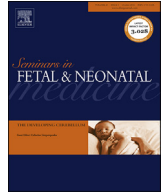




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## Novel strategies to prevent stillbirth

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## A B S T R A C T

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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 that 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.

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## 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.

## 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

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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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