The Journal of Maternal-Fetal and Neonatal Medicine, October 2010; 23(10): 1073–1084

informa
healthcare

REVIEW

Management of subsequent pregnancy after antepartum stillbirth. A review

FRANCESCA MONARI[1] & FABIO FACCHINETTI[2]

[1]*Department of Mother-Infant, University of Modena and Reggio Emilia, Modena Italy, and* [2]*Unit of Obstetrics, Azienda Ospedaliero Universitaria, Modena, Italy*

(Received 17 July 2009; accepted 14 January 2010)

Abstract

In literature, there is a paucity of information about the management of the subsequent pregnancy after stillbirth (SB). we undertook a systematic review of the literature focusing on the evidence for antenatal interventions with the potential to prevent SB and we try to summarise the management of the pregnancy subsequent to a SB. The diverse interventions and their efficacy will be reported according to the possible causes and/or conditions associated to the previous SB. Few of the studies reported SB as an outcome and the evidence was frequently conflicting. Several interventions showed clear evidence of impact on SB, including the scrupulous control of blood sugar by using multiple doses of insulin, frequent antenatal foetal monitoring and timing of delivery in diabetic women; the prophylaxis with low dose of aspirin in high-risk women; or serial sonograms for foetal growth, Doppler studies and antepartum foetal testing in women with previous growth restricted foetus. Other interventions instead reduced know risk factors for SB but failed to show statistically significant impact on SB rate. Overall, early access to care, at least three ultrasounds examinations, screening for the main pregnancy-related disorders and timely delivery are the milestone of appropriate antenatal care in women with previous SB.

Keywords: *Stillbirth, management, antenatal care*

Introduction

Although stillbirth (SB) is one of the most common adverse events in pregnancy, in Western countries, there is a paucity of information on the management and the outcome of the next pregnancy.

Couples often experience feelings of anxiety, failure in self-esteem and apprehension when contemplating pregnancy after a stillborn infant and a question commonly asked by mothers is 'What are the chances this could happen again?'. According to different studies, the recurrence risk for SB is two to 10-fold increased in the next pregnancy [1]. The prognosis varies according to the aetiology of the SB, the gestational age at foetal death, the presence of foetal growth restriction (FGR) and the maternal race. Sharma et al. [2] studying the Missouri maternal cohort data showed that the risk of SB was almost fivefold higher in woman with a prior SB. However, white women had a lower absolute risk for SB recurrence than African Americans.

Instead, when the SB remains unexplained, providing a woman with prognostic information for the next pregnancy is more difficult. Prognostic data are limited and the largest study of pregnancy outcome after an unexplained SB found that the risk of recurrence was no higher than that of the general population [3]. Other more recent studies confirmed that a woman who has had an unexplained SB at term has no greater risk of recurrence than controls. [4,5].

Instead, the recent ACOG practice bulletin on the management of SB concluded that, in low-risk women with unexplained SB, the risk of recurrence is estimated at 7.8–10.5/1.000 with most of this risk occurring before 37 weeks of gestation. The risk of recurrent SB after 37 weeks is very low at 1.8/1.000. In comparison, women with a history of a live birth complicated by preterm FGR have a SB rate of 21.8/1.000 in a subsequent pregnancy (Level A of recommendation) [6].

Moreover a history of SB was associated with significantly higher frequencies of complications in

Correspondence: Prof. Fabio Facchinetti, Unit of Obstetrics, Azienda Ospedaliero Universitaria, Via del Pozzo 71, 41100 Modena, Italy.
E-mail: facchi@unimore.it

ISSN 1476-7058 print/ISSN 1476-4954 online
DOI: 10.3109/14767051003678036

the next pregnancy such as placental abruption, preterm delivery, low birth weight infants, and preeclampsia (PE) [7,8]. There was an increased rate of caesarean section and inductions of labour demonstrating increased anxiety both in patients and providers. In this review we try to summarise the management of the pregnancy subsequent to a SB. The diverse interventions and their efficacy will be reported according to the possible causes and/or conditions associated to the previous SB.

Management according to defined causes and/or circumstances of prior stillbirth

Diabetes

One key method to prevent SB in diabetic women is to scrupulously control blood sugar readings and achieve euglycaemia. Many high-risk centres use a multidisciplinary approach including perinatologists, dieticians and high-risk perinatal nursing staff to aggressively monitor glycaemic control. Increased monitoring is associated with fewer SB, less risk for macrosomia, and less risk for injury to the neonate at the time of delivery. One hallmark of aggressive blood sugar control is the timely and intensive use of insulin, namely in pregestational diabetic women. Multiple doses of insulin (more than twice a day) has been shown to provide better control of blood sugars with decreased hyperglycaemic and hypoglycaemic episodes. Reducing extremes in blood sugar readings may be an important tool to reduce the risk of SB [9].

Another aspect that may contribute to reducing the risk for SB is antenatal foetal monitoring. A mainstay of antenatal foetal surveillance is nonstress testing (NST), with or without determinations of amniotic fluid volume and biophysical profile. Most centres currently use it weekly or twice/week since 28th week [9,10].

Moreover could be counselled regarding the use of foetal movement (foetal kick counts).There is a paucity of data to show that these measures conclusively reduce the risk of SB in diabetic women. However this simple non-invasive technique seems reasonable, inexpensive, and may show other benefits such as improved maternal bonding [9,10], although increasing anxiety.

Brecher et al. [11] reported a retrospective case–control study in which 1935 women who had all types of diabetes experienced weekly or twice/week NSTs or biophysical profiles. They found that women who experienced SBs were more likely to have suboptimal glucose control and a greater time interval from their last foetal surveillance testing [11].

Doppler velocimetry of the foetal or maternal vessels is a recent addition to the tools to monitor foetal condition. As placental resistance increases, foetal umbilical blood flow becomes increasingly retrograde, such that reversed end diastolic blood flow is a strong predictor of subsequent foetal death. Bracero et al. [12] reported that the umbilical artery Doppler velocimetry better identified diabetic pregnancies that ended adversely respect with NST and/or biophysical profile. In a follow-up study [13] these same investigators found that umbilical Doppler velocimetry paired with haemoglobin A1C was much more predictive of adverse pregnancy outcome.

The timing of delivery of the diabetic woman is key to improve outcomes. Given the critical nature of this decision, many centres developed algorithms to aid in the decision-making process. Common indications to delivery include an apparent inability to adhere to treatment regimens, hyperglycaemia despite intensive efforts to gain control, abnormal foetal testing (NST, biophysical profiles, Doppler velocimetry), FGR ($<10\%$ in women who have diabetes) [14]. In insulin-treated diabetic women, apart from reducing the risk of SB, delivery at 38 weeks may impart other benefits, such as reduction in infant size and a lower incidence of shoulder dystocia. However, in women with mild diet-treated gestational diabetes, there was little evidence to support elective labour induction [15].

Intrapartum monitoring is routinely employed in the hopes to ensuring the best possible outcome with the lowest risk for cerebral palsy although, unfortunately, intrapartum foetal monitoring has not realised this goal [15]. However, most authorities agree that intrapartum foetal monitoring can decrease the risk for SB, in particular, it should be employed in women who have diabetes, along with scrupulous control of maternal blood sugars during the course of labour [13].

Hypertensive disorders

During pregnancy the spiral arteries undergo a series of vascular transformations to ensure a more than 10-fold increase in the blood supply to the intervillous space. The spiral arteries are converted from small-diameter, high resistance vessels into larger-diameter vessels with low resistance and high compliance. Doppler ultrasonography provides a non-invasive method for the study of the uteroplacental circulation. In normal pregnancy, impedance to flow in the uterine arteries decreased with gestation, and histopathologic studies suggest that this is due to trophoblastic invasion of the spiral arteries and their conversion into low-resistance vessels. PE and FGR share similar pathophysiologic abnormalities, such as reduced uteroplacental blood flow, endotelial cell disfunction, and a state of imbalance between pro-angiogenic and anti-angiogenic factors. These pathophysiologic abnormalities are

presumed to be the result of a cascade of events secondary to failure of trophoblastic invasion and defective remodelling of the uterine spiral arteries. Because FGR related to placental insufficiency and PE share abnormal placentation as a common pathway, the diagnosis of suspected FGR may represent the initial manifestation of PE [16].

Papageorghiou et al. [17], found that abnormal uterine artery Doppler studies at 22–24 weeks was associated with increased rates of development of PE, FGR and perinatal death. Allen et al. [18] explored the frequency of hypertensive disorders in pregnancy and the associated increase in small for gestational age and SB in a population of 135,466 pregnancies. Adjusted analyses showed a crude relationship between SB and hypertension in pregnancy (RR 1.4, 95%CI = 1.1,1.8), chronic hypertension (RR 2.4, 95% CI = 1.2,5.1) and chronic hypertension with superimposed PE (RR 4.4, 95%CI = 2.2,8.8) [18].

Such associations are extremely interesting although they cannot be interpreted as truly causes of death as in the case of Wigglesworth and Aberdeen classification, rather, hypertensive disorders has to be considered a risk factor [19]. Women with a history of previous PE are at increased risk of PE recurrence as well as for other adverse pregnancy outcomes, such as placental abruption or SB. The recurrence of PE is additionally increased in women with thrombophilia therefore linking the different risk factors [20]. The magnitude of this risk is dependent on gestational age at time of disease onset, severity of disease, and presence or absence of pre-existing medical disorders. It remains to be demonstrated if recurrence of PE is associated with recurrence of SB. However, the objective in the management of these patients is twice: to reduce risk factors by optimising maternal health before conception and to detect obstetric complications as early as possible. A rational approach includes: preconception evaluation and counselling, early antenatal care, first-trimester ultrasound examination for accurate dating and establishing foetal number, frequent monitoring of maternal-foetal well-being, home blood pressure monitoring and timely delivery. For patients with a prior pregnancy complicated by PE with FGR, we recommend serial ultrasound evaluation of foetal growth and amniotic fluid volume. The development of severe gestational hypertension, FGR, or recurrent PE therefore requires maternal hospitalisation [16]

Several approaches have been explored to prevent PE recurrence. Unfortunately, supplementation with fish oil or other prostaglandin precursor [21], vitamin C and E therefore [22,23] have been shown to be ineffective in the prevention of recurrent PE and are not recommended at present, as well as the use of antihypertensives [23].

The Cochrane review shows a reduction in PE, and in maternal death or severe morbidity, in women who used calcium supplementation during pregnancy, (with a minimum dose of 1 g/day), namely for those with low dietary intake. However there was no overall effect on the relative risk of SB or baby death before discharge from hospital (10 trials, 15,141 women: RR 0.89, 95%CI = 0.73,1.09) [24].

A recent Cochrane analysis of antihypertensive drug therapy for mild to moderate hypertension during pregnancy reviewed 40 studies; 24 of them comparing antihypertensive drug with placebo or no antihypertensive drug. The authors reported a halving in the risk of developing severe hypertension (RR 0.52; 95%IC 0.41,0.64) with no difference in the risk of developing PE or proteinuria (RR 0.99) [25].

The impact of various pharmacological agents on perinatal outcomes and SB is unclear and further studies are needed to define optimal approaches for the prevention and treatment of hypertension in pregnant women. Despite the wealth of studies and information available on the impact of anti-hypertensive therapy on maternal outcomes, there is no evidence that these drugs reduce the risk of SB [26].

Examining the effectiveness of low-dose aspirin in preventing perinatal death and PE, the Cochrane review suggests that such antiplatelet agent, has small-moderate benefits when used for prevention of PE [27], but no effects on perinatal death in general population. Coomarasamy et al. [28] performed a meta-analysis on the effectiveness of aspirin preventing PE in women at high risk (previous history of PE, chronic hypertension, diabetes and renal disease).This review showed a significant benefit of aspirin therapy in reducing perinatal death (OR 0.79, 95% CI = 0.64,0.96) and PE (OR 0.86, 95% CI = 0.76,0.96). However there are not data on the relative contribution of SB to perinatal death. Aspirin was also associated with a reduction in rates of spontaneous preterm birth (OR 0.86, 95% CI = 0.79,0.94), and an increase of 215 g in mean birth weight (weighted mean difference 215, 95% CI = 90, 341).Thus meta-analysis concluded that, given the importance of its outcomes and the safety and low cost of aspirin, such prophylaxis should be considered in women at high risk because of history. The intake of 75–100 mg of aspirin daily should be started before 20th week of gestation, probably at 12th week, when the trophoblastic invasion was not yet completed [28]. The impact of anti-platelet agents on risk of SB is less convincing, although the analysis shows a slight trend in the direction of benefit [26].

Despite an increasingly common belief, there are very few data supporting thrombo-prophylaxis with heparin for the prevention of recurrent adverse

perinatal outcome. Just recently, a small randomised controlled trial performed in women at risk because of previous perinatal complications, reported that heparin treatment was found to reduce recurrence of adverse obstetric outcome, including SB [29].

In women where SB was previously associated with an hypertensive disorder the evidence of a worsening of maternal/foetal antenatal conditions (blood-flow resistances in umbilical artery, non reassuring NST, onset of significant proteinuria, etc.) beyond 34 weeks of gestation should be considered an indication for delivery given the increased risk of foetal death, maternal morbidity and abruptio placentae. In all other women with mild pregnancy hypertension some authors would consider delivery at 39 weeks of gestation in the absence of other maternal or foetal complications [16].

Antiphospholipid syndrome

Patients with circulating antiphospholipid antibodies (aPL), notably lupus anticoagulant (LAC) or anticardiolipin antibodies, and trombosis, a pregnancy loss or both, are diagnosed as suffering of antiphospholipid antibodies syndrome (APS). APS diagnosis requires at least one laboratory and one clinical criteria [30].

A plausible explanation for foetal losses in APS is thrombosis of the uteroplacental vasculature and placental infarction. That aPL are prothrombotic is supported by research indicating that these antibodies among others can bind and activate platelets and endothelial cells, inhibit fibrinolysis and may interfere with the protein C pathway [31].

Because aPL are a risk factor for pregnancy loss, dysmaturity and PE and since 'tender-loving care' improves pregnancy outcome in women with unexplained recurrent miscarriage, intense maternofoetal monitoring should always form the basis for management of pregnancy in APS women. This includes frequent antenatal controls, continuity of the care providers, frequent obstetric ultrasound scans, monthly Doppler velocimetry of the umbilical arteries from 16 weeks of gestation, and weekly NST starting at 24 weeks [32].

Current recommendation are that women with APS and without history of thrombosis should receive low-dose of aspirin (0.1 g/day) and prophylactic dose of low molecular weight heparin (LMWH) (5000 UI twice/day) during the pregnancy. This management strategy is documented by small well-controlled prospective studies and is now recommended by the American College of Chest Physicians ACCP (grade 1A recommendation). The treatment is stepwise: starts with aspirin before conception or at positive pregnancy test and adds heparin either with a positive pregnancy test or when foetal heart activity was demonstrated. The treatment should continue untill 6 weeks after the delivery [31]. Frank and Witter [33] recommend LMWH 5000 UI twice/day and 81 mg of low dose of aspirin per day. Postpartum, many haematologists recommend continuous 81 mg of aspirin per day indefinitely and continuous heparin for 6 weeks postpartum [33].

In patients with a history of thrombosis, full anticoagulation is indicated and should be done with heparin or low-molecular-weight heparin. Subcutaneous injection of either unfractionated or low-molecular heparin may be used. In the third trimester, unfractionated heparin will need to be used at an 8-h injection intervals to maintain therapeutic levels as half-life decreases in pregnancy. The target for anticoagulation with unfractionated heparin is an activated partial thromboplastin time with international normalised ratio of 2.5 [33].

Corticosteroids give no additional benefit and should be administered only to women with APS secondary to systemic lupus erythematosus or women with APS and severe thrombocytopenia. In thrombotic APS patients on oral anticoagulants, it is advised to switch from oral anticoagulants to adjusted dose of heparin (LMWH) either before conception or with a positive early pregnancy test and to resume oral anticoagulant therapy postpartum [32].

Comparing active treatment trials with no treatment trials, Tulppala [34] showed no benefit of aspirin over placebo in 12 patients with APS and a history of recurrent foetal loss. Laskin's [35] trial of 88 patients showed active therapy appearing worse than no therapy, and Pattison's [36] trial of 40 patients comparing aspirin to placebo also showed no advantage. Cowchock's [37] study of 19 patients also showed no advantage of aspirin *vs.* usual care.

In the obstetric aPL patient, low-dose aspirin plus heparin ($\sim$10,000 U/day) is recommended but the evidentiary basis for this is not strong and is driven primarily by the results of a single trial [38] with low-dose aspirin as control. In this 90– patient unblinded study, pregnancy loss was 13/45 (29%) with heparin plus aspirin *vs.* 26/45 (48%) with aspirin alone. All but 4 of the 39 losses occurred in the first trimester (OR of pregnancy loss 0.50; 95%CI = 0.30,0.84). Considering that no treatment/supportive care is associated with good outcomes, the need for pharmacological intervention seems doubtful; moreover, no studies consider a foetal loss $>$20th week separately.

Inherited thrombophilia

Several studies, examining the association between inherited thrombophilia and adverse reproductive

outcomes, such as SB, have been performed. However, there are no clear conclusions to be drawn from these studies. Some show a positive relationship between thrombophilias and adverse outcomes, whereas others show no association.

Lockwood [39] showed that thrombophylias have been associated with a 3.6-fold increased risk of SB in a general population. The last meta-analysis of 31 studies, factor V Leiden mutation was associated with late non-recurrent foetal loss (OR 3.26, 95%CI = 1.82,5.83), prothrombin G20210A gene mutation (OR 2.30, 95%CI = 1.09,4.87) and protein S deficiency (OR 7.39, 95%CI = 1.28,42.63). However the definition of late non-recurrent foetal loss varied among studies ranging 14–22 weeks of gestational age. Methylenetetrahydrofolate mutation associated with hyperhomocysteinaemia, protein C deficiency, and antithrombin III deficiency were not associated with pregnancy loss in this meta-analysis [40].

It is important to be cautious when attributing foetal death to thrombophilia in women who test positive for such condition. Thrombophilia is a condition quite common in normal individuals, namely of caucasian etnicithy. Indeed, prospective studies failed to demonstrate an association between factor V Leiden mutation and foetal death, and Gonen et al. did not find either an association between unexplained third-trimester intrauterine foetal death and inherited thrombophilia [41,42]. Thrombophilia is more likely to contribute to a foetal death if there is objective evidence of placental insufficiency (FGR, abnormal blood flow, placental infarction or placental abruption).

Clinicians are often faced with the difficult situation of what to do with a woman with a previous adverse pregnancy outcome, such as SB, who tested positive for thrombophilia. Gris et al. [43] performed a small multicentre randomised controlled trial in 160 thrombophilic women (Factor V Leiden, prothrombin mutation or protein S deficiency) with one prior pregnancy loss at more than 10 weeks. All women received 5 mg folic acid daily preconceptionally and were randomised to low dose of aspirin (100 mg/day) or enoxaparin (40 mg/day) at 8th week. The use of enoxaparin, a LMWH, was associated with a significantly improved OR for live birth i.e. 86% in the enoxaparin group compared with 29% in low dose of aspirin group (OR 15.5, CI = 95% 7.34, $p < 0.0001$). The improvement in live birth rates with enoxaparin was similar for each thrombophilia. Lower birth weight occurred in 10% of women treated with LMWH and in 30% of women treated with low dose of aspirin. Brenner et al. [44] reported that the percentage of live births in women with inherited thrombophilia and recurrent early pregnancy loss increased from 20% without therapy to 75% following treatment with LMWH.

Bloomenthal et al. [45] wrote a summary of published documents outlinking expert opinion on possible management strategies in these women, that is treatment with LMWH (either Enoxaparin 40 mg or Deltaparin 5000 UI sc once/day or twice/day) during pregnancy followed by warfarin for 6–12 weeks in the post-partum.

Similarly the 'Consensus Report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes' made from the Pregnancy and Thrombosis Working Group said that women with a moderate risk assessment (women who had a history of adverse obstetric outcome such severe PE, IUGR $<$5th percentile or foetal loss at $\geq$20 weeks) should do an antepartum therapy with enoxaparin 4.000 UI sc once/day or delteparin 5.000 UI sc once/day to prevent a recurrence of adverse obstetric outcome [46]. Despite such expert recommendations the evidence is totally lacking. There are several ongoing international trials on the efficacy of prophylactic treatment of asymptomatic carriers with a previous adverse obstetric outcome.

Foetal growth restriction

Foetal growth restiction (defined as an extimated foetal weight $<$10th percentile) is the single largest category of conditions associated with SB (43%) and is found in the majority of the cases previously considered unexplained [47]. Improved antenatal detection of FGR is crucial to having a positive impact on SB prevention. In up to 75% of pregnancies, FGR may be missed and it is incorrectly diagnosed about 50% of the time. As a consequence, the required antenatal surveillance is not performed, and timely delivery of the foetus from an unfavourable intrauterine environment is not done increasing the risk of SB. The management of preterm FGR is major clinical challenge. Balancing the risk of a potential SB against the one of a (severe) prematurity with expected neonatal morbidity and mortality is difficult. Based on the literature, Doppler velocimetry is useful in pregnancies complicated by FGR with improved management and timing of delivery of preterm foetuses. There is a natural progression of findings in Doppler studies in FGR. Initially, there are abnormal umbilical artery flare reflecting increased resistance in placental vessels. Absence of reversal of end diastolic velocities in the umbilical artery represents further deterioration. Subsequently, there is blood flow redistribution resulting in 'brain sparing', which is reflected in abnormal middle cerebral artery flare. With further deterioration, there is cardiac failure with retrogade flow in the venous

circulation resulting in abnormal venous Doppler studies. The final steps manifests in central nervous system damage with abnormal NST or biophysical profile and then foetal death [48].

Therefore, in women who had a previous SB associated with FGR a close antenatal surveillance should be performed. It includes: serial sonograms for foetal growth and Doppler studies, (starting at 28 weeks of gestation, usually to every 2–4 weeks) in conjunction with other tests of foetal well-being (foetal kick counts, twice/week NST and amniotic fluid index or biophysical profiles) in the management and timing of delivery [49].

In a randomised controlled trial (The GRIT study) pregnant women with foetal compromise between 24 and 36 weeks with abnormal umbilical artery Doppler waveform and clinical uncertainty whether or not indicate immediate delivery were included. The interventions were 'immediate delivery' *versus* 'delay until the obstetrician is no longer uncertain'. Out of 548 women recruited, outcomes were available on 547 mothers. The median time-to-delivery intervals were 0.9 days in the immediate group and 4.9 days in the delay group. Two SB occurred in the immediate group *versus* 9 in the delay group whereas the neonatal death were 23 in the immediate group *versus* 12 in the delay group. The total deaths prior to discharge were similar in the two groups: 29 (10%) in the immediate group and 27 (9%) in the delay group (OR 1.1, 95%IC 0.61,1.8) [50].

According to the latest ACOG bulletin, the timing of delivery in the growth-restricted foetus should be individualised and it becomes mandatory when there is a non-reassuring foetal assessment or a complete cessation of foetal growth demonstrated with ultrasounds over a 2–4 week interval [49]. However, the evidences that SB recurrence could be reduced with such a management are not available.

Suboptimal care

Stillbirth rates have substantially decreased over the last decades and one reason is the improved perinatal care. Saastad et al. [51] explored a population of 356 SB (>22 weeks of gestation) in 2 Norwegian countries, 31% of them born to non-western women. Sub-optimal care was identified in 37% of deaths and non-western women had both increased risk of SB (OR 2.2; 95%CI = 1.3,3.8) and an increased risk of sub-optimal care (OR 2.4; 95%CI = 1.5,3.9). A common failure in antenatal care for both groups was undiagnosed/inadequate management of FGR or decreased foetal movements. Non-western women were less prone to attend the programme for antenatal care and/or to follow recommendations from health professionals. Moreover inadequate communication was documented in half of them. Thus, possibilities for improvements include a reduction of language barriers, timely diagnosis and management of growth restriction in addition to an adequate intervention in complicated vaginal births.

The association between socioeconomic disadvantage and SB were analysed in a case–control study leaded in Sweden. Women with social deprivation (non-specialised skilled worker), comparing with leading class women, have an increased risk of SB (OR 2.2, IC95% 1.3,3.7) [52]. Moreover, an observational survey performed in Wales showed a significant association between SB, infant mortality and a low socioeconomic status (RR 1.53, IC95% 1.35,1.74). It's interesting, points out that the social disvantage wasn't significantly associated with early neonatal and intrapartum mortality, while it was associated with SB and sudden infant death [53].

One of the most important perinatal death survey is the Confidential Enquiry into Maternal and Child Health (http//www.cemach.org.uk) [54] that is composed by a multidisciplinary group (gynaecologist, midwifes, neonatologyst, anatomopathologyst, family physicians). This group expresses an opinion on the quality of medical care provided. In Table I there is a description of specific suboptimal care occurring in cases of SB.

The most frequent conditions is the lack of FGR diagnosis and/or the inappropriate management in non-western women, caused by difficulties in verbal communication [54]. In our reality this is an important and increasing phenomenon since the latest report of delivery assistance showed that about 25% of pregnant women are migrants [55].

Management according to the presence of risky behaviours

Several unhealthy behaviours have been reported as risk factors for SB. Some of them could be modified through appropriate counselling and/or health promotion campaigns.

Obesity

Several epidemiologic studies have reported an increased risk of SB among obese women when compared with normal-weight subjects. A recent meta-analysis showed that the odds of SB were 1.47 (95% IC 1.08,1.94) and 2.07 (95% IC 1.59,2.74) among overweight and obese pregnant women, respectively [56]. This increased risk seems related to the undiagnosed diabetes mellitus or glucose intolerance or other unrecognised factors that are associated with obesity during pregnancy. Moreover, obesity increases risk of hyperlipidaemia, which reduces prostacyclin secretion and enhances

Table I. Nature of inappropriate care (modified from the 54).

Risk identification	– Failed recognition of high risk condition at the moment of care giving
Foetal growth	– Non appropriate foetal growth monitoring – Absence of diagnosis of foetal growth restiction – Defect of management of foetal growth restriction
Foetal movements	– Defect of management of foetal movement decrease – Absence of explanation about importance in foetal movements changing – Reduction of foetal movements reported by women only after delivery
Clinical management	– Defect in management of women with an high risk personal anamnesis – Defect in management of hypertension/ proteinuria – Absence of a definited health care plan – Defect in management of NSTs prenatal changing – Defect in prescription or repeat oral glucose tollerance test – Inadequate management of diabetic pregnant women – Inadequate involvement of medical staff in health care assistance plan
Communication	– Lacking in communication – Lacking both in oral and written comunication
Life style	– Smoking – Lacking in obstetric controls during the pregnancy
Post-partum	– Inadequate screening after the foetal death – Post-mortem: lack of foetal tessutal samples posting and low qualityof these samples

peroxidase production allowing to vasoconstriction and platelet aggregation. Obese pregnant women also have more apnea-hypoxia events, and more episodes of oxygen desaturation during sleep have been reported, respect with normal weight women. Such episodes could reduce blood/oxygen supply to the foetus, a factor that increases the risk of SB. It has been also proposed that thinner women may better perceive a decrease of foetal movements than heavier women do, and this fact would enable timely medical treatment. Thus, given the numerous other benefits of weight reduction, obese women should be encouraged to undertake a weight reduction programme before attempting a subsequent pregnancy after SB [56].

Smoking

Through several literature surveys it is revealed that pregnancy in smoking women has an increased risk of SB, and all the studies reported that this effect is dose-related. The majority of these studies considered as a cut-off, an use of 1–9 cigarettes/day and more than 10 cigarettes/day [57,58]. Smoke decreases foetal oxygenation through raised blood carboxyhaemoglobin, whereas nicotine reduces prostacyclin secretion which results in vasoconstriction, platelet aggregation and decreased foetal blood flow [59].

Stopping smoking in the first trimester seems to be enough to reduce the association between SB and smoke [59]. Moreover, women who stop smoking habit in the subsequent pregnancy show the same risk of SB as reported in non-smoking women (OR 1.02, IC95% 0.79,1.30). On the other hand, women who continue to smoke have an increased risk for SB (OR 1.35, IC95% 1.15,1.58) [60]. Moreover, a meta-analysis of 13 observational studies showed that smoking in pregnancy increased the risk of placental abruptio (OR 1.9, IC 95% 1.8,2.0) possibly due to an increased oxidative stress and production of free radicals [61]. Smoking is also associated with an increased risk of placenta previa (RR: 1.5 to 3) because it's related to a condition of chronic hypoxia that seems to lead to an increased placental extension and to its possible anomalous localisation [62]. Finally, the relation between smoking and FGR is dose related with a reversal of the effect when women stops such unhealthy behaviour [61]. It therefore seems evident that smoking could negatively interfere with several factors increasing the risk of SB. Although specific data are lacking, refraining from such unhealthy behaviours reasonably expected to reduces recurrence.

Coffee and alcohol

Caffeine is absorbed to the gastrointestinal tract, crosses placenta and reaches foetal tissues including nervous central system. It seems that caffeine induces an increase of catecolamines which leads to a vasoconstriction of the utero-placental bed and the subsequent foetal hypoxia. Moreover, caffeine has a direct effect on the cardiovascular system inducing foetal tachycardia and arrhythmia [63]. However, data on the association between SB and caffeine use are controversial. In a cohort prospective study Wisborg et al. [59] showed a significant increase of SB risk ($>$ 28 weeks of gestation) in women drinking more than eight cups of coffee a day (caffeine: 800 mg/day) [64]. However, no data support the fact that reduction on cups of caffeine consumption could reduce recurrence of SB.

Also for alcohol consumption literature data are controversial as far as its impact on SB. An important prospective study performed in Denmark on a population of 24.768 pregnant women reported that the use of more than five drinks/week increased the

risk of SB (OR 3.65, IC 95% 1.47,9.07). The association between alcohol and SB has been related to an increased production of prostaglandins E, with placental blood-flow reduction and hypoglycaemia. [65]. However, no data support the fact that refraining from alcohol during pregnancy could have an impact of SB recurrence.

Management in the case of totally unexplained stillbirth

The management of pregnancy after an unexplained SB causes great anxiety in women, their partners and families, and their obstetric providers, indeed. Are the subsequent pregnancies of women who have suffered an unexplained SB managed differently from those of other women? To answer this question Robson et al. [66] send a postal survey to Australian Obstetricians, addressing their management in a scenery of subsequent pregnancy after an unexplained SB at term. One quarter of respondents would initiate 'kick counting' before 34th weeks of gestation, the remainders by 36th weeks. Surveillance with NST would be initiated by one-third before 34 weeks, the remainders between 34 and 36 weeks. Regular ultrasound surveillance (for foetal growth, amniotic fluid index and Doppler umbilical flow assessment) was advocated by 87% of respondents; out of them, the half said that should be started at 25–28 weeks of gestation and the remainders said starting at 29–32 weeks. The majority of respondents indicated a frequency of two tests a week. Elective induction of labour at 38 weeks or at the same gestation age of the previous SB would be offered by the majority of care-givers. A minority would offer induction 1 week before the gestation of the previous SB. One-third would offer an elective caesarean delivery to her patient.

In women with unexplained SB, maternal assessment of foetal movement or foetal kick counts could be started at 28 weeks of gestation. In some studies women had to count foetal movements for 1 h three times/week while in other studies women who count fewer than 10 movements/10 h for two successive days were instructed to alert their care provider. A pilot study was performed to validate a protocol in which the patient was instructed to record the elapsed time required to appreciate 10 foetal movements. The mean time interval was 20.9 ± 18.1 min. Patients in whom 2 h elapsed without counting 10 foetal movements were reported to delivery unit for further evaluation. During a 7-month control period, when no formal foetal movement assessment was done (2519 deliveries), the foetal mortality rate was 8.7 per 1000 births. During a next study period (1864 deliveries) the foetal mortality was 2.1 per 1000 and the number of antepartum tests increased by 13%. Interventions for suspected foetal compromise prompted by inadequate foetal activity tripled, resulting in a drop in foetal mortality among patients with decreased movement from 44 to 10 per 1000. This study showed that the count-to-10 foetal movement screening programme is simple and effective in reducing the foetal mortality rate [67]. However, in a recent meta-analysis Froen et al. [47], shows that there is no evidence that any absolute definition of reduced foetal movements is of greater value than maternal subjective perception in the detection of intrauterine foetal death of foetal compromise. Further investigation is required to determine an effective method of identifying patients with reduced foetal movements and to determine the best subsequent management [68].

Despite the lack of conclusive evidence of effectiveness as a surveillance technique for predicting SB [69], most clinicians recommend that women with a previous SB monitor foetal assessment and those reporting decreased foetal movement would have follow-up and foetal surveillance.

Timing of delivery

While in pregnant women with previous SB associated with FGR, it indicates performing serial sonograms for foetal growth and Doppler studies every 2–4 weeks, repeating antepartum foetal testing weekly (traditional biophysical profile and NST) and resolving to delivery when there is a non-reassuring foetal assessment or a complete cessation of foetal growth assessed with ultrasounds over a 2-week interval [49], in women with previous unexplained SB, antepartum testing and timing of delivery are undetectable.

Reddy et al. [48] reported that ante-partum foetal testing, such as twice weekly NST and amniotic fluid index or biophysical profiles, may be initiated at 32 weeks or 1–2 weeks before the gestational age of the previous SB. Moreover this review indicated that timing of delivery should be discussed with the couple and depends on maternal anxiety and cervical ripeness and elective induction at 38–39 weeks or earlier and provide support and reassurance to a couple could be appropriate [48].

Smith and Fretts [70] said that, in high-risk pregnancy, as a women with previous SB, the use of umbilical artery Doppler flow velocimetry is justified because it seems to reduce overall perinatal mortality [71]. Moreover, about timing of delivery, they proposed to schedule delivery of women who are considered at high risk of SB, irrespective of the results of foetal assessment. The primary approach is a routine induction of labour beyond term because the risk of antepartum SB increases from one per 2000 women per week at 37 weeks, to one in 500 at

Table II. Summary of intervention proven or supposed to be helpful in the management of the next pregnancy, according to defined causes or circumstances of previous stillbirth.

Conditions associated to previous SB	Intervention	Outcome
Diabetes	– Scrupulous control of blood sugar readings achieving euglycaemia, reducing extremes in blood sugar values by using multiple doses of insulin (more than twice a day). – Antenatal foetal monitoring: foetal kick counts – NST with or without amniotic fluid determination or biophysical profile weekly (or twice weekly) starting at 28th week. – Doppler of umbilical artery velocimetry – There isn't an optimal timing of delivery. It's indicated to induce delivery in case of inability to adhere to treatment regimens, hyperglycaemia, abnormal foetal testing or FGR. – Induction of delivery at 38th week in insulin-treated women	– Reduce the risk of stillbirth [9] – Not enough data to show the effectiveness in reducing risk of SB [10] – Reduce the risk of SB [10] – Good predictor of worse outcome [12] – Reduce the risk of SB [14] – Reduce the risk of SB [14]
Preeclampsia	– Preconception counselling, early antenatal care and ultrasound datation, frequent monitoring of well-being, timely delivery, early diagnosis of severe hypertension or preeclampsia, home blood pressure monitoring, serial ultrasound evaluation of foetal growth and amniotic fluid volume. – Supplementation with fish oil, vitamin C or E, use of anti-hypertensive drugs – Antihypertensive drugs in mild to moderate hypertension during pregnancy. – Supplementation of calcium (1 g daily) during pregnancy – Prophylaxis with low dose of aspirin (75–100 mg/daily starting before 20th week) in high risk women	– Reduce the recurrence of Preeclampsia but not that of SB [16] – Don't reduce the recurrence of Preeclampsia or SB [21–23] – Don't reduce the risk of Preeclampsia [25–26] – Reduce the risk of preeclampsia, maternal death or severe morbidity. Don't reduce the risk of SB [24]. – Reduce the risk of perinatal death and Preeclampsia [26,27]
Antiphospholipid syndrome	– Antenatal foetal monitoring: frequent antenatal controls, continuity of the care providers, frequent obstetric ultrasound scans, monthly Doppler velocimetry of the umbilical arteries from 16 weeks of gestation on, and weekly NST starting at 24 weeks. – Treatment with low-dose of aspirin (0.1 g/day). – Treatment with low dose of aspirin (0.1 g/day) plus prophylactic dose of low molecular weight heparin *vs.* low dose of aspirin only. – Treatment with low-dose of aspirin (0.1 g or 81 mg/daily) plus prophylactic dose of low molecular weight heparin (5000 UI twice daily). Treatment should continue untill 6 weeks after the delivery.	– Improve pregnancy outcomes resulting in >80% live births in women with unexplained recurrent early miscarriage [33]. – No benefits of treatment in women with recurrent foetal loss [34–36] – Reduce the rate of first trimester pregnancy loss [39]. – Current recommendation: ACOG [34].
Inherited thrombophylia	– Preconceptional treatment with folic acid (5 mg/day) plus enoxaparin (40 mg/day, since 8th week) *versus* preconceptional treatment with folic acid (5 mg/day) plus low dose aspirin (100 mg/day). – Treatment with low molecular weight heparin in trhombophylic women with recurrent pregnancy loss. – Low molecular weight heparin (Enoxaparin 40 mg SC once or twice daily or Dalteparin 5000 U SC once or twice daily) switched to warfarin for 6–12 weeks in the puerperium. – Women with a moderate risk (history of adverse obstetric outcome such severe preeclampsia, IUGR <5th percentile or foetal loss at ≥20th week) should do an antepartum therapy with enoxaparin 4.000 UI sc once a day or delteparin 5.000 UI sc once a day.	– Significantly improves OR for live birth (OR: 15.5 CI95% 7–34) [44]. – Increases the percentage of live births [45] – Current recommendation [46] although the lack of randomised controlled trials. – Current Consensus Report and Recommendations [47] although the lack of randomized controlled trials.

(*continued*)

Table II. (*Continued*).

Conditions associated to previous SB	Intervention	Outcome
Foetal growth restriction	– Serial sonograms for foetal growth and doppler study starting at 28 weeks of gestation, usually every 2–4 weeks, and antepartum foetal testing (foetal kick counts, NST and amniotic fluid index or biophysical profiles)	– Reduces perinatal mortality and on present reduce the risk of SB [49]
Suboptimal care	– Reduction of language barriers, timely diagnosis and management of growth restriction and an increased vigilance towards migrants women.	– Supposed to reduce the risk of SB [52]
Other risk factors	– Weight reduction programme before attempting a subsequent pregnancy after SB in obese women. – Maternal assessment of foetal movement or foetal kick counts in obese women. – Smoking women should be encouraged to stop this abitude. – Encourage to reduce caffeine and alcohol intake.	– Supposed to reduce the risk of SB [57]. – Despite lack of conclusive evidence [54] of effectiveness for predicting stillbirth, most clinicians recommend it – Women who stop smoking have a same SB risk of non smoking women (OR: 1.02; IC95% 0.79–1.30) [61] – No evidence of reducing SB.
None	– Serial sonograms (every 2–4 weeks) for foetal growth and Doppler evaluation of umbilical artery waveforms performed, starting at 28th week. – NST and amniotic fluid index or biophysical profiles, starting at 32nd week or 1–2 weeks before the gestational age at previous SB	– Reduce the risk of perinatal death (level A of recommendation) [50] – Reduce the risk of SB [49]

42 weeks, and one in 200 by 43 weeks [72]. In women with a previous SB, because of the difficulty in doing adequately powered studies, there are no data from randomised trials that directly support routine delivery. However, these interventions might be justified on the basis of epidemiological evidence of an increased risk of foetal death and by the very low risk of neonatal death associated with delivery at term [70]. Thus, this review is concluded by saying that elective delivery at 37–38 weeks would be proposed because it represents an intervention that should prevent placentally related losses but which carry a low risk of neonatal death.

Conclusions

The availability of few randomised clinical trials coupled with the overall acknowledged uncertainty in defining causes of SB did not allow us to prepare a 'systematic review', as defined by the EBM. Nonetheless, we reviewed the studies, reviews and recommendations published in English language in order to collect any information useful for the management of the next pregnancy after a SB. Such limitation should be taken into account when reading this review. However, we hope that despite the lack of scientific guidelines as the outcome, our efforts would help all those clinicians who have no scientific resources to afford such a tremendous responsibility as to help a pregnant women having had a stillborn.

Anyway, we summarised the (few) evidences for the management of such pregnancies in Table II. Overall, appropriate antenatal care is the milestone to better support and protect pregnant women in order to have a successful outcome. They include early access to care, offer of at least three ultrasounds examinations, screening for the main pregnancy-related disorders and timely delivery. Moreover, caring for has a tremendous psychological impact and such 'placebo effect' is an added value of every patient-physician relationship. On the other hand, pharmacological interventions seem of little help except few defined conditions.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Samueloff A, Xenakis EM, Berkus MD, Huff RW, Langer O. Recurrent stillbirth: significance and characteristics. J Reprod Med 1993;38:883–886.
2. Sharma PP, Salihu HM, Oyelese Y, Ananth CV, Kirby RS. Is a race a determinant of stillbirth recurrence? Obstet Gynaecol 2006;107:391–397.

3. Robson S, Chan A, Keane RJ, Luke CG. Subsequent birth outcomes after an unexplained stillbirth: preliminary population-based retrospective cohort study. Aust N Z J Obstet Gynaecol 2001;4:29–35.
4. Onwude JL, Eisman V, Selo-Ojeme DO. Recurrent stillbirths: a matched case-control study of unexplained stillbirths at term. J Obstet Gynaecol 2006;26:205–207.
5. Lurie S, Eldar I, Glezerman M, Sadan O. Pregnancy outcome after stillbirth. J Reprod Med 2007;52:289–292.
6. ACOG practice bulletin. No 102. Management of Stillbirth. Obstet Gynecol 2009 Mar;113(3):748–761.
7. Black M, Shetty A, Bhattacharya S. Obstetric outcomes subsequent to intrauterine death in the first pregnancy. BJOG 2008;115:269–274.
8. Heinonen S, Kirkinen P. Pregnancy outcome after previous stillbirth resulting from causes other than maternal conditions and foetal abnormalities. Birth 2000;27:33–37.
9. Donald J. Dudley, MD. Diabetic-associated stillbirth: incidence, pathophysiology, and prevention. Clin Perinatol 2007;34:611–626.
10. Michael P. Nageotte MD. Antenatal testing: diabetes mellitus. Semin Perinatol 2008;32:269–270.
11. Brecher A, Tharakan T, Williams A, Baxi L. Perinatal mortality in diabetic patients undergoing antepartum foetal evaluation: a case–control study. J Matern Foetal Neonatal Med 2002;12:423–427.
12. Bracero LA, Figueroa R, Byrnr DW. Comparison of umbilical Doppler velocimetry, nonstress testing, and biophysical profile in pregnancies complicated by diabetes. J Ultrasound Med 1996;15:301–308.
13. Bracero LA, Haberman S, Byrne DW. Maternal glycemic control and umbilical artery doppler velocimetry. J Matern Neonatal Med 2002;12:342–348.
14. Hawkins JS, Brian MC. Labor and delivery management for women with diabetes. Obstet Gynecol Clin N Am 2007;34:323–334.
15. Alfirevic Z, Devane D, Gyte GM. Continuous cardiotography (CTG) as a form of electronic foetal monitoring for foetal assessment during labor. Cochrane Database Syst Rev 2006;3:CD006066.
16. Barton JR, Sibai BM. Prediction and prevention of recurrent preeclampsia. Obstet and Gynaecol 2008;112:359–372.
17. Papageorghiou AT, Yu CK, Cicero S, Bower S, Nicolaides KH. Second-trimester uterine artery Doppler screening in unselected population: rewiev. J Maternal Foetal Neonatal Med 2002;12:78–88.
18. Allen V, Joseph K, Murphy K, Magee L, Ohlsson A. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. BMC Pregnancy and Childbirth 2004;4:17.
19. Korteweg FJ, Gordijn SJ, Timmer A, Holm JP, Ravisé JM, Erwich JJ. A placental cause of intra-uterine foetal death depends on the perinatal mortality classification system used. Placenta 2008;29:71–80.
20. Facchinetti F, Marozio L, Frusca T, Grandone E, Venturini P, Tiscia GL, Zatti S, Benedetto C. Maternal thrombophilia and the risk of recurrence of preeclampsia. Am J Obstet Gynecol 2009 Jan;200(1):46.e1–5. Epub 2008 Oct 9.
21. Makrides M, Duley L, Olsen SF. Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by preeclampsia or intrauterine growth restriction (Review). The Cochrane library 2007, Issue 2: 2006 Jul 19;3:CD003402.
22. Rumbold A, Crowther CA. Vitamin E supplementation in pregnancy (Review). The Cochrane library 2007. Issue 2: 2005 Apr 18;(2):CD004069.
23. Rumbold A, Crowther CA. Vitamin C supplementation in pregnancy (Review). The Cochrane library 2007. Issue 2: 2005 Apr 18;(2):CD004072.
24. Hofmeyr GJ, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (Review). Cochrane library 2007. Issue 2: 2006 Jul 19;3:CD001059.
25. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev 2007;1:CD002252.
26. Menezes EV, Yakoob MY, Soomro T, Haws RA, Darmstadt GL, Bhutta ZA. Reducing Stillbirth: prevention and management of medical disorders and infections during pregnancy. BMC Pregnancy Childbirth 2009;9 (Suppl 1):S4. 1–49.
27. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications (Review). The Cochrane library 2008. Issue 4: 2007 Apr 18;(2):CD004659.
28. Coomarasamy A, Honest H, Papaioannou S, Gee H, Khan KS. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. Obstet Gynecol 2003;101:1319–1332.
29. Rey E, Garneau P, David M, Gauthier R, Leduc L, Michon N, Morin F, Demers C, Kahn SR, Magee LA, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. J Thromb Haemost 2009;7:58–64.
30. Derksen RH, De Groot PG. The obstetric antiphospholipid syndrome. J Reproductive Immunology 2008;77:41–50.
31. De Groot PG, Derksen RH. The antiphospholipid syndrome: clinical characteristics, laboratory features and pathogenesis. Curr Opin Infect Dis 2005;18:205–210.
32. Derksen RH, Khamashta M, Branch DW. Management of the obstetric antiphospholipid syndrome. Arthritis Rheum 2004;50:1028–1039.
33. Frank R, Witter MD. Management of the high risk lupus pregnant patient. Rheum Dis Clin N Am 2007;33: 253–265.
34. Tulppala M, Marttunen M, Soderstrom-Anttila V, Foudila T, Ylikorkala O. Low-dose aspirin in prevention of miscarriage in women with unexplained or autoimmune related recurrent miscarriage: effect on prostacyclin and thromboxane A2 production. Hum Reprod 1997;12:1567–1572.
35. Laskin CA, Bombardier C, Hannah ME, Mandel Fp, Ritchie JW, Farewell V, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent foetal loss. N Engl J Med 1997;337:148–153.
36. Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. Am J Obstet Gynecol 2000;183:1008–1012.
37. Cowchock S, Reece EA. Do low-risk pregnant women with antiphospholipid antibodies need to be treated? Am J Obstet Gynecol 1997;176:1099–1100.
38. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). Br Med J 1997;314 253–257.
39. Lockwood CJ. Heritable coagulopathies in pregnancy. Obstet Gynaecol Surv 1999;54:754–765.
40. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and foetal loss: a meta-analysis. Lancet 2003;361: 901–908.
41. Dizon-Townson D, Miller C, Sibai C, Spong CY, Thom E, Wendel G. The relationship of the Factor V Leiden mutation

and pregnancy autcomes for mother and foetus. Obstet Gynaecol 2005;106:517–524.
42. Gonen R, Lavi N, Attias D, Schliamser L, Borochowitz Z, Toubi E, Ohel G. Absence of association of inerithed thrombophylia with unexplained third-trimester intrauterine foetal death. Am J Obstet Gynaecol 2005;192:742–746.
43. Gris JC, Mercier E, Quere I, Lavigne-Lissalde G, Cochery-Nouvellon E, Hoffet M et al. Low-molecular-weight heparin *versus* low dose aspirin in women with one foetal loss and a constitutional thrombophylic disorder. Blood 2004;103:3695–3699.
44. Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost 2000;83:693–697.
45. Bloomenthal D, Von Dadelszen P, Liston R, Magee L, Tsang P. The effect of factor V Leiden carriage on maternal and foetal health. CMAJ2002;167:48–54.
46. Duhl AJ, Paidas MJ, Ural SH, et al. Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcome. Am J Obstet Gynecol 2007;197:457.e1–457.e21.
47. Froen JF, Gardosi J, Thurmann A, Francis A, Stray-Pedersen B. Restricted foetal growth in sudden intrauterine unexplained death. Acta Obstet Gynecol Scand 2004;83:801–807.
48. Reddy U. Prediction and prevention of recurrent stillbirth. Obstet Gynaecol 2007;110:1151–1164.
49. American College of Obstetricians and Gynaecologists. Intrautherine growth restriction. ACOG Pract Bull 12, 2000.
50. The GRIT Study Group. A randomized trial of timed delivery for the compromised preterm foetus: short term outcomes and Bayesian interpretation. BJOG 2003;110:27–32.
51. Saastad E, Vangen S, Frøen JF. Suboptimal care in stillbirth – a retrospective audit study. Acta Obstet Gynaecol Scand 2007;86:444–450.
52. Stephansson O, Dickman PW, Johansson AL, Cnattingius S. The influence of socioeconomic status on stillbirth risk in Sweden. Int Epidemiol 2001;30:1296–1301.
53. Guildea ZE, Fone DL, Dunstan FD, Sibert JR, Cartlidge PH, Social deprivation and the causes of stillbirth and infant mortality. Arch Dis Child 2001;84:307–310.
54. Confidential enquiry into stillbirth and death in infancy. Enquiry comments on 422 stillbirth occurring 1996–97. 8th Annual report. 1999 http://www.cemach.org.uk.
55. La nascita in Emilia-Romagna. 5 Rapporto sui dati del Certificato di Assistenza al Parto (CedAP) – Anno 2007. Novembre 2008. Giunta Regionale. Direzione Generale Sanità e Politiche Sociali.
56. Chu SY, Kim SY, Lau JL, Sychmid CH, Dietz PM, Callaghan WM, Curtis KM. Maternal obesity and risk of stillbirth: a metaanalysis. Review. Am J Obstet Gynaecol 2007:223–228.
57. Stephansson O, Dickman PW, Johansson A, Cnattingius S. Maternal weight, pregnancy weight gain, and the risk of antepartum stillbirth. Am J Obstet Gynecol 2001;184:463–469.
58. Cnattingius S, Lambe M. Trends in smoking and overweight during pregnancy: prevalence, risks of pregnancy complications, and adverse pregnancy outcomes. Semin Perinatol 2002;26:286–295.
59. Wisborg K, Henriksen TB, Secher NJ. A prospective intervention study of stopping smoking in pregnancy in a routine antenatal care setting. Br J Obstet Gynaecol. 1998;105:1171–1176.
60. Odegård RA, Vatten LI, Nilsen ST, Salvesen KA, Austgulen R. Risk factors and clinical manifestations of pre-eclampsia. BJOG 2000;107:1410–1416.
61. Ananth CV, Smulian JC, Demissie K, Vintzileos AM, Knuppel RA. Placental abruption among singleton and twin births in the United States: risk factor profiles. Am J Epidemiol 200;153:771–778.
62. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. Nicotine Tob Res. 2004;S125–S140.
63. Grosso LM, Bracken MB. Caffeine metabolism, genetics and perinatal outcomes: a review of exposure assessment considerations during pregnancy. Ann Epidemiol 2005;15:460–466.
64. Bech BH, Autrup H, Nohr EA, Henriksen TB, Olsen J. Stillbirth and slow metabolizers of caffeine: comparison by genotyper. Int J Epidemiol 2006 Aug;35(4):948–953.
65. Kesmodel U, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake during pregnancy and the risk of stillbirth and death in the first year of life. Am J Epidemiol 2002;155:305–312.
66. Robson S, Thompson J, Ellwood D. Obstetric management of the next pregnancy after an unexplained stillbirth: an anonymous postalsurvey of Australian obstetricians. Aust N Z J Obstetrics Gynaecol 2006;46:278–281.
67. Moore TR, Piacquadio K. A prospective evaluation of foetal movement screening to reduce the incidence of antepartum foetal death. Am J Obstet Gynaecol 1989;160:1075–1080.
68. Heazell AE, Froen JF. Methods of foetal movement counting and detection of foetal compromise. J Obstet Gynaecol 2008;28:147–154.
69. Mangesi L, Hofmeyr GJ. Foetal movement counting for assessment of foetal wellbeing (Review). The Cochrane Library 2008: 2007 Jan 24;(1):CD004909.
70. Smith GCS, Fretts RC. Stillbirth. Lancet 2007;370:1715–1725.
71. Neilson JP, Alfirevic Z. Doppler ultrasound for foetal assesment in high risk pregnancies. Cochrane Database Syst Rev 2000;2 CD000073.
72. Smith GCS. Life-table analysis of the risk of perinattal death at term and post term in singleton pregnancies. Am J Obstet Gynaecol 2001;184:489–496.