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SHORT COMMUNICATION

Randomised controlled trial shows that co-bedding twins may reduce birthweight recovery delay, parenteral nutrition weaning time and hospitalisation

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INTRODUCTION

Multiple pregnancies have been increasing, due to advances in assisted reproductive technology and delayed childbearing (1), and adapting and optimising medical protocols for multiple births have become a priority (2). *In utero* ultrasound has highlighted remarkable social bonds between twins, including the similarity of heart rates, sleep and wake rhythms and early behavioural interactions (3). The co-bedding technique is in line with the co-regulation and synactive theories, where the goal is to provide developmental and health benefits to twins (4,5). Co-bedding essentially prolongs the behavioural bond and *in utero* interactive development between twins and may significantly reduce postnatal stress due to separation.

Although the technique is now widely employed (6), co-bedding was traditionally performed late in hospitalisation, which was questionable given its objective to reduce separation stress at a critical clinical stage. We believe that early co-bedding, as soon as possible after birth, may be of critical importance. To date, there has been a lack of consensus among studies and a paucity of compelling data on the potential clinical benefits of co-bedding (7). Lai et al.'s database analysis in 2012 pinpointed discrepancies in the data produced by co-bedding studies, as well as the absence of data and safety and long-term outcomes (8). Heterogeneous practices, clinical judgement criteria and, most importantly, the delayed co-bedding of stable newborn twins several weeks after birth, may have contributed to this lack of clarity (6,9–12).

We decided to assess the effects of early co-bedding just after birth on twins ventilated with continuous positive airway pressure. We primarily focused on weight gain, but also considered thermoregulation, cardiorespiratory function, comfort and long-term neurodevelopmental outcomes at two years of age.

Neonatology and Cobedding (NEOCOB) was a monocentric prospective study using a randomised unblinded protocol and approved by the Medical Ethics Committee of Nantes, France. We planned to co-bed all twins born between 30 and 34 weeks of gestation, who did not have severe congenital pathologies but needed intubation, in the first 24 hours following birth. If intubated ventilated preterm infants were not eligible for practical reasons, due to the organisation of our unit, noninvasive ventilation support such as continuous positive airway pressure was accepted. Because intrauterine growth restriction (IUGR) has a significant impact on neonatal weight gain, the block randomisation was stratified by whether one or both of the twins were IUGR, in accordance with the usual Fenton curves. Parental consent was requested as soon as possible after birth, and initial resuscitation and randomisation were performed immediately by the hospital's Women's and Children's Clinical Investigation Center to determine the treatment arm.

Abbreviations
ANOVA, ANalysis Of VAriance; IUGR, IntraUterin Growth Restriction; LoS, Length of Stay; NEOCOB, NEOnatology & CO-Bedding; NICU, Neonatal Intensive Care Unit.

The twins were co-bedded in a single cocoon to maximise proximity and contact and each twin and their medical equipment were individually identified by coloured markings and identification stickers. The less stable twin was positioned on the left side of the incubator to facilitate resuscitation management, and a back-to-back position was favoured, at least until they were weaned off ventilatory support, to minimise the risk of accidents. Co-bedding was used until discharge for 15 sets of twins and compared to 17 sets of twins managed separately in individual incubators.

Growth parameters–weight, length and head circumference–were collected daily and, or, weekly, according to current practice. The daily weight gain (g/kg/day) was calculated weekly or over the entire hospital stay according to the following formula, where LoS was length of stay:

$$\frac{\left(\text{Weight}_{\text{Discharge}} - \text{Weight}_{\text{Birth}}\right)/\text{Los}_{\text{Days}}}{\left(\text{Weight}_{\text{Discharge}} - \text{Weight}_{\text{Birth}}\right)/2/1000}.$$

Extrauterine growth restriction was estimated using the LMS method (13). We also recorded the following: weight loss from birth or recovery delay, daily frequency of hyperthermia ($T° > 37.3°C$), hypothermia ($T° < 36.6°C$), tachycardia (heart rate >200 bpm), bradycardia (heart rate <80 bpm) and apnoea (respiratory break >15 seconds). Cardiorespiratory data were automatically extracted from CM system MP-50 recorder (Philips, Eindhoven, The Netherlands). The comfort score was based on the Reversed Amiel-Tison Comfort Scale, and the safety analysis was performed using pharmacovigilance and, or, infection vigilance inspections throughout the hospital stay. The neurodevelopment assessment was based on the Ages and Stages Questionnaire–Third Edition and was performed at two years old using the Loire Infant Follow-Up Team regional medical network.

The primary objective was to compare the daily weight gain of co-bedded and separated preterm twins during hospitalisation. Local data extracted from 2004 to 2006 revealed an average daily weight gain of 10.28 ± 2.74 g/kg/day. We expected to detect a 20% increase in growth rate (12.056 g/kg/day) in the co-bedded group. In a bilateral approach, with a target power of 80% and 5% alpha risk, 29 sets of twins were needed. The sample size calculation was not adjusted with the intracluster correlation correction, but fortunately we increased the sample size target to 32 sets, which gave us satisfactory statistical power. We performed generalised estimating equations, in order to account for the nonindependence of infants within a pair, adjusted by the twin set (cluster) and the birthweight *Z*-score, to reflect our randomisation stratifier of IUGR 0/1. In addition, one or two-way ANOVA and repeated measure ANOVA were performed to analyse the time effects, measured as LoS and interactions. SPSS version 16.0 (SPSS Inc, Chicago, USA) was used for all analyses.

Between September 2008 and March 2012, 32 pairs of twins were randomised to the study (Table 1), and co-bedding was initiated in the first 24 hour after birth for 26 (80%) of the pairs. A further two sets were co-bedded between 24 and 72 hours due to the research team's availability, and one set was reunited at 92 hours for organisational reasons. We analysed 60 newborn infants–28 co-bedded twins and 32 separated twins–as two pairs were transferred prematurely to other NICUs (Fig. 1). The randomisation treatment yielded homogeneous and comparable groups for all the confounding criteria. The main NEOCOB results are presented in Table 2. The daily weight gain during the entire hospital stay was not significantly different between the two groups (p = 0.384). Co-bedding did not significantly influence the weight of the Z-scores (ΔZ score co-bedding -0.68 ± 0.08 versus ΔZ score separated -0.74 ± -0.08, p = 0.562) or the weight gain

Table 1 Comparison of maternal and infant characteristics between Co-bedding and Individual Incubator management

	Co-bedding group	Individual incubator group	p-value
Maternal characteristics[a]			
Spontaneous pregnancy (%)	57.14%	56.25%	0.945
Monochorionic twin pregnancy (%)	35.71%	50%	0.265
Antenatal corticosteroids (%)	92.86%	100%	0.124
Caesarean delivery (%)	46.43%	25%	0.083
Breastfeeding ratio (%)	43.75%	42.86%	0.945
Infant characteristics[b]			
Infant sex: Male (%)	50%	37.5%	0.330
Gestational age (mean ± SE)	32.42 ± 0.17	32.04 ± 0.16	0.119
Birthweight in g (mean ± SE)	1684 ± 53.16	1633 ± 44.40	0.309
Intrauterin growth restriction (%)	10.71%	6.25%	0.532
Birthweight Z-score (mean ± SE)	−0.392 ± 0.150	−0.366 ± 0.137	0.902
APGAR at one minute (mean ± SE)	8.36 ± 0.51	7.81 ± 0.41	0.403
Noninvasive ventilation at inclusion (%)	35.71%	46.88%	0.382
Peripheric lines at inclusion (%)	92.86%	100%	0.124
Grade 3 or 4 intraventricular haemorrhage (%)	0%	0	1

[a]Co-bedding, n = 14; Individual Incubator, n = 16.
[b]Co-bedding, n = 28; Individual Incubator, n = 32.

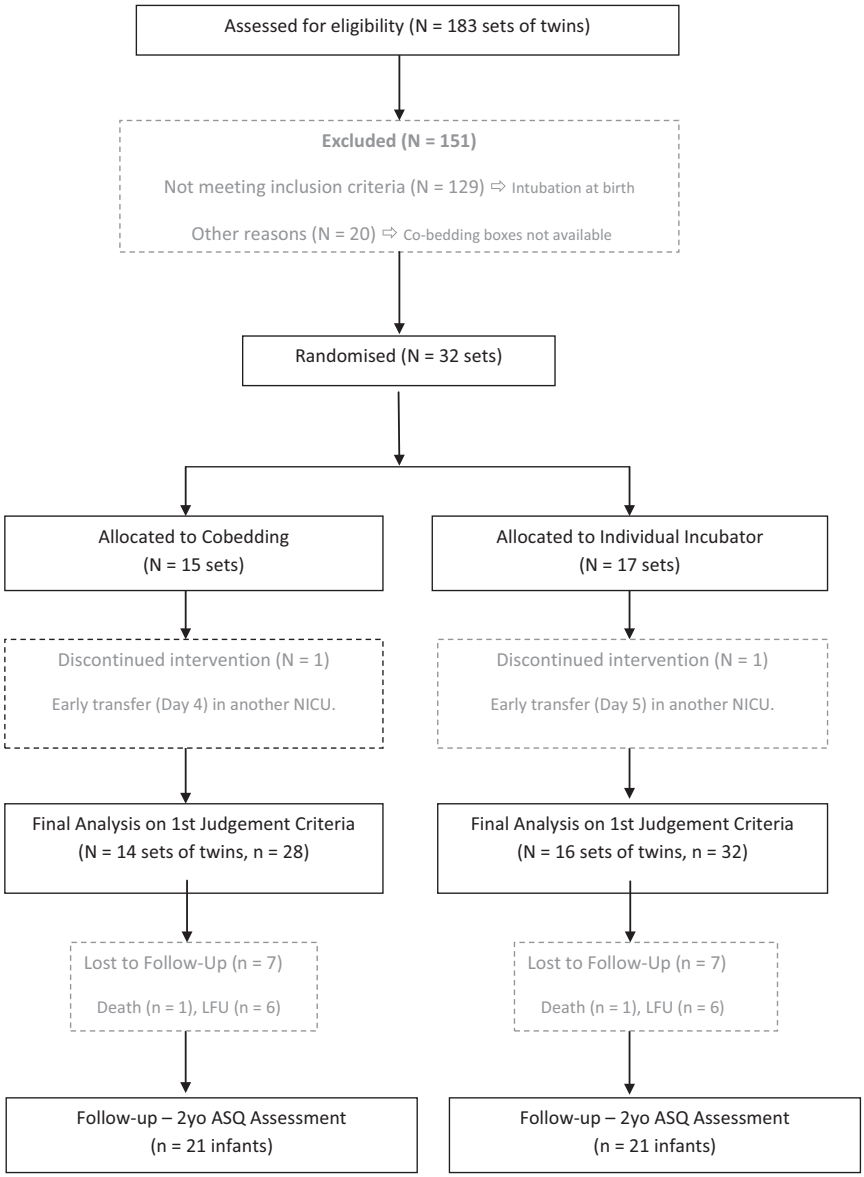

Figure 1 Study population.

trajectories for weeks one, two and three (all p = 0.364). However, we observed trends in the reduced birthweight recovery time in the co-bedding group (p = 0.057) and in the reduced initial weight loss (132.14g ± 48.59 for the co-bedding arm *versus* 156.125 ± 55.11 for the separated arm, p = 0.07). The two groups displayed similar breastfeeding rates: 42.85% in separated arm versus 43.75% in the co-bedded arm (p = 0.95). This rate was significantly higher than the 23% breastfeeding rate measured in the non-enrolled twins (p = 0.031). Trends were detected for the parenteral nutrition weaning delay and LoS, which appeared to be shorter in the co-bedding group (p = 0.063 and p = 0.067, respectively). Bradycardia frequency was identical between the two groups (p = 0.55), as was the frequency of apnoea events (p = 0.141). On the other hand, the co-bedded group displayed a higher frequency of tachycardia (p = 0.088). A repeated measures ANOVA performed on the treatment and number of tachycardia events–repeated over time between the co-bedded versus the separated twins–yielded an interaction term of $F(2–116) = 0.29223$, which confirmed these two patterns (Fig. 2). The rates of tachycardia were consistently higher in co-bedded twins than separated twins (p = 0.0005). The effect of treatment was $F(1–58) = 7.2194$ (p = 0.00939), and the effect of time was $F(2–116) = 4.1707$ (p = 0.01782). The comfort scores were similar between the two groups (p = 0.07), but clinically irrelevant, with no discomfort event reported (p = 1). Thermoregulation patterns appeared to be similar when considering hypothermia (p = 0.487) and hyperthermia (p = 0.347) events. We recorded 10 nosocomial infections. The infection frequency was comparable between the two groups–14% in the

Table 2 Results of main NEOCOB judgement criteria adjusted by generalized estimated equations (GEE) on twin pairs and birthweight Z-score

	Co-bedding Group (N = 28)	Separated Group (N = 32)	Beta	[95% CI]	p-value	Power %
Daily weight gain in g/kg/day (mean ± SE)	9.80 ± 0.46	10.30 ± 0.33	0.540	[−0.68,1.76]	0.384	98.5
Birthweight recovering delay in days (mean ± SE)	**8.76 ± 0.42**	**9.53 ± 0.36**	**1.150**	**[0.033,2.333]**	**0.057**	100
Parenteral weaning delay in days (mean ± SE)	**5.12 ± 0.58**	**8.61 ± 1.32**	**3.431**	**[−0.186,7.048]**	**0.063**	100
Hospitalisation length in days (mean ± SE)	**34.32 ± 1.57**	**40.19 ± 1.74**	**5.896**	**[−0.416,12.209]**	**0.067**	100
Bradycardia frequency* (HR <80 bpm) – (mean ± SE)	56.39 ± 11.33	64.69 ± 10.98	−5.109	[−49.913, 39,696]	0.823	71.84
Tachycardia frequency* (HR >200 bpm) – (mean ± SE)	**55.75 ± 12.31**	**28.91 ± 4.42**	**−29.764**	**[−60.350,0.821]**	**0.056**	100
Apnoea frequency* (Respiratory break >15s) (mean ± SE)	28.79 ± 3.40	42.94 ± 7.24	11.108	[−6.997,29.213]	0.229	100
Hypothermia frequency* (T° <36.6°C) (mean ± SE)	10.00 ± 0.95	14.03 ± 1.65	1.609	[−2.930,6.149]	0.487	100
Hyperthermia frequency* (T° >37.3°C) (mean ± SE)	16.14 ± 1.75	14.00 ± 0.91	−2.402	[−7.409, 2.606]	0.347	98.86
Mean Reversed Amiel-Tison Comfort Score (mean ± SE)	2.69 ± 0.78	1.94 ± 0.55	−1.824	[−5.091,1.442]	0.274	91.48
Noninvasive ventilation duration (mean ± SE)	3.60 ± 0.62	8.80 ± 2.26	4.031	[−1.199, 9.261]	0.131	100
Infectious transmission & material/medication accidents (N - %)	0–0%	0–0%	–	–	1	Nc
Follow-up/2yo ASQ assessment (n, mean ± SE)	n = 21, 264.05 ± 7.81	n = 21, 255.71 ± 6.07	6.938	[−32.099, 18.223]	0.589	92.16

*Mean number of events during NEOCOB physiological monitoring.
Main statistical trends highlighted on secondary clinical judgement criteria are in bold.

Figure 2 A repeated measures analysis of variance with treatment and N of tachycardia events (defined by number of tachycardia events –HR > 200 bpm- per week) repeated over Time between Co-bedded versus Separated twins yielded: Interaction Term ($F(2, 116) = 0.29223$). Rates of tachycardia were consistently higher in co-bedded twins compare with separated twins (Effect of treatment $F(1, 58) = 7.2194$, $p = 0.00939$; Effect of time $F(2, 116) = 4.1707$, $p = 0.01782$).

separated twins versus 18.75% in the co-bedded infants ($p = 0.35$)–as was antibiotic exposure, at 10.67 ± 1.14 days for the co-bedded twins versus 8.25 ± 0.98 for the separated twins ($p = 0.172$). There was no medication or medical equipment incidents or infection transmission noted. Finally, the long-term neurodevelopment outcome data revealed no significant difference in the two-year Ages and Stages Questionnaire score between the two groups ($p = 0.432$).

We believe that this was the first study to explore an integrated set of physiological responses from twins who were early and continuously co-bedded during hospitalisation and received noninvasive support. Our study suggests that co-bedding had no significant impact on the weight gain trajectories in the preterm twins, as shown in previous studies (11,12), but it does highlight potential benefits in terms of birthweight recovery delays, decreased parenteral weaning delays and reductions in the length of hospital stay. Co-bedding was a safe practice, even when used on ventilated and catheterised infants.

Even if they are speculative, the observed trends on parenteral weaning delays and LoS reductions may suggest that co-bedding has an impact on orality maturation. These results seem in line with the initial transitory benefits observed by Byers et al. (9), where an increased average daily weight gain was observed during the first five days after reuniting twins. In accordance with the literature, our study failed to demonstrate clear cardio-respiratory benefits (11). However, the co-bedded twins displayed a significantly higher frequency of tachycardia in the Byer et al. study. One could interpret this finding as discomfort and stress due to constant and lengthy co-bedding. But this idea was not supported by the Reversed Amiel-Tison Comfort Scale scores. As such, we may postulate that there are

possible sensory stimulation properties of co-bedding and neurocognitive benefits on orality, in particular suction and the initiation of breastfeeding, which are major contributors to LoS. Crowded co-bedding may induce constant tactile interaction and efficient awareness, which promotes systemic reorganisation, synaptogenesis and cerebral maturation, namely the synactive theory (5). In this context, increased face and corporal stimuli could foster sensorial acquisition and ultimately explain accelerated parenteral weaning and hospital discharge.

Despite the absence of clear benefits for weight gain, NEOCOB was the first study to investigate an integrated set of behavioural and physiological responses to early co-bedding.

This study had some limitations. Our interpretations on orality maturation induced by co-bedding should be considered with caution due to the absence of direct measures on robust nutrition criteria. Moreover, our study did not have an adequate sample size, as far as the clusterised statistical approach was concerned, to investigate neurodevelopment at two years of age. Larger multicentre studies on early co-bedding efficiency are required to confirm the benefits of co-bedding.

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CONFLICTS OF INTEREST

None to declare.

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