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The implications of high carbon monoxide levels in early pregnancy for neonatal outcomes

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ABSTRACT

Objectives: The aim of this study was to examine the implications of increased maternal Breath Carbon Monoxide (BCO) levels at the first antenatal visit for subsequent birthweight (BW) and neonatal outcomes.

Study design: Secondary analysis of a prospective, observational study. Pregnant women aged ≥18years who understood English were recruited (*n*=250). However, only women who delivered a normally formed baby weighing ≥500g were analysed (*n*=234). At the first antenatal visit, a research questionnaire was completed and a BCO test was performed. Obstetric and neonatal data computerised by midwives at the first antenatal visit and updated after delivery were also analysed.

Results: Results from the receiver operating characteristic (ROC) curve indicated the highest combined sensitivity and specificity for smoking was observed at a BCO cut-off level of 3ppm (sensitivity 85%, specificity 90%). Of the 234 women, 53 (22.6%) had a BCO ≥3ppm but only 36 (15.4%) disclosed smoking to the midwife on routine questioning. A further 23 (9.8%) were classified as non-disclosers based on a research questionnaire and/or a BCO measurement ≥3ppm. No relationship was found between the self-reported number of cigarettes daily in early pregnancy and BW (r=0.05, p=0.78). However, an inverse relationship was found between maternal BCO levels and BW (r=−0.31, p<0.001). BCO levels ≥3ppm in early pregnancy were associated with an increased risk of emergency caesarean section, low birth weight, BW <25th centile, fetal distress and having two or more adverse pregnancy events (all p<0.05). Smoking non-disclosers had babies with decreased BWs (−400.1g, 95% CI 141.1–659.0g, p<0.001), and higher rates of BW <25th centile (56.5% versus 25.3%, p<0.001), small-for-gestational-age (21.7% versus 9.1%, p<0.001) and fetal distress (39.1% versus 16.0%, p<0.01) compared to non-smokers Non-disclosers at the first antenatal visit also had a 22% higher rate of having two or more adverse pregnancy events (p<0.05).

Conclusion: The results showed that an increased BCO level was associated with a lower BW and increased risk of adverse pregnancy and neonatal outcomes. This strengthens the case for universal BCO screening at the first antenatal visit. A high BCO reading should be an indication for referral to stop smoking services referral and close fetal surveillance.

Introduction

Maternal smoking is a global challenge. The prevalence of maternal smoking may have peaked in developed countries but rates of persistent smoking remain high [1–3]. In developing countries the problem continues to escalate [4]. In Europe and America, one in ten women on average report smoking in pregnancy [5,6]. However, these rates are likely underestimated as non-disclosure of smoking is prevalent in pregnancy with rates of up to 73% reported [7].

Non-disclosure of smoking status leads to a number of problems, particularly in pregnancy. Healthcare professionals are missing opportunities to intervene and potentially improve the health of both the woman and her offspring [8]. Furthermore, complications related to smoking, particularly fetal growth

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restriction (FGR), may go unrecognised leading to increased perinatal morbidity and mortality [9].

A number of biochemical markers are used to verify smoking. Cotinine content in urine, blood and saliva demonstrate good sensitivity and reliability for confirming smoking status however, these samples require laboratory analysis increasing the time to receive results and the cost per sample [10,11].

Breath carbon monoxide (BCO) is a quick, inexpensive and practical method to verify smoking status at the point of care [12,13]. Two studies have investigated the relationship between BCO levels and pregnancy outcomes, although, to our knowledge, none to date have assessed the sensitivity or specificity of the BCO cut-off point used to verify smoking [14,15]. Instead, these studies have utilised an arbitrary cut-off point of >5 ppm [14,15]. Reports suggest that this level may be too high and reduce sensitivity for identifying persistent smoking [16,17].

This prospective observational study examined the implications of high maternal BCO levels at the first antenatal visit on subsequent birthweight (BW) and pregnancy outcomes.

Materials and methods

The study is a secondary analysis of data collected from a single-site, prospective, observational study that evaluated the use of BCO screening in identifying maternal smokers (n=250) [17]. All women aged ≥18 years who could understand English were eligible. Women were recruited at the first antenatal clinic appointment at a mean gestation of 12.5 weeks (SD 2.2). Written informed consent was obtained.

The sources of data used in this study included the hospitals online medical record system 'Euroking K2', a purposely designed research only questionnaire and a BCO test.[17] Women's self-reported smoking status was collected on two occasions within the same hospital visit. Smoking status was first collected at the first antenatal clinic appointment and computerised by trained midwives to the Euroking K2system and secondly, in the research questionnaire following the woman's ultrasound dating scan. The woman's clinical, sociodemographic and lifestyle details were also computerised on Euroking K2, whereas education level and exposure to environmental CO were collected on the research questionnaire. BCO tests were performed using the piCO + Smokerlyzer by a single researcher (CR) to limit intra-observer variability (Bedfont Scientific, Kent, UK).

Following delivery, Euroking K2 was updated with pregnancy outcome and delivery details. This data included onset of labour, mode of delivery, suspected fetal distress, Neonatal Unit admissions (NNU: includes high dependency unit and neonatal intensive care unit admissions), gestational age (GA), BW, head circumference (HC).

Suspected fetal distress was recorded in the presence of a non-reassuring cardiotocograph (CTG) when a fetal blood sample was not possible or contraindicated [18]. HC was measured around the broadest part of the forehead above the eyebrow and ears, at the most prominent part of the back of the head. BW was measured and computerised by a midwife within 30 minutes of birth. Low birth weight (LBW) was defined as <2.5kg [19].

BW was converted to percentiles using the Gestation Related Optimal Weight (GROW) bulk centile calculator v8.0.1. The GROW calculator is internationally applicable and recommended by the Royal College of Obstetrics and Gynecologists for the assessment of BW [20,21]. The centiles calculated by the software adjust for a number of known confounding variables of BW and GA such as maternal anthropometry, ethnicity, parity and infant gender.

To reduce the numbers of confounding variables of BW, only women who delivered a live singleton baby, not complicated by chromosomal or congenital abnormalities and weighing ≥500 g were included.

Data were analysed using the statistical software programme SPSS and the online statistical program Vassarstats [22]. The normality of data were assessed using visual inspection of histograms, the skewness and kurtosis of data, as well as the Kolmogorov-Smirnov test. Descriptive statistics were used to assess the study characteristics and proportions of delivery and pregnancy outcome data across groups. The diagnostic accuracy of BCO in determining smoking was assessed using a receiver-operating characteristic (ROC) curve. The BCO level in parts per million (ppm) with the largest combined sensitivity and specificity was used as the cut-off point to distinguish between smokers and non-smokers. Women with a BCO result greater than the cut-off point but who reported as a non-smoker to midwives at their first antenatal appointment were categorised as non-disclosers.

Differences between proportions were evaluated by the test for difference between two independent proportions [22]. Independent samples t-tests were used to assess the mean differences in delivery and pregnancy outcome data between groups.

Non-parametric data were transformed into normally distributed logarithms. Pearson correlations were used to assess the correlations between BW and maternal characteristics and lifestyle data. Multiple linear regression was used to assess the association between maternal BCO levels, GA and BW. Binary logistic regression analyses were used to assess the relationship with BCO levels ≥3ppm and pregnancy outcomes. Ethical approval was received from the Hospitals Research Ethics Committee (17–2015).

Results

Of the 250 women recruited, 234 (94%) were available for analysis. Exclusions included multiple births (n=2), women delivering elsewhere (n=2), miscarriage (n=2), intrauterine death (n=1) and neonatal death due to chromosomal and congenital abnormalities (n=2). Seven cases had missing outcome data.

Of the 234 women analysed, the mean age was 31.0years (SD 5.4), mean BMI was 26.3kg/m^2 (SD 5.9), 36% were nulliparas and 65% had planned their pregnancy. Fifty-one percent were married, 74% were employed and the mean time spent in continuous education was 16.1years (SD 3.5). Five women reported continued alcohol use in pregnancy and eight women continued to use illicit drugs.

At the first antenatal visit, 43% of women reported they had never smoked, 40% reported they were ex-smokers and 17% women reported currently smoking to midwives. Twenty-eight percent of women reported passive smoke exposure on a daily basis. The median BCO level was 1 (IQR 1, range 0–27).

An ROC analysis was conducted to determine the optimal BCO cut-off to indicate current smoking in terms of both sensitivity and specificity. Self-reported smoking status on the research questionnaire was used as the reference in the analysis. The highest combined sensitivity and specificity values crossed the curve at 3 ppm (sensitivity 85% and specificity 90%). The area under the curve (AUC) was 0.93 (95% CI 0.88–0.98). Twenty-three percent (n = 53) of women had a BCO ≥3ppm.

BW at delivery was correlated with the log transformations of the non-parametric variables GA (r=0.52, p<0.001) and maternal BCO (r=−0.31, p<0.001), but not cigarettes per day (r=0.05, p=0.777), maternal BMI (r=0.03, p=0.640), parity (r=0.08, p=0.230) or time spent in passive smoke (r=0.24, p=0.052). Maternal BCO levels explained 10% of the variance in BW whereas GA explained 27%. Results from the multiple linear regression model that included maternal BCO and GA demonstrated a strong association with BW (R=0.57, p<0.001) and explained 32% of the variance in BW.

Table 1 shows the pregnancy and neonatal outcomes of the study cohort analysed by BCO levels <3ppm and ≥3ppm. Women

Table 1
Pregnancy and neonatal outcomes analysed by maternal carbon monoxide levels < and ≥ 3 parts per million (ppm).

Pregnancy/neonatal outcomes	Total $n=234$	< 3 ppm $n=181$	≥ 3 ppm $n=53$	p-value
Onset of labour (%)				
Spontaneous	53.8	55.2	49.1	0.215
Induced	33.9	31.1	43.4	0.048
Elective caesarean	12.3	13.7	7.5	–
Type of delivery (%)				
Spontaneous	56.4	58.5	49.1	0.112
Ventouse	7.6	7.7	7.5	–
Forceps	7.2	5.5	13.2	0.027
Elective caesarean	12.3	13.7	7.5	–
Emergency caesarean	16.5	14.8	22.6	0.087
HC[a] (cm) (mean; SD)	34.9 (1.3)	35.0 (1.3)	34.4 (1.3)	0.013
BW (grams) (mean; SD)	3437.8 (511.6)	3512.4 (497.1)	3180.3 (480.7)	< 0.001
LBW (< 2500 g) (%)	3.4	1.6	9.4	–
SGA (%)	11.4	9.3	18.9	0.027
BW < 25th centile (%)	31.3	26.7	47.2	0.002
GA (weeks) (mean; SD)	39.5 (2.1)	39.6 (2.1)	39.2 (2.0)	0.264
Preterm birth (%)	5.5	4.9	7.5	–
Fetal distress (%)	19.5	16.4	30.2	0.013
NNU admission (%)	9.7	8.7	13.2	0.167
Two or more adverse events[§] (%)	16.2	13.3	26.4	0.011

[*]Tears – includes lacerations and 1st to 4th tears. [a]Missing data $n=16$. p-values compare women with BCO levels <3ppm to women with BCO levels ≥3ppm
[§]Adverse events: A women who had two or more of the following outcomes; SGA, Apgar score <7 at 5 min, NICU admission, fetal distress, preterm birth and/or emergency caesarean section.
HC; Head circumference. BW; Birthweight. LBW; Low birth weight. SGA; Small-for-gestational-age, < 10th centile. GA; Gestational age. NNU admissions; Neonatal unit (includes high dependency unit and neonatal intensive care unit).
- Numbers were too small to statistically analyse.

who had a BCO level of ≥3ppm had a 12% higher rate of induction (p=0.048), 7% higher rate of forceps delivery (p=0.027), 9% higher rate of BW <10th centile (p=0.027), 20% higher rate of BW <25th centile (p=0.002) and a 14% higher rate of fetal distress (p=0.013). Women with a BCO ≥3ppm also had a 13% higher rate of having two or more adverse pregnancy events (p=0.011) and had babies on average 332g lighter than women with BCO levels <3ppm (95% CI-180.5- -483.8g, p<0.001). Fig. 1 shows the proportion of women that delivered a baby within each BW centile analysed by BCO levels above and below the cut-off indicating smoking.

Table 2 shows that BCO levels ≥3ppm in early pregnancy were associated with emergency caesarean section, BW <25th centile, low birth weight (LBW) and fetal distress. Despite no relationship with self-reported smoking (OR 1.3, 95% CI 0.5-3.5, p=0.541, data not shown), a BCO level of ≥3ppm was associated with having two or more adverse pregnancy events (OR 2.8, 95% CI 1.3-6.2, p<0.011).

Results from the research questionnaire and BCO tests showed that although 15.4% ($n=36/234$) of women disclosed currently smoking to midwives at the first antenatal visit, 9.8% ($n=23/234$) did not. The pregnancy outcomes of all women were analysed by their disclosure of smoking status and compared to verified non-smokers (Table 3).

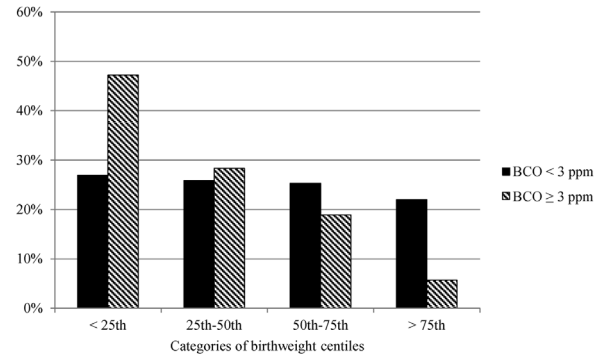

Fig. 1. The proportions of women that delivered an infant within each birthweight percentile analysed by breath carbon monoxide levels (BCO) < 3 ppm and ≥ 3 ppm.

Non-disclosers had a 12% higher rate of SGA, and a 22% higher rate of both fetal distress and having two or more adverse pregnancy events compared to non-smokers (all p<0.01) but not disclosers (p>0.05). Non-disclosers also had lower BWs than

Table 2
Logistic regression analysis of maternal carbon monoxide levels ≥ 3 parts per million (ppm) and pregnancy outcomes.

Pregnancy/neonatal outcome	Odds ratio (OR)	95% CI	p-value
Onset of labour			
Spontaneous	Reference	Reference	Reference
Induced	1.6	0.8–3.0	0.174
Elective caesarean	0.6	0.2–1.9	0.414
Type of delivery			
Spontaneous	Reference	Reference	Reference
Ventouse	1.2	0.4–3.9	0.790
Forceps	2.9	1.0–8.3	0.472
Elective caesarean	0.7	0.2–2.1	0.141
Emergency caesarean	1.8	1.0–4.1	0.050
LBW			
No	Reference	Reference	Reference
Yes	6.3	1.4–27.1	0.014
SGA			
No	Reference	Reference	Reference
Yes	2.3	1.0–5.3	0.059
BW < 25th centile			
No	Reference	Reference	Reference
Yes	2.5	1.3–4.6	0.005
Preterm birth			
No	Reference	Reference	Reference
Yes	1.6	0.5–5.3	0.463
Fetal distress			
No	Reference	Reference	Reference
Yes	2.2	1.1–4.5	0.028
Adverse events[§]			
None	Reference	Reference	Reference
Two or more	2.8	1.3–6.2	0.011

[*]Tears – includes lacerations and 1 st to 4th tears.
[§]Adverse events: A women who had two or more of the following outcomes; SGA, Apgar score <7 at 5 min, NICU admission, fetal distress, preterm birth and/or emergency caesarean section.
BW; Birthweight. LBW; Low birth weight, <2500 g. SGA; Small-for-gestational-age, < 10th centile. Preterm birth; <37 weeks gestation at birth.

Table 3
Pregnancy and neonatal outcomes analysed by maternal cigarette smoking disclosure.

Pregnancy/neonatal outcomes	Total n = 234	Non-smokers n = 175	Disclosers n = 36	Non-disclosers n = 23
Onset of labour (%)				
Spontaneous	53.8	54.3	52.8	52.2
Induced	33.8	31.4	38.9	43.5
Elective caesarean	12.4	14.3	8.3	4.3
Type of delivery (%)				
Spontaneous	56.4	58.3	55.6	43.5
Ventouse	7.7	8.0	5.6	8.7
Forceps	6.8	4.6	8.3	21.7
Elective caesarean	12.4	14.3	8.3	4.3
Emergency caesarean	16.7	14.9	22.2	21.7
HC[a] (cm) (mean; SD)	34.9 (1.3)	34.9 (1.3)	34.4 (1.3)	34.5 (1.1)
BW (grams) (mean; SD)	3437.8 (511.6)	3512.9 (497.4)	3276.1 (473.1)*	3112.8 (511.3)***
LBW (%)	3.0	1.1	5.6	13.0
SGA (%)	11.1	9.1	13.9	21.7***
BW < 25th centile (%)	31.3	25.3	44.4	56.5***
GA (weeks) (mean; SD)	39.5 (2.0)	39.6 (2.0)	39.4 (1.2)	39.4 (2.7)
Preterm birth (%)	5.1	4.6	2.8	13.0
Fetal distress (%)	19.2	16.0	22.2	39.1**
NNU admission (%)	9.8	9.1	8.3	17.4
Two or more adverse events[§] (%)	16.2	13.1	19.4	34.8**

Disclosers; women who self-reported smoking and had a carbon monoxide test ≥ 3 ppm.
Non-disclosers; women who self-reported not smoking but had a carbon monoxide test ≥ 3 ppm.
The * symbols indicate the significance level between 'Non-smokers' and 'Disclosers' as well as 'Non-smokers' and 'Non-disclosers'.
*p < 0.05, **p < 0.01, ***p < 0.001.
[a]Tears – includes lacerations and 1st to 4th tears.
[§]Adverse events: A women who had two or more of the following outcomes; SGA, Apgar score <7 at 5 min, NICU admission, fetal distress, preterm birth and/or emergency caesarean section.
HC; Head circumference. BW; Birthweight. LBW; Low birth weight, <2500 g. SGA; Small-for-gestational-age, < 10th centile. GA; Gestational age. NNU admissions; Neonatal unit (includes high dependency unit and neonatal intensive care unit).

verified non-smokers (−400.1g, 95% CI -659.0- -141.1, p<0.001). Once again, they did not differ to disclosers of smoking. Disclosers of smoking had similar outcomes to non-smoking women, however, disclosers had a lower average BW (−236.8g, 95% CI −450.4 to −23.3g, p<0.05). Fig. 2 shows the proportion of women that delivered a baby within each BW centile analysed by disclosure of smoking status at the first antenatal visit.

Discussion

This study reports an association between adverse pregnancy and neonatal outcomes and BCO levels in early pregnancy. An inverse relationship exists between BCO levels and infant BW. Women with BCO levels ≥3ppm had babies that were smaller in terms of mean HC and BW and had higher rates of SGA. These women also had an almost two-fold higher rate of having two or more adverse pregnancy events.

Forty-four percent of women with BCO levels ≥3 ppm did not report current smoking. Thus, these non-disclosers may not have received the clinical monitoring they required during pregnancy due to the absence of reported risk factors. These findings strongly support the clinical need to introduce universal BCO screening combined with smoking self-report, in the first trimester. Women with BCO levels ≥3 ppm should be referred to stop smoking services and have their pregnancies monitored, particularly for fetal growth trajectories in the third trimester.

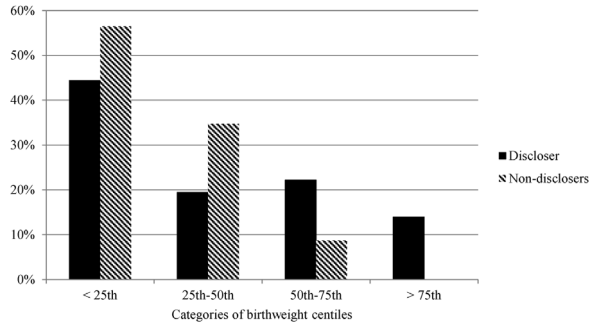

Fig. 2. The proportions of women that delivered an infant within each birthweight percentile analysed by smoking disclosure.

One of the first studies that associated carbon monoxide (CO) with reduced fetal growth was published almost 50 years ago, using results from numerous animal studies. [23] Tissue oxygenation, specifically CO binding to fetal haemoglobin thereby reducing the availability of oxygen, was the proposed mechanism of action.

Almost three decades later, the first study to investigate BCO and BW was published. [14] The study recruited only self-reported maternal smokers and BCO levels were taken at the first antenatal visit and at 36weeks gestation. A weaker correlation was reported between BW and BCO at the first antenatal visit compared to our study (r=−0.22 versus r=−0.31, respectively). However, our study's correlation coefficient was similar to that of the 36week gestation BCO correlation with BW (r=−0.32).

The study concluded that current smokers at the first antenatal visit have already compromised their infant's BW compared to those who quit when they found out they are pregnant. [14] This is not surprising, as longitudinal studies have shown that if women do not quit before pregnancy or soon after confirmation of pregnancy, they are unlikely to quit and remain abstinent subsequently [24,25].

Since then, just one other study investigated this relationship. [15] BCO tests were conducted in the first trimester and at delivery of both smoking and non-smoking women. As with the 1997 study, no ROC curves were calculated and a cut-off of >5ppm was chosen to identify smoking. BCO levels at delivery were highly correlated with BCO levels in the first trimester (r=0.86, p<0.0001). The largest difference in BW was found between women with BCO

levels at delivery of ≤5ppm and women with BCO levels >20ppm (754g). [15].

Although sample size was powered to identify levels of non-disclosure, a limitation of our study was the sample size was insufficient to investigate a number of pregnancy outcomes. Further larger studies are required in pregnancy to investigate the association between BCO and less common adverse outcomes such as pregnancy loss.

To our knowledge, our study is the first to investigate pregnancy outcomes using an ROC curve to obtain the appropriate cut-off for smoking verification. Furthermore, there is a dearth of research investigating the differences in pregnancy outcomes of women who are non-smokers and non-disclosers. Although, a proportion of women categorised as 'non-disclosers' may be 'false-positive', the results of this study indicate that non-disclosers have poor pregnancy outcomes compared with verified non-smokers in early pregnancy.

Although, no significance was found, likely due to sample size constraints, non-disclosers appear to have suboptimal outcomes compared to self-reported smokers possibly due to the reduced clinical monitoring of these pregnancies, as no risk factors were reported. FGR may, therefore, go undetected until much later in pregnancy.

We found that women with BCO levels ≥3 ppm were associated with an increased risk of adverse events including fetal distress and increased risk of emergency caesarean section and NNU admission, all of which are also associated with SGA [26,27]. Furthermore, fetal distress is an indicator for caesarean section, thus is it not surprising these women are more likely to have two or more adverse events [28,29].

SGA is a risk factor for a number of immediate and subsequent adverse outcomes including stillbirth, neonatal death, perinatal morbidity, cerebral palsy and even cardiovascular disease in later life [27]. Despite its potentially serious implications, it is reported that just one quarter of all SGA cases are identified antenatally, however, in low-risk pregnancies the detection rate is as low as one in seven [27].

A recent descriptive study investigating intrapartum and neonatal deaths in Ireland found that although 20% of normally formed infants were SGA at birth, just one case was recognised antenatally [30]. Thus, it was recommended that all risk factors for SGA are identified and managed to reduce deaths [30]. Missing cases of SGA antenatally can increase the risk of serious fetal complications four-fold including, but not exclusive of, cerebral palsy, stillbirth and neonatal death compared to SGA recognition and management during pregnancy [31].

The National Institute for Health and Care Excellence (NICE) recommend BCO screening all women at their first antenatal appointment to ensure women receive smoking cessation advice and referral to smoking cessation services [32]. However, just one out of all 19 maternity units in Ireland currently conduct BCO screening [33].

We found that a high BCO level in early pregnancy was associated with birthweight, despite having no relationship with self-reported smoking. High BCO tests in early pregnancy may, therefore, help to identify women at risk of adverse pregnancy and neonatal outcomes such as fetal distress, emergency caesarean section, LBW and BW <25th centile. Furthermore, non-disclosers of smoking had poorer pregnancy outcomes compared to non-smokers. We therefore recommend that women with high BCO readings in early pregnancy, regardless of self-reported smoking status, are referred to stop smoking services and monitored for FGR throughout pregnancy to prevent adverse events.

Statement of contribution

CR contributed to the conception and design of the study, recruitment of participants, analysis and interpreted of data as well as wrote and revised this original article. RK, EOM and SS contributed to the interpretation of data, drafting and revising of the article. MJT and BE contributed to the conception of the study, interpretation of data as well as the drafting and revising of this article.

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Declaration of interests

None of the authors have any conflicts of interest to declare.

Patient consent

Written informed consent was obtained.

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