# Unprecedented fall in stillbirth and neonatal deaths in twins: lessons from the United Kingdom

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### Running Head: perinatal mortality in twins

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## Background

On June 15th this year, MBRRACE published its report<sup>1</sup> focusing on perinatal deaths in the UK in 2016. While disappointing that the rate of stillbirths in singletons remained static, the report described a significant fall in the rate of stillbirths and neonatal deaths in twin pregnancies. In fact, 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 (Table 1, Figure 1). The neonatal mortality rate in twins 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 (Table 1, Figure 2). Relative to singletons, there has been a significant reduction in the stillbirth rate ratio associated with twin pregnancies from 2.8 (95% CI, 2.47 to 3.17) to 1.6 (95% CI, 1.36 to 1.88), and in the neonatal mortality rate ratio from 4.91 (95% CI, 4.20 to 5.73) to 3.33 (95% CI, 2.80 to 3.98) (Table 2). These reductions are clinically and statistically significant, and unlikely to be a chance finding. They are particularly gratifying in that they reverse the previous trend: there had been a 14% rise in stillbirths in multiple pregnancies in the UK between 2013 and 2014. What might account for this impressive reduction, can it be maintained, and are there any lessons that can be applied to singleton pregnancies to try to effect a similar reduction?

The overall stillbirth rate in the UK remains one of the highest in Europe, with little significant reduction in decades<sup>2,3</sup>, prompting the UK government to make this one of its top healthcare

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priorities. It has set a target of reducing stillbirths by 20% by 2020 and 50% by 2030, and this has now become a top priority on the UK political and medical agendas. Many professional and parent advocacy groups have called for focused research to understand and prevent stillbirth, and the Royal College of Obstetricians and Gynaecologists (RCOG) has launched its 'Each Baby Counts' campaign, with similar aims. The Every Newborn Action Plan aims to reduce the national stillbirth rate to 2 or fewer per 1000 births by 2030.

#### The burden of stillbirth in twin pregnancies

This impressive reduction in the stillbirth and neonatal death rates in twins must be viewed in the context of the epidemiology of twin pregnancies. In the past 30 years, the twin birth rate has risen worldwide, fueled largely by the increasingly widespread use of assisted reproduction techniques and delayed childbirth resulting in advanced maternal age at conception<sup>4-6</sup>. In the USA, for example, the rate of twins rose by 70% between 1980 (19 per 1000 live births) and 2006 (32 per 1000 live births), while in France it has risen by approximately 80% since the beginning of the 1970s. In the UK, the largest increase in the multiple pregnancy rate was recorded between 1990 and 1995, rising by 22% from 11.6 to 14.1 (Figure 3)<sup>7</sup>; by 2015 it had reached 16 per 1000 live births (Figure 3)<sup>7</sup>. In 2015, 10,901 women in the UK gave birth to twins, 169 to triplets, and 3 to quads and above. Approximately one third of twin pregnancies result from assisted reproduction, hence the practice of single embryo transfer now being advocated in many countries. In January 2009, the UK Human Fertilisation and Embryology Authority (HFEA) introduced a policy aimed at reducing the UK IVF multiple pregnancy rate to 10%.

Twin pregnancies are associated with a thirteen-fold increase in the rate of stillbirths in monochorionic, and a five-fold increase in dichorionic, twins compared with singleton pregnancies<sup>8-10</sup>. Monochorionicity-related complications include twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia polycythemia sequence (TAPS) and twin reversed arterial perfusion sequence (TRAP). Although multiple pregnancies comprise only 1.6% of all births in England and Wales<sup>7</sup>, they represent around 20% of preterm births<sup>11</sup>, 5.9% of stillbirths<sup>7</sup>, 18% of neonatal mortality and 10% of all NHS maternity litigation claims in respect of stillbirth<sup>12</sup>. Moreover, the risk of cerebral palsy is six times higher in multiple pregnancy than in singletons.

#### What has led to this reduction in twins' mortality rates?

This major improvement in twins' mortality rates is unlikely to be due to a single factor, but rather to the cumulative effect of a number of important initiatives. The Saving Babies' Lives Stillbirth Care Bundle in England was launched in 2016, so is unlikely to have had a significant impact on the 2016 data recently reported.

The National Institute for Health and Care Excellence (NICE) guideline on the antenatal care of uncomplicated twin and triplet pregnancies was published in 2011<sup>4</sup>, and NICE published its related quality standards (QS) in 2013 (Supplementary material Box 1)<sup>13</sup>. However, dissemination and implementation was patchy<sup>14</sup>. Moreover, there is evidence to 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<sup>14</sup>. This appears to be the case particularly in relation to multiple pregnancies for units that have implemented a model of care that closely matches that set out in NICE QS46<sup>13,14</sup>.

Several patient support groups, including the Multiple Births Foundation (MBF), the National Childbirth Trust (NCT) and the Twins and Multiple Births Association (TAMBA), have conducted audits and national surveys and published a number of reports providing an overview of the care mothers of twins and triplets receive during pregnancy, labor, birth and in the early months that follow<sup>15-17</sup>. Parliamentary questions were also used to obtain information from national datasets to augment this evidence base. These reports have highlighted the deficiencies and inconsistencies in services provided to women with multiple pregnancies; for example, the fact that less than 20% of UK maternity hospitals provide a specialist multiple pregnancy clinic. These reports have been instrumental in keeping the media and political spotlight focused on this area and have been used to exert political pressure on the Department of Health and NHS England to leverage more support for quality improvement initiatives in multiple pregnancies. In response to these efforts, the Department of Health agreed to sponsor a quality improvement programme working with 30 maternity units, the aim of which is to prove that good care, as defined by adoption of the NICE QS, improves outcomes in multiple pregnancies. Furthermore, the project intended to identify barriers to the delivery of good care and provide sufficient resource to create tools and methods to overcome them<sup>14</sup>

Over the past few years, several initiatives have aimed to improve implementation of the NICE guidance on twins. Since 2013, the RCOG has hosted a regular educational meeting on multiple pregnancy, a key focus of which has been the NICE guideline. This course has been replicated in a number of regional educational meetings.

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guideline on the management of twin pregnancies, both uncomplicated and complicated, was published online in 2015<sup>18</sup> and was presented at the ISUOG World Congress in 2015. A summary of the key recommendations is outlined in Supplementary material Box 2. It is likely that every time new guidance is issued and supported with an awareness campaign, it results in greater uptake among clinicians. This is also likely to be, in part, a result of going through hospital trust clinical governance structures.

Over the past 5 years there have been a number of key improvements in fetal therapy for complex monochorionic twins. Severe TTTS affects 10-15% of monochorionic twin pregnancies and is associated with increased fetal loss, perinatal mortality and morbidity<sup>19,20</sup>. A randomized controlled trial of laser coagulation of the entire vascular equator (Solomon technique) compared with standard or selective laser coagulation of the placental vascular anastomoses was published in 2014<sup>21</sup>. The Solomon technique was associated with a reduction in TAPS (3% vs 16% for the standard treatment; OR 0.16, 95% CI 0.05-0.49) and TTTS recurrence (1% vs 7%; OR 0.21, 0.04-0.98). The primary outcome was a composite of the incidence of TAPS, TTTS recurrence, perinatal mortality, and severe neonatal morbidity. The Solomon technique was associated with a reduction in the primary outcome (34% vs 49% for the standard treatment; OR 0.54; 95% CI 0.35-0.82). Since then, this technique has gradually become the standard technique of Laser for TTTS in the UK and elsewhere, and improvements in pregnancy outcomes are expected. Although UK data are yet to be published, European centers have demonstrated a continuous improvement in doubletwin survival rate, likely due to the growing experience and refinements in fetoscopic instruments and techniques<sup>22</sup>. It seems likely that this advance has contributed to the reduction in twins' mortality rates in the UK reported for 2016, although unfortunately the data are not broken down according to chorionicity so this cannot be confirmed<sup>1</sup>.

#### Can this trend be maintained?

As mentioned above, the Saving Babies' Lives Stillbirth Care Bundle in England was launched in 2016 so the impact of this initiative should be seen over the next few years. This care bundle includes four components: firstly, smoking reduction/cessation and all women offered an antenatal test for carbon monoxide level; secondly, identification and monitoring of fetal growth restriction, specifically implementing the use of the 'Growth Assessment Programme' (GAP); thirdly, educating pregnant women about the importance of detecting and reporting reduced fetal movements, and developing consistent care pathway protocols when concerns are raised; and fourthly, effective fetal monitoring during labour by implementing a 'fresh eyes' double checking protocol for CTG traces during labour, and an escalation protocol when there is concern. This policy reflects the goals of the 2014 RCOG 'Each Baby Counts' campaign aimed at reducing intrapartum stillbirths and hypoxic brain injury. However, the first three components are unlikely to reduce the stillbirth rate in multiple pregnancies. There is no evidence that monitoring fetal growth using the GAP reduces the risk of stillbirth in multiple pregnancy. In fact, NICE guidance specifically recommends not using abdominal palpation or symphysis-fundal height measurements to screen for intrauterine growth restriction in multiple pregnancies<sup>4</sup>. The evidence supporting a causal relationship between smoking and stillbirth is derived from studies which mostly excluded twin pregnancies<sup>23,24</sup>. So, while it seems reasonable to assume that smoking cessation will also reduce the risk of stillbirth in twins, this has not been proven. Similarly, the evidence suggesting a potential reduction in the risk of stillbirth with increased awareness and monitoring of fetal movements stems from studies which included only singleton pregnancies<sup>25,26</sup>; it would be inappropriate to extrapolate this potential benefit to twins.

The scope of the current NICE multiple pregnancy guidance<sup>4</sup> is limited to the antenatal care of uncomplicated twin and triplet pregnancies. However, this guideline is currently being updated and its scope expanded to include intrapartum care and complicated twin and triplet pregnancies. It is hoped that, assuming continued effective implementation, this expanded guidance will lead to further improvements in the care of multiple pregnancies. In November 2016, the RCOG also updated its guidance on the management of monochorionic twin pregnancies<sup>27</sup>. One of the key changes in both the ISUOG<sup>18</sup> and RCOG guidelines<sup>27</sup> is the increased frequency of antenatal ultrasound scans for this group (Figures 4 and 5). Timely detection of TTTS and TAPS has been shown to improve perinatal outcome<sup>28</sup>. Longer scan intervals are likely to be associated with a more severe presentation at diagnosis of one of these complications and consequently also with poorer outcomes<sup>29</sup>. There is relatively little evidence supporting the routine examination of dichorionic twins every 4 weeks, or even every 4-6 weeks as recommended by some<sup>30</sup>.

It would obviously be very helpful if future reports break down the mortality figures according to chorionicity, as this would facilitate understanding of which initiatives might be responsible for any changes.

#### Can this be replicated in singletons?

Whether this reported decline in perinatal mortality in twins can be replicated in singleton pregnancies is as yet unknown. However, one would imagine that initiatives such as focused efforts on implementation of evidence-based guidelines, education and training, might also be effective in singletons. One third of stillbirths in singletons occur after 36 weeks' gestation and up to two thirds after 34 weeks; if these at-risk fetuses could be identified and delivered appropriately, many of these stillbirths could potentially be avoided<sup>3</sup>. Over half of stillbirths are related to impaired fetal growth secondary to placental dysfunction<sup>31</sup>. Until recently, two thirds of stillbirths were considered 'unexplained' and therefore thought to be unavoidable. Using a new classification system, however, it has been demonstrated that 43% of stillborn babies were growth restricted<sup>32</sup>. Therefore, a policy of screening for fetal growth restriction, and tailored antenatal surveillance and intervention, could potentially prevent a significant proportion of stillbirths.

#### Conclusion

It is very encouraging that perinatal mortality in multiple pregnancies in the UK has fallen significantly, and it is a testament to the efforts of the many parents, clinicians and support groups involved. However, there is no room for complacency - this stillbirth rate is still higher than in singletons, and more focused efforts are needed. Promoting best practice, updating protocols in line with evidence-based guidelines, education and staff training are continuous efforts which are likely to improve the outcomes of these high-risk pregnancies. National efforts and quality improvement initiatives, such as the UK Multiple Pregnancy Maternity Engagement Project, provide support to clinicians in order to implement best practice. It is uncertain whether the UK will meet its target of reducing stillbirths by 20% by 2020 and 50% by 2030. However, we are optimistic that the recent improvement in perinatal mortality in multiple pregnancies represents a major step on this journey.

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Number of fetuses	Number (%)			Rate per 1000 births			
		Stillbirths			Stillbirths		
	2014	2015	2016	2014	2015	2016	
1	2975 (91.3)	2819 (92.9)	2912 (95.0)	3.96	3.72	3.86	
2	265 (8.1)	200 (6.6)	145 (4.7)	11.07	8.34	6.16	
≥3	6 (0.2)	13 (0.4)	7 (0.2)	9.98	21.81	11.78	
Not known	12 (0.4)	2 (0.1)	1 (0)				
	Neonatal deaths			Neonatal deaths			
	2014	2015	2016	2014	2015	2016	
1	1193 (86.2)	1235 (89.9)	1204 (90.1)	1.59	1.64	1.60	
2	185 (13.4)	125 (9.1)	125 (9.3)	7.81	5.26	5.34	
≥3	5 (0.4)	13 (0.9)	7 (0.5)	8.4	22.3	11.93	
Not known	1 (0.1)	0 (0)	1 (0.1)				

**Table 1.** Stillbirth and neonatal mortality rates according to the number of fetuses by year: United Kingdom and Crown Dependencies, for births in 2014 to 2016<sup>1</sup>.

Number of fetuses	Ratio of mortality rates (RR) Stillbirths					
	2014	2015	2016			
1	Reference	Reference	Reference			
2	2.80 (2.47-3.17)	2.24 (1.94-2.59)	1.6 (1.36-1.88)			
≥3	2.52 (1.13-5.62)	5.86 (3.40-10.10)	3.05 (1.46-6.38)			
	Neonatal deaths					
	2014	2015	2016			
1	Reference	Reference	Reference			
2	4.91 (4.20-12.70)	3.21 (2.67-3.86)	3.33 (2.80-3.98)			
≥3	5.28 (2.19-12.70)	13.62 (7.89-23.53)	7.45 (3.56-15.56)			

**Table 2.** Ratios of mortality rates for stillbirth and neonatal death according to the number of fetuses by year: United Kingdom and Crown Dependencies, for births in 2014 to 2016<sup>1</sup>.

## **Figure legends**

**Figure 1.** Stillbirth rates according to the number of fetuses by year: United Kingdom and Crown Dependencies, for births from 2014 to 2016<sup>1</sup>

**Figure 2.** Neonatal mortality rates according to the number of fetuses by year: United Kingdom and Crown Dependencies, for births from 2014 to 2016<sup>1</sup>

Figure 3. UK multiple birth rate from 1940 to 2015<sup>7</sup>

**Figure 4.** The recommended frequency and content of ultrasound assessments for dichorionic twin pregnancies<sup>18</sup>

**Figure 5.** The recommended frequency and content of ultrasound assessments for monochorionic twin pregnancies<sup>18</sup>

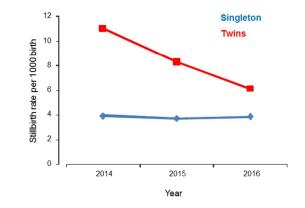


Figure 1. Stillbirth rates according to the number of fetuses by year: United Kingdom and Crown Dependencies, for births from 2014 to 2016

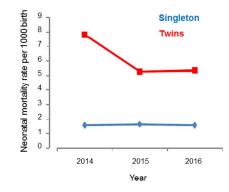


Figure 3

Figure 2. Neonatal mortality rates according to the number of fetuses by year: United Kingdom and Crown Dependencies, for births from 2014 to 2016

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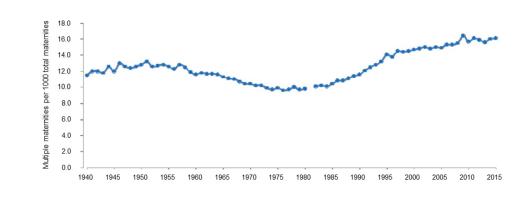
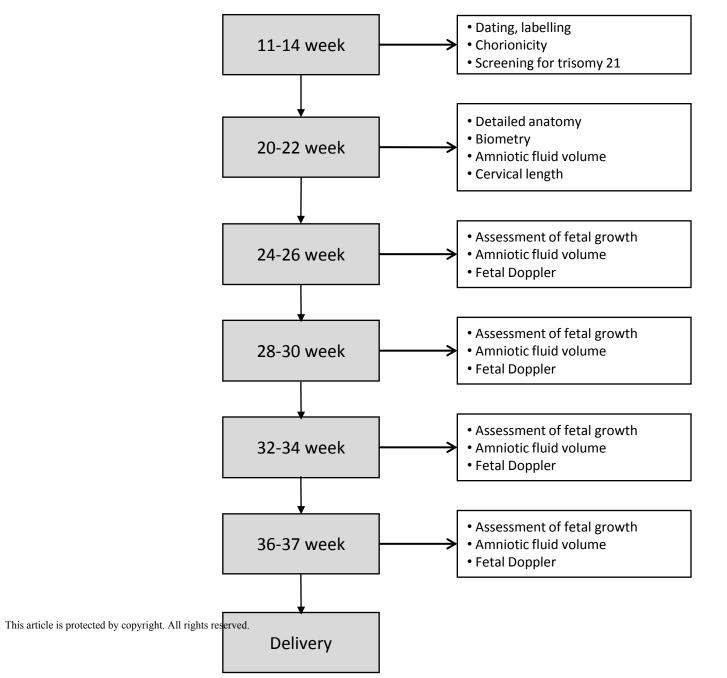


Figure 3. UK multiple birth rate from 1940 to 2015

# **Dichorionic Twin Pregnancy**



# **Monochorionic Twin Pregnancy**

