







Reduction in twin stillbirth following implementation of NICE guidance

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CONTRIBUTION

What are the novel findings of this work?

Implementation of the NICE twin guideline was associated with > 70% reduction in the rate of stillbirth in twins without a concomitant increase in neonatal mortality, rate of admission to the neonatal intensive care unit or rate of emergency Cesarean section. The reduction observed in monochorionic twins was higher than that in dichorionic twins.

What are the clinical implications of this work?

Reduction in stillbirth in twins can be achieved through implementation of guidelines. The reduction in stillbirth in twins represents a promising step towards achieving the UK national target of reducing stillbirths by 50% by 2025. National mortality reports should provide twin data separately for dichorionic and monochorionic pregnancies.

ABSTRACT

Objective There has been an unprecedented fall in the rate of stillbirth in twin pregnancy in the UK. It is contested whether implementation of the National Institute for Health and Care Excellence (NICE) guidance on the antenatal management of uncomplicated twin pregnancies has contributed to this change. The aim of this study was to investigate whether the implementation of NICE guidance was associated with a reduction in the rate of stillbirth in twin pregnancies delivered in a large UK hospital.

Methods This was a retrospective cohort study including all twin pregnancies delivered at St George's Hospital, London, UK, between 2000 and 2018. Data were analyzed according to two time periods: before implementation of the NICE guidance on twins (before June 2013; pre-NICE) and after its implementation (after June 2013; post-NICE). The exclusion criteria were higher-order multiple gestations, pregnancies of unknown chorionicity, pregnancies complicated by miscarriage, those that underwent termination and those diagnosed with vanishing twin. The main outcome was stillbirth. Other outcomes included neonatal death (NND), admission to the neonatal intensive care unit (NICU) and emergency Cesarean section. We planned a priori a sensitivity analysis according to chorionicity. The chi-square test and Mann–Whitney U-test were used to compare outcomes between the study groups.

Results We included in the analysis 1666 twin pregnancies (3332 fetuses), of which 1114 pregnancies (2228 fetuses) were delivered before and 552 pregnancies (1104 fetuses) after June 2013. Of those, 1299 were dichorionic and 354 were monochorionic diamniotic. The incidence of stillbirth was significantly lower in the post-NICE than in the pre-NICE group (3.6 per 1000 births vs 13.5 per 1000 births; $P=0.008$). The reduction in stillbirth rate was from 8.5 to 3.6 per 1000 births ($P=0.161$) in dichorionic and from 33.6 to 3.8 per 1000 births ($P=0.011$) in monochorionic diamniotic twin pregnancies. There was no significant difference in the rates of NND ($P=0.625$), NICU admission ($P=0.506$) or emergency Cesarean section ($P=0.820$) between the two

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groups. The median gestational age at delivery was significantly lower in the post-NICE than in the pre-NICE group (median 36.3 vs 36.9 weeks; $P < 0.001$), as a consequence of a significant increase in preterm birth between 34 and 37 weeks' gestation (39.3% vs 27.0%; $P = 0.002$), but not before 34 weeks ($P = 0.473$).

Conclusions A significant reduction of >70% in the stillbirth rate in twin pregnancies was noted after implementation of the NICE guidance. This reduction was statistically significant in monochorionic, but not dichorionic, twin pregnancies. The improvement in twin pregnancy outcome was achieved without a concomitant increase in NND, admission to the NICU or emergency Cesarean section. © 2020 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

The UK has witnessed an unprecedented fall in the rate of stillbirth in twin pregnancies in recent years^{1–3}. According to the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE) 2018 report, the stillbirth rate for twins was almost halved from 11.07 (95% CI, 9.78–12.47) in 2014 to 6.16 (95% CI, 5.20–7.24) per 1000 births in 2016¹. Furthermore, the neonatal mortality rate in twins also fell significantly during this period, from 7.81 (95% CI, 6.73–9.01) to 5.34 (95% CI, 4.47–6.36) per 1000 live births¹. However, it is important to recognize that, despite this significant improvement, the UK stillbirth rate in twins remains higher than that in singleton pregnancies¹.

One potential contributor to the reduction in stillbirths in the UK is the National Institute for Health and Care Excellence (NICE) guideline on the antenatal care of uncomplicated twin and triplet pregnancies, published in 2011⁴ (Appendix S1) and the related NICE quality standards (QS), published in 2013⁵. Key clinical recommendations in this guideline address the dating of twin pregnancies, determining chorionicity and amnionicity, labeling of the fetuses, prenatal screening for aneuploidy, frequency and timing of antenatal visits and ultrasound screening for fetal growth restriction and twin-to-twin transfusion syndrome (TTTS). The recommendations also specify the gestational age for delivery in uncomplicated multiple pregnancies^{4,5}. The initial results of the Twin and Multiple Births Association maternity engagement quality improvement initiative suggest that adherence to the NICE-QS is associated with lower rates of stillbirth, neonatal death (NND), emergency Cesarean section and admission to the neonatal intensive care unit (NICU)⁶. The maternity engagement quality improvement initiative, which was funded by the UK Department of Health, aimed at improving outcomes in multiple pregnancies by promoting the implementation of the NICE guideline.

The aim of this study was to investigate whether the implementation of the NICE guidance on the antenatal

management of twin pregnancies was associated with a reduction in stillbirth in twin pregnancies delivered in a large UK hospital.

METHODS

This was a retrospective analysis of data collected prospectively in a single tertiary referral center over a 19-year period from 2000 to 2018. Cases were identified by searching the electronic maternity records, prenatal ultrasound database and neonatal records at St George's Hospital, University of London, UK. In this center, pregnancy and delivery characteristics of all births as well as maternal demographics are routinely recorded prospectively. The inclusion criteria were twin pregnancies delivered at St George's Hospital, and therefore with ascertained pregnancy outcome. The exclusion criteria were higher-order multiple gestations, pregnancies of unknown chorionicity, pregnancies complicated by miscarriage, pregnancies that underwent termination and multiple pregnancies diagnosed with vanishing twin. Gestational age was determined by the crown–rump length of the larger twin at the 11–14-week scan or by head circumference if assessed after 14 weeks' gestation^{4,7–9}. Chorionicity was determined by ultrasound evaluation based on the number of placentae and the presence of the lambda or T-sign, and confirmed after birth^{4,8,9}. Pregnancies in which data on chorionicity were not available or could not be ascertained were excluded. The ultrasound electronic records were reviewed to ascertain the prenatal diagnosis of monochorionicity-related complications, including TTTS, selective fetal growth restriction (sFGR), twin anemia–polycythemia sequence (TAPS) and twin reversed arterial perfusion sequence.

The main outcome of this study was stillbirth, which was defined as fetal death after 24 weeks' gestation and before birth. We also aimed to investigate the incidence of NND (defined as death of a neonate up to 28 days postpartum), admission to the NICU and emergency Cesarean section. These outcomes were chosen in view of their reported association with the implementation of the NICE-QS⁶.

The NICE guidance was published in September 2011 and was subsequently implemented at St George's Hospital during 2012. However, in view of the fact that it takes time to embed clinical guidance in routine clinical practice, and to take into account the length of pregnancy, we decided to compare pregnancy outcomes before and after June 2013, considering the two groups to represent pregnancy care before (pre-NICE) and after (post-NICE) implementation of the NICE guideline. The differences in the monitoring and management protocols between the two study periods are listed in Table S1.

Statistical analysis

Categorical data are presented as n (%) and were compared between the two groups using Fisher's exact test or the chi-square test. Continuous data are presented

as median (interquartile range (IQR)). The D'Agostino and Pearson Omnibus test was used to assess the normality of the data. Non-parametric analysis using the Mann–Whitney *U*-test was then used to compare continuous data between the study groups. We planned *a priori* a sensitivity analysis according to chorionicity (dichorionic and monochorionic twin pregnancies). The statistical power for each outcome in the entire study population and in the subgroup analysis according to chorionicity is reported. All *P*-values were two-tailed and

Table 1 Characteristics of study population of twin gestations, according to whether they were delivered before or after implementation of National Institute for Health and Care Excellence guideline on antenatal care of twin pregnancy

Characteristic	Pre-implementation (n = 1114)	Post-implementation (n = 552)	P
Maternal age (years)	33 (29–36)	34 (31–38)	< 0.001
BMI (kg/m ²)	24.25 (21.70–27.70)	24.78 (22.35–28.93)	0.007
BMI ≥ 30 kg/m ²	116 (10.4)	101 (18.3)	0.028
BMI ≥ 35 kg/m ²	41 (3.7)	37 (6.7)	0.159
BMI ≥ 40 kg/m ²	11 (1.0)	9 (1.6)	0.637
Ethnicity			< 0.001
Caucasian	673 (60.4)	269 (48.7)	
Afro-Caribbean	182 (16.3)	64 (11.6)	
Asian	131 (11.8)	64 (11.6)	
Mixed	24 (2.2)	9 (1.6)	
Other	69 (6.2)	106 (19.2)	
Not recorded	35 (3.1)	40 (7.2)	
Smoker	244 (21.9)	15 (2.7)	< 0.001
Nulliparous	498 (44.7)	318 (57.6)	< 0.001
Assisted conception	287 (25.8)	171 (31.0)	0.025
DCDA	882 (79.2)	417 (75.5)	0.102
MCDA	223 (20.0)	131 (23.7)	0.086
MCMA	9 (0.8)	4 (0.7)	1.000

Data are given as median (interquartile range) or *n* (%). BMI, body mass index; DA, diamniotic; DC, dichorionic; MA, monoamniotic; MC, monochorionic.

Table 2 Perinatal outcomes of study population of twin gestations, according to whether they were delivered before or after implementation of National Institute for Health and Care Excellence guideline on antenatal care of twin pregnancy

Outcome	Pre-implementation (n = 1114 pregnancies; n = 2228 fetuses)	Post-implementation (n = 552 pregnancies; n = 1104 fetuses)	P	Statistical power (%)
Live birth	2198 (98.7)	1100 (99.6)	0.008	80.5
Stillbirth (per 1000 births)	30 (13.5)	4 (3.6)	0.008	88.5
Neonatal death (per 1000 live births)	24 (10.9)	14 (12.7)	0.625	9.0
GA at delivery (weeks)	36.9 (34.6–37.6)	36.3 (34.1–37.3)	< 0.001	> 99.9
Preterm birth				
< 37 weeks	502 (45.1)	342 (62.0)	< 0.001	99.9
34–37 weeks	301 (27.0)	217 (39.3)	0.002	99.9
< 34 weeks	201 (18.0)	125 (22.6)	0.473	69.1
< 28 weeks	57 (5.1)	29 (5.3)	0.562	5.7
Admission to NICU (per 100 live births)	659 (30.0)	338 (30.7)	0.506	7.9
Emergency Cesarean section	339 (30.4)	141 (25.5)	0.820	65.3
Birth weight (g)	2390 (1908–2710)	2350 (1958–2603)	0.049	> 99.9

Data are given as median (interquartile range) or *n* (%), unless indicated otherwise. Some percentages are calculated per pregnancy and some per fetus, depending on outcome. GA, gestational age; NICU, neonatal intensive care unit.

P < 0.05 was considered statistically significant. Statistical analysis was performed using the statistical software packages SPSS 20.0 (SPSS Inc., Chicago, IL, USA), Stata 11 release 11.2 (College Station, TX, USA) and GraphPad Prism® 5.0 for Windows (InStata; GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Study population

We included in the analysis 1666 twin pregnancies (3332 fetuses), of which 1114 pregnancies (2228 fetuses) were delivered before June 2013 and 552 pregnancies (1104 fetuses) after June 2013. Of these, 1299 were dichorionic and 367 were monochorionic. There was no significant difference in the proportion of dichorionic and monochorionic twin pregnancies between the two study periods (*P* > 0.05).

The maternal characteristics and pregnancy outcomes of the two study groups are shown in Tables 1 and 2. Women were significantly older (*P* < 0.001) and more likely to be obese (BMI ≥ 30 kg/m²) (*P* = 0.028) in the post-NICE than in the pre-NICE group. In the post-NICE group, more women were from ethnic minority backgrounds (*P* < 0.001), were nulliparous (*P* < 0.001) and had conceived via assisted conception (*P* = 0.025) and fewer were smokers (*P* < 0.001) compared with the pre-NICE group (Table 1).

The incidence of stillbirth in the whole study population was 10.2 per 1000 births, while the incidence of NND was 11.5 per 1000 live births. The incidence of stillbirth was higher in monochorionic diamniotic (22.6 per 1000 births) than in dichorionic (6.9 per 1000 births) twin pregnancies. The rate of admission to the NICU in the study population was 30.2%, while the incidence of emergency Cesarean section was 28.8%. The median gestational age at delivery was 36.6 weeks (IQR, 34.4–37.4 weeks) and the incidence of preterm birth (PTB) prior to 37 weeks' gestation was 50.7%.

Study outcomes

There was a significant reduction in the rate of stillbirth from 13.5 per 1000 births before implementation to 3.6 per 1000 births after implementation of the NICE guidelines ($P = 0.008$) (Figure 1, Table 2). There was no significant difference in the rates of NND ($P = 0.625$), NICU admission ($P = 0.506$) or emergency Cesarean section ($P = 0.820$) between the two study periods. The median gestational age at delivery was significantly lower in the post-NICE than in the pre-NICE group ($P < 0.001$). In the post-NICE group, the incidence of PTB prior to 37 weeks (62.0% vs 45.1%; $P < 0.001$) and between

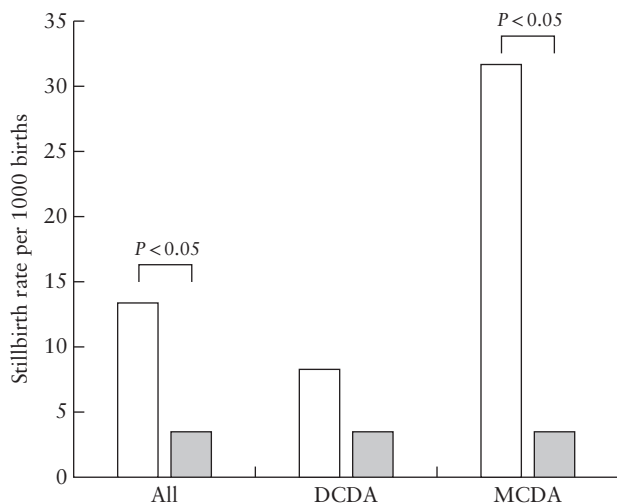


Figure 1 Rate of stillbirth in overall study population and separately for dichorionic diamniotic (DCDA) and monozygotic diamniotic (MCDA) twins, according to whether they were delivered before (□) or after (■) implementation of National Institute for Health and Care Excellence guideline on antenatal care of twin pregnancy.

34 and 37 weeks (39.3% vs 27.0%; $P = 0.002$) was significantly higher than in the pre-NICE group. However, PTB prior to 34 weeks' gestation was similar between the two groups ($P = 0.473$) (Table 2).

Subgroup analysis according to chorionicity

Similar patterns were observed when comparing the outcomes between the two study groups considering separately women with a dichorionic and those with a monozygotic diamniotic twin pregnancy (Table 3). Figure 1 shows the stillbirth rate in dichorionic, as well as monozygotic twin pregnancies (see also Table 3).

In dichorionic twin pregnancies, the incidence of stillbirth was lower in the post-NICE than in the pre-NICE group (3.6 per 1000 births vs 8.5 per 1000 births; $P = 0.161$); however, this difference was not statistically significant (Figure 1, Table 3). The rates of NND ($P = 0.568$), NICU admission ($P = 0.406$), emergency Cesarean section ($P = 0.590$) and incidence of PTB prior to 37 weeks ($P = 0.091$) and between 34 and 37 weeks ($P = 0.181$) was similar between the two groups (Table 3).

In monozygotic diamniotic twin pregnancies the incidence of stillbirth was significantly lower in the post-NICE than in the pre-NICE group (3.8 vs 33.6 per 1000 births; $P = 0.011$) (Figure 1, Table 3). There was no significant difference in the rates of NND ($P = 0.930$), NICU admission ($P = 0.527$) or emergency Cesarean section ($P = 0.577$) between the two groups. PTB prior to 37 weeks (96.9% vs 65.9%; $P < 0.001$) and between 34 and 37 weeks (62.6% vs 36.8%; $P = 0.002$) was significantly higher in the post-NICE than in the pre-NICE group. However, PTB prior to 34 weeks' gestation was similar ($P = 0.869$) between the two groups.

Table 3 Perinatal outcomes of dichorionic diamniotic and monozygotic diamniotic twin pregnancies, according to whether they were delivered before or after implementation of National Institute for Health and Care Excellence guideline on antenatal care of twin pregnancy

Outcome	Dichorionic diamniotic twin pregnancies				Monozygotic diamniotic twin pregnancies			
	Pre-implementation (n=882 pregnancies; n=1764 fetuses)	Post-implementation (n=417 pregnancies; n=834 fetuses)	P	Statistical power (%)	Pre-implementation (n=223 pregnancies; n=446 fetuses)	Post-implementation (n=131 pregnancies; n=262 fetuses)	P	Statistical power (%)
Live birth	1749 (99.1)	831 (99.6)	0.161	31.3	431 (96.6)	261 (99.6)	0.011	87.3
Stillbirth (per 1000 births)	15 (8.5)	3 (3.6)	0.161	31.6	15 (33.6)	1 (3.8)	0.011	87.5
Neonatal death (per 1000 live births)	15 (8.6)	9 (10.8)	0.568	7.7	9 (20.9)	5 (19.2)	0.930	3.7
Preterm birth								
< 37 weeks	355 (40.2)	215 (51.6)	0.091	> 99.9	147 (65.9)	127 (96.9)	< 0.001	> 99.9
34–37 weeks	219 (24.8)	135 (32.4)	0.181	87.1	82 (36.8)	82 (62.6)	0.002	99.9
< 34 weeks	136 (15.4)	80 (19.2)	0.553	49.3	65 (29.1)	45 (34.4)	0.869	39.7
< 28 weeks	45 (5.1)	21 (5.0)	0.543	4.3	12 (5.4)	8 (6.1)	0.885	7.9
Admission to NICU (per 100 live births)	469 (26.8)	234 (28.2)	0.406	5.1	195 (45.2)	99 (37.9)	0.527	57.1
Emergency CS	262 (29.7)	130 (31.2)	0.59	12.2	77 (34.5)	41 (31.3)	0.577	19.6

Data are given as n (%), unless indicated otherwise. Some percentages are calculated per pregnancy and some per fetus, depending on outcome. CS, Cesarean section; NICU, neonatal intensive care unit.

DISCUSSION

Summary of study findings

Implementation of the NICE guidance was associated with a significant reduction of more than 70% (from 13.5 to 3.6 per 1000 births) in the stillbirth rate of twin pregnancies. This reduction was greater in monochorionic (about 90%) than in dichorionic (about 60%) twin pregnancies. Implementation of the NICE guidance was not associated with a significant change in NND, admission to the NICU or emergency Cesarean section, despite an increase in elective delivery at 34–37 weeks' gestation.

Interpretation of findings and comparison with literature

Our findings support the hypothesis that the reduction in the stillbirth rate in twin pregnancies that has been observed in the UK recently, could, at least in part, be attributed to the implementation of the NICE twin guideline^{4,5}. The NICE guidance provided many recommendations (Appendix S1), including the establishment of specialist clinics for twins. Our findings add to the scarce evidence supporting the role of such clinics^{10,11}. Women receiving care in a consultant-led multidisciplinary twins clinic at a metropolitan tertiary center in Sydney, Australia, had lower rates of Cesarean section (55% *vs* 70%) and PTB at 34–36 weeks (26% *vs* 44%) than did those managed in a general antenatal care clinic¹¹. It is of note that the incidence of PTB at 34–36 weeks in our study cohort was significantly higher following implementation of the NICE guidance. Despite this, we found no significant increase in rates of NND or NICU admission.

It should be noted that other factors could have contributed to the significant reduction in the stillbirth rate in twin pregnancies, such as implementation of the guideline of the International Society of Ultrasound in Obstetrics and Gynecology on the use of ultrasound in twin pregnancies⁹. The detection of fetal structural abnormalities and aneuploidy has improved. This could have led to early detection of anomalies, allowing termination of the affected twin. Moreover, early detection of monochorionicity-related complications, mainly TTTS and sFGR, could lead to fetal therapeutic interventions with the risk of early fetal loss. The diagnostic criteria of some of the complications affecting twin pregnancies, such as sFGR, have varied over the years. The use of chorionicity-specific twin charts was implemented at St George's Hospital in 2017, which could have altered the assessment of fetal growth in twins^{12–14}. Furthermore, routine screening for TAPS, a monochorionic-specific complication associated with an increased risk of perinatal mortality and morbidity^{15,16}, was implemented at St George's Hospital in 2012; however, it is unknown whether routine screening is associated with improved pregnancy outcomes¹⁷.

An important finding of this study is the higher incidence of PTB between 34 and 37 weeks' gestation in the post-NICE than in the pre-NICE group. This probably

reflects the implementation of the NICE guidance, which recommends delivery of uncomplicated monochorionic twins by 36 weeks^{4,5}. This also explains why PTB between 34 and 37 weeks' gestation was significantly higher in monochorionic, but not dichorionic, twin pregnancies delivered after implementation of the NICE guideline. As stillbirth can occur only during pregnancy, shortening the pregnancy is likely to be responsible for at least some of the reduction in stillbirth. In this regard, it is important that there were no differences in NND between the two study periods.

In the post-NICE compared with the pre-NICE cohort, women were older and more likely to be obese, nulliparous and to have conceived via assisted conception, which is consistent with national demographic changes in the UK^{18–21}. There were more women from ethnic minorities and fewer who smoked in the post-NICE group. With the exception of lower rates of smoking, these factors would have been expected to increase the stillbirth rate, so they cannot explain the decline in the rate in the post-NICE group.

Clinical and research implications

We have shown significant differences in outcomes for monochorionic and dichorionic twins, and how analyzing them separately makes it possible to gauge the impact of an intervention aimed at twins. It would be very helpful, therefore, if future MBRRACE publications were to report monochorionic and dichorionic twin data separately.

The results of this study and the MBRRACE findings¹ of a reduction in stillbirths represent promising steps towards achieving the UK national target of reducing stillbirths by 50% by 2025. Multiple pregnancies are disproportionately over-represented in stillbirth, neonatal mortality and morbidity^{22–25}, and national efforts are needed to address this inequality. We should strive to reduce the rate of stillbirths in multiple pregnancies to levels similar to, or even lower than, that in singletons, which our study and another from The Netherlands have shown is feasible²⁶.

Strengths and limitations

Strengths of our study include the relatively large number of twin pregnancies and ascertainment of outcome data. Furthermore, we reported the data separately in dichorionic and monochorionic twins, overcoming one of the major limitations of the MBRRACE report.

The retrospective design of this study is a limitation inherently associated with a potential risk of bias. However, as we included all twin pregnancies delivering at St George's Hospital, the risk of selection bias is low. The study population included high-risk cases referred for delivery at our tertiary maternity center. This could have led to stillbirth and neonatal mortality rates that are above the average. However, we decided *a priori* not to perform a sensitivity analysis according to the original planned place of birth. The rationale was that this could potentially artificially reduce the rates of stillbirth and

neonatal mortality in our study population. Furthermore, it would not be consistent with the current national reporting system, according to which birth data are reported according to the hospital of birth.

In view of the observational nature of the study, it was not possible to prove causation. There might be other contributors to the fall in the rate of stillbirth in twins. However, given that the change in gestational age at delivery coincided with the implementation of the NICE guidance, it is highly likely that it contributed to the fall in the rate of stillbirths. Finally, in view of the long duration of the study, it is impossible to avoid the potential effect of changing practice and improved antenatal care. However, as these changes are not specific to twins, they would be expected to lead to a similar reduction in the rate of stillbirths in both singleton and twin pregnancies. Instead, the overall stillbirth rate in the UK remains one of the highest in Europe, with little significant reduction in the past decades^{27,28}.

Conclusions

Implementation of the NICE guidance was associated with a greater than 70% reduction in stillbirths in twin pregnancies. This fall was statistically significant in monochorionic, but not in dichorionic, twin pregnancies. Rates of neonatal mortality, NICU admission and emergency Cesarean section remained unchanged. Future studies in other maternity hospitals are needed to prove that these results can be replicated across the UK.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Appendix S1 Summary of recommendations in National Institute for Health and Care Excellence (NICE) guideline on antenatal management of twin pregnancy (NICE guideline 2011)

Table S1 Change in monitoring and management protocols at St George's Hospital before (pre-NICE) and after (post-NICE) implementation of National Institute for Health and Care Excellence (NICE) guideline on management of twin pregnancies, published in 2011