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Reduction in twin stillbirth following implementation of NICE guidance

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Short title: Stillbirth in twins

Keywords

Stillbirth, twin, multiple pregnancy; NICE; guideline; intrauterine demise; neonatal mortality; admission to neonatal unit; preterm birth; Cesarean section

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.22051

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CONTRIBUTION

What are the novel findings of this work?

Implementation of NICE twin guideline was associated with >70% reduction in stillbirth without a concomitant increase in neonatal mortality, admission to the neonatal unit or emergency Caesarean section. The reduction observed in monochorionionic 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 report the twin data separately in dichorionic and monochorionic pregnancies.

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ABSTRACT

Background: There has been an unprecedented fall in stillbirth in twin pregnancies 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 may have contributed to this change. The aim of this study was to investigate whether the implementation of NICE guidance is associated with a reduction in stillbirth in twin pregnancy.

Methods: This was a cohort study including all twin pregnancies at St George's Hospital, London, UK. Data were analysed according to two time periods: Group 1 (before June 2013) before implementation of NICE twin guidance, and Group 2 (after June 2013) after this implementation. The exclusion criteria were higher order multiple gestations, pregnancies of unknown chorionicity, pregnancies complicated by miscarriage, undergoing termination and pregnancies diagnosed with vanishing twin. The main outcome was stillbirth. Other outcomes include neonatal death (NND), admission to the neonatal unit (NNU) and emergency Caesarean section. Chi-square test and Mann-Whitney U-test were used to compare between the study groups. We planned a priori sensitivity analysis according to chorionicity.

Results: We included 1666 twin pregnancies (3332 fetuses), with 1114 pregnancies (2228 fetuses) before June 2013 and 552 pregnancies (1104 fetuses) from June 2013, in the analysis. Of those, 1299 were dichorionic and 354 were monochorionic diamniotic. The incidence of stillbirth was significantly lower in group 2 compared to the group 1 (3.6 per 1000 births vs 13.5 per 1000 births, p=0.008). The reduction in stillbirth rates was from 8.5 to 3.6 per 1000 births in dichorionic and from 33.6 to 3.8 per 1000 births in monochorionic twin pregnancies. There was no significant difference in the rates of neonatal death (p=0.625), NNU admission (p=0.506) or emergency Caesarean section (p=0.820) between the two groups. The median gestational age at delivery was significantly lower in the post-NICE compared to the pre-NICE twin pregnancies (median 36.9 vs 36.3 weeks, p<0.001), as a consequence of an increase in preterm birth (PTB) between 34 and 37 weeks (27.0% vs 39.3%, p=0.002), but not before 34 weeks' gestation (p=0.562).

Conclusions: A large and significant reduction (>70%) in stillbirth has been noted in twin pregnancies and associated with implementation of 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 neonatal mortality, admission to the neonatal unit or emergency Caesarean section.

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BACKGROUND

The United Kingdom has witnessed an unprecedented fall in the rate of stillbirth in twins by 50%.[1,2,3] According to the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE) 2018 report, the stillbirth rate was almost halved from 11.07 (95% CI, 9.78 to 12.47) per 1,000 births in 2014 to 6.16 (95% CI, 5.20 to 7.24) in 2016. Furthermore, the neonatal mortality rate also fell significantly from 7.81 (95% CI, 6.73 to 9.01) to 5.34 (95% CI, 4.47 to 6.36) per 1,000 live births.[1] However, it is important to recognise that, despite this significant improvement, the UK stillbirth rate in twins remains higher than that in singleton pregnancies.[1]

One potential contributor to this reduction in stillbirths is the National Institute for Health and Care Excellence (NICE) guideline on the antenatal care of uncomplicated twin and triplet pregnancies, published in 2011 (Supplementary material) and its quality standards (QS), published in 2016.[4,5] Key clinical recommendations in this guideline address the dating of twin pregnancies, determining chorionicity and amnionicity, twin labelling, 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 pregnancy. [4,5] The initial results of the Twin and Multiple Births Association (TAMBA) maternity engagement quality improvement initiative suggest that adherence to NICE QS is associated with lower rates of stillbirth, neonatal deaths, emergency cesarean section and admission to the neonatal intensive care unit.[6] The maternity engagement quality improvement initiative, which was funded by the UK Department of Health, aimed at improving the pregnancy outcomes in multiple pregnancies by promoting the implementation of this NICE guideline.

The aim of this study was to investigate whether the implementation of NICE twin pregnancy guidance is associated with a reduction in stillbirth in twin pregnancy in a large UK hospital.

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METHODS

This was a retrospective analysis of prospectively collected data 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. All births, as well as the maternal demographics, are routinely recorded prospectively. The inclusion criteria were twin pregnancies where the birth took place at St George's Hospital, and therefore the pregnancy outcomes are ascertained. The exclusion criteria were high order multiple gestations, pregnancies of unknown chorionicity, pregnancies complicated by miscarriage, pregnancies undergoing termination and multiple pregnancies diagnosed with vanishing twin. Gestational age (GA) was determined by the crown-rump length of the larger twin at the 11-14 week scan or by head circumference (HC) if assessed after 14 weeks' gestation.[4,7-9] Chorionicity was determined by ultrasound evaluation according to the number of placentas and the presence of the lambda or T signs, and confirmed after birth.[4,8,9] 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 (TRAP).

The main outcome in this study was stillbirth. Stillbirth was defined as the death of the fetus after 24 weeks and before birth. We also aimed to investigate neonatal death (NND), admission to the neonatal unit (NNU) and emergency cesarean section. These outcomes were chosen in view of their reported association with the implementation of NICE QS.[6]

The NICE guidance was published in September 2011, and was subsequently implemented at St George's Hospital during 2012. 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 (group 1) and after (group 2) June 2013.
The differences in the protocols between the two study groups are listed in Supplementary Table 1 (Supplementary material).

Statistical Analysis

Categorical data were presented as number (%) and compared using the Fisher's exact test or Chi-square test. Continuous data were 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 Mann-Whitney U-test was then used to compare continuous data between the study groups. We planned a priori 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 was reported. P values <0.05 were considered statistically significant. All p values were two-tailed. The analysis was performed using the statistical software packages SPSS 20.0 (SPSS Inc., Chicago, IL, USA), Stata 11 (release 11.2. College Station, Texas, USA) and GraphPad Prism® 5.0 for Windows (InStata, GraphPad Software Inc., San Diego, California, USA).

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RESULTS

Study population

We included 1666 twin pregnancies (3332 fetuses), with 1114 pregnancies (2228 fetuses) before June 2013 and 552 pregnancies (1104 fetuses) after June 2013, in the analysis. Of those, 1299 were dichorionic (DC) and 354 were monochorionic (MC). There was no significant difference in the proportion of DC and MC twin pregnancies between the two study periods (p>0.05). The incidence of stillbirth in the entire 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 (22.6 per 1000 births) than in dichorionic (6.7 per 1000 births) twin pregnancies. The rate of admission to the NNU in the study population was 30.2%, while the incidence of emergency cesarean section was 28.8%. The median (IQR) gestational age at delivery was 36.6 weeks (34.4-37.4), while the incidence of preterm birth prior to 37 weeks' gestation was 50.7%.

The maternal characteristics and pregnancy outcomes in the two study periods are shown in Tables 1 and 2. Women were significantly older and more likely to be obese in group 2 compared to group 1 (p<0.001 and p=0.028, respectively). There were more women from ethnic minority and fewer smokers (p<0.001 for both) in group 2 compared to group 1. There were more nulliparous women and pregnancies conceived via assisted conception in group 2 compared to group 1 (p<0.001 and p=0.025, respectively) (Table 1).

Study outcomes

There was a significant reduction in stillbirth rates associated with implementation of NICE guidelines from 13.5 to 3.6 per 1000 births (p=0.008, Figure 1, Table 2). There was no significant difference in the rates of NND (p=0.625), NNU admission (p=0.506) or emergency caesarean section (p=0.820). The median gestational age at delivery was significantly lower in group 2 compared to group 1 (p<0.001). Preterm birth (PTB) prior to 37 weeks (61.9% vs 45.1%, p<0.001) or between 34 and 37 weeks (39.3% vs 27.0%, p=0.002) was significantly higher in group 2 compared to group 1. However, PTB prior to 34 weeks' gestation was similar (p=0.562) (Table 2).

Subgroup analysis according to chorionicity

Similar patterns were seen when comparing the two study groups in women with dichorionic, as well as monochorionic, twin pregnancies (Table 3). Figure 1 demonstrates the stillbirth rate in dichorionic, as well as monochorionic twin pregnancies (Table 3).

The incidence of stillbirth in dichorionic twins was lower in group 2 compared to group 1 (3.6 per 1000 births vs 8.5 per 1000 births, p=0.161) (Figure 1, Table 3); however, this difference was not statistically significant. There was no significant difference in the rates of NND (p=0.568), NNU admission (p=0.406) or emergency caesarean section (p=0.590). PTB prior to 37 weeks (p=0.091) or between 34 and 37 weeks (p=0.181) was similar in group 2 compared to group 1 (Table 3).

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In monochorionic twins the incidence of stillbirth was significantly lower in group 2 compared to group 1 (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 ($p=0.930$), NNU admission ($p=0.527$) or emergency cesarean ($p=0.577$). PTB prior to 37 weeks (96.9% vs 65.9%, $p<0.001$) or between 34 and 37 weeks (62.6% vs 36.8%, $p=0.002$) was significantly higher in group 2 compared to the group 1. However, PTB prior to 34 weeks' gestation was similar ($p=0.869$).

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DISCUSSION

Summary of the study findings

Implementation of NICE guidance was significantly associated with a greater than 70% reduction in the stillbirth rate in twin pregnancies (3.6 vs 13.5 per 1000 births). This reduction was greater in monochorionic (almost 90% reduction) than dichorionic (almost 60% reduction) twin pregnancies. Implementation of NICE guidance was not associated with a detrimental change in NND, admission to NNU or emergency CS, despite the increase in elective birth at 34-37 weeks' gestation.

Interpretation of study findings and comparison with published literature

Our findings support the hypothesis that improvement in twin stillbirth rate could, at least in part, be attributed to the implementation of the NICE twin guideline.[4,5] This NICE guidance included many recommendations (Supplementary material), including the establishment of twin-specialist clinics. Our findings add to the scarce evidence supporting the role of such clinics.[10,11] The implementation of a consultant-led multidisciplinary twin clinic at a metropolitan tertiary center in Sydney, Australia was associated with lower cesarean section rates (55% vs. 70%) and fewer late PTB at 34-36 weeks' gestation (26% vs. 44%).[11] Of note, the incidence of PTB at 34-36 weeks in our study cohort was significantly higher following the implementation of NICE guidance. Despite this, we found no significant increase in NND or NNU admission.

The significant reduction in stillbirth rate in twin pregnancy may also have been contributed to by other factors that changed over time, such as the implementation of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) twin guideline.[9] Secondly, the detection rate of fetal structural abnormalities and aneuploidy has improved. This could have led to early detection, allowing termination of the affected twin. Thirdly, early detection of monochorionity-related complications, mainly TTTS and sFGR, could lead to fetal therapeutic interventions with the risk of early fetal loss. Fourthly, 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 outcomes.[17]

An important finding is the higher incidence of PTB between 34 and 37 weeks' gestation in the post-NICE compared to pre-NICE group. This likely reflects the implementation of 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 post-NICE. As stillbirth can occur only during pregnancy, shortening 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 time periods.

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

Clinical and research implications

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

The results of this study and the MBBRACE findings 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 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 feasible.[26]

Strengths and weaknesses

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 MBBRACE report.

The retrospective design is a limitation inherently associated with the potential risk of bias. However, as we have included all twin pregnancies delivering at St George's Hospital, the risk of selection bias is low. The study population includes high risk cases, referred for delivery at our tertiary maternity center. This could have led to above average stillbirth and neonatal mortality rates. 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 stillbirth and neonatal mortality rates in our study population. Furthermore, it would not be consistent with the current national reporting system, where birth data are reported according to the hospital of birth.

In view of the observational nature of the study, it is not possible to prove causation. There might be other contributors to the fall in stillbirths in twins. However, given that the change in gestational age at delivery coincides with the implementation of the NICE guidance, it is highly likely that it has contributed to the fall in 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 twin-specific, they would be expected to lead to a similar reduction in stillbirths in both singleton and twin pregnancies. But the overall stillbirth rate in the UK remains one of the highest in Europe, with little significant reduction in decades.[27,28]

Conclusions

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Implementation of NICE guidance was associated with a reduction (70%) in stillbirths in twin pregnancies. This fall was statistically significant in monochorionic, but not dichorionic, twin pregnancies. Neonatal mortality, NNU 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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FIGURE LEGENDS

Figure 1. The stillbirth rate in the study population before and after the implementation of the NICE guideline.[3]

DCDA: dichorionic diamniotic; MCDA: monochorionic diamniotic

*indicates statistical significance ($p<0.05$)

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Table 1. Characteristics of the twin study population

	Pre-implementation of NICE guideline (n=1114)	Post-implementation of NICE guideline (n=552)	p-value
Maternal age in years, median (IQR)	33 (29-36)	34 (31-38)	<0.001
Maternal body mass index (BMI) in Kg/m^2, median (IQR)	24.25 (21.70-27.70)	24.78 (22.35-28.93)	0.007
Maternal BMI ≥30Kg/m^2, n (%)	116 (10.4)	101 (18.3)	0.028
Maternal BMI ≥35Kg/m^2, n (%)	41 (3.7)	37 (6.7)	0.159
Maternal BMI ≥40Kg/m^2, n (%)	11 (1.0)	9 (1.6)	0.637
Ethnicity, n (%)			<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, n (%)	244 (21.9)	15 (2.7)	<0.001
Nulliparous, n (%)	498 (44.7)	318 (57.6)	<0.001
Assisted conception, n (%)	287 (25.8)	171 (31.0)	0.025
Dichorionic diamniotic, n (%)	882 (79.2)	417 (75.5)	0.102
Monochorionic diamniotic, n (%)	223 (20.0)	131 (23.7)	0.086
Monochorionic monoamniotic, n (%)	9 (0.8)	4 (0.7)	1.000

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Table 2. Perinatal outcomes of the study population

	Pre-implementation of NICE guideline	**Post-implementation of NICE guideline**	**p-value**	**Statistical Power**
Sample size	1114 pregnancies; 2228 fetuses	552 pregnancies; 1104 fetuses		
Livebirth, n (%)	2198 (98.7)	1100 (99.6)	0.008	80.5%
Stillbirth, n (per 1000 births)	30 (13.5)	4 (3.6)	0.008	88.5%
Neonatal death, n (per 1000 live births)	24 (10.9)	14 (12.7)	0.625	9.0%
Gestational age at delivery in weeks, median (IQR)	36.9 (34.6-37.6)	36.3 (34.1-37.3)	<0.001	>99.9%
Preterm birth prior to 37 weeks, n (%)	502 (45.1)	342 (61.9)	<0.001	99.9%
Preterm birth at 34-37 weeks, n (%)	301 (27.0)	217 (39.3)	0.002	99.9%
Preterm birth prior to 34 weeks, n (%)	201 (18.0)	125 (22.6)	0.473	69.1%
Preterm birth prior to 28 weeks, n (%)	57 (5.1)	29 (5.3)	0.562	5.7%
Admission to neonatal unit, n (%)	659 (30.0)	338 (30.7)	0.506	7.9%
Emergency Cesarean section, n (%)	339 (30.4)	141 (25.5)	0.820	65.3%
Birthweight in grams, median (IQR)	2390 (1908-2710)	2350 (1958-2603)	0.049	>99.9%

Some percentages are calculated as per pregnancy and some others as per fetus, depending on the outcome.

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Table 3. Perinatal outcomes of the study population according to chorionicity

	Pre-implementation of NICE guideline	Post-implementation of NICE guideline	p-value	Statistical Power
Dichorionic diamniotic twin pregnancies				
Sample size	882 pregnancies; 1764 fetuses	417 pregnancies; 834 fetuses		
Livebirth, n (%)	1749 (99.1)	831 (99.6)	0.161	31.3%
Stillbirth, n (per 1000 births)	15 (8.5)	3 (3.6)	0.161	31.6%
Neonatal death, n (per 1000 live births)	15 (9.1)	9 (10.8)	0.568	7.7%
Preterm birth prior to 37 weeks, n (%)	355 (40.2)	215 (51.6)	0.091	>99.9%
Preterm birth at 34-37 weeks, n (%)	219 (24.8)	135 (32.4)	0.181	87.1%
Preterm birth prior to 34 weeks, n (%)	136 (15.4)	80 (19.2)	0.553	49.3%
Preterm birth prior to 28 weeks, n (%)	45 (5.1)	21 (5.0)	0.543	4.3%
Admission to neonatal unit, n (%)	469 (28.4)	234 (28.2)	0.406	5.1%
Emergency Caesarean section, n (%)	262 (29.7)	130 (31.2)	0.59	12.2%
Monochorionic diamniotic twin pregnancies				
Sample size	223 pregnancies; 446 fetuses	131 pregnancies; 262 fetuses		
Livebirth, n (%)	431 (96.6)	261 (99.6)	0.011	87.3%
Stillbirth, n (per 1000 births)	15 (33.6)	1 (3.8)	0.011	87.5%
Neonatal death, n (per 1000 live births)	9 (20.9)	5 (19.2)	0.930	3.7%
Preterm birth prior to 37 weeks, n (%)	147 (65.9)	127 (96.9)	<0.001	>99.9%
Preterm birth at 34-37 weeks, n (%)	82 (36.8)	82 (62.6)	0.002	99.9%
Preterm birth prior to 34 weeks, n (%)	65 (29.1)	45 (34.4)	0.869	39.7%

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Preterm birth prior to 28 weeks, n (%)	12 (5.4)	8 (6.1)	0.885	7.9%
Admission to neonatal unit, n (%)	195 (45.2)	99 (37.9)	0.527	57.1%
Emergency Caesarean section, n (%)	77 (34.5)	41 (31.3)	0.577	19.6%

Some percentages are calculated as per pregnancy and some others as per fetus, depending on the outcome.

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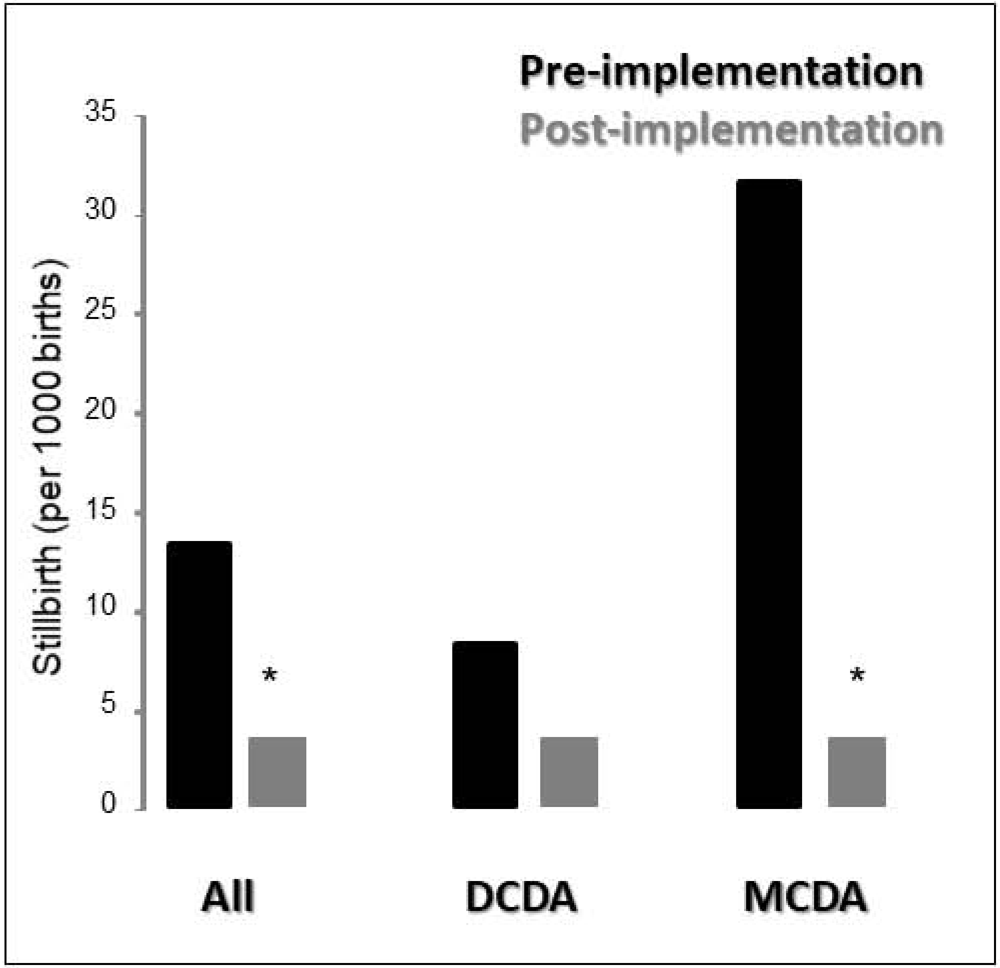

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Figure 1