Embryonic growth discordance and early fetal loss: the STORK multiple pregnancy cohort and systematic review

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STUDY QUESTION: Is there an association between discordance in embryonic growth and fetal loss at the time of the 11–14-week scan in twin pregnancies?

SUMMARY ANSWER: Regardless of the chorionicity, crown rump length (CRL) discordance at 7+0–9+6 weeks is predictive of subsequent single fetal demise in the first trimester.

WHAT IS KNOWN ALREADY: Previous small studies have reported a variable association between discordance in embryonic growth and subsequent fetal loss.

STUDY DESIGN, SIZE, DURATION: Retrospective study of all twin pregnancies of known chorionicity from a large regional cohort over a 10-year period. A total of 1356 twin pregnancies (288 monochorionic and 1068 dichorionic) were included in the study.

PARTICIPANTS, SETTING, METHODS: Women presenting to the early pregnancy unit were included in the study. Logistic regression, ROC curve and Kaplan–Meier analyses were performed to evaluate the association between CRL discordance at 7+0–9+6 weeks and spontaneous single fetal loss diagnosed at the 11–14-week scan. A systematic review was also performed using MEDLINE, EMBASE, CINahl and the Cochrane Library in order to explore the relationship between early growth discordance and single fetal loss in twin pregnancies.

MAIN RESULTS AND THE ROLE OF CHANCE: There were 111 (8.2%) single fetal losses diagnosed at 11–14 weeks in this cohort. At multivariate analysis, CRL discordance percentile [odds ratio (OR) 1.20; 95% confidence interval (CI), 1.12–1.63, P = 0.0001] and CRL 5th centile of at least one twin (OR, 2.21; 95% CI 1.23–4.24, P = 0.023), but not chorionicity (P = 0.486) or maternal age (P = 0.283) was independently associated with the loss of one fetus at the 11–14-week scan. The predictive accuracy of CRL discordance for single fetal loss was high (AUC = 0.93; 95% CI = 0.91–0.94). A significant association was found between the increase in the degree of embryonic discordance and the likelihood of early fetal loss (P < 0.0001).

LIMITATIONS, REASONS FOR CAUTION: Only a high-risk population was analysed. Therefore, the patients studied were not a representative sample from the population of women pregnant with twins.

WIDER IMPLICATION OF THE FINDINGS: Twin pregnancies, in particular those resulting from assisted conception, are scanned frequently, particularly during the early stages of pregnancy. The findings of this study are likely to prove important in counselling parents about the short-term outcome of the pregnancy when an embryonic discordance is present.

STUDY FUNDING/COMPETING INTEREST(S): No external funding was sought for this study. None of the authors has any conflicts of interest to declare.

Key words: growth discordance / miscarriage / twin pregnancies / pregnancy loss / outcome

† All STORK authors’ details are given in the Appendix.

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Introduction

The incidence of twin pregnancy continues to rise, mainly due to the more popular use of assisted reproduction techniques (NICE, 2011). The conception rate in multiple gestations has been reported to be greater than the birth rate with spontaneous reduction from twin to singleton in the early first trimester occurring in a significant minority of cases (Blumenfeld et al., 1992; Landy and Keith, 1998; Oloyede et al., 2012). Although twin pregnancy is associated with increased risk of early fetal loss, perinatal mortality and morbidity, the pathophysiology of early fetal loss has not been completely elucidated. Maternal, fetal and iatrogenic factors may play a role in spontaneous multiple pregnancy reduction. Improvement in ultrasound technique has allowed better visualization of embryonic and extra-embryonic structures in the early stages of pregnancy, which has led in turn to more frequent reporting of this phenomenon.

Studies in singletons have shown that the sonographic demonstration of a heartbeat in the embryo early in the first trimester cannot reliably predict the final pregnancy outcome and that different factors, such as a smaller than expected crownrump length (CRL), mode of conception, maternal age and clinical symptoms such as vaginal bleeding, may help in the stratification of the obstetric risk in early pregnancy (Wilson et al., 1986; Benson et al., 1993; Falco et al., 1996; Mukri et al., 2008). Previous studies have shown that discrepancy in CRL detected early in gestation may be predictive of adverse pregnancy outcome in twin pregnancies (Dickey et al., 1992; Kol et al., 1993; Bora et al., 2009; Palmer et al., 2010; Papaioannou et al., 2011). However, the number of pregnancies included in each study was relatively small, ranging between 77 and 245, and some excluded monochorionic (MC) pregnancies, limiting the clinical applicability to dichorionic twins only (Dickey et al., 1992; Kol et al., 1993; Bora et al., 2009; Papaioannou et al., 2011).

The aim of this study was to quantify the performance of discrepancy in embryonic growth detected at 7+0 and 9+6 weeks of gestation in predicting a subsequent single fetal loss diagnosed at the 11–14-week scan in a large cohort of twin pregnancies. A systematic review of the literature on the relationship between embryonic growth discordance and single fetal loss in twin pregnancies in the first trimester is also presented.

Methods

This was a retrospective study of prospectively collected data in women with twin pregnancies presenting to the Early Pregnancy Units (EPUs) of nine hospitals in the Southwest Thames London region Obstetric Research Collaborative (STORK) between 7+0 and 9+6 weeks of gestation over a period of 11 years from 2000. Scan data were obtained by a computerized search of each hospital’s obstetric ultrasound computer database. The indications for the ultrasound scan between 7+0 and 9+6 weeks include vaginal bleeding, abdominal pain, history of miscarriage or ectopic pregnancy, maternal anxiety and uncertain menstrual dates. All scans were performed transvaginally and the pregnancy was dated according to the larger twin CRL or CRL of the surviving twin in case of single fetal loss (Robinson and Fleming, 1975). In women who conceived using assisted conception, the gestational age (GA) was calculated from the embryo date. Chorionicity was determined by ultrasound evaluation according to the number of placentas and the presence of the lambda or T-signs (Bora et al., 2008; Dias et al. 2011). CRL discordance was calculated as 100 × (larger CRL – smaller CRL)/larger CRL.

Only twin pregnancies attending a routine 11–14-week scan with a prior scan in early pregnancy demonstrating two viable embryos were considered suitable for the analysis. The exclusion criteria included termination of pregnancy, MC monoamniotic twin pregnancies and high-order multiple gestations. A small number of cases (n = 77) analysed in a previous study (Bora et al., 2009) were included in the current analysis. These cases were all from a single institution and constituted 5.6% of the current study population. The main study outcome was the number of viable fetuses at the 11–14-week scan. Fetal demise was diagnosed either if a fetus was found to have no visible heart pulsation or if a fetal pole was not visualized due to presumed re-absorption.

Ethical approval

Ethical approval for this retrospective study was obtained from the local research ethics committee.

Systematic review of embryonic discordance and early fetal loss in twin pregnancies

Search strategy

This review was performed according to a protocol designed a priori and recommended for systematic reviews and meta-analysis (Stroup et al., 2000; Henderson et al., 2010). MEDLINE (1966–March 2012), EMBASE (1974–March 2012), Cinahl (since inception) and the Cochrane Library (since inception) including the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched electronically on 7 February 2013 using combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants ‘CRL discordance’, ‘CRL discrepancy’, ‘early pregnancy growth’, ‘embryo’, ‘twin’, ‘multiple pregnancy’, ‘first trimester’, ‘monochorionic’, ‘dichorionic’, ‘chorionicity’, ‘fetal loss’, ‘miscarriage’ ‘intrauterine death’ (Supplementary data, Table S1). The result of the combined search was limited to studies on humans published in English. Reference lists of relevant articles and reviews were hand searched for additional reports.

Study selection and data extraction

Studies were assessed according to the following criteria: population, outcome and study design. Studies reporting the fetal loss in twin pregnancies with discordance in fetal or embryonic size before 11 weeks of gestation were considered suitable for the analysis. Prospective and retrospective cohort, case–control studies and case series of more than three cases were included. Case reports, case series including less than three cases, conference abstracts and editorials were excluded. The study was registered with the PROSPERO database (registration number: CRD42013004134, http://www.crd.york.ac.uk/PROSPERO). All abstracts were reviewed independently by two authors (F.D. and E.M.). Agreement about potential relevance was reached by consensus, and full text copies of those papers were obtained. Three reviewers (F.D., E.M. and A.K.) independently extracted data regarding study characteristics, outcome and quality using the Strengthening the Reporting of Observational Studies in Epidemiology statement criteria (von Elm et al., 2007). There was no blinding of authorship. Inconsistencies were discussed by the reviewers and consensus reached. For those articles in which information was not reported, but the methodology was such that this information would have been recorded initially, the authors were contacted.

Statistical analysis

Continuous variables were reported as median and inter-quartile range (IQR) and examined by using the Mann–Whitney U-test. Dichotomous variables were reported as numbers or percentages and compared using the χ² test. Logistic regression analysis was carried out in order to assess the association between pregnancy characteristics, such as chorionicity, CRL discordance, CRL <5th centile (Papaioannou et al., 2010) and maternal
age, with fetal loss; for the purpose of this analysis CRL discrepancy was considered as a continuous variable and expressed as percentage (%) of discordance between the twins, while CRL < 5th centile and chorionicity were entered in the regression as categorical variables. The likelihood of prediction of fetal loss at the 11–14-week scan was assessed using receiver operating characteristic (ROC) curve analysis. A time-to-event analysis (Kaplan–Meier) was carried out to evaluate the difference in survival trend in the first trimester according to different degrees of discordance in early pregnancy growth. Between-study heterogeneity was explored graphically within the forest plot and statistically assessed using the $I^2$ statistic, which represents the percentage of between-study variation that is due to heterogeneity rather than chance. Subgroup analysis was performed to investigate the heterogeneity. The statistical analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA), GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego CA, USA) and Meta-disc version 1.4 (Ramón y Cajal Hospital, Madrid, Spain). Statistical significance was set at $P < 0.05$. All $P$ values were two-tailed.

## Results

A total of 1356 twin pregnancies (288 MC and 1068 DC) were included in the analysis. There were 111 (8.2%) single fetal losses in the population analysed with no significant difference in the incidence of single fetal loss between MC and DC twin pregnancies (8.0 versus 8.2%, $P = 0.985$). The GA at the early pregnancy scan in pregnancies without fetal loss (median = 8.5 weeks, IQR = 7.1–9.4) was not significantly different from pregnancies complicated by a single fetal loss (median = 8.6 weeks, IQR = 7.3–9.7, $P = 0.035$). The median CRL discordance in the study population was 5.5% (IQR = 2.3–12.3) and was not significantly different between MC (5.9%, IQR = 2.6–11.2) and DC (5.3%, IQR = 2.2–10.3, $P = 0.515$) pregnancies. The median CRL discordance at 7+0–9+6 weeks was significantly higher in twin pregnancies complicated by a single fetal loss (42.6%, IQR = 30.5–58.3, $P < 0.000$) compared with those without fetal loss (5.0%, IQR = 1.9–9.0). The incidence of fetal loss at 11–14 weeks according to the discordance in CRL at 7+0–9+6 weeks is shown in Table I. The logistic regression analysis demonstrated that CRL discrepancy (odds ratio (OR), 1.20; 95% confidence interval (CI), 1.12–1.23, $P = 0.000$) and CRL < 5th centile of at least one twin (OR, 2.21; 95% CI 1.23–4.24, $P = 0.023$), but not chorionicity ($P = 0.486$), maternal age ($P = 0.283$) or GA at the initial scan ($P = 0.321$) were independently associated with the loss of one fetus at the 11–14-week scan.

CRL discordance between 7+0 and 9+6 weeks was predictive of subsequent single fetal loss at the 11–14-weeks scan (AUC, 0.93; 95% CI 0.91–0.94) with an optimal cut-off at 19% of discordance, which had a sensitivity of 87.4% (95% CI 79.7–92.9) and a specificity of 95.2% (95% CI 93.8–96.3) (Fig. 1). The positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR) and negative likelihood ratio (−LR) were 62.0 (95% CI 53.7–69.4), 98.8 (95% CI 98.0–99.4), 18.1 (95% CI 14.0–23.4) and 0.1 (95% CI 0.1–0.2), respectively. The predictive accuracy of different cut-offs of CRL discrepancy in early pregnancy is shown in Table II. A total of 157 (11.6%) twin pregnancies (31 MC and 126 DC) had a CRL discrepancy ≥ 19% and the single fetal loss rate was significantly higher in this group compared with that showing a discordance in size of less than 19% (62.1 versus 1.2%; $P = 0.000$).

Twin with ≥ 19% of discordance in early pregnancy had a significantly different survival trend during the first trimester of pregnancy (log-rank test, $P < 0.0001$) compared with those with lesser degrees of discordance, with a relative risk of 52.91 (95% CI 31.0–90.4) (Fig. 2). There was a significant association between the increase in the degree of embryonic discordance and the likelihood of early fetal loss ($\chi^2$ test for trend, $P < 0.0001$).

The literature search for the systematic review yielded 436 possible citations; of these, 388 were excluded by review of the title or abstract as they did not meet the selection criteria (Fig. 3). The data on chorionicity, GA at the initial assessment, cut-off of CRL discordance and incidence of single fetal loss, together with comparable data from the current study, are shown in Table III. Pregnancies included in the study by Bora et al. were included in this study population. The chorionicity data were not reported in two studies (Dickey et al., 1992; Kol et al., 2009; Papaioannou et al., 2011). The data on chorionicity, GA at the initial assessment, cut-off of CRL discordance and incidence of single fetal loss, together with comparable data from the current study, are shown in Table III. The incidence of single fetal loss was significantly greater in MC than DC pregnancies (31 MC and 126 DC) (Table I).

### Table I

<table>
<thead>
<tr>
<th>CRL discordance (%)</th>
<th>Viable twins at 11–14 weeks [n (%)]</th>
<th>Single fetal loss [n (%)]</th>
<th>Total (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>954 (99.2)</td>
<td>8 (0.8)</td>
<td>962</td>
</tr>
<tr>
<td>15–20</td>
<td>148 (95.5)</td>
<td>7 (4.5)</td>
<td>155</td>
</tr>
<tr>
<td>21–25</td>
<td>46 (90.2)</td>
<td>5 (9.8)</td>
<td>51</td>
</tr>
<tr>
<td>26–30</td>
<td>68 (87.2)</td>
<td>10 (12.8)</td>
<td>78</td>
</tr>
<tr>
<td>31–40</td>
<td>17 (53.1)</td>
<td>15 (46.9)</td>
<td>32</td>
</tr>
<tr>
<td>41–50</td>
<td>12 (35.3)</td>
<td>22 (64.7)</td>
<td>34</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0 (0)</td>
<td>44 (100)</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>1245 (91.8)</td>
<td>111 (8.2)</td>
<td>1356</td>
</tr>
</tbody>
</table>

$\chi^2$ test for trend, $P < 0.0001$. CRL, crown rump length.

### Figure 1

The ROC curve for the prediction of single fetal loss at 11–14-week scan in twin pregnancies using CRL discordance at 7+0–9+6 weeks of gestation. CRL, crown rump length.
The latest GA was 10 weeks in the study by Papaioannou et al. The incidence of single fetal loss ranged between 4.7 and 33.3%. Given the heterogeneity between articles, meta-analysing the risk of single fetal loss could be considered inappropriate. However, as this data could be of importance when counselling parents, we present a 'summary statistic' in Supplementary data, Fig. S1.

The quality of the studies is summarized in Fig. 4. The study design was mainly retrospective cohort or case–control. Among the studies included, eligibility criteria were described in 75%. Characteristics and follow-up were described in all of the articles. However, none reported efforts to address bias.

Discussion

The data from this cohort confirm that, irrespective of chorionicity, a CRL discordance \( \geq 19\% \) detected between 7\( ^{+0} \) and 9\( ^{+6} \) weeks of gestation is highly predictive of single fetal loss at the 11–14-week scan. The risk of single fetal loss at 11 – 14 weeks was related to the magnitude of CRL discordance at 7\( ^{+0} \) – 9\( ^{+6} \) weeks. Discordance in the fetal size is a relatively common finding in multiple pregnancies. Although a degree of discordance in fetal growth is usually present in all twin pregnancies, inter-twin discordance in size has been associated with a multitude of adverse outcomes including stillbirth, neonatal death, preterm birth, respiratory distress and admission to neonatal intensive care unit (Miller et al., 2012). However, while fetal growth discordance in the third trimester can be used to predict an adverse outcome both in MC and DC twin pregnancies, CRL discordance at 11–14 weeks and mid-trimester size discordance have been shown to be poorly predictive of most adverse outcomes once chromosomal and structural abnormalities have been excluded (Harper et al., 2012; D’Antonio et al., 2013a, b).

In contrast to findings at 11–14 weeks and mid-gestation, the current data demonstrate that embryonic size discordance is strongly associated with early pregnancy fetal loss. The risk of single fetal loss has been reported to decrease with the progressive appearance of the embryonic structures and cardiac activity (Dickey et al., 1990; Sampson and deCrespigny, 1992; Frates et al., 1993). Studies carried out in singletons have shown that a smaller than expected CRL detected early in pregnancy is predictive of subsequent fetal loss in the first trimester (Frates et al., 1993; Mukri et al., 2008). The association between reduced fetal size and pregnancy loss relies on the fact that impaired growth could be due to chromosomal or structural abnormalities, which are commonly associated with delayed fetal growth and intrauterine death. On the other hand, growth discrepancy may reflect a state of severe and early placental dysfunction in one twin. Previous smaller studies in twins have also shown that a discrepancy in early fetal or embryonic size may be predictive of subsequent fetal loss (Dickey et al., 1992; Kol et al., 2008).
The STORK cohort interrogated here is the largest series to date assessing the value of discordance in early pregnancy in predicting fetal loss at 11–14 weeks in twin pregnancies. A particular strength of the current data is that the ongoing pregnancies in this cohort were followed up to delivery and have been reported in other papers (D’Antonio et al., 2012; STORK, 2012; D’Antonio et al., 2013a; D’Antonio et al., 2013b).

The difference between the findings of the current study and those assessing the role of CRL discordance at 11–14 weeks or mid-gestation may be explained by the fact that spontaneous fetal loss is higher during the embryonic stage of pregnancy compared with the late first trimester (Benson et al., 1993). Thus, a discrepancy in growth during the embryonic and early fetal stages might reflect a pathological condition potentially leading to the loss of the fetus. Conversely, a discrepancy in the fetal size

Table III  Studies reporting data on the relationship between CRL discordance before 11 weeks of gestation and fetal loss in twin pregnancies.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Chorionicity</th>
<th>Cases (n)</th>
<th>Fetal losses n (%)</th>
<th>GA at the initial scan (weeks)</th>
<th>CRL discordance cut-off (% or mm)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickey et al., 1992</td>
<td>Retrospective cohort</td>
<td>–</td>
<td>126*</td>
<td>18 (14.3)</td>
<td>5–8</td>
<td>3 mm</td>
<td>38.8</td>
<td>93.5</td>
</tr>
<tr>
<td>Kol et al. (1993)</td>
<td>Retrospective case series</td>
<td>–</td>
<td>46b</td>
<td>2 (4.7)</td>
<td>5–6</td>
<td>60.7c</td>
<td>66.6</td>
<td>100</td>
</tr>
<tr>
<td>Bora et al. (2009)</td>
<td>Retrospective cohort</td>
<td>MC and DC</td>
<td>77</td>
<td>9 (12)</td>
<td>7–9</td>
<td>17</td>
<td>88.9</td>
<td>86.7</td>
</tr>
<tr>
<td>Papaioannou et al. (2011)</td>
<td>Retrospective cohort</td>
<td>DC</td>
<td>231</td>
<td>24 (10.4)</td>
<td>6–10</td>
<td>18.2d</td>
<td>37.5–54.2e</td>
<td>95–90</td>
</tr>
<tr>
<td>Current study (2013)</td>
<td>Retrospective cohort</td>
<td>MC and DC</td>
<td>1356</td>
<td>111 (8.2)</td>
<td>7–9</td>
<td>≥ 19</td>
<td>87.4</td>
<td>95.2</td>
</tr>
</tbody>
</table>

*Twins with no second embryo detected at the first US examination excluded.

bHigh-order multiple gestations excluded.

The mean discordance value (%) in twins experiencing the loss of one fetus (crude values: 50.0 and 71.4%, respectively).

dThe median value in twins with single fetal loss.

eThe detection rate for 5 and 10% false-positive rates, respectively.

Figure 4 Quality criteria of the included articles, as assessed using the strengthening the reporting of observational studies in epidemiology checklist. Note the retrospective design of all the papers included and the fact that none reported efforts to address bias.

1993; Bora et al., 2009; Papaioannou et al., 2011).
in the late first trimester is more likely to represent a state of physiological variation, recognizing that the majority of losses will have already occurred in the very early stages of pregnancy, hence its weaker association with subsequent fetal loss. Twin pregnancies, in particular those resulting from assisted conception, are scanned frequently, particularly during the early stages of pregnancy. The findings of this study are likely to prove important in counselling parents about the short-term outcome of the pregnancy in these cases.

Previous studies carried out in singleton pregnancies have proposed that various factors such as a smaller than expected CRL, heart rate, mode of conception, maternal characteristics and clinical symptoms such as vaginal bleeding might be helpful in predicting the outcome of the pregnancy (Wilson et al., 1986; Frates et al., 1993; Falco et al., 1996; Jauniaux et al., 2005; Mukri et al., 2008). Therefore, the findings of this study may be biased by the fact that patients attending an EPU represent a cohort at increased risk of adverse pregnancy outcomes. However, in view of the fact that pregnancies are usually not routinely scanned until 11 weeks, the results of this study are useful for counselling those women attending for early pregnancy assessment. Another potential weakness of the study is that information regarding maternal characteristics, mode of conception, presence of clinical symptoms and the indications of the scan were not available, thus limiting the robustness of the multivariate analysis. Lastly despite the fact that discordance in the embryonic size can predict early fetal loss, currently there is prevention to ameliorate this predicted poor pregnancy outcome. However, in the multiple regression analysis for the prediction of outcome in the study by Papaioannou et al., there was no significant contribution from the indication for attendance, maternal characteristics or mode of conception. These findings were also noted in the study by Bora et al. where these variables were similar between the group with a viable twin pregnancy and the group with single fetal loss at 11–14 weeks of gestation.

This is the largest series to date assessing the value of embryonic CRL discordance at 7–10–9+6 weeks in predicting subsequent fetal loss at 11–14 weeks of gestation. CRL discordance between 7+10 and 9+6 weeks of gestation is predictive of single fetal loss occurring at a later stage in the first trimester.

Supplementary data
Supplementary data are available at http://humrep.oxfordjournals.org.

Authors’ roles
Study design: F.D., A.K. and B.T. Study data collection and analysis: F.D. and A.K. Writing the manuscript: all authors.

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Conflict of interest
None of the authors has any conflicts of interest to declare.

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Appendix

STORK collaborative authors and contributors:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Authors</th>
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<tbody>
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<td>Mayday University Hospital</td>
<td>Rosol Hamid</td>
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<td>Cheryl Ellis</td>
</tr>
<tr>
<td>Frimley Park Hospital</td>
<td>Anne Deans</td>
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<tr>
<td>Kingston Hospital</td>
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<td>St George’s Hospital</td>
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