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CLINICAL RESEARCH ARTICLE

QTc intervals are not prolonged in former ELBW infants at pre-adolescent age

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BACKGROUND: Whether preterm birth is associated with cardiac conduction or repolarization abnormalities in later life is still poorly explored, with conflicting data on QTc prolongation in former extreme low birth weight (ELBW, <1000 g) infants.
METHODS: Twelve lead electrocardiograms (ECG) at rest, collected in the PREMATurity as predictor of children's Cardiovascular-renal Health (PREMATCH) study in former ELBW cases and term controls during pre-adolescence (8–14 years) were analyzed on corrected QT time (QTc, Bazett) and QT dispersion (QTd). ECG findings were compared between groups (Mann−Whitney), and associations with clinical and biochemical findings were explored (Spearman). In ELBW cases, associations between QTc and perinatal characteristics (at birth, neonatal stay) were explored (Mann−Whitney, Spearman).
RESULTS: QTc and QTd were similar between 93 ELBW cases and 87 controls [409 (range 360–465) versus 409 (337–460); 40 (0–100) versus 39 (0–110)] ms. Age, height, weight, or body mass index were not associated with the QTc interval, while female sex (median difference 11.4 ms) and lower potassium ($r = -0.26$) were associated with longer QTc interval. We could not observe any significant association between QTc interval and perinatal characteristics.
CONCLUSIONS: There were no differences in QTc or QTd between ELBW and term controls in ECGs at rest in pre-adolescents.

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IMPACT:

- This study aimed to assess the differences in QTc and QTd intervals between extreme low birth weight infants (ELBW) and term controls in electrocardiographic measurements at rest during pre-adolescence.
- This analysis confirmed the absence of significant differences in QTc or QTd findings between ELBW cases and term controls, while female sex and lower potassium were associated with a prolonged QTc interval.
- These data suggest that QTc screening strategies—including for pharmacovigilance—should not differentiate between former ELBW cases and term controls.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov Identifier NCT02147457

INTRODUCTION

Preterm birth and gestational age at birth are associated with an increased risk for cardiovascular morbidity and mortality.[1,2] In a large population-based cohort study with an incidence of preterm birth of 5.4%, the adjusted hazard ratio of all-cause mortality in former preterms (23–33 weeks) was 1.44 in young adulthood (<50 years), most pronounced for cardiovascular mortality (1.89), diabetes (1.98), and chronic lung disease (2.28). Interestingly, the increased death risk was found across gestational age up to the ideal term age (39–41 weeks), but most prominent for the most immature group.[3] Besides better understanding of the underlying mechanisms associated with the 'Barker' and 'Brenner' cardiovascular risk hypotheses, be it applied to preterm neonates, either or not associated with growth restriction, there is an obvious need to further explore biomarkers to detect potential higher risk besides the gestational age or birth weight to translate this knowledge to clinical practice or secondary prevention strategies.[4,5]

In a recent meta-analysis on changes in the preterm heart from birth to young adulthood, it was concluded that former preterms have morphological and functional cardiac impairments, proportionally to the degree of prematurity.[6] In contrast to the echocardiographic differences in left and right ventricular systolic functions in former preterm when compared to term controls,

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observations on electrocardiographic (ECG) findings are less conclusive. Whether preterm birth is associated with conduction or repolarization abnormalities later in life is less well explored.[7]

At present, there are conflicting data on the potential QT interval prolongation in former extreme low birth weight (ELBW, <1000 g) infants.[7–10] On the one hand, Bassareo et al.[8] reported that corrected QT (QTc) intervals and QT dispersion (QTd) were significantly prolonged in 24 former ELBW cases compared to 24 term controls (mean, ±SD: 417, 23.6 versus 369, 19.5 ms, and 30.4, 14.1 versus 24.6, 8.2 ms, respectively). Gervais et al.[7] could subsequently not confirm these findings in 49 preterm cases (<30 weeks gestational age) when compared to 53 term born controls. At rest, mean QTc were 408, ±34 and 409, ±SD 31 ms respectively. In subsequent letters, differences in genetic background or in sex distribution were considered, with a strong call for additional data and collaborative studies.[9,10] Finally, a study comparing QTc and QTd intervals between full term born cases with either a low birth weight ($n = 50$) or normal weight ($n = 70$) at an average age of 10 years could neither document significant differences.[11]

Although the majority of the previously mentioned ECG studies were conducted at young adulthood (23.2, ±3.3 years and 18–33 years respectively),[7,8] we considered that the ECG observations, collected as part of the PREMATurity as predictor of children's Cardiovascular-renal Health (PREMATCH) study in former ELBW cases or term controls collected during pre-adolescence (age range 8–14 years) contribute to the available data on this specific aspect in former ELBW cases.[12]

METHODS

Ethics

The study has been conducted in accordance with the Helsinki Declaration for Investigation in human subjects and was registered at ClinicalTrials.gov (NCT02147457). The local Ethics Committee of the University Hospitals Leuven (Belgium) approved the study protocol (June 2014, S56577). Based on good clinical practice guidance and national law, parents or custodians and children provided written informed consent and assent respectively.

PREMATCH study participants

We recruited ELBW cases from a cohort of 140 children born between 2000 and 2005, who survived premature birth after a gestation ranging from 23 to 33 weeks and who had a birth weight of <1000 g.[13] In these ELBW cases, detailed information on perinatal characteristics [*at birth*: birth weight, gestational age, small-for-gestational age, sex, prenatal steroids (lung maturation), tocolysis, pre-eclampsia, preterm pre-labor rupture of membranes (PPROM); chorioamnionitis; *during neonatal stay*: duration of ventilation, days until full enteral feeding, pharmacological treatment (ibuprofen) of a patent ductus arteriosus, postnatal steroids, retinopathy of prematurity (≥stage 3)] was available. Of 140 ELBW children invited, 93 participated (66.4%). The 87 controls were either friends of the cases ($n = 41$) or recruited at an elementary school close to the examination center located in Eksel, Belgium ($n = 46$). Cases and controls were examined at a median age of 11 (range 9–14) years.[14]

Body weight was measured, using the Omron Karada Scan HBF511 (Omron Health Care, Kyoto, Japan) and body height by a wall-mounted ruler. Based on these measurements, the body mass index (BMI, kg/m^2) was calculated. Blood pressure (BP) was the average of three consecutive auscultatory readings obtained according to European guidelines with a standard mercury sphygmomanometer after the children had rested in the sitting position for at least 5 min. The cuffs had a 9 × 18 cm inflatable bladder, but if upper arm circumference exceeded 22 cm, standard cuffs with 12 × 22 cm bladder were used.[14]

In all participants, blood sampling was also intended to be collected during the same assessment. After the children had fasted for at least 6 h and rested for 30 min in the supine position and after application of a Rapydan® patch (70 mg lidocaine/70 mg tetracaine, Eurocept, Ankeveen, The Netherlands) to minimize discomfort, a study nurse collected a venous blood sample, which was immediately spun. Aliquots were stored at −20 °C until analysis. As reported previously, reasons for the unavailability of blood samples were refusal of the child, too low sample volume or inability to collect blood after one or two attempts, so that this information is available in 127/180 included cases (58 ELBW cases, 69 controls).[14] Finally, information on medicine use was collected by a questionnaire before assessment, with an subsequent analysis on medicines labeled as associated with potentially QTc prolongation.[15]

ECG collection and analysis

A 12-lead ECG was collected at rest after 30 min in supine position by a trained assistant. As a quality control measure, research assistants received periodical training on skin preparation, electrode placement and positioning of the participants. The Cardiax® device (RDSM Medical Devices, Hasselt, Belgium) was used for ECG acquisition and automatic determination of standard ECG parameters on the digital traces, thereby excluding observer-related bias. PR and QT intervals, QRS duration, and QRS axis were automatically measured to the nearest 1 ms or °, and have not been calculated manually. QT intervals were corrected for heart rate with the Bazett-formula ($QTc = QT/\sqrt{RR}$).

Based on visual inspection of printouts, the quality of the ECGs used for analysis was assessed by one assessor (T.S.), blinded for group allocation. Additionally, QTd was calculated for all participants for which 50 mm/s printouts were available ($n = 155$). To do so, QT-intervals were measured manually by T.S. using the slope-method on a single heartbeat in all precordial leads (V1−V6) and the reported QTd was calculated as the difference between the maximal and minimal QT interval. No heart rate correction was applied for QTd.[16] The QTd analysis was added because of the observed increased sudden death risk in former preterm neonates, while prolonged QT dispersion has been suggested to be associated with an increased risk of mortality and arrhythmic events in other populations.[1–3,17,18]

Statistical analysis

Clinical, ECG-related, and biochemical measurements in ELBW cases and controls were calculated (median and range) and compared (Mann−Whitney *U* test). In the full dataset, associations between QTc and clinical characteristics (age, height, weight, BMI), and biochemical measurements (sodium, potassium, calcium and phosphate) were subsequently explored (Spearman correlation). Finally, and specific in ELBW cases, associations between (Spearman correlation) QTc Bazett and perinatal characteristics were explored (Spearman's coefficient of rank correlation, or Mann−Whitney *U* test for continuous and discontinuous variables respectively). The MedCalc®, version 20.008 (MedCalc Software Ltd, Ostend, Belgium) was used for these analyses. Post hoc power analysis for the comparison of QTc between cases and controls was performed using G*Power (Heinrich Heine Universität, Düsseldorf, Germany).[19]

RESULTS

Related to the quality assessment, all but one of the ECG prints were classified as good. For this single observation (ELBW case, male), substandard recording was observed in only two leads, so that we included all collected ECG measurements in the analysis. Eighteen cases, and seven control cases took medicines at assessment. Eight medicines in four ELBW cases and four controls respectively were classified as reported to be associated with QTc prolongation (formoterol, by inhalation ($n = 2$), or methylphenidate, oral ($n = 6$)).

The clinical, ECG, and biochemical measurements in ELBW cases and controls are presented in Table 1. The differences in clinical measurements, including in blood pressure, were already reported previously and reflect the specific phenotype in former ELBW cases (smaller, lighter, higher blood pressure). At rest, there was a near significant minor difference in heart rate, higher in former ELBW cases. Related to this minor difference in heart rate, PR and QT intervals were significantly shorter (differences in mean 10 and 2 ms respectively) in ELBW cases, while the QTc interval and QTd were not significantly different between cases and controls (Table 1).

In the analysis of the full dataset of both ELBW cases and controls, associations between QTc and age, height, weight, or BMI were not significant. The QTc interval was not different between cases exposed to any medicine ($n = 25$), or a medicine with potential QTc prolongation ($n = 8$), when compared to non-exposed cases. In this pre-adolescent cohort, the median QTc was

Table 1. Comparison of ELBW cases versus controls for clinical measurements, ECG-related measurement and biochemical measurements, data reported by median and range.

Characteristic	ELBW cases $n = 93$	Controls $n = 87$	p value
Clinical measurements			
Age, year	11 (9–14)	10.8 (9–14)	0.025
Height, cm	145 (124–168)	147 (129–181)	0.027
Weight, kg	35.5 (21.4–71.4)	37.7 (23.5–67.8)	0.043
BMI, kg/m2	16.5 (12.6–27.5)	17.2 (12.7–24.9)	0.053
Male/female	47/46	42/45	
Blood pressure, systolic, mmHg	114 (94–146)	107 (88–132)	<0.001
Blood pressure, diastolic, mmHg	69 (48–88)	65 (52–80)	<0.001
Medicine use, any	18/93	7/87	0.019
Medicine use, QTc prolongation	4/93	4/87	0.635
ECG-related measurements			
Heart rate, bpm	71 (47–104)	67 (48–111)	0.052
PR, ms	124 (94–188)	134 (94–196)	0.005
QT, ms	382 (320–438)	384 (320–442)	0.046
QTc (*Bazett*), ms	409 (360–465)	409 (337–460)	0.870
QTd, ms	40 (0–100)	39 (0–110)	0.673
QRS time, ms	82 (70–104)	84 (68–112)	0.015
QRS axis, °	78 (−24–104)	77 (28–117)	0.628
Biochemical measurements			
Sodium, mmol/L ($n = 127$)	141 (137–146)	140 (134–146)	0.185
Potassium, mmol/L ($n = 127$)	4.38 (3.72–5.92)	4.4 (3.87–5.36)	0.589
Calcium (total), mmol/L ($n = 127$)	2.52 (2.24–2.82)	2.46 (2.17–2.67)	0.001
Phosphate, mmol/L ($n = 127$)	1.52 (0.91–1.96)	1.48 (1.13–1.84)	0.550

ELBW extreme low birth weight, <1000 g, *BMI* body mass index, *ECG* electrocardiogram, *bpm* beats per minute.

Table 2. Analysis on the association of perinatal factors at birth or during neonatal stay in a cohort of 93 former extreme low birth weight infants with QTc interval (Bazett) at pre-adolescent age.

Perinatal factors	Findings	Statistical analysis*
At birth		
Birth weight	815 (430–1000) g	$p = 0.961$
Gestational age	27 (24–33) weeks	$p = 0.887$
Small for gestational age	36/92 (39 %)	$p = 0.442$
Sex (male/female)	47/46	$p = 0.117$
Prenatal steroids (yes)	80/90 (88 %)	$p = 0.218$
Tocolysis (yes)	29/89 (32 %)	$p = 0.575$
Pre-eclampsia (yes)	27/92 (29 %)	$p = 0.616$
PPROM (yes)	18/91 (20 %)	$p = 0.640$
Chorioamnionitis (yes)	4/91 (4 %)	$p = 0.656$
During neonatal stay		
Ventilation, duration	7 (0–131) days	$p = 0.736$
Full enteral nutrition	33 (12–143) days	$p = 0.512$
Ibuprofen (yes)	45/91 (49 %)	$p = 0.836$
Postnatal steroids (yes)	47/92 (51 %)	$p = 0.419$
ROP, ≥stage 3 (yes)	17/91 (19 %)	$p = 0.309$

Data are provided as absolute number and incidence, or median and range. The total number of observations for some factors was sometimes lower (data not always available in all individual cases) (*Spearman's correlation, or Mann−Withney *U* test for continuous and discontinuous factors respectively).
PPROM preterm pre-labor rupture of membranes, *ROP* retinopathy of prematurity.

significantly longer in female versus male [91 females, 89 males: 415 (353–465) versus 401 (337–460) (median difference 11.4) ms, $p = 0.001$] children. For the biochemical measurements, only potassium ($r = -0.26$, 95% CI −0.41 to −0.09, $p = 0.003$) had a weak, but significant negative correlation with QTc values. In Table 1, we explicitly refer to the minor, but significant difference in total calcium (median 2.52 versus 2.46 mmol/L, $p = 0.001$) between ELBW cases and controls, but without significant correlation between calcium and QTc values ($r = -0.05$, 95% CI −0.23 to 0.12, $p = 0.554$). Finally, we could not observe a significant association between QTc and any of the perinatal characteristics explored, either at birth or during neonatal stay (Table 2).

DISCUSSION

In this PREMATCH study cohort, we were not able to observe significant differences in QTc intervals between ELBW cases compared to controls at pre-adolescent age. Using the same criteria applied by Gervais et al. in their Canadian cohort (young adulthood), none of the included patients had a severe increased QTc (>500 ms), while mild increase (>450 ms and >460 ms in male and female respectively) was observed in three ELBW cases (2 male/1 female) and in one control (1 male) (3/93 and 1/87 in ELBW cases and controls respectively). None of them were co-exposed to QTc prolonging medicines, but the absence of a difference in QTc times between subjects either or not exposed to medicines (8 versus 172) is underpowered to draw any strong conclusion. Along the same line, none of the perinatal characteristics (at birth, or during neonatal stay) explored was associated with any change in QTc in former ELBW cases.[7] Finally, we confirmed the observation of Gervais of a modest increase (+8 beats per minute, bpm in their study) in heart rate in former preterms at rest, be that the difference in the PREMATCH study (+4 bpm) did not reach statistical significance (Table 1).[7] So, in essence we confirm the absence of a difference in QTc in a somewhat younger (9–14 years) cohort of former ELBW cases.

These data imply that ELBW itself does not serve as an indicator of an altered risk in QTc interval, irrespective of the epidemiologically higher risk for cardiovascular morbidity and mortality.[1,2] As we have explored this in an ELBW cohort with the a priori highest risk, it seems reasonable to assume that this applies also to less immature former preterms.[3]. In a slightly different population of term small-for-gestational-age infants, Akyuz et al. could neither find any difference in QTd.[11] This suggest that the applicability of QTd as biomarker remains to be explored.

The QT interval also has a pivotal role in drug development and pharmacovigilance as biomarker of ventricular repolarization and potential risk for torsade de pointes. In the absence of recommendations specific for children receiving therapy with QTc interval-prolonging drugs, the existing guidance suggest that partial extrapolation (*event and intervention are believed to behave similar in pediatric patients and adults, but the exposure-response relationship in children is inadequately defined or thought not to be sufficiently similar*) is reasonable.[20]

The current result in pre-adolescent former ELBW cases does not support a priori avoidance of QT prolonging medicines, or the need for additional precautious in this specific population.[21] This is relevant as some QTc prolonging medicines (like attention deficit

hyperactivity (ADHD) disorder medicines, or anti-psychotics) are more commonly prescribed in former preterms.[22,23] Furthermore, our findings are in line with the findings of Gervais, be it with even more confidence as we have collected data at pre-adolescence, the pediatric age where such medicines are commonly initiated.[24]

Obviously, this study must be interpreted in the context of its limitations. The participation rate in former ELBW cases was only 66%, but there were no clinically relevant significant differences in perinatal characteristics between included and non-included cases, as published previously.[25] This paper also reported on the puberty scores (Tanner), reflecting early puberty (breast/genital 2.3, SD 0.87 and pubic 2.2, SD 0.96).[25] We could neither observe a correlation between the QTc time interval and BMI (neither in the full group, nor in the ELBW cases only). This is in contrast to the findings of the Gervais cohort when analyzing the former preterm cases (each increase with 1 point in BMI was associated with a 5-ms increase).[7] A similar pattern with prolonged QTc associated with hypertension and BMI in young adults has recently been reported.[26] Furthermore, only ECGs at rest and in the supine position were collected. We neither performed a priori a formal power calculation for QTc, as recruitment was pragmatic. However, post hoc analysis showed that our study had a power of 90% to detect a difference of 11.45 ms between both groups, supporting the sensitivity of our study to detect minimal differences. Specific for QTd, several authors have raised concerns on the reproducibility of the measurement. ECG traces were therefore blinded for group allocation. Nevertheless, there also remain concerns on the interpretation and meaning of QTd findings.[16,27] Finally, most cases and controls have a Caucasian background, reflecting the composition of the population in Belgium, while the analysis on perinatal characteristics (Table 2) was based on the data as available. This means for instance that for prenatal lung maturation, the majority of survivors were exposed to prenatal steroids (88%), so that such analysis has additional power limitations. As suggested by others, additional analyses on perinatal risk factors associated with QTc interval will necessitate further pooling of available cohorts. However, the association with sex and potassium provide us additional confidence on the sensitivity of the study, as both confirm previous and generally reported findings in QTc intervals.

Despite its limitations, we therefore conclude that we have not observed significant alternations in QTc interval between ELBW cases compared to controls at pre-adolescent age in the largest cohort of cases so far reported, so that only a minor difference (<11.45 ms) could not be excluded. Furthermore, none of the perinatal characteristics (at birth, or during neonatal stay) was associated with any change in QTc in former ELBW cases.

DATA AVAILABILITY

The corresponding author can be contacted to share the raw data, if based on a reasonable request and a study protocol.

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AUTHOR CONTRIBUTIONS

A.R., J.A.-S. and K.A. conceived and designed the PREMATCH study and obtained the funding. The electrocardiographic findings were assessed on quality by T.S., while

T.S., A.R. and K.A. designed and performed the analysis. All authors were involved in the interpretation and drafting of the manuscript, approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare no competing interests.

INFORMED CONSENT

Parents or custodians and children provided written informed consent and assent respectively.

ADDITIONAL INFORMATION

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