were observed for the first time at the same gestational age as in the control group. If the results were plotted according to crown-rump length the emergence of fetal movement patterns occurred, however, almost at the same time as in the control group. It was concluded, that in well controlled diabetic pregnancy there is a delay in functional motor development of the embryonic and fetal nervous system that was shown not to be very specific but mostly dependant on growth delay. On the contrary, breathing movements emerge relatively early as compared to growth.[6] Next step in the investigation was to study the effects of tightly controlled maternal (type-1) diabetes mellitus on the development of fetal behavioral states.[7] These states named 1F to 4F were previously identified as organizational states of fetal eye movements, body movements and fetal heart pattern that could be observed from 38 to 40 weeks of gestation.[8] All the women that participated in the study were treated with continuous subcutaneous insulin infusion (CSII) therapy and were adjusted to an insulin-pump before conception or during early pregnancy. The fetuses were longitudinally studied between 32 and 40 weeks postmenstrual age, at intervals of 2 weeks with 2 hr recordings of fetal heart rate, uterine contractions and of real-time ultrasound scanning for fetal body movements, breathing and eye movements. Four fetal behavioral states were defined by the presence and the combination of following variables: fetal heart rate, body movements and eye movements. They found poorly developed state organization exhibited by the near term fetuses of the diabetic group that was related to maternal parity, but not to pre or postconceptional onset of insulin-treatment. The fetuses of nulliparous diabetic women showed more often asynchrony of transition and interruption of periods of concordant association which resulted in significantly higher percentages of 'no-coincidence' and in low incidence of behavioral states as compared with control fetuses of nulliparous women. On the other hand, in the multiparous diabetic cases studied near term the development of fetal behavioral states was normal, although the low number of those cases must be mentioned. Therefore, the one can conclude that, despite tight control of maternal blood glucose levels, the development of behavioral states was disturbed in fetuses of nulliparous diabetic women. The information about the exact blood levels of glucose before conception and in the early pregnancy that were later shown to may have influence on the results was not provided. These first studies showed that real-time ultrasound observation of fetal movement patterns can be used to assess the development of the motor component of the nervous system and that a tight metabolic control, achieved with continuous insulin infusion, does not prevent these disturbances in development.[6,8,9]

Previously shown a 1-2 weeks delay in the first appearance of all movement patterns which normally emerge during the first 12 weeks of pregnancy was confirmed by the next study by Mulder and co.[10] Breathing movements were again observed for the first time at an earlier age than in the control fetuses. Again one-hour recordings were made once a week between the 7th and 17th week of gestation in the diabetic women that were being treated with continuous subcutaneous insulin infusion therapy and data were compared to those obtained in uncomplicated pregnancy. The new findings were made when the emergence of frequently occurring movement patterns was plotted against fetal crown-rump length, which is usually smaller in diabetic pregnancy, and there was still a general delay in comparison with the control group. It was concluded that delay in motor development therefore does not run completely parallel with the delay in growth which indicates the possible existence of a specific diabetes-related influence on the functional development of the embryonic and fetal nervous system. Hyperglycemia was considered to be responsible, as the delay in the emergence of fetal general movements was most profound in the women whose periconceptional quality of glucose control was poor. When investigators looked in to the developmental trends in the occurrence of movement patterns in diabetic pregnancies they found the similarity to those in the control fetuses, with the exception of startles. It was found that before the 9th week of gestation, fetal movements occurred less frequently which was related to the quality of maternal glucose control. After 12 weeks, the overall incidence was higher than in the control group, due to an increase in the incidence of breathing movements that was generally slower than in the control group.[11]

The generation of body and breathing movements was studied in relation to behavioral states in near-term fetuses and

newborn infants of women with well-controlled type-1 diabetes.[12] Before birth, 2-h recordings were made of fetal heart rate and of fetal body movements, breathing and eye movements while the neonates were studied polygraphically during 6-h for heart rate, body movements, respiration, eye movements and EEG-pattern. The results showed that the generation of body movements was similar in the fetuses of the diabetic and control groups. After birth, the duration per burst was longer in the diabetic group, both in state 1 and state 2, resulting in increased incidences. The incidence of fetal breathing movements was confirmed to be higher and breathing rate was considerably slower in the diabetic group than in control fetuses what indicates altered regulation of breathing movements in diabetic pregnancy. In the neonates, breathing rate was identical in both groups; it was slower in state 1 than in state 2; such a difference was not present before birth, but periodic breathing occurred more often in the infants of diabetic women, especially in state 2. This study showed the continuity of the poor behavioral state regulation from prenatal into postnatal life in the diabetic group which resembled that of more immature fetuses and infants indicating that this cannot be attributed to the instantaneous unfavorable condition, like hyperglycemia before birth.[12]

For further investigation of the impact of early growth delay on subsequent growth (birth weight) and functional development near term (organizational level of fetal behavioral states) the same group investigated 21 and 10 fetuses of diabetic women, respectively.[13] They found no relationship between the degree of early growth delay and birth weight, while the mean growth delay per fetus in early diabetic pregnancy was negatively correlated with the occurrence of no-coincidence between behavioral state parameters at 36 weeks. Those results have shown that disorders occurring in early life may underlie abnormal functional development in later life, whereas (catch up) growth is mainly determined during the second half of pregnancy. These results corroborate their following findings in the fetuses at 32-38 weeks of gestation in type-1 diabetic pregnancy.[14] The occurrence of fetal breathing movements was studied in relation to the fetal heart rate patterns (HRPs) A and B and to Braxton Hicks' contractions by simultaneous 2-h recordings of fetal heart rate and body, eye and breathing movements. During the recordings, breathing activity remained unchanged at all gestational ages studied, in contrast to the gradual decline in fetal breathing movements seen in normal pregnancy. Braxton Hicks's contractions had no effect on FBM, which differs from the specific distribution of FBM during uterine contractions as previously found in uncomplicated pregnancies. They concluded that the (neural) mechanism underlying FBM differs from that in normal pregnancy resulting in breathing movements in late diabetic pregnancy being not influenced by Braxton Hicks' contractions and not showing a clear-cut state-dependency.[14]

To assess the fetal behavioral response to maternal hypoglycemia Reece and coworkers achieved low glucose plasma levels that were sufficient magnitude to elicit counter regulatory hormones and a symptomatic response by insulin clamp technique.[15] The fetuses of insulin-dependent diabetic women was studied in the third trimester by monitoring fetal heart rate and recording fetal body and breathing movements and by performing Doppler waveform analysis with real-time ultrasonography. Maternal levels of glucagon, cortisol, epinephrine, and growth hormone were measured at each plasma glucose level. The results showed that mean number of fetal limb and body movements did not changed depending on maternal blood glucose levels. In addition, no significant reductions in fetal breathing movements or heart rate were observed, although maternal epinephrine and growth hormone levels were significantly increased. These data suggest that fetal well-being remains unaltered in spite of moderate maternal hypoglycemia in diabetic women.[15]

Unlike the previous described methods for observing fetal movements that were used in the clinical practice in the next study the investigators compared third-trimester fetal biophysical activities in normal and well-controlled insulin-dependent diabetic pregnancies.[16] Serial bimonthly fetal biophysical studies were performed from 30 to 38 weeks in 18 normal and 18 well-controlled insulin-dependent diabetic pregnancies. Each study contained 60 minutes of simultaneous ultrasonographic recordings of fetal breathing movements and rates, baseline heart rate, and body movements. Women in the diabetic group maintained good glycemic control and were delivered of normal infants of weights similar to those of nondiabetic gravitas. Their fetuses had higher mean incidences of fetal breathing movement, fetal heart rates, and fetal breathing rates but lower fetal movements and fetal heart rate acceleration counts than did controls throughout the study. Neither short- nor long-term maternal glycemic levels correlated well with fetal biophysical performance. These results confirmed previously reported results that in spite of good maternal glycemic control fetuses of diabetic women behaved differently from those of no diabetic women. As in this study maternal levels of glucose were followed only from the 30th week it is possible that modulation of fetal biophysical activities could be affected by maternal glycemic status before the last trimester.[16]

To assess the effect of type-I diabetes on the quality of general movements (GMs) Kainer and coworkers analyzed GMs longitudinally in 12 human fetuses at two-weekly intervals from 16 weeks until delivery.[17] All fetuses showed normal GMs at 16 weeks, but from 20 weeks onwards until delivery five fetuses developed abnormal GMs. The diabetes optimality-score was significantly lower in the group with abnormal GMs whereas the pregnancy optimality-score did not differ between fetuses

with normal and abnormal GMs. These results indicate that type-I diabetes can have a negative impact on prenatally observed GMs and that consistently normal GMs indicate normal neurodevelopmental outcome at 10 months. Although the very important observation on the effect of type-I diabetes on the quality of general movements relatively small number of observed fetuses can not be denied.

To synthetize we can say that all mentioned published studies confirmed at least slight impact of maternal diabetes mellitus on fetal and even embryonic movements and behavior. The delay of mergence of spontaneous motility was shown to be independent on growth delay and changes of motility could not be explained by the mother glycemic control. Disturbed organization of behavioral states and general movements in fetuses in pregnancies complicated by the diabetes mellitus demand further investigation by the 3D and 4D technologies that will clarify the neurobehavioral changes in these fetuses.

Fetal Behavior in Pregnancies Complicated by Intrauterine Growth Restriction (IUGR)

Intrauterine growth restriction is a common clinical problem which is one of the main risk factors of fetal mortality and morbidity and can have long-term metabolic consequences, such as an increased propensity for some of the most common diseases of adult life like metabolic syndrome, namely obesity, arterial hypertension, hypercholesterolemia, cardiovascular disease and diabetes mellitus type 1. One of the first study on the impact of growth restriction on the fetal behavior focused on fetal breathing and on the course of behavioral state.[18] To achieve that goal Van Vliet and his group used real-time ultrasound scanners to detect fetal eye, body, and breathing movements, and the fetal heart rate of 12 growth-retarded fetuses between 36 and 40 weeks of gestation. The mean incidence of fetal breathing was greater during periods of fetal activity (body and eye movements present, greater heart rate variability) than during quiescence (body and eye movements absent, narrowed heart rate variability) at all gestational ages studied in both low-risk and growth-retarded fetuses. During periods when one of the state variables was in its active condition while the other two were quiet, or the reverse, the incidence of fetal breathing was intermediate between those found when all three state variables were in agreement. After behavioral states had developed, at 38 and 40 weeks, the mean incidence of fetal breathing in the low-risk fetuses was greater during active states than during the quiet state. There was no apparent increase in the degree of linkage between fetal breathing and other expressions of fetal activity after the emergence of behavioral states.[18] In another study by the same group behavioral state observations were carried out on 12 fetuses which subsequently had birthweights below the 10th percentile.[19] Their gestational ages at the time of study ranged from 32 to 40 weeks. Real-time ultrasound scanning was used to detect fetal body and eye movements, and the fetal heart rate was continuously recorded using a clinical fetal monitor. The appearance of states seemed to be delayed in the growth-restricted fetuses since states were present in only three of eight growth-restricted fetuses studied at 40 weeks. Also at 40 weeks, the proportion of discordant association of the state variables was increased in the growth-restricted fetuses as compared to the control. There were no consistent differences between the two groups in the occurrence of defined combinations of parameters of the state variables at earlier ages. The results from this study showed that the growth-restricted fetuses have impaired quality and quantity of somatic motility in comparison to low risk fetuses of equivalent gestational age. These observations suggest that some aspects of central nervous system function are disturbed in growth-retarded fetuses, even in the absence of fetal distress.[19]

Since asymmetrical intrauterine growth restriction occurs earlier than symmetrical or combined one it was important to study the fetal behavior in the group of fetuses that develope growth restriction in earlier gestational age. For that purpose the behavior of 15 asymmetrical intrauterine growth restricted fetuses was compared to that of a control group of healthy fetuses by simultaneous cardiotocographic and ultrasonographic examinations.[20] Behavioral states analysis was carried out according to Nijhuis et al[8] and fetal movements were automatically synchronized with FHR and grouped for each FHRP. There were no statistical differences in the distribution of FHRP between healthy and IUGR fetuses. On the other hand quantitative differences were found when the movements investigated were related to FHRP. Moreover IUGR fetuses showed a reduction of state 1F (quiet sleep) and an increase of periods of no coincidence between behavioral state variable when compared to the control group fetuses. These findings, therefore suggest the existence of quantitative differences in fetal behavior in asymmetrical IUGR fetuses when compared to healthy fetuses.[20] To see wether these differences were caused by the compromised vascularization the degree of vascular peripheral resistance was evaluated by means of pulsed Doppler ultrasonic equipment in the group of asymmetrical growth restricted fetuses and in control group.[21] All fetuses underwent simultaneous cardiotocographic and echographic examinations for two consecutive hours at 36-38 weeks of gestation. The distribution of gross fetal body movements, fetal breathing movements and fetal eye movements was analyzed during the different fetal heart rate patterns. Furthermore, the incidence and organization of fetal behavioral states was investigated. Growth restricted fetuses were divided into two groups on the basis of the presence or absence of end diastolic flow in the fetal thoracic descending aorta. The results were in accordance with previous findings that growth restricted fetuses showed a delay in the integration of behavioral patterns and a lower coincidence of behavioral states. These findings are particularly

evident in the fetuses with a severe increase of peripheral vascular resistance (absence of end diastolic flow in descending aorta) suggesting that a delay in central nervous system development is present in asymmetrical growth retarded fetuses and that there is a possible relationship of this delay to the degree of peripheral vascular resistance.

Since general movements are considered to be important for prediction of fetal neurobehavior next step was to study the effect of severe intrauterine growth restriction on its quality.[22] The study was performed longitudinally in 17 human fetuses and fetal movements were recorded by means of weekly 1 h ultrasound and video registrations, following by neurological examinations after birth. No clear effect of uncomplicated intrauterine growth restriction could be detected on the quality of general movements, but the quality was disturbed. General movements became slow and small in amplitude 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, while they were hardly discernible after further deterioration of the fetal condition. With the exception of 3 infants with cerebral hemorrhages, the quality of general movements observed just before and after birth was identical. 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. This study showed that in contrast to prenatal period 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.[22] In another study by the same group 17 fetuses with intrauterine growth restriction (IUGR), the quantity of general movements and fetal breathing movements were studied both cross-sectionally and longitudinally.[23] In IUGR fetuses, cross-sectional comparisons were made between the quantity of fetal movements and the fetal clinical condition and 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. The quantity of general movements as well as that of breathing movements was low in IUGR group with abnormal fetal heart rate patterns compared to group with normal parameters. In group with reduced amount of amniotic fluid 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 was 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 discouraged the use of quantitative aspects of general movements and breathing movements as reliable indicators of the neurological condition in the individual fetus.[23] On the other hand Ribbert and coworkers showed that the assessment of fetal activity may be of help in fetuses with a marginally reduced FHR variation, in which prolongation of pregnancy is considered desirable to allow further maturation *in utero*.[24] In order to determine changes occurring with time they longitudinally studied fetal heart rate variation, general movements, breathing movements and hemodynamics in 19 intrauterine growth restricted fetuses, who eventually were delivered by caesarean section (CS) because of fetal distress. In 14 of 19 fetuses abnormal velocity wave forms were present from the beginning of the study onwards. FHR variation was initially just within or below the norm and fell further during the last 2 days before CS. General movements and breathing movements fell below the normal range later and in a lower rate of occurrence than FHR variation. FGM showed a more or less consistent fall in time, whereas FBM showed a wide range throughout the period of observation. The poorest outcome occurred in fetuses with reversed end-diastolic velocities and rapid fall in FHR variation. It was concluded that with progressive deterioration of the fetal condition abnormal velocity wave form patterns occur first; FHR variation is reduced subsequently while GMs and FBM are the last to become abnormal.[24]

In another study fetal heart rate (FHR) variation and movements (FA) was investigated in 27 normally grown fetuses and in 18 fetuses with intrauterine growth restriction (IUGR).[25] The results confirmed previously shown decrease of fetal movements in IUGR fetuses as compared to normally grown fetuses at all gestation times. The investigators reported that IUGR fetuses also spent a significantly lower proportion of time exhibiting high FHR variation at 28-31 weeks. If the fetal movements were compared to FHR one can conclude that more of the IUGR fetuses had abnormalities of movements. Finally, within the IUGR fetuses, those with small head circumferences (less than 3rd centile) had lower movement rates during periods

of both low and high FHR variation, though this was only statistically significant for periods of low FHR variation. This published report offered the possibility that objective evaluation of fetal behavior could be used in a clinical setting and could provide a more sensitive method of fetal assessment than biophysical profile scores.[25]

A causal relationship with the impairment of fetal oxygenation has been suggested for a reduction in the incidence of fetal movements and in fetal heart rate variation. To test those hypothesis 16 IUGR fetuses and 13 normally grown fetuses were observed during maternal hyperoxygenation that was applied for 40 min in order to increase fetal PO_2 levels.[26] All IUGR fetuses had abnormal Doppler blood velocity waveforms of the umbilical artery suggesting an impaired uteroplacental exchange. The effect of hyperoxygenation on fetal breathing and body movements and on fetal heart rate was evaluated. In the IUGR fetuses there was a significant increase in fetal breathing and body movements and in heart rate variation during hyperoxygenation as compared to the preceding control period of 40 min. No significant changes in fetal breathing and body movements were found in the normally grown control fetuses. A surprising observation was the increase of the number of heart rate decelerations after discontinuation of the maternal hyperoxygenation. It was concluded that in IUGR fetuses the increase in fetal heart rate variation and the increase in the incidence of breathing and body movements during maternal hyperoxygenation substantiates the relationship between these variables and the oxygenation status of the fetus.[26]

The implementation of 4D sonography was necessary to find out whether the quantity of fetal facial expression and quality of body movements can be used as an additional diagnostic criterion for prenatal brain impairment in fetuses with growth restriction. For that purpose a prospective study was conducted in 50 pregnant women with a growth restricted fetus and in 50 uncomplicated healthy women in the third trimester of pregnancy.[27] 4D ultrasound observation was specially designed to assess whether functional brain impairment and fetal growth restriction had prenatally occurred by the utilization of several behavioral patterns. The results showed that the median value of all movement patterns in the normal fetuses differed from fetuses with intrauterine growth restriction (IUGR). Statistical evaluation revealed significant differences in the distribution of the movements between these groups. A tendency that IUGR fetuses have less behavioral activity than normal fetuses was noted in all observed movement patterns. Correlation reached statistical significance between normal and IUGR fetuses in the third trimester in hand to head, hand to face and head retroflexion. Statistically significant differences could be shown in the distribution of the median values of observation over the five qualitative categories of head and hand movements. These recent data on IUGR fetuses obtained by 4D sonography are stimulating and might result in a more effective strategy to assess development before birth and may encourage future use of 4D ultrasound for quantitative and qualitative assessment of fetal behavior as possible indicators of the neurological condition in IUGR fetuses.[27]

Fetal Behavior in Pregnancies Complicated by Alcohol use in Pregnancy

Alcohol (ethanol) use during pregnancy is important factor which can produce a wide spectrum of effects in the developing embryo and fetus that are dependent on the maternal drinking pattern. The effects of chronic ethanol exposure on the developing conceptus includes ethanol teratogenesis, manifesting in the human as the fetal alcohol syndrome and other alcohol effects while acute ethanol exposure on the near-term fetus include suppressed fetal breathing movements, electrocorticographic activity and electrooculographic activity.[28] One of the first studies on the effect of maternal ingestion of ethanol was conducted in 11 healthy pregnant women at 37 to 40 weeks' gestation and fetal breathing movements, gross fetal body movements, and fetal heart rate were analyzed.[29] It was shown that fetal breathing movements were almost abolished within 30 minutes of the alcoholic drink and remained significantly decreased for 3 hours which confirmed some previous results.[30] On the other hand the incidence of gross fetal body movements before or after ethanol was not different from that on the control day, and the fetal heart rate was not changed after maternal ingestion of ethanol.

Disturbed behavioral state organization has been found in the near term fetuses from pregnancies with maternal alcohol abuse.[31] The abnormalities included frequent interruptions of the periods of concordant association of 2F-parameters, reflected by a high proportion of no-coincidence, and spontaneous awakenings (State 4F), always following stable periods of State 1F. The latter phenomenon was not found previously, neither in normal nor in complicated pregnancies. After birth normal state organization was found. It was suggested that the abnormalities in fetal behavior might have been due to maternal alcohol abuse, whereas a possible withdrawal effect might have occurred *in utero*.[31]

Although disturbed sleep regulation has been observed in neonates of women who drank heavily during pregnancy it was unknown if an occasional drink affects fetal sleeping behavior. For that purpose Mulder and his group examined the effects on fetal behavioral state organization of two glasses of wine in 28 near-term pregnant women.[32] Simultaneous 2-h recordings of fetal heart rate and body, eye, and breathing movements were made on two successive days, once without alcohol exposure and once during maternal alcohol consumption. The study was standardized for time of day and fetal sleep state, i.e. the start of recording was either during quiet sleep or during active sleep. It was found that alcohol intake reduced fetal eye movements,

disorganized behavioral state organization (rapid eye movement sleep was affected in particular), and suppressed fetal breathing activity almost completely. This study revealed that even modest maternal alcohol intake affected fetal behavioral state organization, which reflects an immediate effect on fetal brain function.[32]

Fetal Behavior in Pregnancies Complicated by Drug use in Pregnancy

In utero cocaine exposure is associated with poor head growth, abnormal neurodevelopment, and an increased incidence of sudden, unexplained death, suggesting that in utero cocaine exposure disrupts the central regulation of breathing what is due to altered CNS maturation. Since components of fetal behavioral state organization reflect the successful integration of the central nervous system with a specific developmental timetable, and can be studied by fetal ultrasound techniques, the group of authors developed a strategy for assessing the state organization of the fetus exposed to cocaine in utero by 2D ultrasound techniques.[33] Fetal assessments were accomplished by serial ultrasonographic examination, videotaped, and scored by a scheme developed by the authors. Abnormal or delayed state behavior was identified in 13 of 20 fetuses. State organization was evaluated as suspect or abnormal for 16 of the 20 exposed newborns suggesting that disorganized behavioral state in the fetus successfully predicted abnormal newborn behavior. These findings support the concepts that cocaine exposure disrupts central nervous system development and that fetal assessment of state is predictive of neonatal outcome.[33]

The negative impact of cocaine was report on a series of ultrasound observations on a fetus of the mother who was a user of cocaine until 18 weeks of gestational age, but after this age used it only once at 31 weeks of gestation.[34] It was shown that exposure to cocaine resulted in prolonged periods of inactivity interspersed with periods of increased general activity and an increased number of startles. This was particularly evident immediately following exposure to cocaine but behavior appeared to become more normal with time as the mother stopped using cocaine. The behavioral states of the cocaine exposed fetus were also different from unexposed fetuses. Longer periods were spent in states 1F and 4F and less time in state 2F. Other studies are in agreement with these findings with additional result of fetal (Table 1) being less time in state 4F.[35] Furthermore the incidence of periods where no states were observed was considerably higher. These observations confirmed that maternal cocaine use disrupts the behavior of the fetus indicating a direct effect on the CNS and showed the value of prenatal behavioral observations to assess the effects of neurotoxic agents.

The effect of methadone on fetal neurobehavioral functions was investigated in women attending a substance abuse treatment facility with otherwise uncomplicated pregnancies.[36] Fetal behavior was evaluated at peak and trough methadone levels and the fetal measures included heart rate, variability, periodic accelerations/decelerations, motor activity, and fetal movement-heart rate coupling. The results revealed that fetuses displayed less motor activity, and the integration between heart rate and motor activity was attenuated at peak level of methadone and it was concluded that maternal methadone administration has significant effects on fetal behavioral functions that are independent of maternal effects.[36]

Fetal Behavior in Pregnancies Complicated by other Risk Factors in Pregnancy

Intrauterine adequate levels of thyroid hormones have been shown to be absolutely necessary for early brain development. During pregnancy, both maternal and fetal thyroid hormones contribute to fetal brain development and maternal supply explains why most of the athyreotic newborns usually do not show any signs of hypothyroidism at birth, while thyrotoxic fetuses may develop goitre, tachycardia, hydrops associated with heart failure, growth retardation, craniosynostosis, increased fetal motility and accelerated bone maturation.[37] It was shown that fetal movements and fetal heart rate are the most valuable indicators of thyroid function in the fetus and their intense control is necessary from the beginning of the second trimester in cases of hyperthyroidism during pregnancy.[38]

Fetal body movements and breathing movements as a variables of fetal biophysical profile have been shown to be predictable of impending fetal infection in patients with premature rupture of the membranes.[39] Some viral and bacterial pathogenes have been shown to influence fetal motility. For example, transplacental infection with coxsackie B_3 confirmed by molecular techniques resulted in severe reduction of fetal movements at the 27th week detected by prenatal 2D ultrasound. Late onset of fetal akinesia deformation sequence with mild arthrogryposis was the finding at fetal autopsy following interruption of the pregnancy.[40] Listeria monocytogenes has been increasingly recognized as a cause of intrauterine sepsis with associated perinatal wastage. The most common presentations in pregnancy include premature labor, an influenza-like illness and reduced fetal movements.[41]

Intra-amniotic infections often result in preterm premature rupture of membranes. In a prospective study fetal behavior was observed in 41 cases complicated with preterm premature rupture of membranes.[42] The length of time and the number of fetal breathing and gross body movements were correlated with the amniotic fluid culture results. An episode of fetal activity

Table 1: Additional findings of fetal behavior in high risk pregnancies in published reports

Author	*Year*	*Main findings*
Visser et al[4]	1985	First study on diabetes-related influence on delay emergence of fetal behavioral pattern
Mulder et al[5]	1987	Study on diabetes-related influence on deley emergence of fetal behavioral states
Visser et al[7]	1986	Integrated results on diabetes-related influence on of fetal behavioral pattern trough the gestation
Mulder et al[8,9]	1991	Additional findings on diabetes-related influence on fetal behavioral pattern
Mulder et al[10]	1990	Study on diabetes-related influence on behavioral states in the near-term fetuses
Mulder et al[11]	1992	Indicated that diabetic disorders occurring in early life may influence abnormal functional development in later gestation
Mulder et al[12]	1995	Study on fetal breathing movements in relation to other parameters of fetal well being in late diabetic pregnancies
Reece et al[13]	1995	Findings on how maternal hypoglycemia affects fetal behavioral parameters
Devoe et al[14]	1995	Study on diabetes-related influence on Fetal biophysical activities in third-trimester
Van Vliet[15]	1985	Results on relationship between fetal activity and behavioral states in third trimester growth-restricted fetuses
Van Vliet[16]	1985	Showed that the quality and quantity of the growth-restricted fetal motility is disturbed
Arduini[17]	1988	Showed that the quality and quantity of the assymetrical growth-restricted fetal motility is disturbed
Rizzo[18]	1987	Findings on the influence of fetal blood flow on the IUGR fetal motility
Sival[19,20]	1992	Findings on the IUGR influence on the fetal general movements
Ribbert et al[21]	1993	Showed the dynamic of fetal movements and relations to other parameters of fetal well-being in growth-restricted fetuses
Vindla et al[22]	1997	Findings on fetal movements as the predictor of fetal condition
Bekedam et al[23]	1991	The effects of maternal hyperoxia on fetal breathing movements, body movements and heart rate variation in IUGR fetuses
Andonotopo et al[24]	2006	4D findings on fetal behavior of growth restricted fetuses.
McLeod et al[26]	1998	First study on the effect of maternal ethanol Consumption on fetal body movements
Mulder et al[28,29]	1998	Revealed that even modest maternal alcohol intake affects fetal behavioral state organization
Hume et al[30]	1989	Showed that n utero cocaine exposure affects fetal behavioral state
Hepper et al[31]	1995	A longitudinal study on the effect of maternal cocaine consumption on fetal behavior
Jansson et al[33]	2005	Revealed the fetal behavior response to maternal methadone exposure
Konstantinidou et al[37]	2007	Case report on the effect of Coxsackievirus B_3 on fetal motility
Craig et al[38]	1996	Study on the effect of Listeria monocytogenes on fetal motility
Goldstein et al[39]	1988	Findings on fetal body and breathing movements as Predictors of intraamniotic infections
Del Valle et al[40]	1992	Findings on fetal body and breathing movements as Poor predictors of intraamniotic infections
Sherer et al[41]	1996	Showed that decreased amniotic fluid volume before third trimester is associated with decreased fetal motility
Habek D[42]	2007	Revealed the effect of chronic tobacco hypoxia on the fetal behavior in early pregnancy
Cowperthwaite et al[43]	2007	Showed that fetuses less than 37 weeks GA of mothers who smoke throughout pregnancy have a delayed onset of response to the maternal voice.
Warner et al[44]	2002	Study on influence of mothers hypertension on fetal behavior
Ksilevsky et al[45]	2005	Comparison of fetal behavior in low- and high-risk Pregnancies
de Vries et al[46]	2007	Overview on changes in fetal motility indicative of malfunction of the central nervous system in high-risk
Morokuma et al[48]	2007	First simplified ultrasound screening for fetal brain function based on behavioral pattern.
Ahmed et al[50]	2005	Provided more information of specific movement patterns and quality of movement in the high risk fetuses.
Andonotopo et al[51]	2005	Allowed early diagnosis of a functionally affected anencephalic fetus.
Kurjak et al[52]	2007	New scoring system for fetal neurobehavior assessd By 3D and 4D US

(body movements and breathing movements) of greater than or equal to 30 seconds during 30 minutes of observation was associated with the absence of intraamniotic infection in 100% of the cases. On the other hand, the absence of fetal breathing movements and gross body movements of less than a 50 second duration during 30 minutes of observation was associated with positive amniotic fluid cultures in all cases. If an episode of fetal breathing movements was present but lasted less than 30 seconds and/or the total time of gross body movements was greater than 50 seconds, 64% of patients had an intra-amniotic infection. The conclusion was that the breathing movements could be used as a predictor of intra-amniotic infection. On the contrary, study by Del Valle and his group which enrolled sixty-eight women with the diagnosis of preterm premature rupture of membranes (PROM) showed that the biophysical profile with breathing movements included and the NST are poor predictors of perinatal infectious complications.[43]

To investigate the relation between amniotic fluid volume (AFV) and fetal movements at less than 32 weeks of gestation as assessed by routine biophysical profile (BPP) the study included 352 consecutive nonhypertensive, nondiabetic patients.[44] The results revealed a significant correlation between decreased AFV and decreased fetal movements. Fetal presentation and GA were not significantly different between patients based on score of fetal movements. The authors concluded that decreased AFV is associated with decreased fetal movements irrespective of fetal presentation or gestational age.[44]

Nicotine was shown to have impact on fetal motility in recent published study on fetal movement in early pregnancy that were qualitatively and quantitatively observed by ultrasound monitoring in women smokers and in controls.[45] The study included three groups of 20 pregnant women each: nonsmokers (group 1), smokers of an average of 10 cigarettes daily (group 2), and smokers of an average of >20 cigarettes daily (chronic smokers; group 3). Two-dimensional US study was performed once during gestational weeks 10-20 by the then standard method of fetal movement monitoring:

1. Quantitative measurement of global fetal movements qualitatively verified as brisk or sluggish
2. Quantitative measurement of isolated spontaneous head movements
3. Quantitative measurement of isolated spontaneous arm movements
4. Quantitative measurement of isolated spontaneous leg movements
5. M-mode measurement of fetal heart rate.

The results showed that the ratio of brisk to sluggish fetal movements was higher in nonsmokers compared to smokers. The rate of isolated spontaneous head and arm movements and of the upper cerebral pattern (head and arm movements) was statistically significantly lower in group 3 as compared with groups 1 and 2, whereas no statistical significance was recorded in isolated spontaneous leg movements. The rate of fetal tachycardia was also significant in group 3, whereas tachyrhythmia was recorded in seven children born to group 3 mothers. The described study of the effect of chronic tobacco hypoxia on the components of fetal behavior revealed a positive correlation between global and isolated fetal hypokinesia of the upper cerebral pattern, fetal tachycardia, and tachyrhythmia in the group of mothers who were chronic smokers.[45]

To determine the effects of maternal smoking on fetal spontaneous behavior and auditory processing Cooperwhite and coworkers examined 38 fetuses of smoking and nonsmoking mothers, stratified by gestational age and observed at least 1 hr following smoking.[46] Observations included spontaneous fetal heart rate and body movements (20 min) followed by a 2 min audiotape of the mother reading a story while FHR and body movements were recorded. They found that the fetuses less than 37 weeks GA of mothers who smoke throughout pregnancy have a delayed onset of response to the maternal voice, a subtle difference which may have implications for later language development for prematurely born infants.

The relationship between maternal blood pressure (BP) and fetal behavior were examined in hypertensive compared to normotensive women at 33 and 36 weeks gestational age.[44] As expected, maternal BP was negatively related to GA at birth and birth weight.[47] On average, fetuses of hypertensive women were born 2 weeks earlier (38 weeks GA) and 340 gm lighter. Maternal systolic BP was negatively related to the number of spontaneous body movements observed on ultrasound scan over 20 min and the magnitude of the fetal heart rate acceleration elicited by a vibroacoustic stimulus. At 36 weeks GA, vibroacoustic stimulation elicited differential responding with fetuses in the hypertensive compared to the normotensive group having fewer body movements, a lower magnitude of FHR acceleration, and a lack of cardiac-body movement coupled responses. These findings suggest a relationship between maternal BP and fetal behavior and differential functional development of sensory-motor response systems which need to be characterized in the subgroups of hypertensive disorders observed during pregnancy.

Recent meta-analyses were conducted on archival data of human fetal behavior to identify differential behavior among high-risk fetuses in pregnancies complicated by threatened preterm delivery, maternal hypertension or diabetes compared with low-risk fetuses in uneventful pregnancies, delivering as healthy, full-term infants.[48] There were no differences in spontaneous behaviors when scored using clinical criteria for the nonstress test and biophysical profile; however, there were differences in the magnitude of the behaviors measured in the tests. Developmental differences were observed between those threatening to deliver early and the fetuses of hypertensive and diabetic mothers. The later two groups differed little from one

another but differed from low-risk fetuses in their response to auditory stimulation. It was concluded that differences in behavior among high-risk groups suggest that atypical fetal behaviors may represent adaptation to condition specific insult rather than a generalized response to insult per *se*. The finding that high-risk fetuses showed atypical responses to auditory stimuli indicates a need to examine the relation between fetal auditory function and later language acquisition.

Behavior in Fetuses with Congenital Disorders

Although behavior of fetuses with congenital disorders has been investigated and published in many, mostly case-reports publications systematic approach to the issue lacks mostly because high diversity of disturbances . Although estimation of neurodevelopmental outcome of the fetuses based on the following studies could be possible, a direct precise prognosis is still not available during the prenatal period. The use of 4D US recording could provide more information about the quality of fetal movements leading to the better prediction of neuronal development.

De Vries conducted a literature search on motility in fetuses with congenital disorders. The review included 48 articles describing motility of 104 fetuses.[49] The author divided abnormal motility into two main subcategories: hypo- and hyperkinetic with posture affected in 40/60 hypokinetic and 4/44 hyperkinetic moving fetuses. The majority of the disorders resulted in an adverse outcome. Fourteen percent survived with a handicap, depending on the underlying disorder. The 16 disorders with hypokinetic motility had mainly an autosomal recessive etiology with no possibility of invasive prenatal diagnosis or conclusive sonographic structural anomalies, in contrast to the 17 disorders with hyperkinetic motility. Within the limitations of the studies, a deeper understanding of affected milestones in motor development can be obtained. The author concluded that broadening motor assessment procedures from quantitative to qualitative aspects, including the assessment of behavioral states and emphasizing onset and continuity of motility before and after birth will enhance the reliability and predictive value of motility as a parameter in the assessment of fetal condition.[49]

Ahmed and his group established a behavioral state profile in the eight high risk fetuses by 4D US recording.[50] In the study the authors tried to observe all the behavioral parameters which are related to CNS function. In anencephalic case and cephalocele case, they noticed excessive hypertonic movements, while fetuses affected by homocystinuria and Meckel– Grubber syndrome demonstrated hypotonia. The sequence of occurrence of behavioral parameters was clearly abnormal in those fetuses affected by anencephalic and cephalocele. These findings fully agree with their previous case report on the behavior of an anencephalic fetus.[51] Normal quantity and quality of behavioral parameters was noted in fetuses affected by prune belly, diaphragmatic hernia, and hydrothorax. The quality and quantity of fetal movement in the fetus affected by anchondrogenesis were normal, but it was difficult to observe the movement of extremities due to abnormal fetal posture.

From previously described case report, fetal hand movements in the anencephalic fetus were visible only in one direction (hand to head) and it appeared abnormal and monotonous.[51] Isolated arm movements and isolated leg movements were present but the characteristic of movements showed a forceful quality, they were jerky and appeared incidentally. Decreased variability was observed along with the tendency of movement patterns appearing randomly compared to being sporadic and continuous in a normal fetus. Although it was difficult to establish the movement patterns in the anencephalic fetus, these results proposed that there was a prominent underlying structure. Hands occurred around the specific body part and were directed against the uterine wall. With the malformation of fetal CNS, movement's patterns were abnormal and could exist in spite of a serious reduction in the quantity and change in the fetal CNS.[51]

Antenatal Behavior Screening

Despite the long-standing belief that it is possible to make valid assessment about brain function from observed, no generalized behavior screening method has been developed to identify fetuses that may have central nervous system defects. In the recent study from Morokuma the effort has been made to produce screening test that would be less time consuming and in that way cost effective as compared to their previous study.[52] They devised a brief ultrasound examination to distinguish fetuses with compromised central nervous system function from the general population and evaluated it within their study.[53] The study design compared findings on five behavioral patterns obtained by retrospectively reviewing the ultrasound examinations of 5 fetuses who had abnormal behavior with prospectively obtained findings of 29 normal fetuses. Median time for brief examination criteria was 50 min (range, 30-60 min) with the only case undetectable by this brief ultrasound examination had an eye-movement period significantly longer than the normal upper limit. The assessment of fetal brain function as part of routine antenatal care could be obtained using this method as a screening test although the disadvantage is that is very time consuming.[53]

In the recent study the Zagreb group attempted to produce a new scoring system for fetal neurobehavior based on prenatal assessment by 3D/4D sonography.[54] Parameters that were analyzed were the product of multicentric studies conducted during several years which resulted with the most significant parameters for the assessment of fetal neurological development. There is a similarity between neonatal optimality

test of Amiel-Tison and that new scoring system for the assessment of neurological status in fetuses.[55,56] One of the differences was that the analytical criteria of typical passive and active tone in the neonate cannot be elicited in the fetus: head anteflexion versus retroflexion, ventral versus dorsal incurvations in the axis, both being of the utmost importance postnatally to confirm CNS optimality.[56]

To produce the new scoring test the Zagreb group identified severely brain damaged infants and those with optimal neurological findings by comparing fetal with neonatal findings. In the group of 100 low-risk pregnancies they retrospectively applied new scoring system. After delivery, postnatal neurological assessment (ATNAT) was performed,[70] and all neonates assessed as normal reached a score between 14 and 20, which was assumed to be a score of optimal neurological development. New scoring system was applied in the group of 120 high risk pregnancies in which, based on postnatal neurological findings, three subgroups of newborns were found: normal, mildly or moderately abnormal and abnormal. Based on this, a neurological scoring system has been proposed. All normal fetuses reached a score in the range from 14 to 20. Ten fetuses who were postnatally described as mildly or moderately abnormal achieved prenatal score of 5 to 13 prenatally, while another ten fetuses postnatally assigned as neurologically abnormal had a prenatal score from 0-5. Among this group four had alobar holoprosencephally, one had severe hypertensive hydrocephaly, one had tanatophoric dysplasia and four fetuses had multiple malformations.

That was a preliminary study which is planed to be continued in several collaborative centers. It is hoped that the future database formed using this new score for fetal neurological assessment will help in distinguishing fetal brain and neurodevelopmental alternations due to the early brain impairment occurring *in utero*. Study of a large population will hopefully validate the value of the new test as a predictive marker for fetal neurodevelopmental outcome in both low and high-risk populations.

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