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Original Research

Pregnancy Outcomes Subsequent to Stillbirth—A Single Tertiary-Care Center Experience

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Abstract

Background: Currently, there is little evidence to guide clinical management of pregnancies after stillbirth. Our study aims to evaluate the pregnancy outcome in pregnant women with a previous stillbirth, by applying a standardized protocol for etiologic investigations and subsequent treatment of the underlying etiology. **Methods**: A retrospective cohort study on a group of 100 women with history of stillbirth, occurred in single pregnancy between 2005 and 2021, was performed. All patients were followed up in their subsequent pregnancies (n = 153) in a tertiary university hospital. During the preconception period causes of stillbirth were investigated and a correction of modifiable risk factors was encouraged with a multidisciplinary approach. Data about pregnancy management, obstetric complications, gestational age at delivery, mode of delivery and neonatal outcomes were collected. **Results**: The analysis of previous stillbirth revealed that, by using the ReCoDe classification, the most common identifiable causes of death were fetal growth restriction (21%), placental abruption (11%) and "other placenta insufficiencies" (26.7%), whereas 15.8% of stillbirth was unexplained. Out of 153 subsequent pregnancies, 131 (85.62%) resulted in live births, 15 (9.8%) in a first trimester miscarriage, and 7 (4.57%) in second trimester miscarriage; no cases of stillbirth recurrence occurred. Obstetric complications in subsequent pregnancies included gestational diabetes (21.4%), gestational hypertensive disorders (6.1%), intrahepatic cholestasis of pregnancy (3.8%), fetal growth restriction (7.6%) and preterm birth (19.8%). The mean gestational age at delivery was 38 weeks with a mean birth weight of 2886.63 g. **Conclusions**: Our experience is encouraging as reflecting good outcomes in terms of live birth rate in the subsequent pregnancies, with no cases of recurrence. These results are probably due to extensive preconception investigations with a multidisciplinary approach. A preconception evaluation is, thus, essential to improve maternal and fetal outcome in case of history of stillbirth, aiming to minimize the risk of recurrence.

Keywords: stillbirth; recurrence; fetal deaths; subsequent pregnancy; preconception evaluation

1. Introduction

Stillbirth represents the most fearful obstetric complication and unfortunately continues to be a significant challenge in global public health [1]. Global estimates indicate that every year more than 2.6 million stillbirths occur in the third trimester of pregnancy, and that more than 55% of stillbirths happen in the antepartum period [2–4].

In the last Stillbirth Lancet's Series, every country has been called to eliminate all preventable stillbirths with the goal to achieve a rate of 12 stillbirths or fewer per 1000 total births (resulting in a global average of nine stillbirths per 1000 total births) [5]. The stillbirth rate is considered a marker of antenatal and intrapartum care quality, and of a health system's strength [6,7]. Fortunately, Italy is one of the high-income countries in which the stillbirth rate has declined the most in the last 20 years with a current rate of 3.3/1000 [8]. However, estimating the real global incidence is difficult as the numbers of stillbirths are not accurately recorded in low-income countries where the condition occurs most frequently [9]. Moreover, differences in definitions of stillbirth among countries regarding birth weight and gestational age make challenging the comparisons of perinatal mortality rates [10].

The World Health Organization (WHO) defines "fetal death" as the intrauterine death of a fetus at any time during pregnancy; WHO recommends reporting all fetal deaths $\geq$500 g and, when weight is not available, all fetal deaths occurring at gestational age $\geq$22 weeks [11,12]. For international comparison WHO recommends using the term "stillbirth" referring to a late fetal death that occurs at or beyond 28 weeks of gestation.

The United States National Center for Health Statistics and the International Stillbirth Alliance define stillbirth as a fetal death or loss that occurs after 20 weeks of pregnancy and before or during delivery, with further division into early stillbirth (20 to 27 completed weeks), late stillbirth (28 to 36 completed weeks), and term stillbirth ($\geq$37 completed weeks) [2].

Despite the controversies in terminologies and definitions, stillbirth is the result of the complex interaction among many factors (maternal, fetal and placental disorders). Despite numerous available classified systems, it

may be unexplained for various reasons, including the inadequacy of post-mortem investigations [13]. Unexplained stillbirths, which account for 25–59% of all stillbirths, still pose a challenge to modern obstetrics [14], causing a high degree of anxiety about future pregnancy outcomes among patients, their partners, and caregivers [15]. Categorization of the cause of a previous fetal death can allow to estimate the individual recurrence risk and to plan management strategies for future pregnancies.

There is conflicting evidence in the literature about the likelihood of recurrent stillbirth [14]. This risk is estimated to increase by two to tenfold among women with a prior stillbirth [16–19], regardless of the presence of additional obstetric risk factors [20]. Nevertheless, other studies report conflicting data, suggesting that in the absence of known risk factors, the recurrence risk after an unexplained stillbirth is not increased [21–23].

Moreover, a previous stillbirth is associated with an increased risk of adverse pregnancy outcomes, such as placental abruption, prematurity, fetal growth restriction (FGR) and preeclampsia (PE) [18,19,21,24].

There is currently little evidence to guide clinical management of pregnancies after stillbirth [14,25–27]. Increased antepartum surveillance and early birth is often suggested, but in many cases the benefits of these interventions remain uncertain and may lead to iatrogenic interventions. In fact, those pregnancies tend to be associated with higher rates of induction of labour, and caesarean section (CS), either because of medical concerns as well as because of patient and physician anxiety [21,24,28].

The aim of the present study was to evaluate a cohort of pregnant women with previous stillbirth and to assess the obstetric outcome of the subsequent pregnancy, using a standardized protocol for etiologic investigations and treatment of the underlying etiology.

2. Materials and Methods

A retrospective, observational, single-center cohort study was conducted in our Tertiary University Hospital (Careggi University Hospital, Florence, Italy). The study population included singleton pregnant women with a history of stillbirth between 2005 and 2021, occurred in our or other hospitals. We excluded all multiple pregnancies. These women were referred to our Regional Reference Center for High-Risk Pregnancies after the event of stillbirth for preconception counselling and pregnancy planning and/or for the management of the subsequent pregnancy.

The diagnosis of stillbirth was based on the World Health Organization recommendations and was defined as fetal death at the 22nd week of gestation or later, or birthweight greater than 500 g if the gestational age was unknown [11,12].

Patients were closely followed in our Preconception Clinics for eleven months an average after stillbirth, until a new conception.

Causes of stillbirth were investigated during the preconception period or, at the latest, in early pregnancy. The relevant causes of stillbirth were classified according to the ReCoDe (relevant condition at death) classification [29]. Evaluation of the cause of stillbirth includes a careful collection of information about baseline maternal characteristics (maternal ethnicity, age, pre-pregnancy body mass index [BMI], smoking habits, chronic maternal diseases), obstetric history and the gestational age when the death occurred [14,30–32]. We revised the documentation of the previous pregnancy complicated by stillbirth to obtain information about post-mortem investigations: placental pathology examination, fetal autopsy, fetal chromosomal analysis (from amniotic fluid or intracardiac blood or umbilical cord sampling). If stillbirth occurred in our hospital, we obtained this information from our electronic record systems, otherwise information was obtained from the paperwork provided by the patients. Maternal evaluation included a series of investigations according to a comprehensive protocol as previously published [33]. In brief, the protocol comprised measurement of maternal blood pressure, maternal blood tests for inherited and acquired thrombophilia, thyroid function, indirect Coombs test, screening for diabetes, serology for TORCH (“Toxoplasmosis”, “Others” “Rubeola”, “Citomegalovirus”, “Herpes”), anti-endomysium, anti- transglutaminase, and anti-gliadin antibodies. Genetic tests for the most common polymorphisms associated with celiac disease (HLA DQ2/DQ8) were also performed, as it has already been shown a higher prevalence HLA DQ2/DQ8 in women with a history of stillbirth, mostly in case of suboptimal fetal growth [34]. Patients with celiac disease or gluten sensitivity started a gluten free diet at least 3 months before the conception and throughout the course of the subsequent pregnancy.

During the preconception period, a correction of modifiable risk factors, such as smoking and obesity, was encouraged with a multidisciplinary approach. Overweight/obese patients and those affected by insulin resistance were referred to an endocrinologist and a nutritionist to optimize their BMI before pregnancy. They were treated with diet and physical activity alone or in combination with inositol and/or metformin, based on glycemia and insulinemia values.

Women with chronic systemic comorbidities were managed with a multisciplinary approach, involving a team of specialists such as endocrinologists, rheumatologists, immunologists, nephrologists, cardiologists, nutritionists, and psychologists. In case of autoimmune diseases, during the preconception period, management was modified aiming to optimize the activity disease in order to plan pregnancy in a moment of stability or remission, also changing type of medications to those least harmful for the fetus.

All patients were followed up during their subsequent pregnancies in our high-risk pregnancy Unit. They were screened for PE in the first trimester, using the test sug-

gested by the Fetal Medicine Foundation (FMF), based on maternal factors, uterine artery (UtA) pulsatility index (PI), mean arterial pressure (MAP) and serum placental growth factor (PlGF). A risk cut-off of 1 in 100 was used [35]. Obstetrics ultrasound was performed every 4 weeks in all patients to assess fetal biometry and fetoplacental Doppler.

Acetylsalicylic acid at a daily dosage of 150 mg, initiated before 16 weeks of gestational age, and continued until 36 weeks, was prescribed in women at high-risk of PE, identified by the screening proposed by the FMF or by anamnestic factors according to ACOG recommendations [36,37]. Due to the insufficient evidence supporting the role of anticoagulants in preventing stillbirth recurrence [38], the prophylactic therapy with Low Molecular Weight Heparin (LMWH) alone was prescribed, after a careful obstetrical evaluation, when the previous stillbirth was due to placental causes such as FGR or abruptio placentae or histological findings of placental hypoperfusion (infarctions >20% of the parenchyma, massive fibrin deposition, diffuse villous edema, decidual vasculopathy, incremented syncytial knots, chorangiosis, villous branching anomalies) associated or not with maternal congenital thrombophilia [39]. Prophylactic LMWH was also prescribed in women with thrombophilia to reduce the risk of Venous Thromboembolism, according to the Royal College of Obstetricians and Gynaecologists (RCOG) guidelines [40].

For women with antiphospholipid antibody syndrome (APS), a combination of acetylsalicylic acid plus LMWH was prescribed. As recommended, low-dose Aspirin was started prior to conception, or at least at the beginning of the pregnancy, and a prophylactic-dose of LMWH upon confirmation of intrauterine pregnancy [41]. When indicated hydroxychloroquine was started before the conception in APS women due to the immunomodulatory, mild-aggregate, and anti-inflammatory effects [42].

According to ACOG recommendation about the management of pregnancies after a stillbirth occurred at or after 32 weeks, we started antepartum surveillance once a week at 32 weeks or 1–2 weeks before the gestational age of the previous fetal death. For stillbirth occurred before 32 weeks, timing of antenatal surveillance was individualised based on associated risk factors [14]. The timing of delivery was individualized and shared with the woman and her partner after careful counselling. However, induction of labor has not been proposed before 38–39 weeks of gestation.

A psychological support with a dedicated specialist before conception and during pregnancy was offered to the woman and their families.

Data about the subsequent pregnancies, including pregnancy complications (gestational diabetes [GDM], gestational hypertensive disorders, intrahepatic cholestasis of pregnancy, FGR, preterm birth [PTB]), gestational age at delivery, mode of delivery and neonatal outcomes, were collected consulting medical records from ViewPoint (Seam Group), Argos and Archimed (medical records used in our hospital during outpatient and inpatient visits, respectively).

Birthweight was expressed in percentiles according to the Italian Neonatal Study [INeS] charts [43]. The collected data were entered in an electronic database. Percentages and means have been extrapolated, followed by the creation of charts and tables for a descriptive analysis. We compared the rate of obese women in the stillbirth group and the subsequent pregnancy group by using chi-square test. A p value < 0.05 was considered statistically significant.

3. Results

Our cohort included 100 women with a history of stillbirth. 153 subsequent pregnancies were recorded during the study's observation period.

The causes of previous stillbirth, using the ReCode classification [29], are summarized in Table 1. Among stillbirths, 15.8% were unexplained. The most common identifiable causes of death were FGR (21%), placental abruption (11%) and "other placenta insufficiencies" (26.7%), defined as histopathologic changes of placental insufficiency such as small placentas with decidual arteriopathy, infarctions in central portions of the placenta, abruption and intervillous thrombosis. Chorioamnionitis is identified as the cause of stillbirth in 6% of pregnancies and maternal conditions in another 6% (4% hypertensive disorders, 1% APS, 1% APS associated with systemic lupus erythematosus [SLE]). Neonates with a lethal congenital anomaly were 3%, 1% of cases was associated with nonimmune hydrops, 1% with isoimmunisation and 1% with fetomaternal haemorrhage. We identified only one case (1%) of intrapartum stillbirth caused by asphyxia and one intrauterine fetal death for intrahepatic cholestasis of pregnancy. In this cohort, one patient experienced 2 previous stillbirths, the first one due to chorioamnionitis and the second one to abruptio placenta.

The mean maternal age at the time of stillbirth was 30 years and the mean BMI 25 Kg/m^2 (62% normal weight, 6% underweight, 16% overweight, 16% obese). The mean gestational age at stillbirth was 30 weeks (32% early stillbirth, 36% late stillbirth, 32% term stillbirth) and the mean neonatal weight at birth was 2014 g; 53% (N = 53) of stillborn babies had a birth weight <10° percentile. No differences were found in stillborn gender distribution.

All the 153 subsequent pregnancies were followed up as previously described through a close clinic and ultrasound monitoring.

Prophylactic therapy was carried out as follows: 6 (6%) patients received a prophylactic daily dose (100–150 mg) of acetylsalicylic acid and 57 (57%) received the complete treatment with acetylsalicylic acid associated with LMWH for clinic or histopathological indications. Moreover, 28 women (28%) had a positive screening of thrombophilia, thus they were treated with a daily prophylactic dose of LMWH after positive pregnancy test and until 6 weeks after delivery, with a suspension during labor. For 9

Table 1. Causes of previous stillbirth, according the ReCode classification.

Group		N = 101 (%)
A	1. Lethal congenital anomaly	3 (2.9%)
FETUS	2. Infection	0 (0%)
	3. Non-immune hydrops	1 (0.9%)
	4. Isoimmunisation	1 (0.9%)
	5. Fetomaternal haemorrhage	1 (0.9%)
	6. Twin-twin transfusion	0 (0%)
	7. Fetal growth restriction	21 (20.7%)
B	1. Prolapse	1 (0.9%)
UMBILICAL CORD	2. Constricting loop or knot	2 (1.9%)
	3. Velamentous insertion	0 (0%)
	4. Other	1 (0.9%)
C	1. Abruptio	11 (10.8%)
PLACENTA	2. Praevia	0 (0%)
	3. Vasa praevia	0 (0%)
	4. Other “placenta insufficiency”	27 (26.7%)
	5. Other	0 (0%)
D	1. Chorioamnionitis	7 (6.9%)
AMNIOTIC FLUID	2. Oligohydramnios	1 (0.9%)
	3. Polyhydramnios	0 (0%)
	4. Other	0 (0%)
E	1. Rupture	0 (0%)
UTERUS	2. Uterine anomalies	0 (0%)
	3. Other	0 (0%)
F	1. Diabetes	0 (0%)
MOTHER	2. Thyroid diseases	0 (0%)
	3. Essential hypertension	0 (0%)
	4. Hypertensive diseases in pregnancy	4 (3.9%)
	5. Lupus or antiphospholipid syndrome	2 (1.9%)
	6. Intrahepatic Cholestasis of pregnancy	1 (0.9%)
	7. Drug misuse	0 (0%)
	8. Other	0 (0%)
G	1. Asphyxia	1 (0.9%)
INTRAPARTUM	2. Birth trauma	0 (0%)
H	1. External	0 (0%)
TRAUMA	2. Iatrogenic	0 (0%)
I	1. No relevant condition identified	16 (15.8%)
UNCLASSIFIED	2. No information available	0 (0%)

women, prophylaxis was not performed because of the absence of clinic or anamnestic risk factors or because the previous stillbirth was not associated with any placental findings of hypoperfusion/insufficiency.

In terms of obstetric outcome of the subsequent pregnancies, 131 (85.62%) resulted in live birth, however 15 (9.8%) ended in a miscarriage in the first trimester and 7 (4.57%) in second trimester miscarriage.

Maternal baseline characteristics at the time of subsequent pregnancy are summarised in Table 2. The mean maternal age at subsequent pregnancy was 32.49 years and the mean pre-pregnancy BMI 23.67 Kg/m^2 (62.1% normal weight, 7.85% underweight, 22.2% overweight and 7.85% obese), with a significant reduction in rate of obese women (16% vs 7.85%, *p*-value 0.04) compared to previous pregnancies.

Pregnancy complications reported in subsequent pregnancies include GDM (N = 28, 21.4%), gestational hypertensive disorders (N = 8, 6.1%), intrahepatic cholestasis of pregnancy (N = 5, 3.8%), FGR (N = 10, 7.6%) and PTB (N = 26 ,19.8%). Early PTB (before 34 weeks) occurred in 18 pregnancies (13.7%) whereas late PTB in 8 pregnancies (6.1%).

The mean gestational age at delivery was 38 weeks. The mean birth weight was 2886.63 g; 15 neonates (11.45%) had a birth weight $<10°$ percentile.

Table 2. Maternal baseline characteristics at the time of subsequent pregnancy.

Main maternal characteristics		N = 100	N = 100
		Index pregnancy	Subsequent pregnancy
Age (years)		30.14 ± 5.02	32.45 ± 4.99
BMI (Body Mass Index Kg/m^2)	Mean BMI	25 ± 6.7	23.67 ± 5.64
	Normal weight	62 (62%)	64 (64%)
	Overweight	16 (16%)	19 (19%)
	Underweight	6 (6%)	9 (9%)
	Obese	16 (16%)	8 (8%)
Ethnicity	Caucasian	63 (63%)	63 (63%)
	Others	37 (37%)	37 (37%)
Smoking status		2 (2%)	1 (1%)
Parity		1.07 ± 1.02	2.09 ± 1.04

Regarding the mode of delivery, 73 (55.7%) pregnancies ended in vaginal delivery: 38 (29%) experienced spontaneous labor and 35 had (26.7%) an induction of labor. 17 pregnancies (12.98%) ended in an urgent Caesarean section. In 41 cases (31.3%), an elective CS was performed. The indications for the elective CS were prior CS (n = 34, 82.9%), breech presentation (n = 3, 7.3%), maternal pathology (n = 2, 4.8%) and placenta previa (n = 1, 2.4%). Only in 2 cases (4.8%) the indication for CS was maternal request due to obstetrics history.

Pregnancy outcomes are shown in Table 3.

4. Discussion

Our study describes a cohort of 100 women with a history of stillbirth and pregnancy outcomes of the subsequent 153 pregnancies followed up in our tertiary-care center.

Several studies have found that previous stillbirth is a risk factor for subsequent stillbirth [16,44–47]. However, because of limitations in sample size and/or analysis, very few studies have estimated the recurrence risk in order to improve counselling and management.

In our study population, only in one case we identified a recurrence of stillbirth. However, this patient was referred to our center for a preconception visit only after the second stillbirth. APS and gluten sensitivity emerged from the preconception evaluation; therefore, according to our protocol, in the subsequent pregnancy (third pregnancy) low dose aspirin and LMWH were prescribed, and a gluten-free diet recommended. This pregnancy was uncomplicated, and at term elective CS was performed as per choice of the patient because of the previous CS, without maternal and neonatal complications.

Among women who were managed according to our diagnostic and therapeutic protocol, we did not report any case of recurrence. Our experience is encouraging as reflecting good outcomes in terms of live birth rate in the subsequent pregnancies. These results are likely due to an extensive preconception assessment in addition to a careful and strict obstetric follow up. A preconception evaluation, including a thorough investigation of the causes of stillbirth, is essential to improve maternal and fetal outcome of subsequent pregnancies and to reduce the risk of recurrence. In fact, this approach allows to identify and correct potential risk factors, such as smoking and obesity, to plan the next pregnancy, to institute therapeutic preventive strategies, and to provide an appropriate counselling to the couple. Regarding modifiable risk factors, for example, interventions in the preconception period resulted in our study population in a reduction in the average maternal BMI and statistically significant reduction in rate of obese women at subsequent pregnancy. Moreover, it is important to guarantee psychological support to the woman and her partner before conception and during the subsequent pregnancy as psychological sequelae include depression, posttraumatic stress disorder, and anxiety may adversely affect their relationship and subsequent pregnancy outcome [48].

It seems that the risk of recurrent stillbirth depends on the type of stillbirth. A recent cohort study [49] suggested that previous intrapartum stillbirth, is associated with an increased very high risk of recurrence, while the recurrence risk of antepartum stillbirth is low and may be higher in women with a previous SGA (small for gestational age) stillbirth. In fact, for women with a previous intrapartum stillbirth, the risk of another intrapartum stillbirth is very high (3.59%, RR (relative risk) 36.50, 95% CI (confidence interval) 20.17–66.05). Regarding antepartum deaths, the recurrence risk was higher in women with a previous SGA stillbirth (4.09%, RR 10.39, 95% CI 5.81–18.59) compared with women with a previous AGA (appropriate for gestational age) stillbirth without other risk factors, such as hypertensive disorders of pregnancy and pre-existing diabetes mellitus (0.97%, RR 2.46, 95% CI 1.23–4.91). Therefore, women with previous SGA stillbirth may benefit from careful surveillance, as ultrasound may identify FGR accurately. In a previous study, we found that 33% of stillbirths classified as unexplained were due to an undiagnosed FGR; this percentage was even higher (57%) using Gardosi customised growth curves, which define fetal weight on the

Table 3. Pregnancy outcomes of subsequent pregnancies.

Outcomes		N
Pregnancies after stillbirth	One pregnancy	64 (42.1%)
Total 153	Two pregnancies	25 (16.4%)
	Three or more pregnancies	11 (7.2%)
Pregnancy outcomes	Live birth	131 (86.27%)
Total 153	Early miscarriage	15 (9.8%)
	Late miscarriage	7 (4.57%)
Method of delivery	Spontaneous vaginal delivery	38 (29%)
Total 131	Vaginal delivery, Induced labor	35 (26.7%)
	Urgent C-section	17 (12.98%)
	Elective C-section	41 (31.3%)
Indication for elective C-section	Prior C-Section	33 (80.5%)
Total 41	Breech Presentation	3 (7.3%)
	Maternal pathology	2 (4.8%)
	Maternal request	2 (4.8%)
	Placenta previa	1 (2.4%)
2° and 3° trimester complication	Gestational diabetes mellitus	28 (21.4%)
Total 131	Early preterm delivery	16 (12.2%)
	Fetal growth restriction	10 (7.6%)
	Intrahepatic cholestasis of pregnancy	5 (3.8%)
	Hypertensive disorders	8 (6.1%)

basis of genetically determined growth potential adjusted for maternal characteristics [50].

Since FGR continues to be a leading cause of preventable stillbirth, we performed strict ultrasound monitoring of fetal growth with monthly checks in our study population.

Previous studies found that women with a previous stillbirth due to PTB, FGR, PE, placental abruption are at increased risk of stillbirth in a second pregnancy [16,51].

The tendency for these conditions to recur suggests common pathogenetic factors related to impaired placental function [16,24,51,52]. Screening methods to identify placental disorders during pregnancy and specific interventions may help preventing stillbirth [47]. For these reasons, all patients of our cohort of study underwent a careful assessment of anamnestic risk factors for placental insufficiency and PE screening in the first trimester, using the test proposed by the Fetal Medicine Foundation. When indicated, because of anamnestic risk factors according to ACOG guidelines or positive PE screening, low-dose aspirin prophylaxis has been prescribed. When previous stillbirth was due to placental insufficiency, but low dose aspirin was not indicated due to the absence of sufficient anamnestic risk factors according to ACOG recommendation or negative PE screening, LMWH therapy, from the first trimester, was prescribed.

Although a recent Cochrane review concluded that it was uncertain whether LMWH reduced the risk of stillbirth because of low quality evidence [3], LMWH was often prescribed in clinical practice for the prevention of placental complications. The effect of LMWH in these conditions does not seem related to its anti-coagulant action. It is well known that LMWH exerts beneficial actions on maternal vascular system, and has anti-inflammatory and immunomodulant effects, playing a potential role in embryo implantation and placentation [53]. In fact, LMWH seems to induce cytotrophoblast proliferation causing an ameliorated syncytial fusion in the syncytiotrophoblast layer that in turn secretes pro-angiogenic growth factors in the intervillous space [54]. Restoration of syncytial fusion promotes the expression of anti-coagulant proteins on the syncytiotrophoblast surface preventing the vasculopathy typical of severe placental insufficiency [55]. As an unbalanced inflammatory activation seems to play a key role in determining placental insufficiency, LMWH may be useful because of its anti-inflammatory activity [56]. However, standardised, trials investigating the potential role of LMWH for prevention of placenta-mediated disorders in women at the highest risk of these conditions are needed to confirm our hypothesis [53].

When specific risk factors for stillbirth are identified, the risk of recurrence may be better quantified. For example, maternal complications such as diabetes or chronic hypertension would explain the recurrence of stillbirth in a subsequent pregnancy, especially if adequate preconception control has not been achieved [20].

On the contrary, the evidence surrounding the recurrence risk in women with a previous unexplained stillbirth remains controversial and limited. A retrospective analysis reported adjusted risks for unexplained stillbirth af-

ter one previous stillbirth of 4.18 (95% CI 1.36–12.89), while two other studies reported adjusted risks of 3.11 (95% CI 0.72–13.50) and 1.00 (95% CI 0.23–4.30), respectively [22,57,58].

Data on management of pregnancies after an unexplained stillbirth are scant. Therefore, unexplained stillbirths represent the main challenge for obstetricians and further research is needed to clarify the involved pathogenetic pathways in order to improve the management of subsequent pregnancies [6].

Finally, our findings confirm that the subsequent pregnancies after stillbirth are associated with an increased risk of pregnancy complications, such as GDM, gestational hypertensive disorders, intrahepatic cholestasis of pregnancy, FGR, and PTB, as described previously in literature [17–19,21,24]. However, despite the limited sample of our study, our findings suggest that couples who have experienced a previous stillbirth can be reassured about the success of their future pregnancy when managed with a strict preconception evaluation and antenatal surveillance in a high-risk pregnancy center.

5. Conclusions

Management of the subsequent pregnancy after stillbirth poses a great challenge for obstetricians, given the inadequate quality evidence on stillbirth.

Our experience is encouraging as reflecting good outcomes in terms of live birth rate in the subsequent pregnancies with no cases of recurrence. These results are probably due to extensive preconception investigation with a multidisciplinary approach. A preconception evaluation is, thus, essential to improve maternal and fetal outcomes of subsequent pregnancies and to reduce the risk of recurrence.

Our findings confirm that the subsequent pregnancies after stillbirth are associated with an increased risk of pregnancy complications, therefore, a history of stillbirth should be considered an indication for careful antenatal surveillance in a high-risk pregnancy unit. Further efforts are needed to create a standardized, evidence-based protocol for the management of pregnancies after stillbirth.

Author Contributions

CS had the idea for the article and contribute to draft the manuscript. SC drafted the manuscript. EF, MH, FT collected the data. SV, FP and FM critically revised the work. All authors approved the final manuscript.

Ethics Approval and Consent to Participate

The study follows the principles of the Declaration of Helsinki. Participants gave written informed consent for inclusion in the study.

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Conflict of Interest

The authors declare no conflict of interest. SV is serving as one of the Editorial Board members/Guest editors of this journal. We declare that SV had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to LA.

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