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Stillbirth, potentially preventable cases: an Italian retrospective study

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ABSTRACT

Objective. The reduction in the global burden of child mortality is one of the Millennium developmental goals of the World of Health Organization (WHO). Understanding the pathophysiology underlying every single stillbirth case will allow the achievement of the WHO goal by implementing specific interventions. The aim of the study was to examine stillbirth cases occurred from 2012 to 2020 in a single tertiary obstetric care unit in Italy.
Materials and Methods. Stillbirths were identified by the hospital electronic archive system. Pre-pregnancy/pregnancy related risk factors and post-mortem examinations were recorded.
Results. A total of 53 stillbirth cases out of 19115 deliveries occurred in the study period (overall 2.77 cases every 1000 live births). The most frequent pre-pregnancy risk factors associated to events were maternal overweight/obesity (50.9%), nulliparity (49%), inherited coagulation disorders (26.4%) and sub clinical hypothyroidism (11.3%). The most common pregnancy related risk factors were growth restriction (56.6%), gestational diabetes mellitus (15%), hypertensive disorders of pregnancy (9.4%) and cord knot (7.5%). Among the 53 cases, 12 would have been potentially preventable with a better antenatal care (22.6%), seven of these occurred at a gestational age equal or more that 39 weeks of gestation. A significant drop in stillbirth incidence has been documented from 2019 (3.17 cases every 1000 live births before 2019 *versus* 1.19 cases every 1000 live births from 2019, respectively ($p = 0.039$)), when, a protocol for induction of labor specific for each pre-pregnancy and pregnancy related risk factors has been introduced in clinical practice.
Conclusions. A significant proportion of stillbirth cases are potentially preventable with a better antenatal care.

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INTRODUCTION

Stillbirth is a dramatic event for both the mother and her family with significant psychosocial consequences [1]. It does not only influence the mother future life, but it has an impact as well on providers both from a psychological and a medico-legal prospective [2]. Different definitions for stillbirth have been reported in the literature [3]. The American College of Obstetrics and Gynaecology (ACOG) in the 2020 defined stillbirth as "foetal deaths at 20 weeks or greater of gestation (if the gestational age is known), or a weight greater than or equal to 350 grams if the gestational age is unknown" [3].
The global incidence of stillbirth is around 18.4 cases every 1,000 live births, ranging from 2/1,000 to 40/1,000 in high- and low-income countries, respectively [4-7]. The last Italian Statistical Institute (ISTAT) report described an incidence of stillbirths ranging from 2.7 to 4.7 cases every 1,000 live births [8].
The reduction in the global burden of child mortality is one of the Millennium developmental goals of the World of Health Organization (WHO) [9]. Understanding the pathophysiology underlying every single stillbirth case will allow the achievement of the WHO goal by implementing specific interventions. Therefore, the aim of our study was to retrospectively study every single stillbirth case occurred from 2012 to 2020 in a single tertiary obstetric care unit in Italy.

MATERIALS AND METHODS

This is a retrospective analysis of stillbirth cases, conducted in a single tertiary obstetric care unit in Italy, from January 2012 to December 2020 (Unit of Obstetrics and Gynaecology, Magna Graecia University of Catanzaro, Italy). According to the last ACOG consensus, stillbirth was defined as "foetal deaths at 20 weeks or greater of gestation (if the gestational age is known), or a weight greater than or equal to 350 grams if the gestational age is unknown". All consecutive stillbirth cases, identified through the hospital electronic archive system, meeting the ACOG definition criteria were considered eligible. The key words adopted for the search in the electronic archive system have been stillbirth and intrauterine foetal death. Gestational age was determined according to the foetal crown–rump length measurement (the measurement of the embryos/foetal length from the top of the head, crown, to the bottom of the buttocks, rump, CRL) obtained during the first trimester "dating scan", or the foetal growth at the second trimester "anomaly scan" if the dating scan wasn't available. Four authors (CDC, PQ, MM and RV) extensively and independently reviewed all the included cases. The same authors also evaluated the obstetrical protocols implemented in the clinical practice of the obstetric unit during the study period.
The following maternal characteristics were retrieved: maternal age, body mass index (BMI), parity, nationality (Italian/European *versus* extra European), level of education (low level of education: illiterate, compulsory school *versus* high level of education: high school or graduation), medical history, mode of conception, smoking status, drug and or alcohol abuse and previous pregnancy obstetric complications.
The following data (part of the internal protocol assessment for stillbirth) were also registered: full blood count, glycated haemoglobin (HgbA1c) levels, serology tests for foetal infections (Toxoplasmosis, Rubella, Cytomegalovirus, Parvovirus B19, Syphilis, Hepatitis B, Hepatitis C, HIV), full coagulation spectrum study both for inherited or acquired disorders and urine toxicology; postpartum placental swabs, the results of foetal autopsy (autopsy was routinely offered and performed whenever accepted) and placental pathology examination (microscopic placental analysis was performed in accordance with practice guidelines for placental evaluation) [10, 11].
The following definitions were used for pregnancy related complications:

- Abnormal growth [12-14]. Growth restriction in the new-born. Birth weight less than the third percentile, or 3 out of the following: birth weight < 10^{th} percentile; head circumference < 10^{th} percentile; femur length < 10^{th} percentile. The third trimester growth scan is not routinely offered by the national health care system therefore we evaluate growth restriction on the basis of birth weight.
- Large for gestational age (LGA). Birth weight equal to or more than the 90^{th} percentile for a given gestational age.
- Hypertensive disorders of pregnancy (HDP) [15]. Preeclampsia (PE) was defined as hypertension in pregnancy (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg on at least two occasions four hours apart developing after 20 weeks' gestation in a previously normotensive woman) with one or more of the following new-onset conditions: protein-

uria (> 300 mg in 24 hours) and/or evidence of maternal acute kidney injury (AKI), liver dysfunction, neurological features, haemolysis or thrombocytopenia, or foetal growth restriction.
- Pregnancy induced hypertension (PIH) was defined as persistent hypertension in pregnancy with no other features of PE.
- Chronic hypertension with superimposed PE was defined by onset of significant proteinuria after 20 weeks' gestation in a non-proteinuric woman with pre-pregnancy hypertension.
- Gestational diabetes mellitus (GDM) [16, 17]. Diagnosed in the presence of a positive result of the 75 g Oral Glucose tolerance test. An oral glucose tolerance test for GDM was performed at 16-18 and/or 24-28 weeks, according to the risk stratification criteria proposed by the Italian diabetes society.
- Chorioamnionitis: [18, 19]. Presence of maternal fever (≥ than 38°) in association with at least two of the subsequent: tachycardia, leucocytosis, uterine contraction, and abnormal vaginal discharge.
- Placental abruption [20]. Evidence of a premature separation of the normal-sided placenta from the uterus.
- Post term pregnancy [21, 22]. Gestational age at or beyond 41 weeks of gestation.

Statistical analysis

Continuous and categorical variables are expressed as the mean ± standard deviation and percentages, respectively. The Chi square test for comparisons of proportions has been used. Statistical significance was fixed at an alpha level of 0.05.

Statistical analyses were performed with SPSS 20.0 software (SPSS Inc, Chicago, IL, USA). Ethics approval for this study was obtained from the institutional review board, Regione Calabria Sezione area Centro (Protocol number 27 of the 21st of January 2021).

RESULTS

Stillbirth rate

During the study period, 56 cases have been recorded as stillbirth by the hospital electronic archive system. After revision, three cases were excluded, not meeting ACOG criteria for definition of stillbirth: gestational age lower than 20 weeks with known gestational age (two cases) and birth weight lower than 350 g with unknown gestational age (one case), leaving, therefore, 53 cases. All the included cases have been diagnosed by ultrasound before to give birth.

Table 1. *Stillbirth cases per year from 2012 to 2020.*

Year	Nr of stillbirths	Nr. of live births	Nr. of cases every 1000 live births
2012	5	2195	2.27
2013	5	2152	2.32
2014	7	2242	3.12
2015	10	2184	4.57
2016	5	2236	2.23
2017	6	2146	2.79
2018	10	1943	5.14
2019	3	2011	1.49
2020	2	2006	0.99

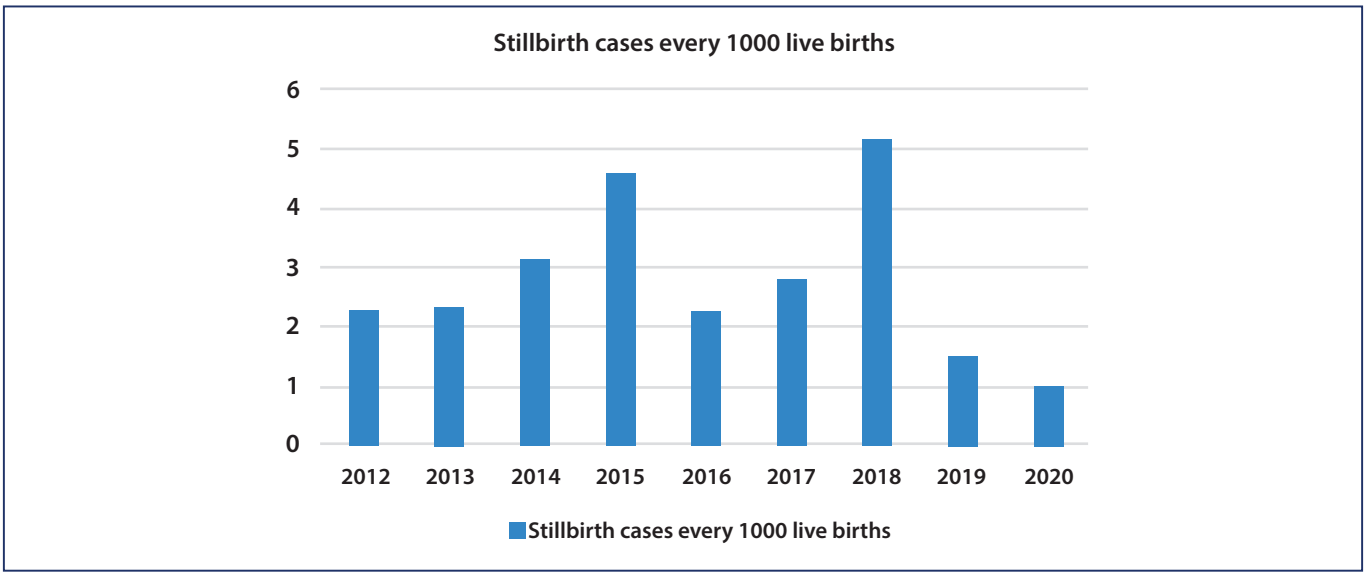

Figure 1. *Stillbirth cases every 1000 live births per year.*

A total of 19115 deliveries took place in the study period. The rate of stillbirth was, therefore, 2.77 per 1000 live births. A description of the number of stillbirth cases diagnosed per year is available on **Table 1** with a visual representation on **Figure 1**. Forty-eight cases out of 15098 deliveries (0.31%), took place until December 2018 (3.17 per 1000 live births) in comparison to 5 cases out of 4017 deliveries (0.12%) from January 2019 (1.19 per 1000 live births). Therefore, a significant reduction in the rate of stillbirths has been demonstrated ($p = 0.03$).

Maternal characteristics and pre-pregnancy risk factors

Mean maternal age at diagnosis was: 31.6 ± 4.2 years. Almost half of the study population was at her first pregnancy 26/53 (49%). Mean BMI was 26.6 ± 4.08. Obese women were 9/53 (16.9 %). All women but 3 (50/53, 94.3%) were of Italian origin, one European and two were extra European (African).
Six women had a low level of education as compared to 40 with a medium/high level of education, unknown for 6/52 women.
One patient was affected by sickle cell anaemia, two by idiopathic thrombocytopenia, one by type II diabetes mellitus, six (6/53, 11.3%) by subclinical hypothyroidism (a dosage of thyroid-stimulating hormone (TSH) level above 2.5 mU/L at the first trimester of pregnancy), 14/53 (26.4%) were affected by coagulation disorders (Heterozygous mutation of both Factor V Leiden and Factor II 2/14; Protein S deficiency 5/14; heterozygous mutation of Factor V Leiden 6/14; both heterozygous mutation of Factor V Leiden and Protein S deficiency 1/14). Of these last only 4/14 were aware of the disorder and under treatment with low weight heparin, the remaining 10 were diagnosed during hospital stay.
Six women out of 53 (11.3%) declared to smoke cigarettes, no one declared to use drug or drink alcohol. Four women had experienced at least one previous abortion during the first trimester of pregnancy; one of these had a second trimester Intrauterine foetal death (20 weeks of gestation). Four pregnant women reported a previous pregnancy complicated by intrauterine growth restriction/Preeclampsia.
A visual representation of the pre-pregnancy risk factors prevalence is reported on **Figure 2**.

Pregnancy characteristics and related risk factors

Mean gestational age at stillbirth diagnosis was 32.39 ± 5.02 weeks of gestation. One case was a late term pregnancy (41 weeks of gestation). All pregnancies had a spontaneous conception with a single foetus.
Thirty of the 53 foetuses (56.6%) were males. One foetus was diagnosed with Trisomy 13 at delivery: one presented generalized hydrops and one a single umbilical artery at the post-mortem examination.
No cases of congenital infections (Toxoplasma, Rubella, Cytomegalovirus, Parvovirus B19, Syphilis, HIV, HBV, and HCV) occurred in the study population. In eight cases (8/53, 15.09%) pregnancy was complicated by GDM, one needed treatment

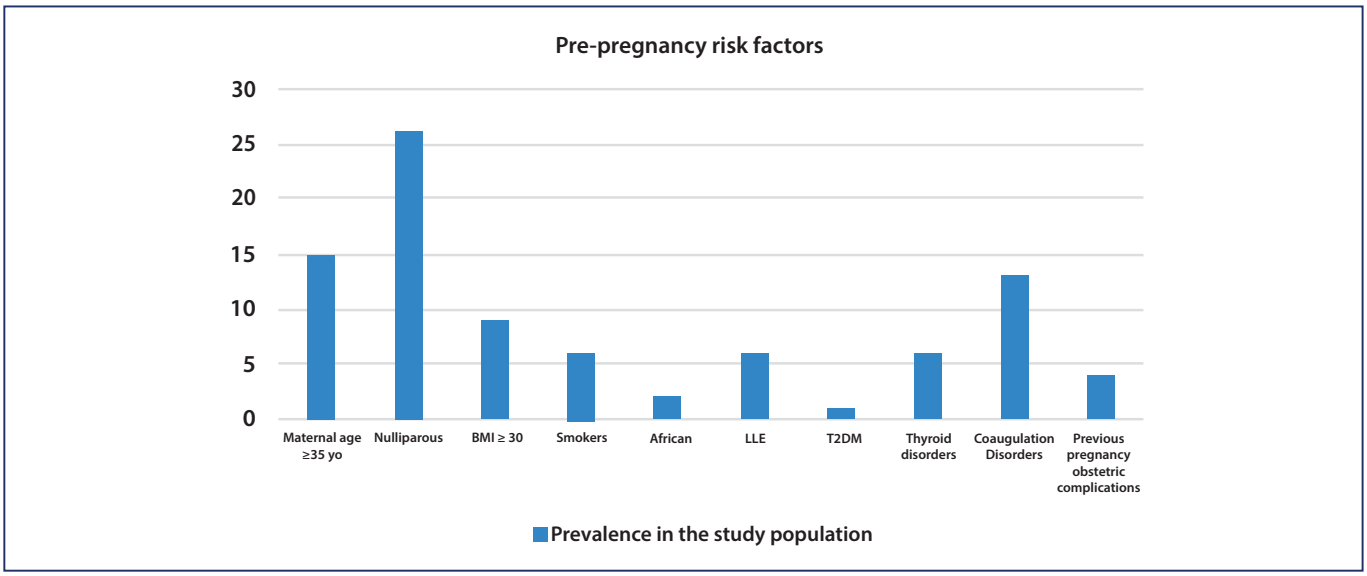

Figure 2. *Visual representation of the pre-pregnancy risk factors prevalence.*
Yo: Years Old; BMI: Body Mass Index; LLE: Low Level of Education; T2DM: Type 2 Diabetes Mellitus.

with Insulin, the remaining only diet ad exercises; of these, only one foetus was considered as large for gestational age at birth.
In five cases (5/53, 9.4%) pregnancy was complicated by one of the hypertensive disorders of pregnancy (HDP), two cases were diagnosed as gestational hypertension and three as preeclampsia. All pregnancies complicated by an HDP had a reduced amniotic fluid volume.
Six stillborn foetuses were LGA. Five out of six did not undergo the oral glucose tolerance test for GDM although four out of five were at risk for GDM according to the risk stratification criteria proposed by the Italian diabetes society.
A new-born growth below the 10th centile was document for 30/53 (56.6%) cases, 26/30 (86.6%) were growth restricted (new-born weight below the 3rd centile) whereas 4/30 (13.3%) were small for gestational age (new-born weight below the 10th centile).
A reduced amniotic fluid volume (oligohydramnios: deepest vertical pocket of amniotic fluid less than 2 cm) was described at the admission scan in 21/53 cases (39.6%). Of these, one was the consequence of Preterm Pre labour Rupture of Membranes (PPROM), 16/21 (76.1%) associated to a growth restricted foetus and or to an HDP.
Chorioamnionitis has been reported in two cases, one of these was also a Preterm Pre labour rupture of membranes. A visual representation of pregnancy related risk factors available on **Figure 3**.
Mode of delivery has been via caesarean section for 24/53 (45.2%) women. Indications were placental abruption for 3/24 cases (12.5%); previous caesarean section 3/24 cases (12.5%); elective caesarean section due to a refuse for induction of labour 18/24 (75%). A placental examination was performed for 20/53 (37.7%) cases. Different patterns have been reported: 11/20 (55%) sub chorionic ischemic haemorrhagic foci; fibro sclerotic placental areas in 6/20 (30%) cases; placental calcification areas 4/20 (20%) cases; placental abruption in 3/20 (15%) cases.
A summary of pre-pregnancy/pregnancy related risk factors with placental evaluation for each of stillbirth cases is available on **Table 2**.
Placental abruption occurred in three cases, one of these associated with a SGA foetus, whereas no association with PE has been described.
A true tight knot of the umbilical cord was documented after delivery in 4/53 cases (7.5%), while umbilical cord around the stillborn baby neck or body was described in 15/53.
Placental abruption occurred in three cases, one of these associated with a SGA foetus, whereas no association with PE has been described.
A true tight knot of the umbilical cord was documented after delivery in 4/53 cases (7.5%), while umbilical cord around the stillborn baby neck or body was described in 15/53.

DISCUSSION

Almost 2 million babies are stillborn every year. The vast majority occur in low/middle-income countries [23]. Whereas high income countries such as United Kingdom or United States of Amer-

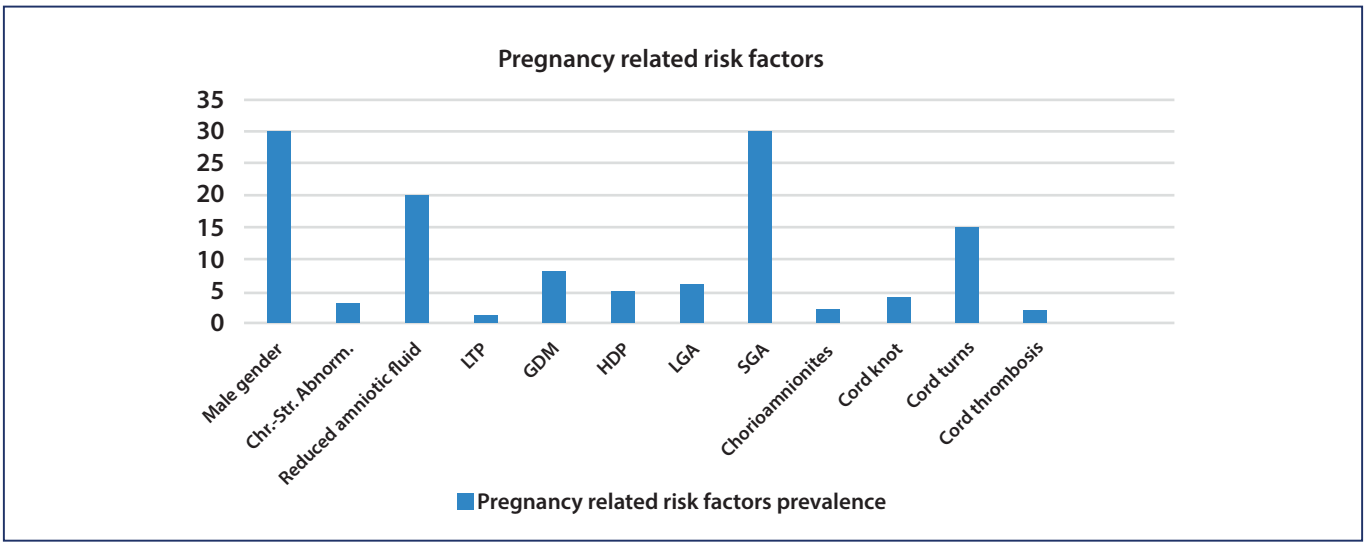

Figure 3. *Visual representation of pregnancy related risk factors.*
Chr-Str. Abnorm: Chromosomal-Structural abnormalities; LTP: Late Term Pregnancies; GDM: Gestational Diabetes Mellitus; HDP: Hypertensive Disorders of Pregnancy; LGA: Large for Gestational Age; SGA: Small for Gestational Age

Table 2. *Stillbirth cases description.*

NS	Pre-pregnancy risk factors	Obstetric risk factors	GA	Placental examination
FR	Unexplained	Unexplained	26	Placental weight 200 g; cord length 40 cm, central insertion Placenta histology unavailable
MM	-	Growth restricted new-born (1°) Cord Thrombosis	28	Placental weight 150 g; cord length 50 cm, central insertion, proximal chord thrombosis Placenta histology unavailable
AV	Unexplained	Unexplained	37	Placental weight 495 g, cord length 60 cm, central insertion Subchorionic ischaemic haemorrhagic foci
PN	42 yo	LGA	37	Placental weight 500 g, cord length 60 cm, central insertion Subchorionic ischaemic haemorrhagic foci
MF	Unexplained	Unexplained	40	Placental weight 495 g, cord length 50 cm, central insertion 1 cm peripheral area haemorrhagic necrosis
MLG	Para 0 Sickle cell	Placental abruption	30	Placental weight 200 g, cord length 50 cm, central insertion Placental abruption
VF	Para 0	Growth restricted new-born (1°)	23	Placental weight 80 g, cord length 20 cm, central insertion. 2 cord turns around neck and body
ZB	Para 0, African, LLE, BMI ≥ 30, SS	-	31	Placental weight 300 g, cord length 50 cm, central insertion. Placental histology unavailable
FG	35 yo, LLE, BMI ≥ 30 Idiopathic Thrombocytopenia	-	37	Placental weight 400 g, cord length 50 cm, central insertion. Fibro sclerotic placental areas Subchorionic ischaemic foci 1 cord turn around body
LC	Overweight	LGA	39	Placental weight 650 g, cord length 50 cm, central insertion.
AP	Para 0, SS Coagulation disorder: Heterozygous Factor V Leiden and Factor II Mutation	Growth restricted new-born (2°)	26	Placental weight 110, cord length 50 cm, central insertion. No abnormal placental histological findings.
AS	Para 0	Growth restricted new-born (1°)	24	Placental examination unavailable
VL	38 yo, Idiopathic Thrombocytopenia and Coagulation disorder: Heterozygous Factor V Leiden Mutation	Growth restricted new-born (1°)	30	Placental weight 200g, cord length 30 cm Subchorionic ischaemic haemorrhagic foci N 2 cord turns around neck
AS	LLE, BMI ≥ 30 Type II Diabetes Mellitus	SUA	37	Placental weight 500g, cord length 50 cm, central insertion. Fibro sclerotic placental areas Subchorionic ischaemic foci N 1 cord turn around foetal arm
AR	-	SGA (9°)	33	Placental weight 330 g, cord length 60 cm, central insertion Fibro sclerotic placental areas Subchorionic ischaemic foci
PD	Para 0, 35 yo	Growth restricted new-born (1°)	35	Placental weight 250 g, cord length 50 cm, central insertion. Placental histology unavailable N2 cord turns around neck and body
SM	37 yo Previous SGA foetus	Growth restricted new-born (1°)	34	Placental weight 240g, cord length 50 cm, central insertion. Fibro sclerotic placental areas Subchorionic ischaemic foci
CA	Para 0, BMI ≥ 30, SS	GDM insulin GH	40	Placental weight 500 g, cord length 60 cm, central insertion Placental histology unavailable
MI	35 yo, LLE, BMI ≥ 30	GH Growth restricted new-born (2°)	31	Placental weight 200 g, cord length 60 cm, central insertion. Subchorionic ischaemic foci

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NS	Pre-pregnancy risk factors	Obstetric risk factors	GA	Placental examination
RS	Para 0 Coagulation disorder: Protein S deficiency	-	36	Placental weight 500 g, cord length 60 cm, central insertion Placental histology unavailable
SA	Para 0, BMI ≥ 30	LTP True Knot of the umbilical cord	41	Placental weight 500 g, cord length 80 cm, central insertion interstitial blood extravasations cord vascular congestion One true cord knot
MC	Para 0 Thyroid disorders: hypothyroidism	True Knot of the umbilical cord	39	Placental weight 460 g, cord length 60 cm, central insertion interstitial blood extravasations cord vascular congestion One true cord knot
PR	-	Growth restricted new-born (1°)	32	Placental weight 280 g, cord length 50 cm, central insertion Placental histology unavailable
MM	Unexplained	Unexplained	39	Placental examination unavailable
NV	Para 0 Coagulation disorder: Heterozygous Factor V Leiden Mutation Known and treated	GDM diet	40	Placental weight 500 g, cord length 60 cm, central insertion Placental histology unavailable N1 cord turn around foetal body
RC	-	SGA (6°) Placental abruption	38	Placental weight 450 g, cord length 60 cm, central insertion Placental abruption
NP	-	GDM diet PE Growth restricted new-born (1°) Chorionamnionites	31	Placental weight 200 g, cord length 60 cm, central insertion. interstitial blood extravasations cord vascular congestion evidence of acute chorionamnionites
SD	-	Growth restricted new-born (1°)	32	Placental examination unavailable
PA	35 yo, SS, LLE Thyroid disorders: hypothyroidism	GDM diet	38	Placental weight 575 g, cord length 50 cm, central insertion. Placental calcification areas N 2 cord turns around foetal body
RD	Para 0	Growth restricted new-born (1°)	38	Placental weight 300 g, cord length 50 cm, central insertion Subchorionic ischaemic foci
AA	Previous SGA foetus, SS; BMI ≥ 30 Coagulation disorder: Heterozygous Factor V Leiden Mutation, known and treated	Growth restricted new-born (1°)	26	Placental weight 5 0g, cord length 25 cm, marginal insertion. Subchorionic ischaemic foci Placental calcification areas
GS	37 yo, LLE, BMI ≥ 30 Poliabortivity (one Second trimester spontaneous IUFD (19 weeks) Coagulation disorder: Heterozygous Factor V Leiden Mutation known and treated	SGA (6°)	30	Placental weight 240 g, cord length 40 cm, central insertion Haemorrhagic endovasculitis Necrotic trophoblast Placental infarctions
PN	Previous pregnancy GDM SGA Coagulation disorder: Heterozygous Factor V Leiden Mutation	GDM diet Growth restricted new-born (1°) True Knot of the umbilical cord	28	Placental weight 100 g, cord length 25 cm, central insertion Placental histology unavailable N1 true cord knot
ES	38 yo	Growth restricted new-born (2°)	38	Placental weight 230 g, cord length 55 cm, central insertion Fibro sclerotic placental areas Subchorionic ischaemic foci Placental calcification areas N1 cord turn around foetal body
SA	Para 0 Thyroid disorders: hypothyroidism	Growth restricted new-born (1°)	26	Placental examination unavailable
CG	35 yo Previous pregnancy PE and SGA	Trisomy 13 Growth restricted new-born (1°)	23	Placental examination unavailable
SD	Para 0, 36yo	PE Growth restricted new-born (1°)	27	Placental weight 100 g, cord length 20 cm, marginal insertion Placental histology unavailable

NS	Pre-pregnancy risk factors	Obstetric risk factors	GA	Placental examination
AC	Para 0, 35 yo	GDM diet	39	Placental examination unavailable
SC	BMI ≥ 30 Coagulation disorder: Heterozygous Factor V Leiden and Factor II Mutation	Growth restricted new-born (1°)	31	Placental weight 120 g, cord length 35 cm, central insertion Necrotic trophoblast Placental infarctions
GA	Thyroid disorders: hypothyroidism Overweight	LGA	29	Placental weight 400 g, cord length 60 cm, central insertion Subchorionic thrombotic areas Placental infarctions
LR	42 yo	Chord thrombosis	34	Placental weight 425 g, cord length 50 cm, central insertion. Fibro sclerotic placental areas N 2 cord turns around neck Chord thrombosis
SA	Para 0, 36 yo Thyroid disorders: hypothyroidism Coagulation disorder: Protein S deficiency	LGA	27	Placental examination unavailable
DA	-	Hydrops LGA	29	Placental weight 1000 g, cord length 42 cm, central insertion interstitial blood extravasations
SS	Para 0 Thyroid disorders: hypothyroidism Coagulation disorder: Heterozygous Factor V Leiden Mutation	Growth restricted new-born (2°)	31	Placental weight 200 g, cord length 50 cm, central insertion Ischaemic Haemorrhagic placental areas N1 cord turn around neck
FR	Para 0	Growth restricted new-born (1°)	26	Placental examination unavailable
MF	Para 0 Coagulation disorder: Heterozygous Factor V Leiden Mutation And Protein S deficiency	GDM diet LGA	35	Placental weight 560 g, cord length 60 cm, central insertion. Ischaemic Haemorrhagic placental areas N1 cord turn around neck
VR	Coagulation disorder: Protein S deficiency Known and treated	Growth restricted new-born (1°)	29	Placental weight 100 g, cord length 30 cm, marginal insertion Intervillous thrombosis
EA	Para 0, 35 yo, African	GDM diet PE Growth restricted new-born (1°)	29	Placental weight 150 g, cord length 45 cm, central insertion Ischaemic Haemorrhagic placental areas
PM	-	Growth restricted new-born (2°) Placental abruption	35	Placental weight 300 g, cord length 50 cm, central insertion. Placental abruption
SR	Coagulation disorder: Protein S deficiency	Growth restricted new-born (1°)	30	Placental weight 140 g, cord length 25 cm, central insertion Ischaemic Haemorrhagic placental areas
SD	-	True Knot of the umbilical cord	35	Placental examination unavailable
CG	Para 0	Growth restricted new-born (1°) PPROM Chorioamnionites	28	Placental weight 150 g, cord length 35 cm, central insertion Ischaemic Haemorrhagic placental areas Placental calcification areas Acute chorionamnionitis
FC	SS Coagulation disorder: Protein S deficiency	SGA (9°)	33	Placental examination unavailable

NS: patient initial name and surname; Yo: Years old; Para 0: nulliparous; LLE: Low level of education; BMI: Body Mass Index; SS: Smoker status; SGA: Small for gestational age; IUFD: Intrauterine Foetal Death; PE: Preeclampsia; LGA: Large for gestational age; GDM: Gestational diabetes mellitus; LTP : Late term pregnancy; GH: Gestational hypertension.

ica report a stillbirth rate that varies from 3.75 to 6 cases every 1000 live births [23, 24].

In our population, stillbirth rate had been lower than other countries and Italian regions, even if our population carries a significant proportion of women considered to be "at risk" for adverse pregnancy outcomes, principally due to advanced maternal age [25], overweight/obesity and GDM [26]. We documented an overall rate for stillbirth of 2.77 out of 1000 live births, ranging from 3.17 cases every 1000 live births before 2019 to 1.19 cases every 1000 live births after.

Four cases have been concluded to be unexplained. No pre-pregnancy or pregnancy related risk factors

have been detected for these pregnancies. According to the last American College of Obstetrics and Gynaecologists stillbirth consensus [3] the most frequent pre-pregnancy risk factors detected in our study population have been maternal overweight/obesity, nulliparity, sub-clinic hypothyroidism and coagulation disorders.

In our unit a complete evaluation both for inherited and acquired coagulation disorders has been historically, routinely performed in the occurrence of a stillbirth case. According to the above-mentioned consensus inherited coagulation disorders should not have to be considered as risk factors for foetal death [3]. Although there is evidence that support the association of inherited coagulation disorders with stillbirth in the presence of a foetal growth restriction [27]. Interestingly our retrospective study has shown that a significant proportion of women were affected by inherited coagulation disorders (mutation on factor V and or Factor II of the coagulation, Protein C or S deficiency) and, more than half carried pregnancies as well complicated by foetal growth restriction. At the occurrence of a stillbirth case, to prevent recurrent cases, it appears crucial to test women not only for acquired but as well for inherited coagulation disorders.

Growth disorders have been the most common pregnancy related risk factors. It has been already proven how infants born at the extremes of birth weight have a higher risk of adverse perinatal outcome [28]. Indeed, in our study population more than half cases were affected by growth disorders. In detail, small for gestational age/growth restricted new-born accounted for 56.6% of cases and 11.3% were large for gestational age. Among these last, four out of six cases did not undergo the oral glucose tolerance test to rule out GDM, even if all of them were "at risk" for glucose intolerance during pregnancy according to the risk stratification criteria proposed by the Italian diabetes society [17]. Considering the high prevalence of GDM in our region [26, 28] is therefore likely that these cases were related to a potential undiagnosed GDM. It is well known that a missed GDM diagnosis associates with a higher rate of stillbirth [29, 30]. In order of frequency the medical conditions that affected more our study population were inherited coagulation disorders (26.4%), GDM (15%) and hypertensive disorders of pregnancy (9.4%). No one case resulted to be affected by a congenital infection. National guidelines recommend monitoring pregnant women for Toxoplasmosis and Rubella although Cytomegalovirus is routinely checked as well. A great attention is given to prevent infections during pregnancy; indeed, our study population has proven the non- significant role that these conditions have on stillbirth rate [31]. Thirty per cent of cases occurred at term, (≥ 37 weeks of gestation). In high income countries, one-third of stillbirths occur at term [32]. Potentially preventable stillbirth cases, defined as those in whom if the probable cause of death may have been diagnosed or prevented by enhanced prenatal care, include placental insufficiency, medical complications of pregnancy, hypertensive disorders of pregnancy, preterm labour, intrapartum, and multiple gestations. From our retrospective analysis a 22.6% (12/53) of potentially preventable cases have emerged. Pregnancy complicated by growth disorders (growth restriction or overgrowth 7/12), GDM 4/12 and or HDP 1/12 would have had benefit from a timed induction of labour.

This data agrees to what has been proven by a study investigating stillbirth in a large cohort that has found a 22.3% of potentially preventable cases with an adequate antenatal care [33].

Our study has highlighted a significant drop in stillbirth incidence from 2019, the year during which the first internal protocol for induction of labour specific for each pre-pregnancy/pregnancy related complication has been approved and introduced in clinical practice, in agreement to national and international guidelines (a summary available on **Table 3**).

We did observe that, 31.2% (15/48) of the cases occurred before 2019, were "term" stillbirths (≥ 37 weeks of gestation) and 80% (12/15) of these were potentially preventable applying the subsequently introduced protocol for induction of labour.

This is the most relevant strategy introduced in our department from 2019, the only one that can potentially explain the drop in the stillbirth incidence of our unit.

Therefore, it appears evident that the application of a rigorous protocol for induction of labour may have a pivotal role in the reduction of stillbirth's rate.

From 2019, five stillbirth cases were recorded, four were pregnancies at risk for adverse outcomes, only one diagnosed with a true cord knot at delivery, otherwise low risk. An impaired growth occurred for 4/5 cases. Italian health care system does not routinely offer a third trimester growth scan to pregnant women, moreover no national guidelines are available for the management of growth restricted foetuses therefore these both,

Table 3. *Internal protocol for induction of labour introduced on January 2019 [references 19-22, 34-37].*

Advanced maternal age	39 weeks of gestation
Obesity (BMI ≥ 30 at dating scan)	39 weeks of gestation
Coagulation disorders under treatment	40 weeks of gestation
Late term pregnancy (≥ 41 weeks of gestation)	41 weeks of gestation
Small for gestational age (Estimated foetal weight < 10th centile, normal Doppler 37 weeks of gestation)	37 weeks of gestation
Type 1/2 Diabetes Mellitus	38 weeks of gestation
Gestational diabetes mellitus well tolerate well tolerate on diet **Gestational diabetes mellitus well tolerate under medication** **Gestational diabetes mellitus not well tolerate under medication**	40 weeks of gestation 39 weeks of gestation 37-38 weeks of gestation
Hypertensive disorder of pregnancy well tolerate under medication	37 weeks of gestation
Premature rupture of membranes with positive swab for Beta Agalactiae Streptococcus at term	Immediate induction of labour
Premature rupture of membranes with negative swab for Beta Agalactiae Streptococcus at term	At 24 h from the spontaneous rupture of membranes
Premature rupture of membranes after 34 weeks of gestation	Induction of labour
Hepatic cholestasis	37-38 weeks of gestation according to Biliary acid levels
Persistent reduced foetal movements	37 weeks of gestation

may have played a crucial role in the stillbirth's incidence from 2019.

Seven out 53 (13.2%) cases occurred at a gestational age major of equal to 39 weeks of gestation (one without any risk factor, two with a cord knot detected at delivery the remaining complicated by either growth disorder or GDM). The Arrive Trial published on 2018 [38], taught us that an induction of labour at 39 weeks of gestation, even for low-risk pregnancies, associates with a lower rate of perinatal death. Considering the heavy impact that every single stillbirth case has, the implementation of an induction of labour strategy at 39 weeks even for low-risk pregnancy should be seriously considered. World Covid-19 pandemic has been demonstrated to associate with a 2.3% rate of stillbirth for affected pregnant women [41, 42], our retrospective analysis did not consider 2021 therefore further study will be aimed to assess the impact of pandemic on stillbirth incidence.

Almost half of our study population (45.2%) did refuse an induction of labour in favour of an elective caesarean section, this rate is much higher than the one recommended by the World of health organization. Alarmingly stillbirth in our unit has practically become a non-obstetric indication to caesarean section according to women attitude [39, 40]. Psychological counselling protocols are crucial to reduce women's attitude toward caesarean section rather than induction of labour, however, historical practice is difficult to change and require a certain time [43, 44]. A summary of the study of the study major findings is available on **Table 4**.

Limitations

Our study presents several limitations: first, the retrospective design of the study, secondly the limited period of time available from our electronic database, that has been introduced only in 2012 and finally the limited agreement from families to post-mortem autopsy due to religious belief.

Table 4. *Key points.*

1	The overall rate of stillbirths has been 2.77 out of 1000 live birth
2	Inherited Coagulation disorders, not traditionally considered as potential risk factors for stillbirth accounted for 26.4% of our study population
3	Small for gestational age/growth restricted new-born accounted for 56.6% of our study population. This pregnancy-related complication has been persistently present through years among stillbirth cases
4	A significant drop in stillbirth incidence has been reported from 2019 the year of the introduction of an internal rigorous protocol for Induction of labour specific for each pre-pregnancy, pregnancy related complication. (3.17 cases every 1000 live births before 2019 versus 1.19 cases every 1000 live births from 2019, respectively, p = 0.039)
5	22.6% of all cases would have been prevented with a better antenatal care (appropriate management of growth disorders, timed induction of labour for each of the obstetric complications, universal induction of labour at 39 weeks of gestation for low-risk population)
6	A Caesarean section has been performed for 45.2% of women, more than half of this population (75%) refused an induction of labour in favour of an Elective Caesarean Section

CONCLUSIONS

Analysing each stillbirth case relevant information have emerged. Twenty percent of cases were potentially preventable with a better antenatal care (appropriate management of growth disorders, timed induction of labour). Inherited coagulation disorders as well as acquired, should be routinely checked to prevent recurrent cases. Psychological support and extensive obstetric counselling are crucial to help women in acceptance and trust to the unit moreover to reduce unnecessary caesarean section.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

P.Q., G.S., M.M.: Protocol/project development. PQ., FI, VZ: Data collection or management. P.Q.: Data analysis. P.Q., G.S., M.M.: Manuscript writing/editing. R.V., C.D.C., M.M., C.V., F.Z.: Writing - review & editing. R.V., C.D.C.: Supervision.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

Ethics approval for this study was obtained from the Institutional Review Board, Regione Calabria Sezione area Centro (Protocol number 27 of the 21st of January 2021).

Informed consent

Informed consent was waived because of the retrospective nature of the study and the analysis used anonymouse clinical data.

Data sharing

Data are available under reasonable request to the corresponding author.

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