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Fetal Cyclic Motor Activity in Diabetic Pregnancies: Sensitivity to Maternal Blood Glucose

ABSTRACT: *Spontaneous fetal movement in the last third of human gestation is dominated by irregular oscillations on a scale of minutes (cyclic motility, CM). The core properties of these oscillations are stable during the third trimester of gestation in normal fetuses, but disrupted by poorly controlled maternal diabetes. Here we investigated whether fetal CM is linked to short-term instabilities in maternal glucose metabolism. The fetuses of 40 mothers with type I ($n = 28$) or gestational ($n = 12$) diabetes were studied one to six times between 27 and 40 postmenstrual weeks of gestation. Fetal movement and maternal blood glucose concentration were measured during two separate periods of fetal activity in each session. Fetal CM was quantified with spectral analysis. Early in the third trimester, changes in the rate of oscillation in fetal CM between the two periods of activity were inversely related to changes in maternal blood glucose levels. Fetal CM was unrelated to concurrent maternal blood glucose levels at any point in the third trimester. The pattern of results suggests that disruption of the temporal organization of spontaneous fetal motor activity in pregnancies complicated by maternal diabetes represents an acute response to fluctuations in the metabolic environment rather than an alteration of CM development.* © *2003 Wiley Periodicals, Inc.* Dev Psychobiol 42: 9–16, 2003.

Keywords: *cyclic motility; fetal movement; gestation; blood glucose; maternal diabetes*

The spontaneous motor activity of the human fetus in the second half of gestation has a rich temporal structure, characterized by persistent but irregular oscillations on a time scale of minutes (Robertson, 1990; Robertson, Dierker, Sorokin, & Rosen, 1982), which persists for at least the first 4 months after birth (Robertson, 1982, 1987, 1993a). The core properties of these oscillations (rate, strength, and irregularity) are remarkably stable during the third trimester of gestation in normal fetuses (Robertson, 1985), a time of substantial change in many other aspects of neurobehavioral organization (Lecanuet, Fifer, Krasnegor, & Smotherman, 1995). Quantitatively similar fluctuations in spontaneous motor activity have been documented in the fetal rat (Smotherman, Robinson, & Robertson, 1988), and fetal sheep (Robertson & Bacher, 1995; Robertson et al., 1996), and qualitatively similar fluctuations appear to exist in a variety of other species (Corner, 1977; Hamburger, 1963). Based on findings in the fetal rat (Robertson & Smotherman, 1990), fetal sheep (Robertson & Bacher, 1995), and neonatal humans (Robertson, 1993b), the irregular fluctuations appear to emerge from interactions among distributed sources of activity in the motor system rather than being driven by a localized pattern generator.

The functional significance of cyclic motor activity (CM) in the human fetus is unknown, but the continuous alternation between brief periods of increased and decreased activity may play a role in prenatal neuromuscular development (Robertson, 1989). In fetal sheep, CM is sensitive to the spontaneous uterine contractions that normally occur during the last third of gestation, similar to Braxton-Hicks contractions in humans (Robertson et al., 1996). In the rat, CM is influenced by fetal exposure to cocaine (Simonik, Robinson, & Smotherman, 1994), and

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regulates behavioral responsiveness to perioral stimulation before and after birth (Bacher, Robertson, & Smotherman, 2000; MacLennan, Smotherman, & Robertson, 1998; Reilly, Robertson, MacLennan, & Smotherman, 1997). After birth in humans, CM is sensitive to sound and tightly coupled to visual attention (Bacher & Robertson, 2001; Robertson, Bacher, & Huntington, 2001), and it appears to regulate social interaction with an adult (Huntington, 2001). Thus, while human fetal CM is relatively stable during the third trimester of gestation, findings in other animals and in humans after birth suggest that CM is sensitive to biologically significant stimulation and may regulate adaptive interactions with the environment.

Maternal diabetes provides an opportunity to study the effects of an abnormal metabolic environment on the prenatal development of CM in humans. Other aspects of fetal neurobehavioral organization are influenced by the altered metabolic environment (Devoe, Youssef, Castillo, & Croom, 1994; Dierker, Pillay, Sorokin, & Rosen, 1982; Doherty & Hepper, 2000; Kainer, Prechtl, Engele, & Einspieler, 1997; Mulder, Leiblum, & Visser, 1995; Mulder, O'Brien, Lems, Visser, & Prechtl, 1990; Mulder & Visser, 1991a, 1991b, 1992; Mulder, Visser, Bekedam, & Prechtl, 1987; Mulder, Visser, Morssink, & de Vries, 1991; Visser, Bekedam, Mulder, & van Ballegooie, 1985), and infants of diabetic mothers remain at increased risk of compromised developmental outcome despite significant advances in the clinical control of maternal diabetes before and during gestation (Aberg, Westbom, & Kallen, 2001; deRegnier, Nelson, Thomas, Wewerka, & Georgieff, 2000; Nelson et al. 2000; Reece & Homko, 1994, 2000; Rizzo, Metzger, Burns, & Burns, 1991; Rizzo, Metzger, Dooley, & Cho, 1997; Schwartz & Teramo, 2000; Vaarasmaki, Hartikainen, Anttila, Pramila, & Koivisto, 2000). Fetal CM is altered in pregnancies complicated by maternal diabetes, but the effects seen early in the third trimester disappear by the end of gestation (Robertson, 1988; Robertson & Dierker, 1986).

A central, unanswered question is whether the effects of maternal diabetes on fetal CM represent an altered developmental trajectory or an acute response to short-term instabilities in maternal metabolism. There is some evidence that fetal behavior is sensitive to concurrent maternal blood glucose levels in diabetic and nondiabetic pregnancies, although the results have been mixed. Some studies have reported increased fetal movement (Aladjem, Feria, Rest, Gull, & O'Connor, 1979; Eller, Stramm, & Newman, 1992; Gelman, Spellacy, Wood, Birk, & Buhi, 1980; Goodman, 1980; Miller, Skiba, & Klapholz, 1978; Richardson, Briggs, Toomey, Burry, & O'Grady, 1983), some have reported decreased fetal movement (Allen & Kisilevsky, 1999; Devoe, Searle, Castillo, & Searle, 1987; Edelberg, Dierker, Kalhan, & Rosen, 1987; Holden, Jovanovic, Druzin, & Peterson, 1984), and others have reported no effects (Bocking, 1989; Bocking, Adamson, Carmichael, Patrick, & Probert, 1984; Bocking et al., 1982; Lewis, Trudinger, & Mangez, 1978; Natale, Patrick, & Richardson, 1978; Natale, Richardson, & Patrick, 1983; Patrick, Campbell, Carmichael, Natale, & Richardson, 1982; Reece et al., 1995; Wladimiroff & Roodenburg, 1982) of elevated maternal blood glucose. However, the previously reported effects of maternal diabetes on fetal CM (Robertson & Dierker, 1986) were accounted for by a subgroup of fetuses whose mothers' blood glucose was least well controlled. Therefore, in the present study we investigated whether fetal CM is linked to concurrent maternal blood glucose levels during the third trimester in pregnancies complicated by preexisting or gestational diabetes.

SUBJECTS AND METHODS

Subjects

The singleton fetuses of 40 diabetic mothers were studied one to six times (3 ± 1, mean $\pm$ *SD*) between 27 and 40 postmenstrual weeks of gestation. Twenty-eight of the mothers had Type I diabetes, and 12 had gestational diabetes (American Diabetes Association, 2001; Kjos & Buchanan, 1999). All but 3 of the mothers with gestational diabetes were insulin dependent at the time the fetus was studied. Hobel antenatal risk scores (Hobel, Hyvarinen, Okada, & Oh, 1973) were 10 to 60 (26 ± 15). Fetal ages were calculated from the date of the mother's last menstrual period if she was certain of the date and her menstrual cycles before the pregnancy were regular ($n = 25$). For the remaining cases, fetal ages were estimated from a physical and neurological examination of the newborn (Ballard, Novak, & Driver, 1979), ultrasound measurement of fetal crown–rump length or biparietal diameter, or the average of the estimates based on the newborn examination and fetal ultrasound measurement(s). The fetuses were subsequently born between postmenstrual Weeks 37 and 41 (39 ± 1), with no major physical malformations. Birth weights were 2.98 to 5.78 (3.92 ± 0.62) kg; 18 of the fetuses had birth weights greater than two standard deviations above the mean for their gestational age (Usher & McLean, 1969). Data from an additional 7 fetuses were not used because they were born before 37 postmenstrual weeks of gestation.

Procedures

Fetal movement was detected by two strain gauges on the mother's abdomen while she rested in a semireclining position, tilted slightly to minimize the possibility of maternal hypotension. The procedures used to record and process the outputs of the strain gauges have been reported in detail previously (Robertson, 1985). Data collection took place in a quiet room with subdued lighting and began approximately 2 hr after the

mother's morning or noon meal. Mothers were asked not to smoke or drink beverages containing caffeine on the day they were studied. Glucose levels in maternal venous blood were determined (Beckman Instruments, Palo Alto, CA) from 1-ml samples taken at 30-min intervals from a heparinized indwelling needle in the mother's hand.

Data Analysis

Three fetal age intervals of 30 to 31 days were defined: 191 to 220 postmenstrual days of gestation (dGA), 221 to 250 dGA, and 251 to 281 dGA. Fourteen fetuses were studied at least once between 191 to 220 dGA, 29 were studied at least once between 221 to 250 dGA, and 30 were studied at least once between 251 to 281 dGA. If a fetus was studied more than once during a fetal age interval, the session with the greatest variation in maternal blood glucose levels which contained usable fetal movement data was used in the analyses reported here.

For each fetus at each of the study sessions, two artifact-free periods at least 8 min long with sufficient fetal motor activity and at least two maternal blood glucose measurements were required for analysis. Usable data were obtained from 12 of the 14 fetuses studied between 191 to 220 dGA, 25 of the 29 studied between 221 to 250 dGA, and 29 of the 30 studied between 251 to 281 dGA. The resulting periods were 8 to 53 (20 ± 8) min long and were separated by 0 to 151 (62 ± 44) min.

Fetal movement time series were constructed for each period by measuring the duration of fetal movement (excluding breathing movements, identified by their distinctive small amplitude, repeating waveform) in successive 5-s intervals to the nearest 0.2 s. Average maternal blood glucose level during each period of fetal activity was estimated from piece-wise linear interpolations between the levels in the blood sample(s) obtained immediately before, during, and immediately after the period of activity.

Fetal CM in each period of activity was quantified with spectral analysis using algorithms described in detail previously (Robertson, 1985). A peak in a movement spectrum was considered to reflect the presence of cyclic organization in fetal motor activity if it exceeded the 95% confidence limits of white noise. For the largest peak meeting this criterion, the frequency, height, and width of the peak at half-maximum were calculated to quantify the rate, strength, and irregularity, respectively, of the corresponding oscillation in fetal movement.

RESULTS

Spectral analysis of the movement time series revealed evidence of cyclic organization (CM) in 22 of the 24 periods of fetal activity at 191 to 220 dGA, 48 of the 50 periods of fetal activity at 221 to 250 dGA, and 59 of the 60 periods at 251 to 281 dGA. Table 1 shows the rate, strength, and irregularity of the fetal CM and the concurrent maternal blood glucose levels during each of the two periods in each fetal age interval.

There was no evidence of systematic differences on any CM measure, or on maternal blood glucose, related to fetal age or period. An Age (221–250 dGA, 251–281 dGA) $\times$ Period (1,2) analysis of variance on each variable revealed no main or interaction effects ($ps > .10$). There were insufficient numbers of fetuses with complete data at all three ages ($n = 4$), at both 191 to 220 dGA and 221 to 250 dGA ($n = 5$), or at both 191 to 221 dGA and 251 to 281 dGA ($n = 7$) to justify age comparisons involving the earliest fetal age interval. For each age interval considered separately, there were no differences between Period 1 and Period 2 on any of the variables (paired t tests, $ps > .10$), and no differences associated with the type of diabetes (Type I or gestational) or the fetus' later birth-weight classification as appropriate or large for gestational age (t tests, $ps > .05$).

Figures 1–3 show each fetal CM measure plotted against concurrent maternal blood glucose level during each period for each fetal age interval. There were no linear (Table 2) or second-order relations between the rate, strength, or irregularity of fetal CM and concurrent maternal blood glucose levels ($ps > .05$). There were no relations when fetuses of mothers with Type I or gestational diabetes were considered separately, and no relations when fetuses later classified as appropriate or large for gestational age were considered separately ($ps > .05$).

Figure 4 shows the *change* in each fetal CM measure (from Period 1 to Period 2) plotted against the corresponding *change* in maternal blood glucose level for each fetal age interval. At 191 to 220 dGA, there was a strong

Table 1. Fetal CM and Concurrent Maternal Blood Glucose

	191–220 dGA		221–250 dGA		251–281 dGA	
	Period 1 $n = 10$	Period 2 $n = 12$	Period 1 $n = 24$	Period 2 $n = 23$	Period 1 $n = 28$	Period 2 $n = 29$
CM rate (cpm)	0.55 (0.27)	0.43 (0.22)	0.43 (0.16)	0.43 (0.26)	0.55 (0.45)	0.69 (0.48)
CM strength (cpm^{-1})	0.60 (0.15)	0.51 (0.15)	0.60 (0.17)	0.64 (0.23)	0.65 (0.22)	0.59 (0.19)
CM irregularity (cpm)	0.51 (0.19)	0.49 (0.12)	0.52 (0.18)	0.57 (0.20)	0.52 (0.19)	0.55 (0.20)
Blood glucose (mg/dL)	124 (70)	124 (51)	108 (46)	113 (39)	104 (37)	95 (33)

Note: Mean (*SD*). dGA is fetal age in postmenstrual days and cpm is cycles/min.

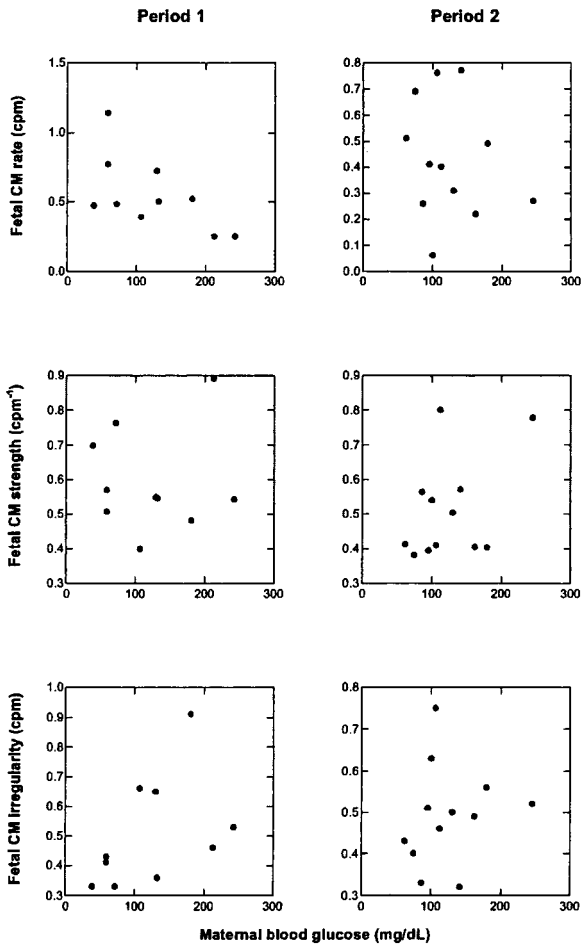

FIGURE 1 The rate, strength, and irregularity of fetal CM and concurrent maternal blood glucose level for each fetus during Period 1 ($n = 10$ with CM) and Period 2 ($n = 12$ with CM) at 191 to 220 dGA.

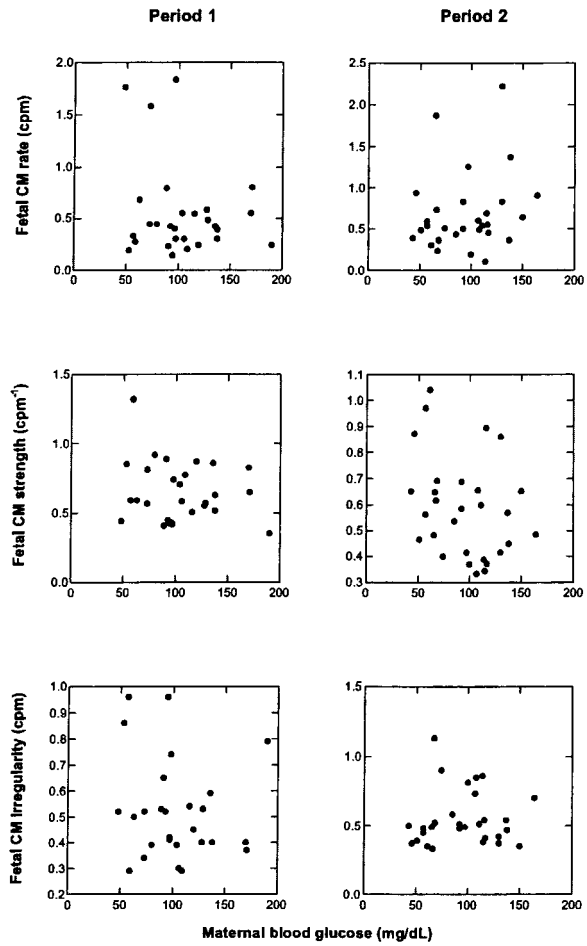

FIGURE 2 The rate, strength, and irregularity of fetal CM and concurrent maternal blood glucose level for each fetus during Period 1 ($n = 24$ with CM) and Period 2 ($n = 23$ with CM) at 221 to 250 dGA.

negative linear relation between the change in the rate of fetal CM and the change in maternal blood glucose level between Periods 1 and 2 (adjusted $r^2 = .83$, $p < .001$). The dominant oscillation in fetal motor activity became slower if maternal blood glucose level increased, but faster if maternal blood glucose decreased. At both 221 to 250 dGA and 251 to 281 dGA, there was a small linear relation between the change in the strength of fetal CM and the change in maternal blood glucose between Periods 1 and 2 (adjusted $r^2 = .17$, $p = .03$, and adjusted $r^2 = .13$, $p = .04$, respectively), but the relation was positive at 221 to 250 dGA and negative at 251 to 281 dGA. When the multiple tests on the data at each age were evaluated with $\alpha = .05/k$ (where k is the number of tests) to control Type I errors (Miller, 1966), only the negative relation between the change in CM rate and the change in maternal glucose at 191 to 220 dGA remained. The results did not change when fetuses of mothers with Type I or gestational diabetes were considered separately, or when fetuses later classified as appropriate or large for gestational age were considered separately.

DISCUSSION

The results demonstrate that early in the third trimester of diabetic pregnancies the mechanism responsible for fetal CM is sensitive to *changes* in maternal blood glucose occurring on a time scale of 2 hr or less. Fetal CM became slower if maternal blood glucose level increased and faster if maternal blood glucose level decreased. In contrast, the findings provide no evidence that fetal CM is sensitive to the concurrent *level* of maternal blood glucose within the range we observed. This pair of results suggests that relatively short-term fluctuations in maternal glucose metabolism, rather than chronically elevated blood glucose, per se, is the effective perturbation of the intrinsic cyclic patterns in spontaneous fetal motor activity in diabetic pregnancies.

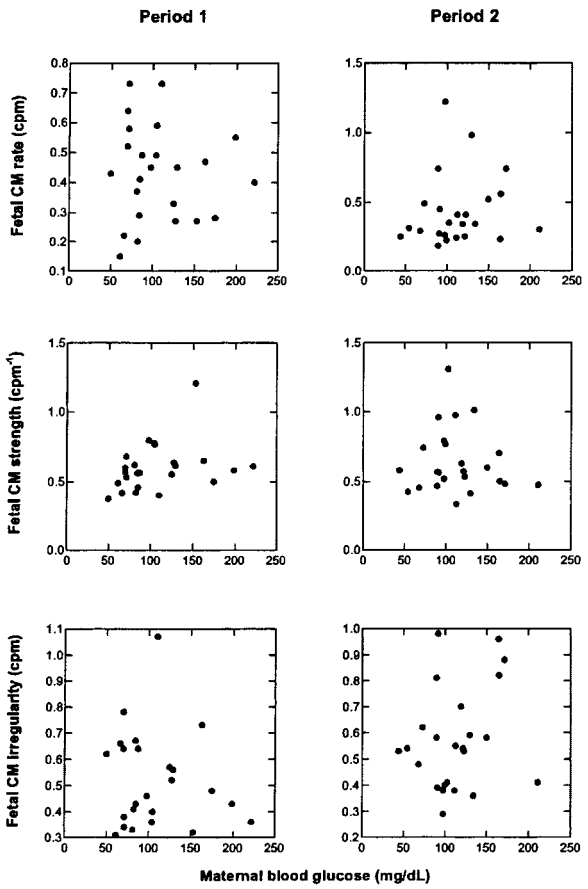

FIGURE 3 The rate, strength, and irregularity of fetal CM and concurrent maternal blood glucose level for each fetus during Period 1 ($n = 28$ with CM) and Period 2 ($n = 29$ with CM) at 251 to 281 dGA.

The finding that the temporal organization of fetal motor activity is sensitive to changes in the metabolic environment also may help explain some of the inconsistent results reported in previous studies (discussed earlier) in which fetal movement—but not its temporal organization—was measured. In those studies, fetal movement was measured at different intervals and for different durations during rapid fluctuations in maternal blood glucose levels induced by oral or intravenous glucose loads. Depending on the relative timing of the sampling of fetal motor activity and its shifting rate of oscillation, changes in the overall amount of fetal motor activity might not be detected. Furthermore, the results of a study by Edelberg et al. (1987) suggest that the amount of fetal motor activity, as well as its cyclicity, may be more sensitive to the change in maternal blood glucose level than to an elevated steady state. In that experiment, a clamp technique was used to hold maternal blood glucose at 120 mg/dl for 3 hr, but the decrease in fetal movement was transient, occurring only during the first hour.

The results also showed that the rate of oscillation in fetal CM is more sensitive than the strength or irregularity of oscillation to changes in maternal blood glucose levels. This finding is consistent with the results of other experiments that were designed to probe the mechanism responsible for CM in the rat fetus and human neonate. In the fetal rat (Robertson & Smotherman, 1990), chemical transection of the spinal cord at the midthoracic level was used to uncouple CM generated by rostral and caudal sources. The rate of oscillation in spontaneous motor activity generated above the transection was slower than the rate of oscillation in motor activity generated below the transection. The strength and irregularity of CM were not affected by the uncoupling of rostral and caudal sources. In the human newborn (Robertson, 1993b), a brief pulse of auditory white noise during active sleep was used to perturb CM. The sound elicited a brief burst of general motor activation which was followed by slower oscillations in motor activity. A similar slowing of CM occurred at the transition from active to quiet sleep. Neither the strength nor the irregularity of CM was affected by the noise perturbation or the state change.

Table 2. Correlation Between Fetal CM and Concurrent Maternal Blood Glucose

	191–220 dGA			221–250 dGA			251–281 dGA		
	Period 1 $n=10$	Period 2 $n=12$	Per 2-Per 1 $n=10$	Period 1 $n=24$	Period 2 n = 24	Per2-Per1 $n=23$	Period 1 $n=28$	Period 2 $n=29$	Per 2-Per 1 $n=28$
CM rate (cpm)	−.61 (.29)	−.21 (.00)	−.92 (.83)*	−.05 (.00)	.13 (.00)	−.25 (.02)	−.21 (.01)	.20 (.00)	−.04 (.00)
CM strength (cpm^{-1})	.07 (.00)	.42 (.10)	.32 (.00)	.30 (.05)	−.08 (.00)	.46 (.17)**	−.19 (.00)	−.31 (.06)	−.40 (.13)**
CM irregularity (cpm)	.46 (.12)	.16 (.00)	.24 (.00)	−.12 (.00)	.22 (.01)	−.38 (.10)	−.16 (.00)	.04 (.00)	−.18 (.00)

Note: Linear correlation (adjusted squared correlation). For Per 2-Per 1, the correlations were calculated using the change in CM and the change in maternal blood glucose from Period 1 to Period 2. dGA is fetal age in postmenstrual days and cpm is cycles/min.

*$p < .001$; **$.01 < p < .05$.

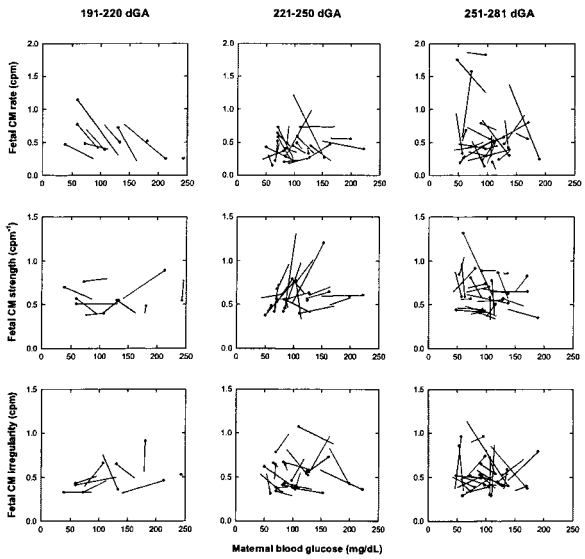

FIGURE 4 The change in the rate, strength, and irregularity of fetal CM and the change in maternal blood glucose level between the two periods of activity for each fetus with CM in both periods ($n = 10$ at 191–220 dGA, $n = 23$ at 221–250 dGA, and $n = 28$ at 251–281 GA). Lines connect the two measurements for each fetus; filled circles are Period 1.

The uncoupling experiment with fetal rats demonstrates that changes in the rate of oscillation in spontaneous motor activity can be caused by a shift in the relative influence of rostral and caudal sources of CM. This suggests that the CM slowing observed in the sound perturbation experiment with human newborns may reflect increased rostral activity during stimulus-induced arousal or spontaneous state changes. If so, then the sensitivity of the rate of fetal CM to variations in maternal blood glucose levels in diabetic pregnancies might reflect transient changes in fetal arousal or state organization induced by fluctuations in the metabolic environment over 1 or 2 hr. The results do not provide any indication of the mechanism that might link dynamic aspects of the metabolic environment and fetal CM. However, there is some indication that CM in fetal sheep might respond to transient changes in blood oxygen levels (Robertson et al., 1996), and hypoxemia in the human fetus during the third trimester is known to be associated with poor control of mothers' blood glucose levels in diabetic pregnancies (Schwartz & Teramo, 2000).

Finally, the results revealed that fetal CM is more sensitive to fluctuations in maternal blood glucose levels during the early part of the third trimester of gestation than during the middle or end of the third trimester. This result may help explain previous findings that early-third-trimester differences in CM between fetuses of diabetic mothers and normal fetuses disappear by the end of gestation (Robertson & Dierker, 1986) and remain absent after birth, even in neonates with clinical evidence of prenatal exposure to an abnormal metabolic environment (Robertson, 1988).

Taken together, the pattern of results across studies suggests that changes in the temporal organization of spontaneous motor activity in fetuses of diabetic mothers are likely to reflect a short-term sensitivity to fluctuations in the metabolic environment early in the third trimester rather than an altered developmental trajectory for CM. The results provide no evidence that the transient effects of maternal glucose metabolism on fetal CM might directly account for any of the increased risk of poor general developmental outcome in children of diabetic mothers. However, the finding that patterned neural activity in the fetus is sensitive to short-term changes in maternal glucose metabolism in the case of CM does suggest that it might be reasonable to examine other aspects of fetal neural function, which may be more closely related to long-term developmental outcome, from this dynamic perspective.

NOTES

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