Fetal behaviour and the sudden infant death syndrome (SIDS)

J Smoleniec, D James

Abstract

To examine whether differences in sleep maturation could be identified before birth, behavioural studies were carried out in 28 fetuses. Studies were possible in all 28 fetuses at 28 weeks, but only in 26 fetuses at 36 weeks (two fetuses delivered before 36 weeks). The risk of sudden infant death syndrome (SIDS) was determined using the Oxford SIDS scoring system. The fetuses at greater risk of SIDS had coincidence of behavioural characteristics for a significantly lower percentage of the time than those at low risk. This difference reached significance ($p \leq 0.05$) only at 36 weeks.

(Arch Dis Child 1995; 72: F168–F171)

Keywords: fetal behaviour, SIDS, sleep states, REM.

Despite the reduction in its incidence,¹ sudden infant death syndrome (SIDS) remains the commonest cause of death in normal infants.² There are many theories for its aetiology and pathogenesis; indeed, it is likely to be a multifactorial phenomenon.³ One theory of causation relates to a disturbance in sleep-wakefulness maturation in some infants during the first few months of life, resulting in an increased vulnerability to SIDS.^{1 4 5–9}

The suggestion that these patterns may be altered in infants at risk of SIDS led us to speculate whether such alteration in behaviour could be detected before birth.^{10–13} We therefore undertook a pilot study of fetal behaviour in pregnant women who were at high or low risk of having a baby die from SIDS.^{14 15}

Methods

The antenatal case records of women with singleton pregnancies who booked in at 18 weeks at St Michael's Hospital, Bristol, were used to calculate a SIDS risk score, using the antenatal component of the 'Oxford SIDS Score (OSS)'.^{14 15} The OSS comprises 15 variables each of which has a risk coefficient. The score is the product of the relative coefficient.^{16–18} The variables are listed in table 1.

Eleven out of the 15 variables can be determined antenatally, with the remaining four being determined postnatally. The OSS uses a cutoff point value to create two SIDS risk groups – namely, a low and a high risk. The OSS has been validated in Avon.¹⁵ In that study a cutoff score of 2.0 was used to define the high risk group. The sensitivity was found to be 55.3% and the specificity 78.3%. The risk of SIDS in the high risk group was

7.5/1000 live births – double that of the general population. By increasing the cutoff point score, the SIDS incidence in the high risk group increases (as does the specificity), but the sensitivity and the proportion of the population from which to recruit high SIDS risk pregnancies decreases. A slightly higher cutoff point value of 2.5 was used in this pilot study in order to reduce the size of the high risk group but not to such a degree as to jeopardise recruitment. It was intended that by aiming for an increased difference in median SIDS scores between the two groups, an association between OSS and fetal behavioural states, if present, would be detected more easily.

The selection of pregnant women for the study occurred after the booking visit and the 18 week detailed fetal scan. The 'antenatal' OSS (11 variables maximum) was calculated by one of the antenatal clerks, and equal numbers of women at high or low risk were identified. Mothers who were eligible for the study were invited to participate by JS. After delivery the SIDS risk scores were recalculated using the full OSS and allocation to the two SIDS risk groups was appropriately adjusted using a cutoff point of 2.5. The comparison of fetal behavioural results was made between the two SIDS risk groups determined using the full OSS. The person performing the fetal behavioural studies (JS) was unaware of the risk status of the pregnancy.

Twenty eight singleton fetuses were included in the study. Behavioural assessment was carried out at 28 weeks in all 28 fetuses and again at 36 weeks in 26, two fetuses having delivered before 36 weeks. The behavioural assessments used a technique described before.¹⁹ This involved continuous ultrasound visualisation of the fetus for 60 minutes with two ultrasound transducers (Hitachi EUB-26 with a 3.5 MHz linear array probe, and Concept 2000, Dynamic Imaging with a 3.5 MHz curvilinear array probe). Simultaneous recording of the

Table 1 Components of Oxford Scoring System^{14 15}

<i>Antenatal characteristics:</i>	
Partner's social class	
Mother's age and birth order	
Interval from last pregnancy	
Known dates of last menstrual period	
Cigarette smoking	
Maternal drug addition	
Mother takes barbiturates	
Multiple births	
Previous SIDS	
Infection during pregnancy	
Congenital defect	
<i>Postnatal characteristics:</i>	
Month of delivery	
Sex of infant	
Gestation	
Birthweight	

Department of
Obstetrics and
Gynaecology, St
Michael's Hospital,
Bristol
J Smoleniec

Department of
Obstetrics and
Gynaecology, Queen's
Medical Centre,
Nottingham NG7 2UH
D James

Correspondence to:
Professor James.

Accepted 28 February 1995

Table 2 Heart rate and body movements and fetal behavioural state^{11 19 21 22}

State	Fetal heart rate	Gross fetal movement
1F	'Flat', low baseline variability. Small (<15 bpm) accelerations with startle	Absent, except for occasional startle
2F	High baseline variability, frequent accelerations of 15 bpm or more	Frequent movements
4F	Sustained tachycardia in excess of 160 bpm ('sum-mated accelerations')	Continuous movements

bpm=beats per minute.

fetal heart rate (was undertaken using a Hewlett Packard 8040A recorder. The fetal heart rate, together with observed fetal limb and body movements, were recorded on a poly-graphic recorder (Hewlett Packard 7745a) at a paper speed of 3 cm/minute.

The behavioural assessments were performed between 0900 hours and 1600 hours. The mothers were asked not to eat or smoke for two hours before each study.

The safety of ultrasound equipment used in this study had been previously checked by an independent expert using a National Physical Laboratory (London) ultrasound beam cali-brator and found to be safe regardless of the duration of exposure.²⁰ The ultrasound spatial peak temporal average intensity (I_{spta}) of ultra-sound with the Hitachi EUB-26 and 3.5 MHz linear array (the machine with the greater intensity) was 6.53 mW/cm². This was well below the 100 mW/cm² recommended as the safe upper limit by the American Institute of Ultrasound in Medicine (AIUM) statement on mammalian in vivo biological effects, revised and approved in 1987. The I_{spta} of a Hewlett Packard 8040A with a 1 MHz continuous wave Doppler fetal heart rate monitor is 6.0 mW/cm².

Each assessment was analysed according to fetal behavioural state criteria, as described before.^{19 21} The low and high risk groups were compared in terms of coincidence of behav-ioural characteristics.²¹ Coincidence exists when a fetus manifests the features of fetal heart rate and gross body movements consis-tent with a behaviour state (1F, 2F, or 4F) for three minutes or more (table 2). In this pilot study eye movements were not used as the third physiological variable for two reasons. Firstly, it is not discriminatory if used for evaluation of fetal behaviour before 36 weeks; Arduini *et al* have suggested that there may be as much as a 26% error introduced when eye movements are included.²² Secondly, the eye may not be visible in up to 20% of studies.¹⁹

For each study the coincidence was calcu-lated by adding the individual periods of coin-cidence in 1F, 2F, and 4F and expressing them as a percentage of total study time.

Non-parametric methods were used for statistical analysis (Fisher's exact test for com-parison of frequencies and the Mann-Whitney U test for comparison of medians).

Results

Using the 'antenatal' component of the OSS, 15 fetuses were recruited as 'low risk for SIDS' and 13 as 'high risk'. Correction of the groups

using the full OSS after delivery resulted in 18 being in the low risk group and 10 in the high risk group. Behavioural data (coincidence) at 28 weeks and at 36 weeks were compared between the two SIDS risk groups, as defined by the full OSS (table 3). Apart from the two from the high risk group delivered before 36 weeks, one of the studies at 28 weeks was rejected because of poor quality fetal heart rate recording.

The median number of episodes of coinci-dences in 1F and 2F and the median number of transitions (changes between episodes of coincidence – from 1F to 2F, or vice versa) are shown in table 4. There were no significant dif-ferences between the high and low risk groups at 28 or 36 weeks.

The median per cent duration of coinci-dence for the two risk groups at 28 and 36 weeks is shown in table 5. The median per-centage of the time the fetuses exhibited coin-cidence was lower in the high risk groups at both 28 and 36 weeks. However, this was not significant at 28 weeks and just failed to reach significance at 36 weeks ($p=0.06$). Similarly, comparison of frequencies for the two groups using a coincidence cutoff point of 70% and 75% at 28 and 36 weeks, respectively, revealed a significant difference at 36 weeks only (table 6).

Follow up enquiries at nine to 12 months of all the infants studied showed that there have been no deaths and that no major developmen-tal problems had been recognised.

Discussion

Altered sleep and arousal patterns have been found in babies at risk of SIDS as early as the first week after delivery.¹⁰ Behavioural research on normal newborns and fetuses has shown a continuity in sleep state development.¹¹ Abnormal fetal behaviour has been associ-ated with neurodevelopmental problems in

Table 3 Coincidence (%) at 28 and 36 weeks' gestation and full Oxford SIDS risk score (OSS)

Risk	OSS	28 weeks (%)	36 weeks (%)
'Low' (OSS <2.5)	0.05	100	87
	0.17	86	77
	0.2	93	80
	0.24	15	100
	0.3	67	83
	0.33	76	87
	0.4	82	60
	0.4	100	31
	0.4	63	93
	0.46	92	98
	0.46	80	90
	0.5	90	96
	0.58	93	88
	0.96	38	89
	1.67	61	96
	1.79	90	100
'High' (OSS >2.5)	1.98	PQ	93
	2.23	50	98
	3.4	43	83
	3.64	67	59
	3.89	72	63
	5.26	100	88
	5.46	86	63
	8.2	41	70
	9.63	48	100
	12.6	74	70
	45	95	PREM
	84.2	82	PREM

PREM=preterm delivery; PQ=poor quality.

Table 4 Median number (range) of episodes of coincidence and median number of transitions between episodes of coincidence

Risk group	28 weeks				36 weeks			
	n=	1F	2F	Transitions	n=	1F	2F	Transitions
Low (OSS <2.5)	17	1 (0-3)	3 (0-6)	1 (0-6)	18	1 (1-4)	2 (1-4)	1 (1-5)
High (OSS >2.5)	10	1 (0-2)	1.5 (1-4)	1 (0-3)	8	1 (1-3)	1.5 (1-30)	1 (1-3)

None of these differences is significant.

infancy.^{12 13} Therefore, one might speculate that fetuses at increased risk of SIDS^{14 15} would exhibit altered fetal behaviour or sleep states. This pilot study using the Oxford SIDS risk prediction scoring system found a significant difference in behavioural development between the high and low SIDS risk group at 36 weeks' gestation, thereby supporting the hypothesis. At 28 weeks, coincidence as a means of detecting behavioural differences may be poorly discriminated, given that behavioural states are established only at 36 weeks using conventional behavioural state criteria.²¹ The advantage of using coincidence to study the development of fetal behaviour is that it increases with gestation and is an index of development of fetal behavioural states.²³ However, coincidence alone does not imply that linked transitions of behavioural state physiological variables from one state to another within three minutes have occurred.²¹ Furthermore, as sleep maturation after birth has been reported to be associated with a risk of SIDS, it was important in this study that the fetal equivalent of infant sleep states, REM and non-REM – namely, 2F and 1F, respectively – were both represented in the 36 week studies. In all the 36 week studies there was at least one linked transition between states 1F and 2F. Larger studies need to be undertaken to confirm this finding.

A number of methodological limitations must be acknowledged. There are several risk scores which have been developed to identify the infant that is at increased risk of dying from SIDS.¹⁴ The factors involved are largely environmental and socioeconomic and relate partly to the increased risk of infection in the first two months of life. Two SIDS risk scoring methods (the Oxford Record Linkage Study and the Sheffield Method) have been evaluated in the south-west of England.¹⁵ Both methods were equally effective at predicting SIDS, being able to identify a group with a two- to three-fold greater risk of SIDS than the general population. These were still insensitive screening methods, with about half the SIDS cases occurring in the low risk group. Arguably, the best use for SIDS scoring techniques is to

Table 5 Median per cent coincidence and SIDS risk

Gestation	OSS	No	Median	Interquartile range	Range
28 Weeks	<2.5	17	82*	63–92	15–100
	>2.5	10	73	53–85	41–100
36 Weeks	<2.5	18	89.5**	84–96	31–100
	>2.5	8	70	63–84	59–100

OSS=Full Oxford SIDS Score; *not significant ($p=0.58$); ** $p=0.06$.

Table 6 Number of fetuses exhibiting coincidence of 70% or more at 28 weeks and 75% or more at 36 weeks

Gestation (weeks)	Risk group	No	Coincidence Cutoff point	
			Below	Above
28	Low (OSS <2.5)	18	6	12*
	High (OSS >2.5)	10	4	6
36	Low (OSS <2.5)	18	2	16**
	High (OSS >2.5)	8	5	3

OSS Full Oxford SIDS Score; *Not significant; ** $p=0.01$.

identify prospectively populations at high risk of SIDS for research into the patterns, mechanisms, or prevention of SIDS,¹⁵ as in this study.

The limitations of adapting the OSS for antenatal use have been illustrated in this pilot study. Three cases scored as high risk on the basis of factors available at recruitment converted to low risk cases when delivery factors were added into the calculations to produce the full OSS. This is not surprising as only 11 of the 15 factors in the full OSS were used for the allocation of risk at recruitment in this study. Another pertinent criticism is that the person performing the fetal behavioural studies (JS) may not have been totally 'blind' to the risk status of the patient, thus introducing bias. We think this is unlikely mainly because if any bias were introduced it would have resulted in a much greater difference between the groups.

Fetal behavioural research utilises methods that are cumbersome and time consuming. Nevertheless, a consensus on the features of normal fetal neurobehavioural development has been reached.^{19 24} Fetal neurobehavioural studies can identify fetuses with neurodevelopmental abnormality.^{11 13 25} Thus it would seem to be an appropriate method for the examination of sleep-arousal patterns in the fetus. The increase in the median coincidence in the two groups between 28 and 36 weeks was of a similar order of magnitude to that found by others.^{24 26} However, the values for both groups at both gestations are greater than that reported by others. The most likely explanation for this observation is that eye movements were excluded from the behavioural analysis. For example, we have separately reported coincidence in the order of 60% when all three variables were used, in contrast to the 85% in this study.¹⁹ Arduini *et al* have also reported this.²²

Interestingly the two preterm deliveries in the high risk group had the highest coincidence values in all the 28 week studies (82% and 95%, respectively) and it is tempting to consider an 'advanced maturation' hypothesis. These findings may be a reflection of the small numbers and the use of only two variables in this pilot study. The proposed larger study which includes eye movements will clarify this issue.

The starting point for considering that sleep-arousal patterns may be disturbed is the simple observation that the commonest time for SIDS to occur is when the infant is asleep⁴ and at an age which coincides with a period of rapid sleep maturation. Over the first two to three months of life there is a progressive decline in

the amount of active sleep and a rapid increase in quiet sleep. Periods of wakefulness diminish in frequency with longer intervals between these periods during the night.

In infants at risk of SIDS there is a disturbance in sleep organisation and arousal with decreased motility in rapid eye movement (REM) sleep and decreased waking time in the early morning.⁷ This disturbance is evident from the first week of life and can persist until 2 to 3 months of age.¹⁰

Electroencephalogram (EEG) research during this period of infant development has revealed the emergence of 'sleep spindles' during quiet sleep. This is thought to indicate the development of interconnections between higher control nervous system centres (fore-brain inhibitory mechanisms) and the brainstem.³⁰ Sustained forebrain inhibition over the brainstem is a necessary part of normal sleep maturation in order to sustain prolonged periods of sleep.³ The developmental synchrony between sleep maturation and homeostatic brain stem mechanisms, especially cardiorespiratory control, is considered to have a critical influence on arousal threshold.^{4,8} Thus failure of arousal because of abnormal sleep maturation at a critical period in autonomic regulatory maturation could place a susceptible infant at risk of SIDS.

There is a disagreement over whether the disturbances of sleep maturation in SIDS represent an accelerated⁶ or delayed^{4,5,9} process. The accelerated maturation hypothesis proposes that early maturation for sleep and waking results in a higher threshold for arousal at a critical time. It is supported by the association of an increased thyroid hormone concentration, a marker of accelerated neurological development that has been reported in infants dying from SIDS.^{32,33}

The delayed maturation hypothesis is also supported histologically by the observation of the persistence of reticular spine density in the brainstem of SIDS babies which normally decreases 34 weeks after conception.⁶ This hypothesis is also supported by the findings of this study.

Finally, we emphasise that fetal behavioural research, as described in this report, is not harmful to the fetus.^{19,26} This conclusion has been reinforced by many authors.³⁴⁻³⁶

- 1 Wigfield RE, Fleming PJ, Berry PJ, Rudd PT, Golding J. Can the fall in Avon's sudden infant death rate be explained by changes in sleeping position. *BMJ* 1992; 304: 282-3.
- 2 Milner AD, Ruggins N. Sudden infant death syndrome. *BMJ* 1989; 298: 689-90.
- 3 Milner AD. The relationship between sleep and the sudden infant death syndrome. *BMJ* 1987; 295: 1366-8.
- 4 Gould JB. The relationship between sleep and the sudden infant death syndrome. *Ann NY Acad Sci* 1988; 533: 62-77.
- 5 Haddad GG, Walsh EM, Leistner HL, Grodin WK, Mellins RB. Abnormal maturation of sleep states in infants with aborted sudden infant death syndrome. *Pediatr Res* 1981; 15: 1055-7.
- 6 Sterman MB, Hodgman J. The role of sleep and arousal in the sudden infant death syndrome. *Ann NY Acad Sci* 1988; 533: 48-61.
- 7 Schectman VL, Harper RM, Wilson AJ, Southall DP. Sleep state organisation in normal infants and victims of the sudden infant death syndrome. *Pediatrics* 1992; 89: 865-70.
- 8 Hunt CE, Brouillette RT. Sudden infant death syndrome: 1987 perspective. *J Pediatr* 1987; 110: 669-78.
- 9 Guilleminault C, Coons S. Sleep states and maturation of sleep: a comparative study between full-term normal controls and near-miss SIDS infants. In: Tildon JT, ed. *Sudden infant death syndrome*. New York: Academic Press, 1983: 401-11.
- 10 Harper RM, Leake B, Hoppenbrouwers T, Sterman MB, McGinty DJ, Hodgman J. Polygraphic studies of normal infants and infants at risk of the sudden infant death syndrome: heart rate and variability as a function of state. *Pediatr Res* 1978; 12: 778-85.
- 11 Pillai M, James DK. Are the behavioural states of the newborn comparable with those of the fetus? *Early Hum Dev* 1990; 22: 39-49.
- 12 Pillai M, James DK. Absence of fetal breathing and abnormal fetal behaviour in prolonged preterm ruptured membranes - case report. *Ultrasound Obstet Gynecol* 1992; 2: 44-7.
- 13 Horimoto N, Koyanagi T, Meada H, Satoh S, Takashima T, Minami T, et al. Can brain impairment be detected in utero? *Arch Dis Child* 1993; 69: 3-8.
- 14 Peters TJ, Golding J. Prediction of sudden infant death syndrome: an independent evaluation of four scoring methods. *Statistics in Medicine* 1986; 5: 113-26.
- 15 Brooks JG, Pleming PJ, Berry PJ, Golding J. Evaluation of the Oxford and Sheffield SIDS Risk Prediction Scores. *Pediatr Pathol* 1992; 14: 171-9.
- 16 Fedrick J. Sudden unexpected death in the Oxford record linkage area: An analysis with respect to time and place. *Br J Prev Soc Med* 1973; 27: 217-24.
- 17 Fedrick J. Sudden unexpected death in infants in the Oxford record linkage area. *Br J Prev Soc Med* 1974; 28: 93-7.
- 18 Fedrick J. Sudden unexpected death in infants in the Oxford record linkage area: Details of pregnancy, delivery and abnormality in the infant. *Br J Prev Soc Med* 1974; 28: 164-71.
- 19 Pillai M, James DK. Behavioural states in normal mature human fetuses. *Arch Dis Child* 1990; 65: 39-43.
- 20 Pillai M. The development of behaviour in normal and high risk fetuses. (MD Thesis.) University of Bristol: 1992: 13-24.
- 21 Nijhuis JG, Prechtl HFR, Martin CB, Bots RSGM. Are there behavioural states in the human fetus? *Early Hum Dev* 1982; 6: 177-95.
- 22 Arduini D, Rizzo G, Giorlandino C, Valensise H, Dell'acqua S, Romanini C. The development of fetal behavioural states: a longitudinal study. *Prenat Diagn* 1985; 6: 117-24.
- 23 Arduini D, Rizzo G, Massaccesi M, Romanini C, Mancuso S. Longitudinal assessment of behavioural transitions in healthy human fetuses during the last trimester of pregnancy. *J Perinat Med* 1991; 1: 67-92.
- 24 Nijhuis JG, Martin CB, Prechtl HFR. Behavioural states in the human fetus. In: Prechtl HFR, ed. *Continuity of neural functions from prenatal to postnatal life. Clinics in developmental medicine*. Oxford: Blackwell Scientific, 1984: 65-79.
- 25 Pillai M, Garrett C, James D. Case report: Bizarre fetal behaviour associated with lethal congenital abnormalities. *Eur J Obstet Gynaecol* 1991; 39: 215-8.
- 26 Pillai M, James D. Development of human fetal behaviour: a review. *Fetal Ther* 1990; 5: 15-32.
- 27 Hellbrugge T. The development of circadian rhythms in infants. Coldspring Harbor Symposium. *Quant Biol* 1906; 25: 311-23.
- 28 Parmalee AH. Sleep patterns in infancy. A study of one infant from birth to eight months of age. *Acta Paediatrica* 1961; 50: 160-70.
- 29 Parmalee AH, Wenner WH, Schulz HR. Infant sleep patterns from birth to eight months of age. *J Pediatr* 1964; 65: 576-82.
- 30 Wu HS, Gould JB, Lee AFS, Fineberg H. Factors affecting sleep spindle activity during infancy. *Dev Med Child Neurol* 1980; 22: 344-51.
- 31 Parmalee AH, Stern E. Development of states in infants. In: Clemente C, Purpura D, Myer F, eds. *Sleep and the maturing nervous system*. New York: Academic Press, 1972: 199-228.
- 32 Peterson DR. Epidemiology of the sudden infant death syndrome - problems, progress and prospects. A review. In: Tildon JT, ed. *Sudden infant death syndrome*. New York: Academic Press, 1983: 89-97.
- 33 Chaco MA, Tildon JT. Elevated values of triiodothyronine in victims of the sudden infant death syndrome. *J Pediatr* 1981; 99: 758-60.
- 34 Bakketeig LV, Eik-Nes SH, Jacobsen G, Ulstein MK, Brodtkorb CJ, Balstad P, et al. Randomised controlled trial of ultrasonographic screening in pregnancy. *Lancet* 1984; ii: 207-11.
- 35 Salvensen KA, Bakketeig LS, Eik-Nes SH, Undheim JO, Okland O. Routine ultrasonography in utero and school performance at age 8-9 years. *Lancet* 1992; 339: 85-9.
- 36 Ter Haar GR. Safety of routine ultrasound. *Ultrasound Obstet Gynecol* 1992; 2: 237-8.