Assessment of Fetal Neurobehavior in Special Cases

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ABSTRACT

In utero life and particularly fetal brain development and fetal behavior and more specifically assessment and imaging of the fetal nervous system, is a field of great interest in perinatal medicine, with many unanswered questions. Human brain development is a very complex, but also extremely structured process commencing the first weeks after conception and continuing for a very long time, even throughout adult life. As already mentioned fetal neurobehavior can be affected by many parameters and can be altered by environmental, racial, and maternal factors, by maternal disease, administration of drugs and neurotrophic agents, and many other factors. We analyze some special circumstances that affect fetal neurobehavior.

Keywords: Fetal neurobehavior, Fetal neurology, KANET.

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INTRODUCTION

In utero life and particularly fetal brain development and fetal behavior and more specifically assessment and imaging of the fetal nervous system, is a field of great interest in perinatal medicine, with many unanswered questions.¹⁻⁴ Human brain development is a very complex, but also extremely structured process commencing the first weeks after conception and continuing for a very long time, even throughout adult life. Establishing the anatomical integrity of the CNS is of utmost importance in fetal medicine to verify the wellbeing of the fetus, but it is not always enough.⁵⁻⁹ Motoric disabilities, mental impairment, and behavioral problems can occur even with an anatomical intact CNS, without the presence of any anatomical anomalies.¹⁰⁻¹² So whenever any of these functional problems occur, it is always a challenge to identify—if possible—when and how this problem could have happened, especially in cases when suspected to be responsible are antenatal, intrapartum, or postnatal incidents.¹³⁻¹⁶ If a specific incident is not identified environmental factors should also be considered, as it happens, e.g., in cases of prematurity when the conditions of *in utero* life are imitated to protect the premature neonate, mainly regarding feeding and nurturing, but still the risk of morbidity and complication remains high, especially regarding the brain development and nerve function.¹⁷⁻²² The degree that the fetus may be affected and the degree of neurological compromises in such cases, most of the times cannot be estimated, with the clinical pictures varying significantly, ranging from mild behavioral and learning disabilities to the most severe form of neurological impairment which is cerebral palsy (CP). But even when an anatomical abnormality or variation is detected antenatally, as it happens in the case of fetal ventriculomegaly, e.g., we cannot be certain to what extent the fetus will be affected, be able to offer complete counseling to the parents regarding the prognosis. In neonates, children, or adults certain clinical examinations can show the severity of the neurological damage that may have been caused by an injury, a tumor, or an infection.²³⁻²⁶ Until recently, there were no structured methods of assessing the neurological integrity of the fetus during *in utero* life and therefore we could not be certain or even distinguish normal from abnormal fetal neurological behavior. As mentioned above, the development and maturation of the fetal nervous system is an extremely structured process and this neuronal development is reflected by certain neurobehavioral

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patterns of the fetus that correspond to each trimester, or even week of pregnancy.²⁷⁻²⁹ The study of this developmental process and mainly being able to recognize the normal fetal neurobehavior that should be expected for each period of pregnancy, can help us understand firstly the normal state for *in utero* life. By understanding the normal fetal neurobehavior, we could then identify abnormal patterns and if possible link them to different anatomical and chromosomal abnormalities or even various insults that may affect fetal CNS and neurobehavioral integrity.³⁰⁻³² Ultrasound technology offered the unique possibility to examine the fetus *in utero* and detect various anatomical and chromosomal abnormalities. Further evolution of ultrasound technology and particularly 3D ultrasound allowed us to view the fetus in explicit detail, being able to view fetal parts and characteristics in a similar way that a neonate is looked at, and even further technological advance, 4D ultrasound, offered the possibility to view all these explicit details in real-time. Characteristics such as hand and feet movements, facial alterations and eye blinking can be assessed prenatally with 4D ultrasound technology, as one would observe and examine a newborn. The first test that succeeded to combine all the parameters and form a scoring system that would assess the fetus in a comprehensive and systematic approach, in the same way, that neonatologists perform a neurological assessment in newborns, to determine their neurological status during the first days of their life, is the Kurjak antenatal neurodevelopmental test

(KANET). Kurjak antenatal neurodevelopmental test has already been shown to be useful in the standardization of neurobehavioral assessment with the potential for antenatal detection of fetuses with severe neurobehavioral impairment. Kurjak antenatal neurodevelopmental test has also succeeded to verify the good neurological outcomes of fetuses that had normal KANET scores, showing a great positive predictive value and offering reassurance for the neurological outcome of these pregnancies.^{29–34} The first results prove that the prenatal neurological findings as estimated by the KANET test, are in concordance with their postnatal outcome. As already mentioned, fetal neurobehavior can be affected by many parameters and can be altered by environmental, racial, and maternal factors, by maternal disease, administration of drugs and neurotrophic agents, and many other factors.

ETHNICITY AND FETAL BEHAVIOR

Hanaoka et al. studied whether fetuses of different ethnical backgrounds behave differently *in utero* and alter the assessment of fetal neurobehavior as anthropometric characteristics in the different populations can give a different picture, and especially for the Asian population what has been noted is a shorter palpebral fissure, a wider soft nose within wide facial contours, a smaller mouth width, and a lower face smaller than the forehead height, parameters that can differentiate the result.^{35–37} The authors applied KANET to Asian (Japanese) and Caucasian (Croatian) populations and noted the differences in their scores, and also to the particular parameters that can be different. They calculated the KANET scores for both groups and what they noticed was that although the total KANET scores of both groups were within normal ranges, there was a difference in some parameters that finally altered the score, but not to a statistically significant degree. The parameters of KANET that were noted to have some differences were mainly the following: isolated eye blinking and facial alteration or mouth opening. As mentioned by the authors part of these differences could be attributed to different anthropometric characteristics which were also mentioned above such as shorter, wider, and shallower noses for the Japanese

population and also greater intercanthal width in relation to a shorter palpebral fissure, a smaller mouth width, a lower face, smaller than the forehead height, and a wider, shallower soft nose within wide facial contours. The characteristics of the Caucasian face are a high-bridged, long nose, deep-set eyes, and a sharply sculpted face. The authors conclude that even when considering these anthropometric differences ethnicity is a parameter that should be considered when evaluating fetal behavior. Regarding the remaining parameters of KANET isolated head anteflexion, and isolated leg movement was noted to also differ between the two populations, but not to a statistically significant degree. So, there may be some expected ethnic differences in fetal behavior and they should be kept in mind when assessing fetal neurobehavior, but overall these differences do not affect the final total KANET score (normal, abnormal, borderline) and the assessment of the fetus, but especially in borderline cases this should be taken into consideration and close follow-up should be continued in these cases (Figs 1 to 3).

FETAL SEX AND FETAL BEHAVIOR

While assessing specific characteristics of newborns differences have been noted between newborns of different sex and this has been attributed to the different maturational process of the neurobehavior between the two sexes. Differences in newborns have been noted in startle movements (male newborns are thought to have more frequent movements), in reflex smiles and bursts of rhythmic mouthing (female newborns present them earlier and more frequently), prone head reaction, and grip strength.^{38–40} There have been some studies on sex difference in fetal behavior assessed by two-dimensional (2D) sonography^{41–43} or fetal actocardiography using a single wide array Doppler transducer.^{44,45} Studies have shown that there may be differences in fetal behavior according to fetal sex and especially mouthing movements (they are increased in female fetuses), while female fetuses appear to require significantly fewer stimuli than males to habituate, suggesting that habituation in the human fetus is affected by fetal sex, and these differences have to do with “central type” developmental differences in the

Fig. 1: A complete KANET with a normal score of a fetus at 34 weeks. Most parameters such as leg, hand, and finger movements are seen, and also facial alterations

Fig. 2: Facial alterations, finger movements as part of normal KANET at 36 weeks. Special attention is paid to finger movements as detailed movements are a landmark of adequate neurological integrity of the fetus

Fig. 3: Fetal facial alterations, grimacing, tongue expulsion, and smiling are important elements that verify the neurological integrity of the fetus and important parameters of KANET

nervous system of the fetuses.⁴⁶ Taste stimuli of the mother also seem to affect fetuses of different sex differently. When pregnant women ingested dark chocolate there was an increase in fetal response and fetal movements, which was more apparent in female fetuses.⁴⁷ Hata et al. by using 4D ultrasound and applying KANET for the evaluation of neurobehavior in both male and female fetuses showed that there was no significant difference in the total KANET score between male and female fetuses, and when they further analyzed each parameter of KANET they found no significant difference in none of the eight parameters, concluding that fetal neurobehavioral and developmental process of the fetal nervous system has no apparent difference between male and female fetuses.³⁸ There are studies particularly on neonates^{39,40,44} that have shown differences in some parameters of neurobehavior (e.g., general movement, smiling, and mouthing) between males and females, and most of these parameters are parts of the KANET test, but as far as fetuses are concerned these studies used 2D ultrasound

to assess fetuses and what is more that could not be confirmed by the only study that assessed fetuses with 4D ultrasound and the complete KANET.

DIABETES AND FETAL BEHAVIOR

It has been well established that different maternal or environmental factors can affect fetal development and fetal neurobehavior. Especially gestational diabetes is a well-known risk factor for both maternal and fetal complications so that it could affect the fetus either directly or indirectly, by affecting the condition of the mother.⁴⁸⁻⁵⁰ Gestational diabetes is a condition that is increasing through the years and is a known risk factor for maternal and fetal complications and affects fetal behavior.⁵¹ In a hyperglycemic environment, there is a decrease in the number of fetal movements, and the effect of diabetes on fetal activity could be attributed to the immaturity of the development of the sensory-motor response

system that characterizes fetuses of diabetic pregnancies, rather than solely a direct effect of glucose levels on the fetus.^{52,53} Studies have also shown that fetal breathing and body movements of diabetic pregnancies are decreased and are altered due to poor behavioral organization, even when glycemic control is adequate and often fetuses of diabetic women had higher numbers of fetal breathing movement and fetal heart rate rhythms, but the fetal movements were lower. Studies show that in diabetic pregnancies hypoglycemia rather than hyperglycemia increases fetal activity and that in these pregnancies hyperglycemia is related to a decrease in the frequency of fetal movements.^{53–56} However, in most of these studies, a structured and homogeneous method of assessing fetal activity was lacking. Antsaklis et al. attempted to assess the fetal behavior of fetuses in conditions of diabetes by applying KANET to fetuses of diabetic mothers.⁴⁸ What they showed was that there are identifiable differences in the fetal behavior between diabetic and non-diabetic fetuses with the non-diabetic group having overall higher KANET scores. They also identified which specific parameters—movements differ between the two groups, with the biggest difference between the two groups being for isolated eye blinking, facial alterations, and finger movements, while there was also a small difference for isolated hand movements, but this was not statistically significant, concluding that glycemic control affects fetal neurobehavior and possibly early identification of undiagnosed diabetes in pregnancy and good glycemic control, may be crucial for fetal neurodevelopment.

HYPOTHYROIDISM AND FETAL BEHAVIOR

Maternal thyroid function is directly related to the development and function of the fetal and neonatal neurological system. Thyroid hormones play an important role in the myelination and differentiation of neuronal cells of the fetus and as a result good control of maternal thyroid function, especially during the first weeks of pregnancy when the fetus is dependent entirely on the maternal thyroid, are important for the formation and development of fetal nervous system and neurobehavior.^{57–61} Several studies have shown the significant effect that maternal hypothyroidism, whether overt or subclinical, has on the neurodevelopment and cognitive functions of neonates.⁶² Neurophysiological tests on neonates of pregnant women with overt hypothyroidism proved that these neonates are negatively affected and that they have a higher incidence of verbal and non-verbal cognitive delays, but also that motor and intellectual functions are also adversely affected. What is more maternal hypothyroidism may indirectly affect fetal brain development through pregnancy-related complications as preterm birth, IUGR, and CP with their possible detrimental effects on the future neurological development of the offspring?^{63–65} Dieb et al. showed that fetuses of hypothyroid mothers had lower KANET scores, compared to fetuses of mothers with normal thyroid function.⁵⁷ They reported abnormal fetal neurological behavior in cases of overt maternal hypothyroidism, proving the importance of well-controlled thyroid function of pregnant women.

PSYCHOTROPIC DRUGS AND FETAL BEHAVIOR

The effect of psychotropic drugs on fetal behavior during pregnancy has been a great challenge in fetal neurology. Prenatal administration of selective serotonin reuptake inhibitors (SSRIs) and antidepressants has been related to neonatal psychiatric, anxiety, and withdrawal symptoms up to 3 years of life and even

with cases of autism.⁶⁶ It has been reported that fetuses of pregnant women with depression showed differences in their behavior during the second and third trimester of pregnancy, as it happened for fetuses of pregnant women who were under treatment with anticonvulsants, with the effects of these drugs being evident even up to school age for these children.^{67–72} Even regarding the activity of the fetuses of mothers who had depression there were some differences noted, even for different trimesters. However, all these studies used 2D ultrasonography to evaluate fetal behavior, a technique that limits the assessment of fetal neurobehavior, without structured methods of assessment for the duration of the examination and the parameters that were assessed. Hata et al. used 4D ultrasonography and KANET to assess the fetuses of pregnant women who were under treatment with psychotropic drugs for different conditions (schizophrenia, depression, anxiety, epilepsy, panic disorders, OCD, personality disorder) and found no significant difference in the total KANET score. There were also no significant differences in any of the eight parameters between the groups, suggesting that psychotropic drugs may not affect fetal behavioral development *in utero*. However their study population was limited (10 cases) and their study group was not homogeneous as it consisted of women with different conditions and under different treatment methods-medications, and these factors were suggested by the authors as a limitation for safe conclusions (Figs 4 to 6).

FETAL RESPONSE TO VIBROACOUSTIC STIMULATION

Vibroacoustic stimulation (VAS) has been routinely used in everyday obstetrical clinical practice to stimulate fetuses, to cause fetal heart rate acceleration during a non-stress test (NST) or biophysical profile, and to detect fetal response and therefore to evaluate fetal well-being, fetal hearing impairment, and neurobehavioral development.^{73–76} Fetal responses to different stimuli throughout pregnancy and especially during the third trimester have been proposed as a method to assess functional neurodevelopment of the fetus and indirectly to assess the fetal condition and particularly brain maturation and CNS integrity.^{76–79} Ogo et al. showed that for fetuses of gestational age <36 weeks VAS did not appear to have a diagnostic value as a significant response was not noted in these fetuses, whereas in fetuses after 36 weeks of gestation the response appeared to be notable, and with an application of KANET they identified specific changes after VAS, which was significant increases in the frequencies of eye blinking and also in startle movements, and what the authors mentioned was that these changes possible reflected the functional maturation of the auditory system of the fetus, which does not reach an adequate level before 37 weeks. The decreased maturation of the fetal auditory system appeared to be responsible for the decreased response after VAS to fetuses of gestational age 24–27 weeks, whose auditory system has not yet developed, whereas, for later gestational age, that is after 28 weeks, but before 36 weeks (at 28–31 and 32–35 weeks) also had decreased response to VAS as the fetal auditory system has not been completely formed. What is more, the authors managed to identify which specific fetal parameters increase in fetuses after 36 weeks after VAS, which was eye blinking and startle movements, and the attributed this to the fact that eye blinking is related to central dopamine system maturation, which occurs at about 36 weeks of gestation, while eye blinking and startle movement after 36 weeks of gestation, might represent an advanced stage of the fetal brain

Fig. 4: Fetal mouthing and tongue expulsion as part of KANET in a fetus at 33 weeks

Fig. 5: Abnormal KANET at 36 weeks in a fetus with metabolic syndrome. The neonate died 1 week after delivery

Fig. 6: Fetus with trisomy 13 and abnormal KANET. The neonate was delivered and died on day 52 post-delivery

and CNS maturation and response to external stimulation, so that the other parameters of fetal behavior are not altered.

ANTENATAL CORTICOSTEROID ADMINISTRATION AND FETAL BEHAVIOR

Antenatal administration of corticosteroids has been related to a reduction of fetal activity, mainly of body and respiratory movements.⁸⁰ It is also well documented that these changes in fetal behavior are not permanent and that they last on average about 1–2 days, with a maximum duration reaching up to 4 days.⁸¹ Changes have also been documented regarding the Doppler studies of the fetus, mainly ductus venosus, and umbilical Doppler but without affecting the overall uteroplacental circulation.⁸² Also, a decrease of the biophysical profile score has been documented after administration of corticosteroids antenatally.^{83,84} Betamethasone is a stronger risk factor for reduction of fetal movements compared to dexamethasone, although this effect appears to be transient in both cases.^{82–85} What is more, the effect of corticosteroids on fetal behavior and neurological development has been proved by studies about direct administration of corticosteroids intrauterine, which caused the fetus vasoconstriction and hypoxemia, located especially in the area of thalamus, diencephalon, and pons. However, the effect of corticosteroid administration as already mentioned is transient and does not appear to alter the overall perinatal outcome, so that decisions regarding the management of pregnancy and delivery, should be carefully taken when corticosteroids are administered in pregnancy and their effect may be obvious in the cardiotocograph or the biophysical profile of the fetus, to which corticosteroids were administered. Antsaklis et al. studied the effect of corticosteroids on fetal neurobehavior by applying KANET to 65 singleton pregnancies after 28 weeks, who were administered corticosteroids. Compared to the control group there was an overall decrease of 2 at the KANET scores when performed 24–48 hours after corticosteroid administration. These reductions of KANET were not reported in the follow-up examination 2 weeks later for the same fetuses. While comparing betamethasone to dexamethasone, dexamethasone appeared to have a smaller effect on the KANET score, but this difference was not statistically significant. It is really important therefore when applying KANET to have a good knowledge of the maternal history and drug administration that could potentially affect fetal behavior, to avoid misinterpretations.

CONCLUSION

Verifying the integrity of the fetal nervous system is a very difficult and at the same time very complex procedure. Assessment of fetal anatomy has reached a very high level via 2D, but especially through 3D ultrasound, as has an assessment of chromosomal abnormalities of the fetus with molecular genetics, who could affect the nervous motoric, behavioral and mental status of the fetus. Assessment of fetal neurobehavior has up to a level been standardized with 4D ultrasound and with KANET, a method that by applying 4D ultrasound to the fetus assesses its neurobehavior in real-time in a similar way that neonatologists assess the newborn in real life. Many multicentric studies have examined and confirmed the validity of KANET on different populations, both low and high risk. However, in this new field of fetal medicine, fetal neurology, and fetal neurobehavior there is still a lot to be discovered and to be learned. Fetal behavior is a very complex situation, susceptible

to many genetic, epigenetic, environmental, and anatomical parameters. Common maternal conditions such as maternal diabetes and thyroid disease, administration of medications that are used frequently in pregnancy such as antenatal corticosteroids and psychotropic drugs, or even ethnic and fetal sex differences can alter the way a fetus is behaving. All these parameters should be taken into consideration when fetal neurobehavior is assessed, as we should take into consideration the full maternal medical history. Assessment of fetal neurobehavior opens a new era in fetal medicine, as many of the so thought routine techniques that we apply in obstetrics could be proved that could be further improved by assessing the fetal neurobehavior at the same time.

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