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Novel strategies to prevent stillbirth

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A B S T R A C T

This article reviews three new and emerging risk factors for stillbirth that may be modifiable or might identify a compromised fetus. We focus on fetal movements, maternal sleep, and maternal diet. Recent studies have suggested than a sudden increase in vigorous fetal activity may be associated with increased risk of stillbirth. We review the papers that have reported this finding and discuss the implications as well as potential future directions for research. There is emerging literature to suggest that maternal sleep position may be a risk for stillbirth, especially if the woman settles to sleep supine. This risk is biologically plausible. How this knowledge may be utilized to assist stillbirth reduction strategies is discussed. Finally, we examine the somewhat limited literature regarding maternal diet and pregnancy outcome. Introducing probiotics into the diet may prove useful, but further work is required. The possible next steps for research are considered, as well as some potential intervention strategies that may ultimately lead to stillbirth reduction.

1. Introduction

There are a wide range of established risk factors for stillbirth; however, most of these risk factors have modest effect sizes and may not be modifiable once the woman is pregnant. Additionally, the findings from the large Stillbirth Collaborative Network Study [1], a case–control study, found that established risk factors such as ethnicity, gestational diabetes, smoking, drug addiction, overweight/obesity, accounted for little of the variance between cases and controls (19%). Thus to achieve a major stillbirth reduction in high-income countries it is necessary to ‘think outside the box’ and explore novel risk factors. If these novel risk factors are found to be associated with stillbirth, primary prevention strategies might be developed.

In this review we focus on three more recently explored risk factors for stillbirth that may be modifiable or might identify a compromised fetus: increased fetal movements, maternal sleep, and maternal diet. We also consider possible next steps for research as well as some potential intervention strategies that may ultimately lead to stillbirth reduction.

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2. Increased fetal movements

Maternal perception of reduced fetal movements has long been associated with increased risk of small for gestational age infants, fetal growth restriction (FGR), and stillbirth [2–4]. However, there is emerging evidence to suggest that an increase in fetal movement (particularly if this is sudden) is also associated with stillbirth, with four recent studies reporting this.

The first to report this was a case–control study from New Zealand. Stacey et al. recruited 155 women who experienced a late stillbirth and 310 controls, who were interviewed in pregnancy and subsequently delivered a normal healthy baby. They demonstrated that maternal perception of increased strength and frequency of fetal movements, as well as frequent vigorous fetal activity, were associated with a reduced risk of late stillbirth. However, they also found that a single episode of vigorous fetal activity was associated with an almost sevenfold increase in late stillbirth risk [adjusted odds ratio (aOR): 6.81; 95% confidence interval (CI): 3.01–15.41] [5]. In 2015, a Swedish group presented an analysis of an online survey and found that 10% of a population of 215 women reported a sudden increase in fetal movements in the 48 h before the stillbirth [6]. Then a large international cohort study of 1714 stillbirth mothers reported that 16.4% of women reported “a little more” or “significantly more” fetal movement during a pregnancy that ended in stillbirth at $\geq$28 weeks [7]. Some of the comments made by mothers supported the Swedish study's findings in that the increase was sudden and occurred in the 48 h before the stillbirth, e.g. "overall movement was the same except for the last 24 h with a big spike in movement during the day and then nothing by evening" [7]. A recent case–control study from the same group also found that 16% of cases reported an increase in fetal movement over the last two weeks of the pregnancy. Additionally they reported that a sudden single episode of vigorous fetal activity described as "crazy" was associated with a very similar increase in late stillbirth risk also described by Stacey et al. (aOR: 4.59; 95% CI: 2.36–8.89) [8]. Of note, the controls tended to describe vigorous activity occurring on more than one occasion and did not use words like crazy but instead described this movement as "strong" or "powerful". Furthermore, multiple episodes of vigorous movement was associated with less risk in both case-control studies (aOR: 0.58; 95% CI: 0.33–1.03; and aOR: 0.44: 95% CI: 0.26–0.76, respectively; both $P < 0001$) [5,8].

3. Intervention

Studies reporting the potential association between a single episode of vigorous fetal movement and stillbirth are recent; however, as this has been found in four separate studies we would argue that care providers should consider their response when women report an episode of vigorous fetal movements described using words like "crazy". International clinical practice guidelines with respect to management of pregnant women perceiving absent or reduced fetal movements recommend that these women should contact their maternity services for further assessment of fetal wellbeing [9–11]. It would seem logical to assume that the same advice should be given to women presenting with a sudden increase in fetal movement. It should be noted that presently the utility of these symptoms to identify women at significantly increased risk of stillbirth is limited by a lack of understanding regarding how women describe them, and the large variation in what is currently considered to be "normal" fetal activity. Nevertheless, with about 10–15% of women reporting this kind of change it is probably important to change current nomenclature from guidelines written for reduced or decreased fetal movements only, to include women perceiving any kind of alteration from their baby's normal pattern of movements. Furthermore, studies are required to better understand maternal perception of increased fetal movements and also how and why better understanding of this fetal behavior might be to identify fetuses at highest risk of antepartum stillbirth.

4. Where to from here?

It is feasible that women could be educated about extremes of fetal activity, rather than RFM, alone and that an episode of sudden increased fetal movement could be managed in the same way as a decrease; however, as shown in a recent systematic review, there are currently no proven strategies for the investigation and management of women presenting with decreased fetal movement [12]. Nevertheless, earlier studies have demonstrated a reduction in stillbirth numbers associated with maternal awareness and care provider education. For example, the rate of stillbirth fell by 30% after the introduction of such a package in Norway [13]. The Scottish Government Health Department set up a Stillbirth Working Group in 2011. The group has required clinicians to have a documented discussion about fetal movement in mid pregnancy, and the stillbirth rate has been steadily falling in Scotland since then [14]. On the back of this change there is currently a large multicenter stepped-wedge cluster-randomized trial in the UK, funded by the Scottish Government, that began in August 2014 and is nearing completion [15]. The study (called AFFIRM: Can Promoting Awareness of Fetal movements and Focussing Interventions Reduce Fetal Mortality?), aims to test the hypothesis that rates of stillbirth may be reduced by introduction of an education intervention consisting of strategies for increasing pregnant women's awareness of the need for prompt reporting of decreased fetal movements, alongside a management plan for care providers to appropriately identify cases of placental insufficiency with timely delivery in confirmed cases. The study also plans to evaluate whether it does any harm (e.g. by increasing maternal anxiety, rates of caesarean section or induction of labour), and, if proven effective, how it may be implemented to best effect in different settings across the globe. It is a prominent care provider concern that education and raising awareness about changes in fetal movements might provoke maternal anxiety, and yet it is important to note that several studies have found that such interventions typically reduce anxiety levels [13,16].

Another study currently underway in Australia and New Zealand is the "My Baby's Movements phone app trial" [17]. This project is also using a step-wedge randomized approach to examine the effectiveness that an educational phone application reminder about fetal movements might have on stillbirth, recruiting in 27 maternity hospitals in Australia and New Zealand. Similar to the AFFIRM study [15], this group is also interested in any "harms" which may result from such education and awareness such as maternal anxiety and increased cost associated with investigation of women presenting with RFM.

Whatever the outcome of these two large studies, it seems pertinent to add to existing guidelines what clinicians should do in the event that women report a sudden single episode of vigorous fetal movement, with the guidance also referring to such a change rather than simply reduction.

5. Maternal sleep

Maternal sleep is a novel and relatively unexplored factor in stillbirth research. It is only in the past decade that intense interest in maternal sleep and pregnancy outcomes has occurred. This is somewhat surprising since sleep is an essential component of health; it consumes approximately one-third of human existence, yet poor sleep can severely impair the other two-thirds. In 2011, a meta-analysis of stillbirth risks [18] reported a number of important and potentially modifiable risk factors for stillbirth: maternal obesity, age, smoking, primiparity, hypertension, diabetes, small for gestational age fetuses, and placental abruption. Recent estimates suggest that about 10% of stillbirths are attributable to the global epidemics of obesity, hypertension, and diabetes [19]. Importantly, sleep has been demonstrated to play a role in many of these risk factors.

Sleep is an important modulator of neuroendocrine function and glucose metabolism; there is a clear association between sleep loss and development of obesity [20]. Both insufficient sleep and sleep-disordered breathing (SDB) are important contributors to conditions such as hypertension [21–23] and diabetes [24] in the non-pregnant state. Addressing such underlying sleep problems prior to pregnancy is one strategy that could help women begin their pregnancies in better health, particularly since obesity, pre-existing hypertension, and diabetes are three of the largest contributors to stillbirths [19].

5.1. Maternal sleep-disordered breathing

Sleep-disordered breathing (SDB) is a spectrum of nocturnal respiratory abnormalities that range from habitual snoring to obstructive sleep apnea. It is widespread yet often undiagnosed, especially in women, as about 90% with SDB are not aware of its

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presence [25]. Increased weight promotes SDB and, importantly, an increase in weight by only 10% is associated with a sixfold increase in the development of significant SDB [26]. In addition to the link between SDB and pre-existing hypertension and diabetes, there is now increasing evidence that maternal SDB is independently associated with gestational hypertension/pre-eclampsia [27–31], eclampsia [31], and gestational diabetes [31–33]. Notably, half of pregnant women with hypertension have unrecognized obstructive sleep apnea [34]. Furthermore, in pre-eclampsia, sleep is associated with adverse hemodynamic changes that can be minimized by positive airway pressure therapy [35]. This raises the possibility that at least a proportion of the >200,000 stillbirths that are attributable to pre-eclampsia and eclampsia [19] could potentially be avoided with better identification and management of underlying disorders such as SDB that are amenable to treatment.

Fetal growth restriction increases the risk for stillbirth. A fetal size <10th centile has been shown in meta-analyses to be associated with a fourfold increased risk of stillbirth, with a population attributable risk of 23% [18]. Whereas there are several causes for FGR, particularly related to placental problems, maternal SDB likely plays a role. Multiple studies using subjective and objective methods of SDB assessment have reported an association with FGR [30,36–38] although this finding is not universal [27,39]. However, rather than a single measure of fetal size at birth, a link with decrease in fetal growth velocity between the third trimester and birth has been reported [40]. Recent data have demonstrated a slowing in serial fetal growth measures across the last trimester in fetuses of women with untreated obstructive sleep apnea, regardless of whether the birth weight was <10th centile, a trajectory not observed in women who received positive airway pressure treatment [41]. It is physiologically plausible that maternal SDB promotes FGR via mechanisms which are established to lead to placental dysfunction including hypoxemia, hypercapnia, and activation of inflammatory pathways, all of which may contribute to poor placental oxygen and nutrient exchange [42]. The accumulation of supporting evidence of a role for SDB in FGR further emphasizes that identification and treatment of maternal SDB may be a novel intervention to improve fetal wellbeing.

Whereas the above studies suggest that maternal SDB plays a role in key risk factors known to be associated with stillbirth, most studies are not large enough to examine the direct link between SDB and stillbirth. Owusu et al. [43] found no association between maternal SDB and stillbirth in Ghana, although this study was very small and underpowered for stillbirth. Large epidemiological studies have also failed to find an independent association between SDB and stillbirth [31] or perinatal death [44]. None of these studies, however, were designed to specifically investigate these relationships. Two case–control studies of stillbirth have collected data on maternal sleep [45,46]. Neither study found a link between SDB symptoms and stillbirth.

5.2. Maternal sleep position

It is well known that maternal posture, especially the supine position, in late pregnancy can have a profound impact on maternal cardiovascular parameters [47,48]. Marked physiological alterations occur during pregnancy including a 30–50% increase in cardiac output [49–51]. From a physiological standpoint, in the supine position there is compression by the gravid uterus of the abdominal blood vessels, with the consequent reduction of venous filling load and cardiac output [52] impaired uterine perfusion, and subsequent impairment of gas exchange with the fetus resulting in fetal heart rate decelerations. Notably, a shift from the supine position to the left lateral position has been documented to improve cardiac hemodynamics by a significant increase in venous return, stroke volume, and cardiac output [53]. The change in maternal position from supine to lateral likely relieves compression on the vena cava from the gravid uterus and the increasing venous return leads to an increase in stroke volume and thus cardiac output [53]. The increase in cardiac output may be as much as 28–35% when moving from supine to left lateral in the third trimester [53,54]. These observations underpin the recommendations that a left-lateral position be adopted when fetal heart rate abnormalities are identified in labour [55].

Despite knowledge of such hemodynamic alterations in the supine position in pregnant women who are awake, little consideration has been offered to the supine position during sleep. Since one-third of the human lifespan is spent asleep, the fetus is exposed to repetitive and possibly prolonged episodes of maternal supine sleep. A seminal publication from the Auckland Stillbirth Study suggested that maternal supine sleep plays a role in late stillbirth (stillbirth at 28 weeks' of gestation or beyond) [45]. In this case–control study, women who experienced a stillbirth reported having settled to sleep in the supine position more than twice as often on the presumed night before their baby's death (aOR: 2.54; 95% CI: 1.04–6.18), compared with controls [45]. In addition, an increased odds of stillbirth was found with infrequent getting up to toilet, long sleep duration, and daytime napping, all of which could also support prolonged vena caval compression.

There are limitations to this study, such as the inability to confirm the reported sleep position and the potential of recall bias in the approximately three weeks between a stillbirth and completion of the structured interview. However, the authors pointed out that women would often frame their recall of position settled in at night by reference to things such as their preference for facing “away from the door” or sleeping facing their spouse, meaning it was likely that they recalled their sleep position correctly. Furthermore, women who have experienced such a devastating loss will often report that events around the time of the stillbirth will be forever seared into memory. For example, findings from investigations of risk factors for sudden infant death syndrome (SIDS) demonstrate that women are able to remember many details of the events leading up to and around the time of their baby's death [56,57].

Although the findings of Stacey et al. [45] have been attributed to chance, reverse causation, and/or different sources of bias [58], other studies have supported a potential role for supine sleep. Subsequent cross-sectional study in Ghana – a country with very high perinatal mortality rates [59] – found that women who reported sleeping at least some of the night supine had an eightfold odds of stillbirth compared to women who reported only side sleep (aOR: 8.0; 95% CI: 1.5–43.2) after accounting for other risk factors [43]. Supine sleep was also independently associated with low birth weight in this study, and, when low birth weight was added to the stillbirth model, the odds ratio for the statistical significance between supine sleep and stillbirth was eliminated (aOR: 4.9; 95% CI: 0.80–31.4). This finding suggests that low birth weight might mediate the effects of supine sleep on stillbirth or that the low birth weight baby is more vulnerable to the effects of supine sleep. Whereas this was a relatively small study, unlike Stacey et al. [45] where cases were stillbirths, the pregnancy outcomes in the Ghanaian study [43] were unknown to the investigators at the time of enrolment.

In a recent matched case–control study of stillbirths in Australia, Gordon et al. [46] have reported similar findings to the original data from Stacey et al. [45]. Women who delivered stillborn babies reported supine sleep position over the previous month at increased odds (aOR: 6.3; 95% CI: 1.2–34.0). Moreover, preliminary findings of a new case–control study from the New Zealand group have further confirmed their earlier results in that women who

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settled to sleep in the supine position had more than three times the odds of stillbirth (aOR 3.48; 95% CI: 1.67–7.27) [60]. This adds even more evidence to the now accumulating data that maternal supine sleep is a risk for stillbirth.

In the Australian Stillbirth Study, fetuses who were small for gestational age were over-represented in the stillbirth group [46]. This, in addition to the finding that maternal sleep practices such as SDB [36,40,41] and supine sleep [43] may be associated with fetal growth problems, suggests that growth-restricted fetuses may constitute an especially vulnerable group. Taken together, the accumulating evidence endorses the triple-risk model [61] that maternal sleep position may be an additional stressor to an already vulnerable fetus. Moreover, it is physiologically plausible since the reduction of maternal cardiac output in the supine position might impede utero-placental blood flow and increase the risk of poor fetal growth and subsequently stillbirth.

If the role of maternal sleep position is causative, approximately one-quarter to one-third of stillbirths might be prevented by simply asking women to change their sleep position [43,45]. In order to confirm or refute these emerging findings, a large case–control study has recently been completed in the UK that was designed to focus on maternal sleep position [62]. In addition to supine sleep, this study was adequately powered to identify whether right-sided sleep position is a risk factor for stillbirth and also to examine whether maternal sleep position is a particular risk factor for the already compromised fetus.

5.3. *Parallels with sudden infant death syndrome (SIDS)*

Supine sleep as a potential modifiable risk factor for late stillbirth mirrors data from studies of SIDS [63–68]. Although an increased odds of prone sleep had been noted in SIDS as early as 1970 [66], it was not until 1988 that Beal [69] summarized several case–control studies and stated that all had found prone position to be more frequent in SIDS compared to control infants. Data from a prospective cohort further supported these findings [70]. Interestingly, some of the same concerns that have been voiced recently in response to the article by Stacey et al. [45] associating maternal supine sleep and stillbirth were also voiced following the initial studies regarding infant sleep position and SIDS. For example, recall bias of maternal sleep position was a critique of Stacey's work [71,72] and was also raised as a concern in the early SIDS reports [73].

Nonetheless, it was not until data from the UK [65] and New Zealand [68] were published that infant sleep position in SIDS started to become of interest to public health policy-makers. Subsequently, following national implementation of interventional health campaigns in New Zealand, the UK, and Australia, the proportion of infants sleeping prone was markedly reduced; in New Zealand the reduction was from 43% to <5% [67]. The incidence of SIDS in these countries also fell substantially following the public health messages of “Back to Sleep” [67,74,75]. As other countries followed, a fall in the overall infant mortality rate and the post-neonatal mortality rate [76,77] meant that more attention could be given to deaths for which no sufficient explanation could be found.

As suggested by Platts et al. [62], it is possible that similar principles regarding sleep position in SIDS could apply to late stillbirth. In the 1990s randomized controlled trials were considered in the investigation of SIDS but rejected due to the large sample size needed and ethical constraints in randomizing babies to be placed in a sleeping position associated with increased risk of death [78]. Doubt remained regarding the robustness of the available data linking infant sleep position to SIDS, especially since the vast majority of prone-sleeping infants did not die. Similarly, the current literature reporting an association between maternal supine sleep and stillbirth is limited to case–control studies [45,46,60] and one small cross-sectional study [43]. Given that the majority of pregnant women spend some time sleeping in the supine position [79] it is highly likely that the majority of babies of supine-sleeping mothers do not die either. The parallels between studies of SIDS and stillbirth are striking – as is the balance between the ethical issues of withholding information that has the potential to save lives and the knowledge that implementation of something that is not proven could have adverse consequences [77,78]. Public health campaigns for SIDS, nonetheless, had support and were launched around the world with significant reductions in SIDS rates. It is quite possible that reduction in the stillbirth rate is likely to require a similar population-based public health intervention, albeit not without similar criticism.

6. Potential interventions

If supine sleep position is a potential fetal stressor, then avoidance (or minimization) of this sleep position might be one strategy to reduce stillbirth risk. It could be assumed that supine sleep is infrequent in late pregnancy due to maternal discomfort; however, the majority of women spend some time asleep on their back [79]. Importantly, of those who do have supine sleep, the median duration is about one-quarter of their sleep period. This constitutes a significant amount of time during which a fetus could be exposed to a potential stressor in a cyclical pattern as often as every night, and therefore demonstrates a clear window of opportunity for intervention. There has been a little research, however, exploring ways in which such an intervention might be achieved.

Simply advising pregnant women to settle to sleep on the left side may be one way of reducing supine sleep. Data from a video study [80] in which women were asked to settle to sleep on their left side – without any other advice or techniques to maintain non-supine sleep – resulted in less supine sleep and an average of 59% of time in bed on their left side. This suggests that simple instruction may be enough, at least partially, to change maternal behavior.

Another potentially useful strategy is positional therapy. The concept of positional therapy within respiratory medicine is long-established, effective, and safe, and avoidance of supine sleep has known benefits for reducing supine-dependent SDB in the general population [81,82]. The tennis ball technique, where a tennis ball is sewn into the back of sleep wear, is the classic example of simple positional therapy [83] although elevation of body position has also shown to be helpful in pregnant women with SDB [84]. Pregnant women frequently use body pillows to maintain comfort during the night; such pillows are typically advertized as aids for aches, pains, spinal misalignment, and indigestion and are widely available for purchase. These pillows could easily be used to help maintain a left-sided sleeping position. A small pilot study designed to capture the impact of a sleep position device on length of supine sleep time in pregnancy has shown promising results: for the 60% of participants who spent time sleeping supine without the device, the average time supine was reduced from 56 to 12 min [8].

7. Where to from here?

Whereas further case–control studies will provide additional data either in support – or otherwise – of the emerging findings regarding the role of maternal supine sleep in stillbirth, other studies are currently in progress to determine whether positional intervention can significantly reduce or eliminate the proportion of time pregnant women spend in the supine sleep position. Whereas small, objective studies are feasible and will shed light on whether positional devices are useful and capable of significantly reducing supine sleep time in committed and well-educated pregnant

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women, generalizing such findings to more disadvantaged or high-risk groups will be difficult. Future research should also determine whether there are any harms, such as loss of sleep quality or increased maternal anxiety, associated with positional therapy. Furthermore, adherence to any intervention during pregnancy will always remain challenging.

Rather than focus on objective measures of sleep position, one approach to reduce supine sleep time may be achieved by education of healthcare providers and women themselves. Lessons could be learned from the above-mentioned studies focused on RFM in Norway [13] and Scotland [14] that have both shown promising reduction in stillbirth rates following introduction of maternal education and a specific pathway of care for responding to women who present with RFM. Given the potential to significantly reduce the stillbirth rate, there appears to be little reason why advocating settling to sleep on the left side should not also be strongly recommended as part of a care pathway for pregnant women.

8. Diet

Examination of the role of diet as it relates to stillbirth is complex, as macronutrients, micronutrients, dietary patterns, vitamins, trace elements, and essential fatty acids all need to be considered.

A Cochrane review of “Antenatal dietary education and supplementation to increase energy and protein intake” found clear evidence that the risk of stillbirth was significantly reduced for women given a balanced energy and protein supplementation [relative risk (RR): 0.60; 95% CI: 0.39–0.94; five trials, 3408 women] [85]. They also reported that nutritional education did not affect stillbirth rates (RR: 0.37; 95% CI: 0.07–1.90; one trial, 431 women). Furthermore the studies examining high-protein supplementation and isocaloric protein supplementation did not report data on stillbirth risk. It should be noted that these trials were conducted in low- and middle-income countries, except one in low-income black women in Harlem, New York City [86].

It is well established that folic acid supplementation taken before conception reduces the risk of neural tube defects. During pregnancy there is an increased demand for folate. A Cochrane review examined folic acid supplementation during pregnancy for maternal health and pregnancy outcomes [87]. They found no conclusive evidence of benefit of folic acid supplementation during pregnancy on pregnancy outcomes, including stillbirths/neonatal deaths (RR: 1.33; 95% CI: 0.96–1.85; three trials, 3110 women). Two relevant studies have been reported from the Nurses' Health Study II (11,072 women and 15,950 pregnancies) in which pre-pregnancy dietary patterns were not associated with stillbirth [88] and pre-pregnancy folate intake was also not associated with stillbirth [89].

A meta-analysis of 12 randomized controlled trials (RCTs) comparing recommended dietary allowance of multiple micronutrients with iron and folic acid alone did not decrease the risk of stillbirth (OR: 1.01; 95% CI: 0.88–1.16) [90]. Another meta-analysis of multiple micronutrient supplementation during pregnancy came to the same conclusion (RR: 0.98; 95% CI: 0.88–1.10; 13 trials) [91]. Another large RCT in Bangladesh, reported after these meta-analyses were done, also came to the same conclusion [92]. A large study of almost 60,000 pregnancies in Bangladesh, supplemented with vitamin A or beta-carotene, did not reduce stillbirths compared with placebo [93].

The majority of RCTs have been conducted in low- and middle-income countries where dietary deficiencies are widespread, and these have been negative. It seems unlikely that dietary supplements (e.g. high-protein, multiple micronutrients, vitamins) would be beneficial in high-income countries where deficiencies are relatively infrequent.

There may also be some lessons from animal husbandry. Zinc supplementation treatment decreases stillbirth in pigs [94], but omega-3 fatty acids have been shown not to affect stillbirth rates in pigs [94] or rabbits [95].

Probiotics are live micro-organisms, which, when given in sufficient amounts, confer a health benefit. There have been no clinical trials of probiotics powered to assess possible impact on stillbirth risk in human clinical trials. In Japan, a fertilizer has been developed from a byproduct of fermented marine animal resources, which contains thermophilic bacteria. The compost is distributed over the soil or sprayed on to leaves. As the thermophilic bacteria might affect the health of the animals that feed on them, a study was undertaken of the effects of oral administration of an extract of this compost to pigs [96]. The stillbirth rate was markedly lower in those fed the extract compared with controls. This intriguing study raises many questions including: whether this reduction would also be seen in humans, whether this effect is specific to these thermophilic bacteria, or if other probiotics might produce the same effect? Even if such effect could be demonstrated, marketing a compost extract for pregnant women would be challenging!

9. Intervention

Even if a dietary intervention could be found, it is probably too late to do much about altering the diet once the woman is pregnant. Therefore education would need to start before the woman became pregnant. As overweight/obesity is an established risk factor for stillbirth, advice to reduce weight before getting pregnant may be important.

10. Conclusions

The recent stillbirth priority-setting partnership mentioned in the Introduction identified eleven relevant research priorities. This review considers evidence and intervention strategies for three of these, namely:

1. Do modifiable ‘lifestyle’ factors (e.g. diet, vitamin deficiency, sleep position, SDB) cause or contribute to stillbirth risk?
2. Which antenatal care interventions are associated with a reduction in the number of stillbirths?
3. Would more accessible evidence-based information on signs and symptoms of stillbirth risk, designed to empower women to raise concerns with healthcare professionals, reduce the incidence of stillbirth? [1]

Of these, maternal sleep position has the strongest evidence for an association with late stillbirth and has a plausible biological mechanism. In our opinion public health messages promoting avoidance of supine sleep position should be implemented and the effects on stillbirth evaluated. A single episode of sudden increase in fetal movements is an intriguing new finding; whereas this needs further exploration, maternity care providers should be alert not to discount these kinds of reports from pregnant women, especially if they express concern that this behavior is out of the ordinary for their baby. Diet is unlikely to be a contributing factor, at least not in high-income countries. However, the potential role of probiotics and risk of stillbirth needs to be further explored.

Practice points

- Care providers should consider evaluating fetal wellbeing if the mother reports a single episode of vigorous fetal movement described using words like “crazy.”
- Clinical practice guidelines should be updated to include confirmation of fetal wellbeing after maternal perception of

sudden increased fetal movement, as for reduced fetal movement.
- Maternity care providers should consider asking women to avoid the supine sleep position, especially when settling to sleep in late pregnancy.
- Public awareness of the importance of eating a healthy diet and maintaining an ideal body weight is important for women planning a pregnancy.

Research directions

- Prospective studies are required to better understand maternal perception of a sudden increase in vigorous fetal movements and also how and why better understanding of this fetal behavior might be to identify fetuses at highest risk of antepartum stillbirth.
- Prospective studies are required to explore the effectiveness of a "settle to sleep on the side" message in late pregnancy in reducing stillbirth rates, as well as effective ways to enable pregnant women to avoid spending time sleeping supine in late pregnancy.
- Research is needed to examine whether the benefit of probiotics for stillbirth reduction seen in animal studies is transferable to human populations.
- Combining findings from case–control studies could increase the power to detect interactions between different factors and detect further associations with stillbirth.

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