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ORIGINAL ARTICLE

How many roads lead to stillbirth rate reduction? A 30-year analysis of risk factors in a Northern Italy University care center

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ABSTRACT

Background: Stillbirths affect more than 2.5 million pregnancies worldwide every year and the progress in reducing stillbirth rates is slower than that required by World Health Organization. The aim of the present study was to investigate which factors were associated with stillbirths in a University Hospital in the North of Italy, over a time span of 30 years. The goal was to identify which factors are potentially modifiable to reduce stillbirth rate.

Methods: Retrospective case-control study (358 stillbirths, 716 livebirths) subdivided into two study periods (1987–2006 and 2007–2017).

Results: The prevalence of conception obtained by assisted reproductive technologies, pregnancy at advanced maternal age, and complications of pregnancy such as preeclampsia, fetal growth restriction (FGR), and other fetal diseases (abnormal fetal conditions including fetal anemia, fetal hydrops, TORCH infections) increased through the years of the study. Despite a rising prevalence, the last 10 years showed a significant reduction in stillbirths associated with preeclampsia and FGR. Similarly, the risk of stillbirth related to abnormal fetal conditions decreased in the second study period and a history of previous stillbirth becomes a nonsignificant risk factor.

Conclusions: Altogether these results suggest that in pregnancies perceived as "high risk" (i.e. previous stillbirth, preeclampsia, FGR, abnormal fetal conditions) appropriate care and follow-up can indeed lower stillbirth rates. In conclusion, the road to stillbirth prevention passes inevitably through awareness and recognition of risk factors.

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Assisted reproduction; fetal growth restriction; malformation; preeclampsia; stillbirth

Introduction

Every year more than 2.5 million stillbirths occur worldwide [1]. Despite this high prevalence, the burden of stillbirths still remains greatly underappreciated [2] and few national and international intervention plans address stillbirths [3]. In high-income countries stillbirths are difficult to prevent and occur mainly in the antepartum period and very preterm [4]. Moreover, many stillbirths are associated with a failure in identifying risk factors, leading to underestimate the hazard, with a lack of appropriate standard of care [5]. All these aspects contribute to the too slow progress in reducing stillbirth rates [6]. Indeed, the progress is slower than that required to meet the targets set by the World Health Organization [7] to end preventable stillbirths [8]. On the other hand, it was suggested that the decreasing of stillbirth rate passes through the improving of prenatal care and monitoring before labor for many conditions such as preeclampsia, poor fetal growth, fetal asphyxia, and improving care and expediting delivery for several conditions such as placental abruption and fetal distress [9]. According to these evidences, one of the first issues to reduce stillbirth rate is the recognition of risk factors. This knowledge is crucial in planning effective public health initiatives and antenatal education, increasing awareness of stillbirth, improving care, and monitoring during pregnancy [10]. Therefore, the present study aimed at investigating which factors were associated with stillbirths and their trend over a long

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Supplemental data for this article can be accessed here.

time period. The final goal was to identify which elements are potentially modifiable to reduce stillbirth rate.

Materials and methods

Data collection

The study is a retrospective case-control study carried out in a University Hospital in the North of Italy.

Stillbirth was defined as fetal death at or more than 22 completed weeks of gestation, according to the World Health Organization's International Statistical Classification of Diseases 10th revision [11]. All stillbirths occurred in a 30-year period (1987–2017) were considered, using the archive of the Unit of Human Pathology (in Italy all stillbirths underwent autopsy by law). Eligible cases for the study included singleton pregnancies with nonmacerated fetus. From a database of 2937 consecutive unselected perinatal autopsies performed at the Unit of Human Pathology, we identified 358 singleton pregnancies eligible for recruitment.

Controls were randomly selected (using a computer-generated sequence of random numbers) among women who delivered singleton liveborn baby in the same years as cases; data were extracted from the database of the Unit of Obstetrics and Gynecology in the same institution. Exclusion criteria were multiple pregnancies and stillbirths. Among 29 063 liveborn singleton deliveries, we randomly collected 716 babies as controls, with a 1:2 case:control rate. With a significance level targeted at 0.05, this sample size achieves 80% power to detect an odds ratio (OR) of 1.5 for the most common risk factors (prevalence in controls = 25%); an OR of 2.0 for unusual risk factors (prevalence in controls = 5%); an OR of 3.75 for very infrequent risk factors (prevalence in controls = 1%).

Sociodemographic variables, maternal and obstetric history, fetal characteristics, and pregnancy outcomes were obtained from routinely collected, prospectively entered, anonymized data from the obstetric clinical databases.

Definitions

Preeclampsia was defined as new-onset hypertension (blood pressure >140/90) with significant proteinuria after 20 weeks of gestation.

Maternal obesity was defined as prepregnancy body mass index at or greater than 30 kg/m^2.

Gestational diabetes was diagnosed at 24–28 weeks of gestation; until 2010 it was diagnosed with a 100-g oral glucose tolerance test with two or more values over the ranges established by Carpenter et al. [12] [plasma glucose: fasting <5.2 mmol/L (95 mg/dl), 1 h <10 mmol/L (180 mg/dL), 2 h < 8.6 mol/L (155 mg/dL), 3 h <7.7 mmol/L (140 mg/dL)]. Since 2010 gestational diabetes was diagnosed with a 75-g glucose tolerance test with at least one value at or over the ranges established by International Association of Diabetes and Pregnancy Study Groups [13] [fasting <5.1 mmol/L (<92 mg/dL), 1 h < 10.0 mmol/L (<180 mg/dL), 2 h < 8.5 mmol/L (<153 mg/dL)]. Congenital abnormalities include karyotype abnormalities and/or gene mutations and/or single severe malformations or multiple malformations or deformations or dysplasia.

Fetal growth restriction (FGR) was diagnosed *in utero* through repeated longitudinal measurements that demonstrated a reduction in fetal growth velocity with abdominal circumference less than 10th centile, in absence of congenital anomalies.

Smokers include women who declared to use cigarettes and continue to smoke in pregnancy (irrespective of the number of cigarettes/day).

Statistical analysis

Baseline characteristics of the study population were expressed as median and range for continuous variables and as frequency and percentage for categorical variables.

Since Kolmogorov-Smirnov test suggested a nonnormal distribution for the continuous variables analyzed in the present study, nonparametric tests were used. At univariate analysis, baseline maternal, pregnancy, and fetal characteristics both in cases and controls were compared with the Wilcoxon two-independent samples test for continuous variables and the chi-square test for categorical variables. Univariate and multivariate unconditional logistic regression was performed in order to calculate OR with 95% confidence intervals (CI) for the risk of stillbirth according to the investigated risk factors. Multivariate logistic models included as covariates the gestational age and the characteristics that were associated with stillbirth at univariate analysis.

Population attributable risk (PAR) with 95% CI was calculated using unadjusted OR for the modifiable risk factors that were significant at univariate analysis.

The population was subdivided into two study periods in order to evaluate the prevalence in time and the association with stillbirth of the identified risk factors. The chosen intervals were 1987–2006 and 2007–2017. This interval was chosen to obtain a

comparable sample-size between the two study periods, in order to allow accurate statistical analysis to highlight the differences in the last 10 years compared to the previous 20 years. The apparently greater number of stillbirths occurred in the last 10 years ($n = 174$ versus $n = 184$ in the previous 20 years) is not related to an increased stillbirth rate but just to increased global population (since the 2006), due to the fusion of a spoke with our Hub. The above described univariate and multivariate statistical analyses were performed for both study periods.

p-values $< .05$ were considered statistically significant. The analysis was performed with SAS Software, version 9.4.

Results

Significant differences were observed between stillborn cases and liveborn controls including differences in maternal characteristics, previous pregnancies outcomes, and current pregnancy outcomes: women with stillbirth were significantly older than women with livebirth (median age of cases: 33 years, range 14–50; controls: 31 years, range 15–44, $p = .003$; univariate OR 1.04 [1.01–1.06]) and they were more frequently obese (14% versus 7%, $p = .005$; OR = 2.26 [1.27–4.01]), smokers (14% versus 9%, $p = .04$; OR = 1.80 [1.01–3.21]), and affected by pregestational type 2 diabetes (2% versus 0%, $p = .003$; OR = 12.19 [1.46–101.62]). Previous pregnancies history was more frequently affected by adverse outcomes in women with stillbirth than controls, including previous FGR (2% versus 0.003%, $p < .002$; OR 8.16 [1.72–38.62]), previous stillbirth (4% versus 1%, $p < .0001$; OR = 7.14 [2.25–12.63]), and previous preeclampsia (1% versus 0.003%, $p < .03$; OR 5.06 [0.98–26.19]) with an overall effect of 8% versus 1%, $p < .0001$; OR = 6.69 [2.91–15.40] in cases with more than one of the above mentioned conditions. The index pregnancy was more frequently obtained by medical-assisted reproductive technologies (4% versus 2% $p = .05$; OR = 2.21 [1.00–4.90]) and affected by preeclampsia (11% versus 1%, $p < .001$; OR = 13.10 [5.81–29.52]). Fetal characteristics in index pregnancies also differed between cases and controls, showing higher prevalence of FGR (12% versus 2%, $p < .0001$; OR = 7.79 [4.05–15.00]), fetal congenital abnormalities (11% versus 1% $p < .0001$; OR 10.51 [4.85–22.77]), and other abnormal fetal conditions (i.e. fetal anemia, hydrops, TORCH infections; 12% versus 2% $p < .0001$; OR = 6.21 [3.39–11.37]) in cases rather than in controls. Characteristics of stillborn cases and liveborn controls are summarized in Supplementary Table 1 and the overall prevalence of specific risk factors and the correspondent PAR are shown in Supplementary Table 2.

At multivariate analysis, risk factors significantly associated with the risk of stillbirth were pregestational diabetes (OR 13.48 [1.14–159.79]), previous FGR (OR 7.74 [1.11–53.86]), current preeclampsia (OR 3.59 [1.01–12.73]), and current fetal congenital abnormalities (OR 4.15 [1.35–12.83]) (Supplementary Table 1).

Our focus was to evaluate the prevalence in time and the association with stillbirth of the identified risk factors in the last 10 years compared to the previous 20 years. Notably, the prevalence of preeclampsia and FGR increased through the last 10 years of the study but, surprisingly, a significant decrease in stillbirth associated with preeclampsia and FGR was observed (preeclampsia: OR = 38.52 [9.12–162.75] prevalence 0.5% during period 1987–2006 versus OR = 3.74 [1.23–11.34] prevalence 1.4% during period 2007–2017; FGR: OR = 12.49 [4.72–33.02], prevalence 1.4% during period 1987–2006 versus OR = 4.60 [1.84–11.49], prevalence 2.0% during period 2007–2017). It resulted in a consistent reduction of PAR over the two investigated time periods: from 17% [4–47] to 4% [0–13] for preeclampsia and from 14% [5–30] to 7% [2–17] for FGR (Table 1). The proportion of early- versus late-FGR does not change through the years, counting 85% early-FGR and 15% late-FGR cases in both study periods.

An increased prevalence of women aged 40 years or over (2.9% versus 7.4%) and pregnancies obtained by assisted reproductive technologies (0.5% versus 2.9%) was also observed. Despite the similar ORs obtained for these factors over the two study periods, the PAR [95%CI] was increased from 2% [−1–9] to 5% [−1–14] and from 1% [0–8] to 3% [0–10] for advanced maternal age and assisted reproductive technologies, respectively (Table 1). In women aged 40 years or over, 14% of stillbirths occurred after the 38th week of gestation and 7% after the 39th week of gestation.

Moreover, an increased prevalence of abnormal fetal conditions was observed over the two time periods (1.1% versus 3.2%) but, fortunately, the ORs and the PAR decreased (OR = 12.36 [4.19–36.44] period 1987–2006 versus OR = 3.98 [1.86–8.51] period 2007–2017; PAR over the two time periods: from 10.99% [3.35–27.81] to 8.61% [2.65–19.18]).

PAR for the modifiable risk factors over the last 10 years is summarized in Figure 1.

Discussion

The present study investigated factors associated with stillbirths over a long time period. Our data highlight that some changes occurred in the prevalence of

Table 1. Association estimates for stillbirth risk according to separate study periods and correspondent population attributable risk (PAR) for the identified risk factors.

		Study period 1 (1987–2006) *N* cases/controls = 184/368			Study period 2 (2007–2017) *N* cases/controls = 174/348		
Category	Specific characteristics	Univariate OR [95% CI]	Prevalence in controls (%)	PAR (% [95% CI])	Univariate OR [95% CI]	Prevalence in controls (%)	PAR (% [95% CI])
Maternal characteristics	Age ≥ 40 years	1.70 [0.66–4.75]	2.9	1.94 [−0.99–8.77]	1.67 [0.90–3.10]	7.4	4.75 [−0.76–13.53]
	Obesity	2.11 [0.85–5.25]	8.3	8.37 [−1.30–25.98%]	**2.25 [1.07–4.74]**	6.4	**7.36 [0.41–19.24]**
	Smoking	NE	0	–	1.37 [0.65–2.90]	8.6	3.11 [−3.13–14.10]
	Diabetes	NE	0	–	6.08 [0.63–58.79]	0.3	1.44 [−0.11–14.28]
	Any baseline pathology	**2.16 [1.30–3.59]**	9.5	**9.91 [2.73–19.77]**	1.11 [0.68–1.83]	15.2	1.69 [−5.14–11.16]
Previous pregnancies	Previous preeclampsia	6.07 [0.63–58.72]	0.3	1.36 [0.10–13.56]	4.04 [0.36–44.81]	0.3	0.86 [−0.18–11.18]
	Previous stillbirth	**20.07 [2.44–164.92]**	0.3	**5.54 [0.44–33.53]**	3.16 [0.70–14.31]	0.9	1.97 [−0.28–11.00]
	Previous FGR	NE	0	–	4.07 [0.74–22.44]	0.6	1.73 [−0.15–10.97]
Current pregnancy	Assisted reprod technol	3.03 [0.50–18.29]	0.5	1.09 [−0.27–8.59]	2.06 [0.84–5.05]	2.9	2.96 [−0.46–10.42]
	Preeclampsia	**38.52 [9.12–162.75]**	0.5	**16.94 [4.23–46.78]**	**3.74 [1.23–11.34]**	1.4	**3.79 [0.34–12.94]**
	FGR	**12.49 [4.72–33.02]**	1.4	**13.50 [4.81–30.31]**	**4.60 [1.84–11.49]**	2.0	**6.74 [1.6–17.43]**
	Congenital abnormalities	**13.58 [5.16–35.74]**	1.4	**14.60 [5.35–32.07]**	**6.27 [1.68–23.48]**	0.9	**4.35 [0.58–16.23]**
	Other fetal conditions	**12.36 [4.19–36.44]**	1.1	**10.99 [3.35–27.81]**	**3.98 [1.86–8.51]**	3.2	**8.61 [2.65–19.18]**
	Male sex	1.22 [0.86–1.75]	51.0	10.24 [−7.83–27.57]	1.39 [0.97–2.01]	47.0	15.57 [−1.68–32.19]

Note. Significant ORs and PARs are in bold.
CI: confidence intervals; OR: odds ratio; PAR: population attributable risk; BMI: body mass index; FGR: fetal growth restriction; NE: not estimable, due to small number of cases (diabetes, previous FGR) or >20% of missing data (smoking).
"Any baseline pathology" includes one or more of these characteristics: autoimmune disease/thrombophilia, diabetes, hematological disease (including severe anemia and/or congenital hemoglobinopathies), chronic hypertension, thyropathy (defined as overt hypothyroidism and/or autoimmune thyroiditis in patients taking oral levothyroxine therapy), and other pregestational pathology.
"Other fetal conditions" include fetal anemia or hydrops or TORCH infection.

certain stillbirth-associated risk factors during the last 30 years: the prevalence of conception obtained by assisted reproductive technologies, pregnancy at advanced maternal age, and complications of pregnancy such as preeclampsia, FGR, and other fetal diseases (abnormal fetal conditions including fetal anemia, fetal hydrops, TORCH infections) increased through the years of the study. Despite a rising prevalence, the last 10 years showed a significant reduction in stillbirths associated with preeclampsia and FGR. Similarly, the risk of stillbirth related to abnormal fetal conditions decreased and a history of previous stillbirth becomes a nonsignificant risk factor in the last 10 years.

Considering the framework of the country in which the study was performed, these results are very interesting: in Italy, antenatal care is free of charge and it includes routine monthly appointments, comprising ultrasound scans (at first, second and, if indicated, at third trimester of pregnancy). Additional care and referrals to specialist services are provided when needed. At the present day there are no specific national intervention plans to reduce stillbirth rate and national guidelines on antenatal care for women with previous stillbirths do not exist.

Our results suggest that interventions in some areas could contribute to increasing awareness of the potentially modifiable risk factors, thus reducing stillbirth rates.

Maternal age

Childbearing later in life is a growing trend associated with potentially adverse pregnancy outcomes [14]. Advanced maternal age is most commonly encountered in primigravid women who delay pregnancy due to lifestyle choices or underlying subfertility, but also in multiparous women continuing childbearing [15]. Indeed, advanced maternal age is an independent risk factor for stillbirth in both nulliparous and multiparous women [16]. Our results are in agreement with the trend of delaying pregnancy, showing an increased prevalence of women aged 40 years or over during the last 10 years. Obviously, maternal age cannot be modified during pregnancy, but the risks related to ageing should be considered in intervention programs to lower stillbirths. For example, epidemiological studies show that women aged 40 years or older have a similar stillbirth risk at 39 weeks of gestation as 25–29 year olds at 41 weeks of gestation [17,18]. According to this evidence, the Royal College of Obstetricians and Gynaecologists (RCOG) considers the option of earlier induction of labor as a clinical practice that would reduce late antenatal stillbirths in advanced maternal age [19].

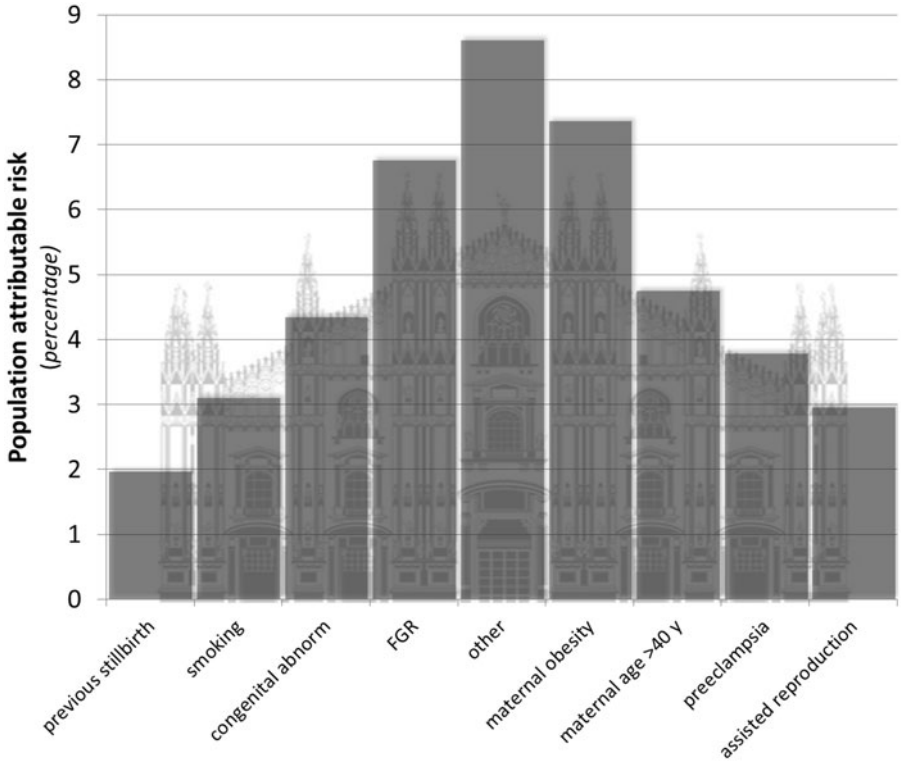

Figure 1. Population attributable risk (PAR) for stillbirth during the period 2007–2017. Bars represent population attributable risk (expressed as percentage). PAR indicates the proportion of cases that would not occur in the population if the risk factors were eliminated. The figure shows the main risk factors observed in the studied population. Data are shown mimicking the shape of the "Duomo," the most famous landmark in Milan, the city where the study was performed (Northern Italy, EU). The attributable risk depends on the prevalence of the risk factor and the strength of its association with stillbirth. Some factors cannot be modified (e.g. history of previous stillbirth, advanced maternal age, conception obtained by assisted reproductive technologies, presence of fetal congenital abnormalities) and others are difficult (but not impossible) to change during pregnancy (e.g. maternal overweight, smoking). Nevertheless, proper interventions, pregnancy care, and follow-up can lower stillbirth rates. Specific comments for each risk factor in the text. "Other" includes fetal anemia, fetal hydrops, TORCH infections. FGR: fetal growth restriction.

Obesity

Obesity in pregnancy is an independent risk factor for stillbirth and the risk seems to increase with increasing gestational age [20–24] and maternal weight [25]. Our results agree with previously published Italian data [26], confirming that high maternal body mass index is a specific risk factor for stillbirth in Northern Italian population.

Prevention strategies to reduce obesity-related risk of stillbirth pose a challenge, yet they are achievable. Preconceptional weight optimization is the ideal scenario and it may be obtained by providing information about obesity-related risks and encouraging weight loss and lifestyle modification during family planning consultations [27]. Other interventions include tailoring nutritional needs with adequate supplementations before and during pregnancy (i.e. folic acid dosage); discussing the importance of a healthy diet and appropriate daily physical exercise during pregnancy in order to prevent excessive weight gain. Specific risk assessment should be considered for obese women, also addressing the risk of comorbidities associated with obesity (including for example fetal malformations, gestational diabetes, preeclampsia, sleep apnea); adequate antenatal care with specific consideration for maternal and fetal surveillance should be provided [28].

Previous stillbirth

The recurrence of stillbirth from one pregnancy to the subsequent one has been widely acknowledged, for example, a recent meta-analysis reported a nearly fivefold increase in the relative risk [29]. In our population a previous stillbirth was a significant risk factor for subsequent stillbirth during the first study period (1987–2006), whereas it became nonsignificant during the last 10 years (2007–2017). This result may be related to the additional medical examinations and ultrasound scans frequently performed in women who experienced stillbirth [30]. Clinical guidelines suggest

serial assessment of growth by ultrasound biometry, screening for gestational diabetes, and individual assessment for timing of birth at a specialist maternity unit as special attentions needed to lower stillbirth recurrence risk [31].

Assisted reproductive technologies

Women who undergo advanced reproductive technologies show an increased risk of perinatal mortality [20]. Although many confounder factors could be responsible for a significant portion of this excess mortality (such as the presence of multiple gestations and an advanced maternal age), assisted conception nevertheless seems to be an independent risk factor for stillbirth [25]. Our results show a significantly increased prevalence of assisted conception in cases, with a significant population attributable risk and increased access in the last 10 years compared to the previous 20 years. Therefore, pregnancies obtained by assisted reproductive technologies should be perceived and monitored as "high risk pregnancies" in order to reduce stillbirth rate.

Preeclampsia

Preeclampsia has been frequently reported as a risk factor for stillbirth [32,33]. Recent reviews highlight that a huge number of stillbirths are attributable to preeclampsia and eclampsia, especially in low and middle income-countries [34]. Nevertheless, other studies in high-income countries found that preeclampsia seems to result in reduced risk [26]. These results suggest that several factors may play a "protective" role against stillbirth in this subpopulation: for example, widespread access to antenatal care, the fact that women are educated concerning the clinical presentation as well as the risks associated with preeclampsia, prompting early diagnosis, and timely delivery [35]. In agreement with this observation, our results show a low but consistent reduction of stillbirth related to preeclampsia in the last 10 years although the prevalence of preeclampsia was increased. Therefore, it is reasonable to think that many fetal deaths could be prevented by timely detection and appropriate management of maternal preeclampsia. Current evidences do not support the use of prophylactic low-dose aspirin solely for the prevention of stillbirth [36]. On the contrary, low-dose aspirin could be useful for the prevention of preeclampsia in women at high risk [36]. This strategy for preeclampsia prevention may lead, in turn, to a reduction of preeclampsia-related stillbirth rate.

Fetal growth restriction

Identification and appropriate management of the growth-restricted fetus represents an important opportunity for stillbirth prevention [20]. Past and recent data show that abnormally grown fetuses reported an incidence of stillbirth severely higher than appropriate-for-gestational-age counterparts, placing FGR as one of the strongest factors associated with stillbirth [37]. Our data reported a low but consistent reduction of stillbirth related to FGR in spite of an increased prevalence of FGR in the last years. Although the rate of neonatal death in early-FGR was not evaluated in the present study, results suggest that a correct management of pregnancies affected by abnormal fetal growth could decrease the rate of stillbirths.

Congenital abnormalities and other fetal conditions

A large number of stillborn fetuses exhibit congenital abnormalities including single or multiple malformations, deformations or dysplasia [38], with or without chromosomal or genetic anomalies. Although many deaths from congenital malformations are currently considered "unavoidable" (e.g. cases related to abnormal fetal karyotype), it is reasonable to think that a proportion of these deaths can be averted by primary prevention measures. Folate supplementation for the prevention of neural tube defects, avoiding teratogen exposure and appropriate hygiene standards all represent possible interventions during the periconceptional period. Our data suggest a decreasing prevalence of congenital anomalies both in livebirths and stillbirths. The general reduction of congenital anomalies could be related to improved early antenatal detection by ultrasound (hence to a possible increase in early legal interruptions of pregnancy before the age of viability). Conversely, ultrasonographic antenatal detection of curable fetal diseases improved intrauterine interventions (e.g. fetal transfusion for anemia) resulting in pregnancy progression and stillbirth reduction.

Strengths and limitations

This study includes a large obstetric cohort of stillbirth, with detailed clinical and obstetric data. Nevertheless, the study is limited by the retrospective case – control

study design: sometimes in the first years of the study some data were missing (>20%) (i.e. smoking); in order to achieve powerful results in the multivariate analysis, smoking was excluded from the model. However, sensitivity analyses were performed with the inclusion of all risk factors, providing comparable results.

In conclusion, our data show how stillbirth risk factors evolved over more than a quarter of a century, reflecting the changes in society with respect to lifestyle choices and health-related issues. The suggestion is that prompt recognition and careful follow-up of many feto–maternal conditions may lead to a lowering incidence of stillbirths in spite of a growing prevalence of high risk pregnancies. Knowledge about risk factors plays a pivotal role in increasing awareness, thus helping to reduce stillbirth rates.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Authors' contributions

Conception and design of the article by LA. LA performed the literature search, drafted the manuscript, collected, and analyzed data. MM and SR expanded the literature research. MM contributed to collect data. SR performed statistical analysis. GB and AMM revised database. AV and CR actively discussed results. All authors read, edited, and approved the final manuscript.

References

[1] Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. Lancet. 2016;387(10018):587–603.
[2] Heazell AE, Whitworth MK, Whitcombe J, et al. Research priorities for stillbirth: process overview and results from UK stillbirth priority setting partnership. Ultrasound Obstet Gynecol. 2015;46(6):641–647.
[3] Frøen JF, Friberg IK, Lawn JE, et al. Stillbirths: progress and unfinished business. Lancet. 2016;387(10018):574–586.
[4] McClure EM, Goldenberg RL. Improved data informs efforts to end preventable stillbirths. Lancet Glob Health. 2016;4(2):e70–e71.
[5] Gardosi J, Giddings S, Buller S, et al. Preventing stillbirths through improved antenatal recognition of pregnancies at risk due to fetal growth restriction. Public Health. 2014;128(8):698–702.
[6] Flenady V, Wojcieszek AM, Middleton P, et al. Stillbirths: recall to action in high-income countries. Lancet. 2016;387(10019):691–702.
[7] World Health Organization. Every newborn: an action plan to end preventable deaths. Geneva (Switzerland): World Health Organization; 2014.
[8] Lawn JE, Blencowe H, Oza S, et al. Every newborn: progress, priorities, and potential beyond survival. Lancet. 2014;384(9938):189–205.
[9] Woods R. The measurement of historical trends in fetal mortality in England and Wales. Popul Stud (Camb). 2005;59(2):147–162.
[10] Nuzum D, Meaney S, O'Donoghue K. The public awareness of stillbirth: an Irish population study. Br J Obstet Gynaecol. 2018;125(2):246–252.
[11] World Health Organization. Definition and indicators in family planning maternal and child health and reproductive health. Geneva: WHO Press; 2006.
[12] Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. Am J Obstet Gynecol. 1982;144(7):768–773.
[13] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676–682.
[14] Lean SC, Derricott H, Jones RL, et al. Advanced maternal age and adverse pregnancy outcomes: a systematic review and meta-analysis. Plos One. 2017;12(10):e0186287.
[15] Guedes M, Canavarro MC. Characteristics of primiparous women of advanced age and their partners: a homogenous or heterogenous group? Birth. 2014;41(1):46–55.
[16] Liu S, Joseph KS, Kramer MS, et al. Relationship of prenatal diagnosis and pregnancy termination to overall infant mortality in Canada. JAMA. 2002;287(12):1561–1567.
[17] Reddy UM, Ko CW, Willinger M. Maternal age and the risk of stillbirth throughout pregnancy in the United States. Am J Obstet Gynecol. 2006;195(3):764–770.
[18] Wyatt PR, Owolabi T, Meier C, et al. Age-specific risk of fetal loss observed in a second trimester serum screening population. Am J Obstet Gynecol. 2005;192(1):240–246.
[19] RCOG. Induction of labour at term in older Mothers Scientific Impact Paper No. 34; February 2013.
[20] Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol. 2005;193(6):1923–1935.
[21] Chu SY, Kim SY, Lau J, et al. Maternal obesity and risk of stillbirth: a metaanalysis. Am J Obstet Gynecol. 2007;197(3):223–228.
[22] Smith GC. Predicting antepartum stillbirth. Curr Opin Obstet Gynecol. 2006;18(6):625–630.
[23] Kristensen J, Vestergaard M, Wisborg K, et al. Prepregnancy weight and the risk of stillbirth and neonatal death. Br J Obstet Gynaecol. 2005;112:403.e8.

[24] Reddy UM, Laughon SK, Sun L, et al. Prepregnancy risk factors for antepartum stillbirth in the United States. Obstet Gynecol. 2010;116(5):1119–1126.
[25] Yerlikaya G, Akolekar R, McPherson K, et al. Prediction of stillbirth from maternal demographic and pregnancy characteristics. Ultrasound Obstet Gynecol. 2016;48(5):607–612.
[26] Facchinetti F, Alberico S, Benedetto C, et al. A multicenter, case–control study on risk factors for antepartum stillbirth. J Maternfetal Neonat Med. 2011;24(3): 407–410.
[27] ACOG committee opinion. Challenges for overweight and obese women. Committee Opinion No. 591; Obstet Gynecol. 2014;123:726–730, reaffirmed 2016.
[28] Modder J, Fitzsimons KJ, Centre for Maternal and Child Enquiries, et al. CMACE/RCOG joint guideline: management of women with obesity in pregnancy. London: Centre for Maternal and Child Enquiries and the Royal College of Obstetricians and Gynaecologists; 2010.
[29] Lamont K, Scott NW, Jones GT, et al. Risk of recurrent stillbirth: systematic review and meta-analysis. BMJ. 2015;350:h3080.
[30] Gravensteen IK, Jacobsen EM, Sandset PM, et al. Healthcare utilisation, induced labour and caesarean section in the pregnancy after stillbirth: a prospective study. Br J Obstet Gynaecol. 2018;125(2):202–210.
[31] RCOG. Late intrauterine fetal death and stillbirth green-top Guideline No. 55. London: RCOG; 2010.
[32] Simpson LL. Maternal medical disease: risk of antepartum fetal death. Semin Perinatol. 2002;26(1):42–50.
[33] Gardosi J, Madurasinghe V, Williams M, et al. Maternal and fetal risk factors for stillbirth: population based study. BMJ. 2013;346:f108.
[34] Allen VM, Joseph K, Murphy KE, et al. The effect of hypertensive disorders in pregnancy on small for gestational age and stillbirth: a population based study. BMC Pregnancy Childbirth. 2004;4(1):17.
[35] Wapner RJ, Lewis D. Genetics and metabolic causes of stillbirth. Semin Perinatol. 2002;26(1):70–74.
[36] Silver RM, Varner MW, Reddy U, et al. Work-up of stillbirth: a review of the evidence. Am J Obstet Gynecol. 2007;196(5):433–444.
[37] De Lange TE, Budde MP, Heard AR, et al. Avoidable risk factors in perinatal deaths: a perinatal audit in South Australia. Aust N Z J Obstet Gynaecol. 2008; 48(1):50–57.
[38] American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 743: Low-dose aspirin use during pregnancy. Obstet Gynecol. 2018;132(1): e44–e52.