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Stillbirths: the way forward in high-income countries

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Stillbirth rates in high-income countries declined dramatically from about 1940, but this decline has slowed or stalled over recent times. The present variation in stillbirth rates across and within high-income countries indicates that further reduction in stillbirth is possible. Large disparities (linked to disadvantage such as poverty) in stillbirth rates need to be addressed by providing more educational opportunities and improving living conditions for women. Placental pathologies and infection associated with preterm birth are linked to a substantial proportion of stillbirths. The proportion of unexplained stillbirths associated with under investigation continues to impede efforts in stillbirth prevention. Overweight, obesity, and smoking are important modifiable risk factors for stillbirth, and advanced maternal age is also an increasingly prevalent risk factor. Intensified efforts are needed to ameliorate the effects of these factors on stillbirth rates. Culturally appropriate preconception care and quality antenatal care that is accessible to all women has the potential to reduce stillbirth rates in high-income countries. Implementation of national perinatal mortality audit programmes aimed at improving the quality of care could substantially reduce stillbirths. Better data on numbers and causes of stillbirth are needed, and international consensus on definition and classification related to stillbirth is a priority. All parents should be offered a thorough investigation including a high-quality autopsy and placental histopathology. Parent organisations are powerful change agents and could have an important role in raising awareness to prevent stillbirth. Future research must focus on screening and interventions to reduce antepartum stillbirth as a result of placental dysfunction. Identification of ways to reduce maternal overweight and obesity is a high priority for high-income countries.

Introduction

In high-income countries, there is an expectation that every pregnancy will end with the birth of a healthy baby. Yet about one baby out of every 200 (who reaches 22 weeks’ gestation or more) is stillborn. Public perception is that stillbirths are a thing of the past, but these are not rare events. The effect of a stillbirth on parents is devastating and long term: to many of these parents the death of their baby before birth is no less a death than is the death of any other child. As highlighted in the first paper of The Lancet’s Stillbirths Series, families are often left with intense grief and damaging psychological and social problems for many years.

Although improvements in maternity care resulted in a dramatic reduction in stillbirth in high-income countries beginning in the 1940s, more recently, the decline has slowed or halted. Examination of recent trends in stillbirth rates by gestational age in the USA shows some improvements in late gestation stillbirth (28 weeks or more) but little reduction in the early gestational age stillbirth (figure 1).

A closer look at trends in late gestation stillbirth rates across 12 high-income countries over the past 20 years reveals substantial reductions in most of these countries. Norway and the Netherlands have shown the largest reductions (50% and 40%, respectively) during this time. Norway now has the lowest rate at 2.2 stillbirths per 1000 births and the UK the highest at 3.8 stillbirths per 1000 births across these high-income countries. Although differences in rates can relate to population characteristics, practices, and policies around registration and reporting (including termination of pregnancy) rather than quality of care, these findings suggest that further reductions in stillbirth rates are possible in many high-income countries (figure 2, see webappendix p 1 for data sources).

Key messages

- The variation in stillbirth rates clearly shows that further reduction in stillbirth is possible in high-income countries.
- Women from disadvantaged backgrounds continue to experience stillbirth rates far in excess of non-disadvantaged women in high-income countries and an increased focus on appropriate programmes is needed to address this disparity.
- Maternal overweight and obesity, and smoking are the most important potentially modifiable risk factors for stillbirth in high-income country settings. Implementation of preconception care for all women could reduce these risk factors. Smoking cessation programmes in pregnancy are effective and should be implemented as part of routine care.
- Factors relating to suboptimum professional care contribute to a substantial proportion of stillbirths. Implementation of perinatal mortality audit at the national level is an important step towards addressing quality of care.
- Data for stillbirth are inadequate. A thorough investigation of stillbirth is essential. This includes placental histopathology for all stillbirths and parents being given the option of a high-quality autopsy. Consensus on definition and classification is needed.
- Antepartum stillbirth related to placental dysfunction and very preterm birth are major contributors to stillbirth in high-income countries. Further research is needed on underlying mechanisms to aid early detection and effective management of women at increased risk.
In the fifth paper of The Lancet’s Stillbirths Series, we present priority areas for stillbirth prevention, and interventions and research to address these priorities in high-income countries. We use 500 g or more, or 22 weeks’ gestation or more, to define stillbirth, unless otherwise stated.

### Priority areas in reducing stillbirth in high-income countries

Future improvements in prevention of stillbirth must target specific causes, risk factors, and vulnerable groups. To identify priorities for stillbirth prevention, we drew on an article published alongside the Stillbirths Series, which presents important risk factors for stillbirth and, additionally, we undertook a detailed analysis of causes and associated disorders for stillbirths through application of one classification system to stillbirths across six high-income countries.

### Risk factors

#### Ethnic origin and socioeconomic status

However, disparity is assessed, links with stillbirth and other adverse birth and longer term outcomes are starkly evident in high-income countries. Inuit-inhabited areas of Canada have stillbirth rates nearly three times higher than the rest of Canada. Indigenous Australian women have almost twice the risk of non-indigenous women as do African-American women in the USA when compared with white women. In the Netherlands, a 30–80% increased risk of stillbirth was shown for minority populations, which make up 15% of the total population. A review in Nordic countries reported a link between stillbirth and social differences, with most of the 35 studies showing a relative risk of stillbirth between 1.4 and 1.9 for the groups with greatest deprivation. Reports from the UK and New Zealand show a similar picture.

The reasons for these disparities differ between countries and regions. Bryant and colleagues described determinants of disparity in obstetric outcomes as having their roots in maternal behaviours, genetics, the physical and social environments, and access to and quality of health care. Some groups, such as American-Alaskan women and Australian and Canadian indigenous women, have high rates of no antenatal care, which is associated with three times the stillbirth risk. Late attendance for antenatal care, also associated with increased risk, can explain some of the disparity in stillbirth rates in high-income countries. Lack of access to care is one of the factors contributing to higher stillbirth rates in remote and rural areas.

Low educational attainment (less than year 10) is associated with almost twice the odds of stillbirth. However, links with other factors are complex. One US report showed that, although education conferred a 30% reduction in stillbirth risk for white women who had more than 12 years of education, there was only a 9% reduction seen for black women and a 4% reduction for Hispanic women with similar levels of education. A review in Nordic countries reported a link between stillbirth and social differences, with most of the 35 studies showing a relative risk of stillbirth between 1.4 and 1.9 for the groups with greatest deprivation.

### Other maternal characteristics

The most important, potentially modifiable risk factors for stillbirth are maternal overweight and obesity before pregnancy (body-mass index [BMI] ≥25 kg/m²), and smoking during pregnancy. Obesity is one of the leading factors contributing to the overall burden of disease worldwide. With up to 58% of women of childbearing age either overweight or obese, the number of attributable stillbirths across high-income countries is in the vicinity of 8064 each year.

Maternal age of more than 35 years is also an important factor that is associated with a 65% increase in the odds...
of stillbirth and could be responsible for almost 4226 stillbirths in high-income countries each year. Primiparity is an important risk factor for stillbirth, contributing to about 15% of stillbirths in high-income countries. The increasing prevalence of women with a combination of important risk factors such as primiparity, maternal age of more than 35 years, and high BMI could potentially lead to an increase in stillbirth rates. The risk of fetal death rises with advancing gestational age, increasing from one in 2000 women remaining pregnant per week at 37 weeks to one in 50 at 42 weeks, and to one in 200 by 43 weeks. The increased risk of stillbirth in later gestations is higher for women of advanced age.

With steadily increasing rates and well established increased risk of stillbirth, multiple pregnancy and the use of assisted reproductive technology are important factors in high-income countries. Although the contribution at the population level is small (around 1%), women with a previous stillbirth have an almost three-times increased risk of stillbirth in a subsequent pregnancy. Previous caesarean section has also been associated with an increased risk of stillbirth. Meta-analysis of six studies showed a 20% increase in the odds of stillbirth. Although confounding due to the reasons for caesarean section cannot be excluded, this finding is concerning and requires further investigations, particularly in view of the increasing rates of births with caesarean section.

Causes and contributing disorders

Further prevention of stillbirths in high-income countries must target specific causes of death and the clinical scenarios in which they occur. However, accurate data on causes is hampered by inadequate post-mortem investigation protocols and differences in approaches in classification, as demonstrated by the wide variation in the reported proportion of unexplained stillbirths of 10–70%. Reports of causes are often rudimentary, hard to compare, and without description of the often complex clinical scenarios involved. We collaborated with groups across six high-income countries in classifying cohorts of stillbirths and neonatal deaths using the Causes of Death and Associated Conditions (CODAC) classification (panel 1). Many classification systems have been developed and various systems seem to have valuable features. CODAC did best in retaining information about stillbirth in an assessment by the International Stillbirth Alliance, and was therefore chosen for this analysis. Another benefit of the CODAC system is that for every stillbirth case, three levels of codes are allowed, which enables reporting for each case by groups of disorders or scenarios rather than attributing death to a single event or disorder. In this cohort of 915 perinatal deaths, including 617 stillbirths of 22 weeks’ gestation or 500 g or more (66% ≥28 weeks or ≥1000 g), autopsy and placental examinations were done in 45% and 73% of cases, respectively. Results are presented in figure 4.

Panel 1: Methods for classification of stillbirths and neonatal deaths

Consecutive series of stillbirths and neonatal deaths (defined as 22 weeks’ gestation at birth or 500 g birthweight) date of birth were included from every participating study team from seven regions as follows: Groningen University, Netherlands; Queensland Maternal Perinatal Quality Council, Queensland, Australia; Norwegian Institute of Public Health, Norway; CDC Georgia, USA; Brown University, Providence, USA; Alberta Perinatal Health Program, Canada; and Centre for Maternal and Child Enquiries, UK. Terminations of pregnancy and neonatal deaths after 7 days of life were excluded. With the Causes of Death and Associated Conditions system, cases were classified according to usual practices within each region and submitted in a de-identified format for analysis. Descriptive analysis was done in SPSS of causes and associated disorders for stillbirths and neonatal deaths separately. Subgroup analysis was undertaken by gestation of less than 28 weeks and 28 weeks or more.
### Figure 4: Causes and contributing factors for stillbirth in high-income countries

The line connectors represent the clinical scenarios of combined factors found in more than 1% of cases. The thickness of the line represents frequency. The slimmest and thickest lines represent 1% and 6%, respectively. COD=cause of death. PAD=provisional anatomic diagnosis. PPROM=preterm premature rupture of membranes.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Contributing as COD or associated condition</th>
<th>Scenarios</th>
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<tbody>
<tr>
<td><strong>Level I categories</strong></td>
<td>%</td>
<td>Level II subcategories</td>
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<tr>
<td>Infection</td>
<td>12</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Intrapartum</td>
<td>3</td>
<td>Extreme prematurity</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>6</td>
<td>Cardiovascular and lymphatic vessels</td>
</tr>
<tr>
<td>Fetal</td>
<td>4</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Cord</td>
<td>9</td>
<td>Infection or inflammation</td>
</tr>
<tr>
<td>Placenta</td>
<td>29</td>
<td>Circulatory disorders—other non-abruptions</td>
</tr>
<tr>
<td>Maternal</td>
<td>7</td>
<td>Unspecified or other</td>
</tr>
<tr>
<td>Unknown</td>
<td>30</td>
<td>With no autopsy</td>
</tr>
<tr>
<td>Associated perinatal</td>
<td>NA</td>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Associated maternal</td>
<td>NA</td>
<td>Maternal BMI ≥30 kg/m²</td>
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<tr>
<td><strong>Series</strong></td>
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</table>

Placental pathology

Placental pathologies accounted for one in four deaths across all gestational ages, and were contributory or causal in more than half of cases. Infarctions and thrombi were reported to be causal or to contribute in 13% of stillbirths; the corresponding figure for placental abruptions was 14%. These data are consistent with an estimated population-attributable risk (PAR) of abruption for stillbirth of 15%. Obstetric disorders with placental origins such as abruptions, infarctions, and small for gestation placentas are part of a large group of clinical scenarios associated with maternal hypertension, smoking, small for gestational age (SGA), and multiple pregnancy. Several studies confirm placental pathology as an important source of information in most stillbirths.\(^{32,38}\) replacing the former so-called unexplained group.\(^{34}\) However, caution is needed not to over-interpret placental findings because causality is often unclear.\(^{30,40}\)

Fetal maternal haemorrhage, reported in published studies to cause 5–14% of stillbirths,\(^ {33}\) was only detected in 2% of cases. Because screening for this disorder is not done routinely, the true incidence of substantial fetal maternal haemorrhage is probably underestimated.\(^ {42}\) Fetal growth restriction owing to placental insufficiency is identified in about 40–60% of stillbirths, also in otherwise unexplained stillbirths.\(^ {41}\) Classification in CODAC does not allow SGA to be coded as a cause of death, but, even so, this disorder was a contributing factor in 11% of stillbirths.

### Infection

The second largest contributor in our CODAC analysis was infection, causing 12% of stillbirths—a finding similar to that from other reports.\(^ {44}\) However, the contribution of infection is probably underestimated due to lack of investigation. Infection-related stillbirth is more frequent in pregnancies at early gestations.\(^ {44}\) In our cohort, infections contributed to 6% of stillbirths at 28 weeks’ gestation or more and to 15% of stillbirths at less than 28 weeks in most cases in scenarios of chorioamnionitis and preterm prelabour rupture of membranes (PPROM), often leading to intrapartum deaths. Common bacteria and viruses implicated in stillbirth in high-income-country settings are parvovirus B19, group-B streptococcus, *Listeria*, *Escherichia coli*, enteroviruses, cytomegalovirus, and influenza virus.\(^ {43}\) The fact that most infectious stillbirths were classified as unspecified in our cohort shows the potential for improvement in identification of the infectious agents in stillbirths.

### Umbilical cord abnormalities and cord accidents

Umbilical cord abnormalities and cord accidents can cause or contribute to fetal death.\(^ {45,46}\) However, since many cord incidents, including true cord knots and nuchal cords, are also common in livebirths, this diagnosis should be made with caution.\(^ {47}\) In our Series, 9% of stillbirths were deemed to be caused by cord complications and were considered contributory in a further 8%.

### Medical and pregnancy disorders

Whereas 7% of stillbirths were caused by maternal medical disorders, these were contributing factors in 24% of cases. The most frequent conditions were hypertensive disorders and diabetes. The estimated
PAR for pre-existing hypertension across a selection of high-income countries ranges from about 7% to 14% and for pre-existing diabetes from about 3% to 5%, indicating the important contribution these disorders continue to make to stillbirth in modern high-income-country settings.6 Although pre-eclampsia is associated with a 60% increased risk of stillbirth in modern obstetric settings, it has a low PAR (3%) based on a prevalence of 5%.6

Intrapartum deaths
Only 3% of stillbirths were caused by intrapartum events, with most deaths occurring in extremely preterm infants. Overall, 9% of stillbirths occurred intrapartum, but the causes had antepartum origin for most.

Congenital abnormalities
Congenital anomalies were identified as causal in 6% of stillbirths and as contributing to the death in another 5%. This finding is consistent with other reports showing that 6–12% of stillbirths are associated with anomalies.41,45 However, this might be an underestimate because of lack of testing and poor test sensitivity.

Unexplained
Although 30% of stillbirths remained without a known cause, this outcome was largely associated with failure to do the appropriate investigations. Only 5% of stillbirths were classified as unexplained despite full assessment (including autopsy and placental investigations) according to local guidelines.

Suboptimal care
Studies in high-income countries have shown that suboptimal care is associated with about 10–60% of stillbirths and neonatal deaths.47–62 The main factors relate to delayed recognition of emerging clinical disorders, and, if noted, an inadequate or delayed response (webappendix pp 2–6). Failure to use updated best practice protocols and non-compliance with existing protocols has an important role, as does poor communication between staff. For the woman herself, suboptimal care factors include inadequate antenatal care attendance, inadequate diabetes management, and smoking. Although intrapartum stillbirths now make up a small proportion of late gestation stillbirths in high-income countries,63 concerns have been raised regarding the contribution of suboptimal care in these cases.64

Interventions to reduce stillbirth in high-income countries
Interventions to prevent stillbirth have been recently reviewed44–46 and are summarised in the third paper of this Series.69 On the basis of these findings, we present interventions and strategies to address the priority areas identified in the first paper of this Series.1 These interventions fall into three main strategic areas: improvement of health and wellbeing of women before, during, and after pregnancy; detection and management of women at risk during pregnancy; and improvement of information and standards of maternity care (table 1).

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Description</th>
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<tbody>
<tr>
<td>Improvement of general health of women before, during, and after pregnancy</td>
<td>Culturally appropriate preconception care for women throughout reproductive years to ensure adequate folic acid intake, optimum weight and diet, cessation of smoking, education about the harms of alcohol, and risk reduction for women with substance use</td>
</tr>
<tr>
<td>Detection and management of women at increased risk</td>
<td>Culturally appropriate accessible routine antenatal care; early ultrasound assessment of gestational age</td>
</tr>
<tr>
<td>Diabetes or overweight and obesity</td>
<td>Screening and individualised pregnancy care plan, including dietitian counselling (exercise and diet) and post-partum weight management; routine weighing at first antenatal visit</td>
</tr>
<tr>
<td>Smoking, alcohol, and illicit drug use</td>
<td>Screening and intervention</td>
</tr>
<tr>
<td>Screening for placental insufficiency or FGR and hypertension</td>
<td>Screening for risk factor; increased awareness and timely evaluation of women reporting decreased fetal movements; doppler for high-risk pregnancies; monitoring and treatment with low-dose aspirin for those at risk</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>Single embryo transfer for in-vitro fertilisation</td>
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<tr>
<td>Post-term pregnancy</td>
<td>Induction after 41 weeks’ gestation</td>
</tr>
<tr>
<td>Raising awareness</td>
<td>Parent organisations as change champions; raising public awareness</td>
</tr>
<tr>
<td>Improvement of information and standards of maternity care</td>
<td>Implementation of national perinatal mortality audit programmes that incorporate evidence-based clinical guidelines</td>
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<td>Improve data access with systems to more effectively use routinely collected data; consensus on a minimum dataset for monitoring pregnancy outcomes on a large scale; education for maternity care providers to improve vital statistics data</td>
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<td></td>
<td>Implement international classifications system to enable comparisons within and across countries</td>
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<td>Implement high-quality stillbirth investigations protocol, including placental histopathology for all stillbirths</td>
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<td></td>
<td>Ensure access to the option of a high-quality autopsy for all parents after a stillbirth</td>
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FGR=fetal growth restriction.

Table 1: Interventions and strategies to address priority areas for stillbirth prevention
Improvement of health and wellbeing of women before, during, and after pregnancy

The stillbirth rate is an important measure of the quality of maternity care but also of women’s general health. Preconception care is increasingly recommended as an effective intervention to improve the general health and wellbeing of women across the reproductive lifespan, specifically an adequate diet and exercise, optimum folic acid intake, and smoking and alcohol cessation. This care grows in importance with increasing prevalence of risk factors in modern societies, such as advanced maternal age, diabetes, and obesity. Although strong evidence for preconception care to improve pregnancy outcome is currently not available, since many risk factors have very early origins, preconception care could reduce stillbirth through reduction of such factors.

With regard to disadvantaged women, employment and education are central to improving outcomes for these women. Further, some risk factors are known to be associated with socioeconomic disadvantage, including smoking, overweight, and obesity, and low education. For this reason, regular attendance for antenatal care is particularly important for disadvantaged women. However, organisational, personal, and financial factors can be important barriers to antenatal care attendance. These include transportation problems, not knowing where to access care, having a poor understanding of or attaching a low value to care, ambivalence or fear about the pregnancy, and high levels of stress. One study concluded that “poverty may be the overriding factor preventing access to care; obstacles appear to be deeply rooted in the experience of being poor, disadvantaged and vulnerable”. Therefore, providing appropriate maternity services for such women remains an important challenge.

Detection and management of women at increased risk

Routine antenatal care

Quality antenatal care, including identification of those for whom additional care is needed, through screening for risk factors, should be accessible to all women. Early ultrasound determination of gestation (10–12 weeks’ gestation) to provide an accurate baseline for continuing fetal surveillance allows optimum timing of early delivery if required and reduces the rate of induction of labour for suspected post-dates pregnancy.

Overweight and obesity

Recent guidelines from the US Institute of Medicine and the UK National Institute for Health and Clinical Excellence (NICE) provide comprehensive recommendations for healthy weight management before, during, and after pregnancy. Although there is some indication that excessive gestational weight gain can be reduced through lifestyle interventions, a review by Dodd and colleagues highlights the present lack of evidence for effective antenatal interventions to improve pregnancy outcomes for these women. Several studies addressing obesity in pregnancy are underway and their findings will further clarify how to help women of reproductive age achieve and maintain healthy weight. Weighing all women at the first antenatal visit assists in risk assessment and allows women to be informed of their recommended weight gain, which can increase the likelihood of correct weight gain.

Diabetes

Outcomes for women with diabetes have improved in high-income settings, but there is clear evidence of a need for further practice improvement. Although high-quality evidence is not available, provision of quality preconception care for women with pre-existing diabetes could assist in avoiding unplanned pregnancy and ensuring optimum weight, glycaemic control, and folic acid intake before conception. Women, particularly those of childbearing age, with risk factors based on history and present weight should be screened for diabetes. Weight management, monitoring, and intervention to achieve optimum glycaemic control throughout pregnancy is crucial to ensuring best possible outcomes for women with diabetes.

Smoking and alcohol

High-level evidence showing the benefits of smoking cessation interventions in pregnancy has been available.
for some time; however, implementation remains suboptimal in many settings. NICE guidelines that recommend a comprehensive approach to detection and intervention for women who smoke may help to address this gap. Because alcohol use in pregnancy is often linked with use of other drugs and smoking, joint targeting of these behaviours might help. Health promotion and psychological and educational interventions have been associated with positive maternal behavioural change, including lower rates of binge drinking. Women should be advised about the harms of smoking and alcohol intake and be aware that no safe level of alcohol consumption has been established.

**Placental insufficiency and fetal growth restriction**

Prevention of stillbirth associated with placental insufficiency, which is often associated with fetal growth restriction, is dependent on detection of women at risk and appropriate timing of birth. The evidence for antepartum testing to detect pregnancies at risk has been extensively reviewed and reveals the paucity of data on which to guide practice. Abdominal palpation to identify fetal growth restriction, although a standard part of antenatal care, results in a substantial proportion of missed cases. The use of serial fundal height measurement with a tape measure can improve detection of fetal growth restriction. However, evidence of benefit is lacking.

Customised growth charts improve prediction of morbidity and mortality in newborn babies; however, further research is needed to establish the risk and benefits of their use as a screening method in the antenatal period. Maternal perception of decreased fetal movements is associated with fetal growth restriction and stillbirth. Although formal counting by use of kick charts cannot be recommended, there is some indication that increased vigilance by both care providers and women about decreased fetal movements might reduce the risk of stillbirth. Planned early delivery, based on the presence of risk factors, is increasingly used to avert late gestation stillbirth. However, this intervention needs to be weighed against the risks associated with intervening at a given gestational age and risks related to unintended, late preterm birth (34–36 weeks).

**Hypertension**

Impaired placentation can cause some of the most important obstetric complications such as pre-eclampsia and intrauterine growth restriction, and is associated with increased fetal morbidity and mortality. Two high-quality meta-analyses have shown that aspirin reduces the risk of several adverse pregnancy outcomes, including perinatal death. These data have prompted NICE in the UK to recommend its use among women at high and moderate risk. However, further research is needed to more clearly define the target population and effect on longer term outcomes. Calcium supplementation reduces the risk of pre-eclampsia, although issues remain regarding the target population such as the role of dietary intake and the risk of pre-eclampsia. The use of fetal and umbilical doppler blood flow measurements in high-risk pregnancies with fetal growth restriction is the only intervention that has been shown, in a systematic review of randomised trials, to prevent stillbirth and neonatal death, and should be included in the management of such pregnancies.

**Multiple pregnancy**

With a steady increase of multiple births in high-income countries because of increases in rates of assisted reproductive technology and pregnancies in women of advanced maternal age, multiple pregnancy is an important area on which to focus attention. The rate of multiple pregnancy with the use of assisted reproductive technology can be reduced by limitation of the number of embryos transferred. Improvement in routine data collection to include chorionicity will aid efforts to reduce adverse outcome.

**Post-term pregnancy**

In the Cochrane systematic review on induction for post-term labour, induction (versus expectant management) at or beyond 41 weeks of gestation was associated with a reduction in perinatal mortality, and the review concluded that induction should be offered to all women at or beyond 41 weeks of gestation.

**Preterm birth and infection**

As many very preterm stillbirths are associated with PPROM and infection, antibiotics could theoretically reduce stillbirth, but they have shown little effect in high-income-country settings. However, treatment of periodontal disease during pregnancy might be promising: a
Panel 3: High-income country research priority methods

With the Child Health and Nutrition Research Initiative (CHNRI) method described in the second paper of this Series, research question lists were developed relating to discovery, epidemiology and development, and delivery in high-income countries. These lists consisted of 32, 50, and 53 questions, respectively.

Scorers included key researchers in the relevant field of stillbirth prevention, identified through Medline searches of first authors in recent stillbirth publications and hand searching of conference proceedings at annual International Stillbirth Alliance conferences from 1996 to 2009 for keynote and invited speakers. Snowball sampling was used to recruit other key researchers and clinicians in the field as scorers. There were 21 scorers each for the epidemiology and development and delivery lists. Discovery scores were provided by six scorers.

Research priority scores were calculated across five criteria for each list and standard CHNRI value weightings were applied. The criteria used for scoring the delivery and discovery lists included answerability, efficacy, deliverability, burden reduction, and equity. For the epidemiology and development list, answerability, attractiveness, feasibility, relevance, and equity were used. Average expert agreement was also calculated per question.

reduction in stillbirth (RR 0.49, 95% CI 0.26–0.94) was shown in meta-analysis of three trials110–112 including 1894 women (PM, personal communication; figure 5). Although of interest, this finding needs to be confirmed in large scale trials.

Improving information and standards of care

Perinatal audit

Perinatal audit has been described as: “The systematic, critical analysis of the quality of perinatal care, including the procedures used for diagnosis and treatment, the use of resources and the resultant outcome and quality of life for women and their babies”.113 Although high-level evidence is not available,114 a review of before-and-after studies115 in low-income and middle-income countries showed a 30% reduction in perinatal mortality associated with the introduction of perinatal audit. Studies in high-income countries also indicate benefit (see web-appendix p 7). In Norway, multidisciplinary perinatal audit has been implemented since 1986.116 Since then, perinatal mortality decreased from 13·8 to 7·7 per 1000 births, and better cooperation between hospitals and the implementation of nationwide protocols have been attributed to the audit. In the UK, nationwide confidential inquiries into stillbirths have shown improvements in obstetric management.117 In Australia and New Zealand, guidelines on perinatal mortality audit have been developed and disseminated118 and although uptake was shown to be suboptimum,119 an active guideline implementation programme in Australia120 and a national audit in New Zealand121 have shown improvements.

In the Netherlands, perinatal audit has been implemented in most obstetric units through a joint effort by the government and professional colleges.122–124 In the USA, several Fetal and Infant Mortality Review (FIMR) programmes have been established to review these deaths and make recommendations for improvements in health care and public health in general. However, these programmes are not uniform in approach and, although many suggestions for improvements in care have been defined, no structured assessment of efficacy has been reported.125 Perinatal audit can be organised by panels of external experts, who will confidentially analyse anonymous reports and feed back to the care providers involved such as the Centre for Maternal and Child Enquiries in the UK, or by unit-based teams such as in the Netherlands, Australia, and New Zealand. These two approaches both have advantages and disadvantages. The value of the impartiality of the expert panel approach can be offset by the advantages of the unit-based approach, which includes better information about the death, the knowledge of how their care is organised, and where it can be improved most efficiently. Further, clinician ownership of the process can assist in implementation of practice improvements. Irrespective of the model, the presence of a skilled, independent, and accepted chairperson is important to guide the discussion. The essential elements of effective perinatal mortality audit are shown in panel 2.

Investigations for stillbirths

Comprehensive investigation of stillbirths provides essential information for high-quality perinatal mortality audit. Ascertainment of a cause is often challenging because of the complexity of the situation in which the baby dies126 and the difficulty of clear determination of causation.127 The value of stillbirth investigations has been extensively reviewed.128 A comprehensive maternal history, comprehensive testing to exclude infection, clinical examination of the baby, macroscopic and histopathological examination of the placenta and umbilical cord, and a full perinatal autopsy are valuable in the work-up of stillbirths and are common components of existing protocols.129–131 Amniocentesis is the optimum method to identify infective causes of stillbirth and for cytogenetic studies, particularly when an autopsy cannot be done.

All parents should be offered the option of a high-quality autopsy examination after a stillbirth. In most high-income countries, parental consent is needed. It is difficult to determine whether autopsy rates are changing in those countries because few serial studies emanate from one location,132 but recent studies point to a fall in perinatal (including stillbirth) autopsy rates.133–135 The major limiting factor seems to be parental consent,136 and cultural and religious beliefs resulting from demographic changes in high-income countries might add to the downward pressure on perinatal autopsy rates.137 The autopsy is rated to be useful to establish a cause of death or in counselling after a stillbirth in 21–60% of autopsies, although many studies do not provide sufficient information to gauge this critically.138 For example, the expertise of those doing the autopsy is often not detailed, but the quality of autopsy is better when done by perinatal rather than general anatomic
The interpretation and reporting of placental pathology can also be variable and is done better by perinatal pathologists. If parents do not consent to an autopsy, other non-invasive tests, such as the babygram (full body radiograph), fetal ultrasound examination, and MRI, could assist.

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<thead>
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<th>Research Priority Score (RPS)</th>
<th>Average Expert Agreement (AEA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The effects of periconceptual environment, including nutrition and micronutrient status, on embryonic development</td>
<td>82.2 80.9 0.79</td>
</tr>
<tr>
<td>Development of repositories of well phenotyped human samples from stillbirths or other related conditions and matched controls, with clear arrangements for access, and appropriate ethical and other legal permissions in place</td>
<td>82.1 78.0 0.70</td>
</tr>
<tr>
<td>Characterising the fetal response to an adverse intrauterine environment to develop improved means of clinical assessment of fetal wellbeing</td>
<td>80.3 74.9 0.68</td>
</tr>
<tr>
<td>Defining pathophysiological pathways leading to stillbirth associated with maternal disease, in particular type 1 and type 2 diabetes mellitus</td>
<td>79.0 74.8 0.70</td>
</tr>
<tr>
<td>Defining pathophysiological pathways leading to increased rates of growth restriction and decreased rates of pre-eclampsia among smokers</td>
<td>76.6 76.3 0.67</td>
</tr>
<tr>
<td>Development of improved statistical, biometric, and bioinformatic technologies for data interpretation and clinical prediction of outcome</td>
<td>74.8 72.5 0.71</td>
</tr>
<tr>
<td>The effect of maternal obesity, with or without insulin resistance, on fetal and placental development</td>
<td>73.7 71.9 0.78</td>
</tr>
<tr>
<td>The role of normal and abnormal coagulation in normal and abnormal pregnancy</td>
<td>72.7 70.8 0.67</td>
</tr>
<tr>
<td>Understanding the fetal or placental function and control of the timing of parturition in post-dates pregnancy</td>
<td>70.9 64.5 0.63</td>
</tr>
</tbody>
</table>

RPS=research priority score. AEA=average expert agreement. All scores are out of 100, apart from AEA which ranged from 0.50 to 0.79.

Table 2: Top ten research priorities in discovery science

<table>
<thead>
<tr>
<th>Research Priority Score (RPS)</th>
<th>Average Expert Agreement (AEA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiological information</td>
<td>87.2 82.9 0.72</td>
</tr>
<tr>
<td>What factors contribute to the excess in stillbirth rates in minority populations?</td>
<td>83.7 78.3 0.71</td>
</tr>
<tr>
<td>What maternal lifestyle consumptions (caffeine, alcohol, cannabis) are associated with stillbirth and what are their relation with other relevant disorders and causes of stillbirth?</td>
<td>83.7 76.8 0.64</td>
</tr>
<tr>
<td>What care factors relating to health-care professional practice, care setting, and the mother and family are associated with potentially avoidable stillbirth?</td>
<td>79.4 75.4 0.65</td>
</tr>
<tr>
<td>How relevant is antenatal detection of fetal growth restriction to the prevention of stillbirth?</td>
<td>84.3 78.3 0.71</td>
</tr>
<tr>
<td>What is the contribution of other maternal bacterial infections in pregnancy (eg, group B streptococcal infection, bacterial vaginosis) to stillbirth?</td>
<td>84.3 78.3 0.71</td>
</tr>
</tbody>
</table>

RPS=research priority score. AEA=average expert agreement. LMIC=low-income and middle-income countries. HIC=high-income countries. All scores are out of 100, apart from AEA which ranged from 0.44 to 0.72.

Table 3: Top five research priorities in epidemiological information and top five in epidemiological measurement
nevertheless, little evidence exists for valid alternatives to the autopsy if women do not take up referrals. on the basis of early work by tugwell and colleagues, and henderson-smart and co-workers described an iterative process of evidence-based health care that integrates best available evidence with patients’ preferences, clinical expertise, and cost considerations, underpinned by high-quality systematic reviews. growing evidence suggests that evidence-based health care improves process of care, and use and costs of health services. a comprehensive overview of interventions to increase the uptake of best practice is provided in the fourth paper of this series.

raising community awareness
most prospective parents remain unaware that stillbirths are a possibility at all and, specifically, that particular lifestyles increase their own risk of stillbirth. parent-based organisations and groups argue for increasing public awareness of risk in pregnancy so women can be informed in the choices they make: parents who are unaware that stillbirth is even a possibility will not be alert to warning signs and are less likely to seek medical advice until it is too late. successful campaigns, such as that around sudden

<p>| Table 4: Top ten research priorities in development and delivery |
|---------------------------------|-----------------|-----------------|-----------------|---------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Rank (weighted)</th>
<th>RPS (weighted)</th>
<th>RPS (unweighted)</th>
<th>AEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>How can smoking cessation programmes be most effectively implemented as part of routine antenatal care?</td>
<td>1 (1)</td>
<td>76.5</td>
<td>76.4</td>
<td>0.74</td>
</tr>
<tr>
<td>How can perinatal audit and facility quality improvement be most effectively undertaken to reduce stillbirth rates?</td>
<td>2 (2)</td>
<td>75.4</td>
<td>73.5</td>
<td>0.66</td>
</tr>
<tr>
<td>In pregnancies with established intrauterine growth restriction, what is the optimum mode and timing of birth to reduce stillbirth and neonatal and infant mortality and severe morbidity?</td>
<td>3 (3)</td>
<td>73.0</td>
<td>73.1</td>
<td>0.68</td>
</tr>
<tr>
<td>What is the role of screening in early pregnancy with markers of placental function in reduction of the risk of stillbirth, neonatal and infant death, and major morbidity?</td>
<td>4 (6)</td>
<td>70.8</td>
<td>69.2</td>
<td>0.58</td>
</tr>
<tr>
<td>In high-risk pregnancies, does fetal umbilical artery doppler ultrasound reduce the risk of stillbirth, neonatal and infant mortality, and major morbidity?</td>
<td>5 (4)</td>
<td>69.8</td>
<td>69.9</td>
<td>0.61</td>
</tr>
<tr>
<td>For women who report decreased fetal movements, what is the optimum management to reduce the risk of stillbirth in term and preterm pregnancies?</td>
<td>6 (7)</td>
<td>69.5</td>
<td>69.6</td>
<td>0.63</td>
</tr>
<tr>
<td>What is the role of fetal growth monitoring with growth curves adjusted according to individual characteristics in detection of abnormalities in fetal growth and reduction of stillbirth, neonatal and infant mortality, and morbidity, and which characteristics, if any, result in optimal performance of such an approach?</td>
<td>7 (5)</td>
<td>69.3</td>
<td>69.5</td>
<td>0.61</td>
</tr>
<tr>
<td>What characteristics of antenatal care are associated with a reduction in the risk of stillbirth?</td>
<td>8 (10)</td>
<td>67.9</td>
<td>67.4</td>
<td>0.62</td>
</tr>
<tr>
<td>For disadvantaged populations, how can access to optimum anteprtum and birthing care be improved?</td>
<td>9 (13)</td>
<td>66.5</td>
<td>66.1</td>
<td>0.64</td>
</tr>
<tr>
<td>In pregnancies with impaired fetal growth, what regimens of fetal surveillance are associated with a reduction in adverse pregnancy outcome including stillbirth, neonatal and infant mortality, and major morbidity?</td>
<td>10 (11)</td>
<td>66.4</td>
<td>66.8</td>
<td>0.58</td>
</tr>
</tbody>
</table>

rps=research priority score. aea=average expert agreement. all scores are out of 100, apart from aea which ranged from 0.43 to 0.74.
infant death syndrome.\(^{155}\) clearly show that parent organisations can be powerful change agents and have an important part to play in stillbirth prevention.

**Stillbirth research priorities**

Although already many opportunities for improvement exist within present evidence, significant research gaps still need to be addressed. Following the method described in the second paper of this Series,\(^{43}\) research themes in discovery science, epidemiology, and development and delivery were developed and scored by international working groups and the top ranking issues are summarised here. Panel 3 describes the methods used in this study.

**Research priorities in discovery science**

Table 2 lists the research priorities in discovery science. The content of the top ten was not strongly affected by the weighting procedure. Early pregnancy environment was highlighted as the top priority, which is consistent with accumulating evidence that complications in late gestation are related to placental development in early pregnancy.\(^{156}\) Priorities 2, 6, and 10 all related to the development of improved infrastructure for pregnancy research in terms of repositories, analytical methods, and the so-called omic characterisation of normal and abnormal pregnancy.

**Research priorities in epidemiology and development and delivery**

Results for these two areas were consistent with the findings for discovery research, with a focus on factors that are most likely to affect antepartum stillbirth rates. The two highest ranked epidemiology issues and the top development and delivery issue related to maternal lifestyle and equity factors include: (1) identification of maternal factors that contribute to excess stillbirth rates in minority populations; (2) other lifestyle factors such as alcohol, cannabis, and caffeine intake; (3) ways to foster smoking cessation programmes; and (4) periconceptual intake of folic acid. Other top scoring issues related to detection of fetal growth restriction including use of antenatal customised growth charts, markers of placental function, and decreased fetal movements. Others dealt with ways to improve information such as ascertainment of stillbirth and improved routine data collection, implementation of perinatal audit, and investigation of stillbirth. Identification of important characteristics of antenatal care also ranked among the highest scoring issues, along with risk scoring and cost-effective methods for screening for diabetes in pregnancy (tables 3 and 4).

**Conclusions**

Many stillbirths in high-income countries are potentially preventable. The disparity associated with disadvantaged populations requires urgent attention through improvement of living standards for women, and provision of culturally appropriate accessible antenatal care. A greater awareness of risk factors for stillbirth is needed at the community, health-care provider, and policy levels.

The absence of quality data on stillbirths is a major impediment to stillbirth prevention. The proportion of unexplained stillbirths associated without adequate investigation remains high in many high-income countries. Improvements in investigation and reporting practices, including consensus of definition and classification systems, is urgently needed. Implementation of perinatal mortality audit at a national level could result in important reductions in stillbirth in high-income countries through improvement of quality of data and standards of maternity care.

However, a substantial proportion of stillbirths lack an obvious maternal risk factor and are thought most likely to portray an incompletely understood abnormality of placental function, which might or might not be associated with impaired growth. Future research should focus on screening and interventions to reduce antepartum stillbirth and stillbirth associated with extremely preterm birth and infection. Identification of ways to reduce maternal overweight and obesity is also a priority for high-income countries. Effective research collaborations are needed to carry out often large-scale research needed to address stillbirth in high-income countries.

Parents have the greatest stake of all in the wellbeing of their baby, and must be part of the drive to reduce stillbirth. Parents and health professionals working collaboratively (in such models as the International Stillbirth Alliance\(^{157}\)) have a powerful part to play in bringing stillbirth to public attention and pushing for the prioritisation of stillbirth in research and maternity services.

**Contributors**

VF compiled the report with contributions from all authors. All authors read and approved the final report.

**The Lancet’s Stillbirths Series steering committee**


**Declarations**

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention. This report also includes data made available by the Australian Institute of Health and Welfare (Canberra, ACT). The authors are responsible for the use made of the data in this report.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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References