Fetal movements as a predictor of health

Running headline: Fetal movements

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We have no conflicts of Interest.

Abstract

The key determinant to a fetus maintaining its health is through adequate perfusion and oxygen transfer mediated by the functioning placenta. When this equilibrium is distorted, a number of physiological changes including reduced fetal growth occur to favor survival. Technologies have been developed to monitor these changes with a view to prolong intrauterine maturity whilst reducing the risks of stillbirth. Many of these strategies involve complex interpretation, for example Doppler ultrasound for fetal blood flow and computerized analysis of fetal heart rate changes. However, even with these modalities of fetal assessment to determine the optimal timing of delivery, fetal movements remain integral to clinical decision making. In high risk cohorts with fetal growth restriction, the manifestation of a reduction in perceived movements may warrant an expedited delivery. Despite this, there has been little evolution in the development of technologies to objectively evaluate fetal movement behavior for clinical application. This review is an attempt to synthesize currently available literature on the value of fetal movement analysis as a method of assessing fetal wellbeing, and show how interdisciplinary developments in this area may aid in improvements to clinical outcomes.

Key words: Fetal movements, fetal monitoring, biophysical profile, fetal growth restriction, stillbirth

Abbreviations
FGR - Fetal growth restriction
SGA - Small for gestational age
BPP - Biophysical profile
CTG - Cardiotocograph
cCTG - Computerized cardiotocograph
FHRV - Fetal heart rate variability
STV - Short term variation
Key Message

The association between normal fetal movements and the physiological state in utero is clear. Its correlation with reassuring and pathological features of existing monitoring techniques support its clinical use, but this is dependent upon establishment of an accurate and objective assessment tool.
Introduction

An obstetric clinician’s role during the antenatal period lies principally in early detection and optimal management of maternal and fetal conditions that may influence the pregnancy and its outcome. The main objective of antenatal care in the third trimester is to reduce the risk of stillbirth. Whilst some stillbirths are related to chromosomal or structural abnormalities which may carry a poor prognosis irrespective of the timing of delivery, other pathologies may benefit from early detection.

In a large population-based cohort study of 2675 stillbirths from 1997-2003, 43% were attributable to fetal growth restriction (FGR) (1), and it is in this group where detection may influence care. In the past, FGR and small for gestational age (SGA) were terms used almost synonymously, but the notion where FGR may exist in a fetus whose biometry is within the normal percentiles is emerging. This problem is even more challenging to tackle, and one that will require new screening strategies that rely not only on fetal biometry. Whilst fetal monitoring modalities have developed to help optimize the timing of delivery, perceived fetal movements remain crucial in that clinical decision-making.

Hypoxia

Adequate oxygenation of the fetal tissues is central to fetal wellbeing. The importance of fetal movements as a marker of health has been demonstrated in sheep models with fetal behavior being reflective of fetal brain function. In hypoxemic intra-uterine environments, movements are significantly reduced, as a mechanism to conserve energy consumption (2). However, with prolonged hypoxemic exposure, fetal movements can return to normal patterns; presumably as part of a compensatory mechanism until the fetus becomes acidemic (3).

Physiology of fetal growth restriction

The physiological adaptations of the fetus during periods of hypoxemia are characterized by redistribution of blood flow. This alteration of tissue perfusion maintains sufficient oxygenation to the vital cerebral, cardiovascular and endocrine organs that are essential in the homeostatic response. The shift in the perfusion equilibrium to the detriment of the peripheral and hepato-enteric circulation has consequent effects on fetal growth. Failure of these compensatory mechanisms to
sustain adequate perfusion for basal functioning of the developing fetus results in hypoxia to those tissues. Lactic acid accumulates as a result of anaerobic metabolism that ensues to preserve the functioning of those organs, and in the setting of placental insufficiency, there is a reduced clearance of carbon dioxide. Consequently, acidemia develops which is lethal unless rapidly corrected. These compensatory changes have been shown to affect fetal growth, Doppler blood flow and heart rate variability as well as fetal behavior. These physiological changes have facilitated the development of fetal monitoring techniques with triggers to most appropriately time delivery.

Our understanding of ‘at risk’ babies is mainly derived from our monitoring of severe fetal growth restriction, and before we begin to consider the physiology of those at risk within the normal percentile range, it is important to fully appreciate the mechanisms involved in these fetuses. Management of severely growth-restricted fetuses is a delicate balance between iatrogenic preterm delivery and prolonging intrauterine maturity, with the risks of stillbirth and chronic acidemia to the fetus.

Whilst in Europe, the clinical decisions for delivery are largely based on Doppler investigations and fetal heart tracing identify hemodynamic decompensation and acidemia (4), in the US, management has been established through assessment of biophysical profile (BPP) that is based on the ultrasound evaluation of amniotic fluid volume, fetal tone, breathing and movement, with fetal heart rate assessment (5). There is evidence that an abnormal BPP score, in particular reduction in fetal breathing and amniotic fluid volume, is a late change that follows arterial and venous Doppler derangement (6). As such, its use may have a role in prolonging intrauterine maturity. Whilst biophysical scoring is a composite measurement of physiological function, individual components of fetal movement have also been associated with fetal wellbeing.

**Movement patterns**

Fetal movement patterns are determined by neurological development of the fetus and its metabolic state. Early studies have shown that behavioral states of the normal fetus change throughout gestation, with periods of quiescence ranging on average from 6 minutes in the second trimester, up to 37 minutes in the late third (7). It has been suggested that the reduction in movements is due to improved coordination due to neurological maturity, in addition to reduced amniotic fluid and intra-uterine space
(8). Movement patterns also alter diurnally, with demonstrably increased fetal activity during the evening compared with that of the day (9).

Fetal movements and outcome
Numerous studies have shown that fetal movement provide an important measure of fetal health; 25% of women perceiving decreased fetal movements have poor birth outcomes, and more than half of stillbirths are preceded by decreased fetal movements (10). However, within a low risk population, the detection of growth restricted fetuses that requires intensive monitoring through self referral to emergency obstetric services in response to a reduced perception of fetal movements, remains poor. Whilst this maybe reflective of the inter-patient subjectivity of quantifying movements, it is also important to consider that the correlation of perception and concurrent ‘true’ movements detected by ultrasound is at best modest, with concordance as low as 37%, and false positive rates of up to 30% (11). Moreover, in-keeping with the data seen with biophysical profiling, a perceived reduction of movements is often a late sign which can already signify irreversible fetal compromise (12).

Even if we consider that currently, the only practical modality of quantifying fetal movements is through maternal perception. There is still no consensus regarding what ‘alarming number’ of kicks would be clinically significant, and accordingly the Royal College of Obstetricians and Gynaecologists does not recommend the quantification of movement through the use of kick charts (13).

When we consider the evidence from both animal and human studies, it is clear that the fetal movement patterns are still not well defined. The observation of movements diminishing during hypoxic conditions, but to later return to normal in the chronic hypoxic setting, is of critical importance in the management of antenatal patients. Are we currently being falsely reassured by this in the clinical setting? Moreover, would longitudinal quantification of these movements aid in reducing stillbirths? Currently, the only practice supported by strong evidence for screening of fetal growth restriction is fetal biometry and Doppler studies (14). However, whilst this allows detection of those babies which are SGA, i.e. size less than the 5th or the 10th percentile, we know that the majority of term stillbirths are within the normal weight
percentiles (15). This poses an important dilemma that there is currently no strategy to
 tackle: how do we determine ‘at risk’ fetuses that are not meeting their growth
 potential, but lie within two standard deviations of the mean? These are truly growth
 restricted fetuses that are failing to meet their growth potential secondary to a
 pathological process, as opposed to being simply SGA. Arguably the former is the
 cohort that is most at risk. This cohort of patients may be falsely reassured following
 an ultrasound scan with conventional parameters. The capability to objectively
 characterize movement patterns may aid understanding normality and allow detection
 of fetuses at risk, who can then be offered further antenatal surveillance and
 organization of a timely delivery.

Existing methods for assessing fetal health

Cardiotocography (CTG)

CTG is a well-established method of monitoring fetal wellbeing. Its underlying
 principal is that compensatory changes of heart rate patterns can be predictive of fetal
 hypoxia. Four features are typically described in the interpretation of a CTG trace;
 each of which will be discussed below in its relation to fetal wellbeing:

Fetal heart rate variability (FHRV)

Antenatal electronic fetal monitoring of FHRV is an important predictor of fetal
 wellbeing in SGA pregnancies (16). Profound reductions in FHRV are thought to
 represent acute fetal compromise. Unlike clinical assessment of FHRV on a
 traditional CTG, which has well acknowledged intra-observer variability, and does
 not alter perinatal mortality (17), computerized CTG (cCTG) produces objective
 measures of FHRV based on the Dawes-Redman criteria previously published (18).
 One such measure, short term variation (STV), is a statistical summary measure of the
 variation in inter-beat intervals of 3.75s epoch of averaged fetal heart rate recordings,
 excluding pronounced accelerations and decelerations. Reduction of STV to below 3
 milliseconds within 24 hours of delivery has been shown to be predictive of an
 increased risk of metabolic acidosis and early neonatal death (16). Whilst there is a
 clear correlation between fetal acidosis and a reduction in fetal movements (19), the
 use of movement as an objective measure for detecting acidosis has not translated into
 clinical use. As such, interpretation of cCTG based on STV remains essential for
prenatal surveillance of fetuses with suspected fetal growth restriction to detect acute fetal distress requiring delivery (14). STV is recognized to be lower in FGR fetuses compared to control groups, even while remaining above the critical threshold of 3 milliseconds, with a positive predictive value for acidemia of 77% (20); attempts to better predict fetal acidemia outside the context of acute fetal distress are being made by further cCTG characterization of the accelerative capacity of the fetal heart rate (20,21).

Baseline fetal heart rate

The baseline fetal heart rate fluctuates under the influence of centrally mediated sympathetic and parasympathetic tone producing variability, which alters with increasing gestational age as these systems mature at different rates (22), and between different fetal behavioral states, the prevalence of which also changes with gestational age. Diurnal variation in FHRV is also seen, as well as a certain amount of intrinsic variability (23). Increases in normal values for STV are seen with advancing gestational age with lower rates of increase in FGR fetuses (21). Ultrasound-CTG studies (24) and fetal magnetocardiogram studies (25) demonstrate that the relative time spent in each fetal behavioral state is unchanged between normally grown and growth restricted fetuses, leading to the suggestion that autonomic dysregulation of FHR control, even when not acutely distressed, underlies the observed differences in FHR variation between these groups. Whether this represents a loss of autonomic control or an inability of the fetal heart to respond to autonomic control has yet to be demonstrated.

Accelerations

Fetal heart accelerations are an indication of normal neurological function, mediated through the somatic nervous system. In a study investigating the association of accelerations with fetal movements, 52 fetuses under CTG surveillance were simultaneously scanned by ultrasound. They demonstrated that 99.6% of large accelerations and 82.4% of small accelerations were associated with concurrent fetal movements (26). Conversely, the absence of accelerations has been noted during fetal
sleep cycles. This physiological phenomenon may be reflective of the parasympathetic dominance during periods of rest.

Decelerations
Late decelerations are typically associated with fetal distress. Schifrin et al demonstrated with the use of concurrent real time ultrasonography, that late decelerations occurring following a normal CTG trace with a stable baseline and variability may be strongly suggestive of fetal breathing movements (27). Fetal breathing is an important component of biophysical profiling, and typically associated with fetal wellbeing (5). The findings are supportive of previous observations that isolated decelerations with a normal baseline and variability are not usually associated with adverse outcome (28).

Doppler ultrasonography
Doppler ultrasound provides valuable information on the impedance to blood flow through vessels. In the setting of placental insufficiency and fetal growth restriction, changes are first seen in the umbilical artery that is reflective of high placental impedance. However, this typically only manifests after 30% of the placenta is affected (29). As a compensatory mechanism, blood is preferentially redirected to the brain that is reflected in lower impedance to flow in the middle cerebral arteries. Late changes are reflected in the venous system as demonstrated by changes in flow velocity pattern of the ductus venosus. Its compromise (demonstrated by ‘a’ wave reversal) is reflective of altered cardiac function as a result of altered shunting of oxygenated blood from the umbilical vein into the fetal heart and is suggestive of poor prognosis.

The understanding of the sequence of Doppler changes being reflective of hemodynamic compensation in early growth-restricted fetuses has gradually evolved to improve neonatal outcome (30). However, management strategies to prolong intrauterine maturity of late fetal growth restriction is less clear, in part because subcritical failure of placental function may not result in Doppler changes or severe growth restriction.

Biophysical profile (BPP)
Investigators have previously related Doppler changes to BPP to improve surveillance for high risk babies (31). In a large cohort of 987 patients, Crimmins et al found that all biophysical parameters became abnormal in severely growth-restricted fetuses at <34 weeks gestation, with hemodynamic redistribution and changes in venous Dopplers. In the less severe group involving patients >34 weeks gestation, but also exhibiting cerebrovascular redistribution on Doppler, they demonstrated that BPP changes were generally a late feature, with normal findings still seen within a week of stillbirth. These results suggest that the biophysical parameters that were assessed in this high risk cohort may have been such a late feature that they were not clinically useful in the prevention of stillbirth, indicating that the current management strategies based on Doppler techniques remain the most predictive of adverse outcome.

However, complex Doppler investigations are typically only performed in specialized units and once fetal growth restriction is suspected. Bardakei et al compared the performance of the umbilical artery Doppler with a modified BPP score in fetuses >36 weeks gestation (32). The data suggests that the detection of adverse perinatal outcomes was superior with BPP than with umbilical artery Doppler. Either this is suggestive that more comprehensive Dopplers then just of the umbilical artery are essential with surveillance of late fetal distress, or that the sensitivity of the BPP maybe improved with gestational maturity.
**Assessment of fetal movements**

**Maternal sensation**

Despite the development of ultrasound scanning and Doppler technologies, maternal perception remains the most common method of quantifying movement as a marker of fetal health. Reduced movements have been associated with poor outcome in terms of growth restriction and stillbirth, with the UK Confidential Enquiry into Stillbirths and Deaths in Infancy indicating that 16% of all stillbirths are preceded by a reduction of perceived activity (33). When the outcome measures are broadened to consider neonatal outcomes such as intrauterine growth restriction in addition to stillbirths, the incidence of reduced fetal movements is found to be even greater, experienced by 25% of those who subsequently delivered with adverse outcome (10).

Unfortunately, our comprehension of fetal movement patterns still does not provide clear guidance on the quantification of perceived movements which can be classified as ‘normal’ or ‘safe’. In fact, the advice of a minimum threshold of 10 fetal movements per 12-hour period, that often forms the basis for counseling patients, originated from data involving high risk populations who were studied as inpatients on wards (34). This is obviously proving problematic in itself with not only being a skewed population, but also due to the confounding effects of psychological impact whilst being a hospital inpatient. Despite the lack of consensus in clinical guidelines, ‘kick counting’ has been established as a common method of screening high risk patients in many healthcare settings. However, in a major study involving 68,000 women randomized to counting or not, no significant difference in outcomes for the two groups were observed, and authors concluded that once perceived movements were reduced, it was often too late to save the baby (35).

**CTG**

Rayburn et al investigated overall CTG interpretation in comparison to perceived fetal movements quantified by the mother (36). In 206 high risk individuals, they found that 97% of women with an active fetus had normal CTG parameters. Moreover, in the presence of reduced fetal movement with an abnormal CTG, the outcomes were invariably poor. However, in larger populations where CTG is used in the setting of triaging women who present with reduced movements, Valentin et al report a poor
concordance between perceived movements and abnormal CTG findings; with 84% found to have reassuring CTGs (12). Whilst it is not clear from these data if the sequence of natural events are reduced movements prior to heart rate changes, or vice versa, their use in conjunction has a good sensitivity when both are abnormal.

**Actograph**

Due to the significant time involved with performing movement characterization using ultrasound, there have been efforts to find alternative tools to analyze fetal movements. During the 1980s, an actograph function was introduced to fetal heart rate monitoring by CTG. The actograph separates high frequency Doppler signals indicative of the fetal heart rate, from low frequency signals indicative of fetal movements. A number of early studies showed promising results of capturing major fetal movements, reporting concordance of movements with concurrent real time ultrasonography of as high as 95% (37,38). However, in later studies, as actograph was more widely available and it was incorporated into most CTG devices, it was reported that false positive rates were unacceptably high and the authors urged caution in its clinical use (39). The actograph is not currently widely used in either clinical or research settings.

**Ultrasound and BPP**

Given that Manning first proposed the BPP as an important technique in the assessment of wellbeing in 1979, it is surprising that technology to objectively quantitate and potentially qualitatively analyze different types of movement in relation to fetal health has not progressed as quickly as other modalities of fetal monitoring. Ultrasound remains the gold standard in total quantification, and whilst numerous groups have comprehensively characterized fetal movement patterns (40,41), the most common clinical application of using movement as a component of antenatal surveillance remains the BPP or a modified variant.

The BPP describes five parameters which reflect normal function and perfusion to different organ systems; the underlying principle that hypoxia to any of those systems can be detected on scan and heart rate tracing, with a composite score to reflect overall fetal well being [5]. Nageotte et al compared the performance of BPP with a contraction stress test; an assessment performed to assess a CTG response to an
iatrogenically induced uterine contraction; where a negative result was predictive of tolerance to labor. In their high-risk series, no significant difference was observed between the perinatal outcomes for those with negative BPP from those with a negative contraction stress test (42). Whilst it is clear even from the early work that this ultrasound based assessment has value in antenatal surveillance, its utilization has been limited certainly within Europe due to its negative performance as compared with fetal heart monitoring (43). As both CTG and BPP changes are reflective of neuroendocrine and neurophysiological responses to hypoxic stress, their similarity in performance seems plausible.

New technologies
Other approaches that have been trialed for fetal movement monitoring include magnetocardiograph recordings (a non-invasive technique in which changes in the magnetic field near the maternal abdomen due to the electrical activity of the fetal heart are acquired and interpreted) (44) and multi-Doppler sensor systems (45). However, neither of these techniques has yet been compared with concurrent ultrasound or maternal sensation.

More recently, the utilization of MRI in fetal medicine has aided the development of cine MRI. This technique allows for accurate assessment of global fetal movements (46), even in late gestation that may otherwise be limited with ultrasound. However, its use is limited to the research arena due to the resources needed, as well as the time-intensive post capture analysis required.

Some studies have explored maternal wearable fetal movement monitoring (47-50), but none of these systems are in routine clinical use. A number of studies have investigated the potential for measurement of vibrations of the maternal abdomen as a predictor of fetal movements. Such systems have the advantages of being non-transmitting, being usable in a home setting, and potentially low in cost. Mesbah et al developed a fetal activity monitor based on accelerometers, with the first to introduce a method to account for maternal movement artifact as a technique to improve specificity (47). Whilst their overall sensitivity was good at 76% when compared to real time ultrasonography, their specificity remained low at 56%. A similar study
from Girier et al. also involving an accelerometer based system, reported a true detection rate of 62% and an average false detection rate of 40%, concluding that only large fetal movements are registered by an accelerometer system and that accelerometers are prone to signal artifacts due to maternal movement (48). Two groups have proposed fetal movement monitors based on capacitive acceleration sensors to detect oscillations of the maternal abdomen (49,50). Nishihara et al reported an agreement between subjective maternal sensation and their sensor of 87.7%. Whilst using similar technology, Ryo et al. reported that their sensors were most effective in picking up gross fetal movements (with prevalence adjusted bias-adjusted kappa values ranging between 0.69 and 0.83), but less effective in detecting breathing or isolated limb movements as detected with ultrasound.

It is clear that all passive forms of fetal monitoring that record the physical signals of the fetus through the maternal abdomen are inferior to the gold standard of ultrasound. However, the potential of utilizing methods such as accelerometry or phonography have the advantage of capturing automated, longitudinal data in the out-of-hospital setting where it is most needed even if they systematically under-record. The future in utilizing these methods to record movement signals will only be optimized through the use of multiple sensors over the maternal abdomen to maximize the likelihood that movement is registered, but with the hindrance that undesirable artifacts that is not fetal in origin will naturally increase. How sensitive and the manner in which signals are processed is a key element to the performance of these types of device, and accuracy levels can vary significantly between analysis techniques and sensing modality. Astute strategies to tackle this problem include the introduction of a reference sensor to identify and remove maternal movement artifact. Complex signal processing and development of intricate algorithms will determine the successes of these devices in clinical practice. Whilst it is also unrealistic to expect that any one algorithm will provide a high yield in accurate detection of all movements, a compromise will need to be made in accuracy with the type of movement behaviors that might be useful to discern.

Longitudinal, prospectively collected data from such devices could finally allow clinicians and researchers to reach a consensus on normal fetal movement patterns
according to gestation, and whether these will translate into a useful tool in our management of babies at risk of stillbirth.
Conclusion

Considering therapeutic strategies available to improve fetal health, there are few available for any condition and the key to favorable outcome is most importantly determining the optimal time for delivery. The importance of such a strategy is essential, none more so than for growth restricted fetuses. The ability to detect and appropriately time delivery will determine if a mother will take home a healthy but potentially iatrogenically premature baby, one with residual effects of chronic hypoxic starvation, or worse be faced with delivery of a still-born. It is clear that our management strategies have developed over the past 30 years, and whilst the indications for delivery has very recently been clearly defined in the small population of growth restricted fetuses <32 weeks gestation (30), the strategies for later gestations, where the burden of stillbirth is greater, is less clear. Moreover, even within this cohort, the detection is still reliant on direction from mothers reporting reduced fetal movements. The difficulties for this ‘late’ group lie not only in consensus regarding the most appropriate monitoring techniques, but perhaps more importantly in identifying our target population, given that the babies most at risk, lie within the normal growth percentiles.

The evidence presented advocates that fetal movements have an important role in antenatal surveillance, but we are currently lacking the technology to utilize this important marker of wellbeing. There is an urgent need for new technologies, or better application of existing ones, to objectively assess fetal movements in the low risk setting and to characterize how these may relate to fetal health. In doing so, the ability for us to improve management of FGR, more precisely determine optimal delivery timing and potentially reduce stillbirths, may be possible.
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