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Subsequent pregnancy after stillbirth: obstetrical and medical risks

Abstract

Objective: To evaluate obstetric outcome after stillbirth according to placental and prothrombotic risk factors.

Methods: Obstetric outcomes of women with prior stillbirth and subsequent pregnancies were reviewed. Data on the immediate subsequent pregnancy included fetal loss, stillbirth, obstetric/medical complications, gestational age and birth weight at delivery, mode of delivery, thrombophilia, and prescribed medication. Placental stillbirth was defined as stillbirth associated with placental abruption, intrauterine growth restriction (IUGR), or histological evidence of placental infarcts. Controls were unselected women who gave birth at our center during a single calendar year. Factors influencing recurrence risks were estimated.

Results: Seventy-three subsequent pregnancies were identified. Five out of 73 (6.8%) women had a repeat stillbirth, significantly higher than controls (relative risk 22.2, 95% confidence interval 8.9–55.4). Four out of five repeat stillbirth cases occurred <37 weeks gestation. Hypertensive complications, diabetes and abruption were higher, while gestational age and birth weight at delivery were significantly lower than controls. Prior placental stillbirth was associated with a 10.5 times higher risk of IUGR in the subsequent pregnancy compared with non-placental stillbirth. All five repeat stillbirth cases occurred in thrombophilic women.

Conclusion: Women with prior stillbirth face an increased risk of pregnancy complications and stillbirth recurrence, especially with concurrent thrombophilia. Most repeat stillbirth cases occur preterm.

Keywords: IUFD; placental stillbirth; pregnancy after IUFD; pregnancy after stillbirth; stillbirth; thrombophilia pregnancy complications.

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Introduction

Late pregnancy stillbirth is an extremely difficult experience for couples and anxiety following such an experience often extends onto the following pregnancy. A limited number of studies have looked at obstetric and neonatal complications in pregnancies after stillbirth, with findings that are sometimes conflicting. Some studies have found evidence for increased risks of prematurity, low birth weight, placental abruption and medical interventions [3, 4, 12, 13, 16], while others found no such risks [14]. The risks of recurrent stillbirth have also not been clearly outlined, with several studies finding an increased risk of up to 10-fold higher, while others finding no such increase [3, 12, 14, 16, 20]. The conflicting results make it difficult and sometimes frustrating to counsel such couples as they contemplate a new pregnancy. Revealing the presumed cause or associated obstetric disorders related to the stillbirth can enable the design of prevention strategies and contribute to a more precise prognosis regarding subsequent pregnancies. Several causes of fetal death, including preeclampsia, abruption, and some cases of unexplained stillbirth with growth restriction [2, 7, 12, 22] have been related to placental dysfunction. Therefore, risk factors for placental dysfunction in pregnancy can possibly influence more than one pregnancy and affect recurrence risk.

In the current study, we aimed to evaluate pregnancy outcome in the subsequent pregnancy after a stillbirth pregnancy in a well-defined cohort of women with extensive post-stillbirth evaluation. Furthermore, we sought to outline risk factors for adverse obstetric outcomes in the following pregnancy, with specific emphasis on placental and pro-thrombotic factors.

Materials and methods

Women who were diagnosed at Sheba Medical center, Israel, with antenatal stillbirth after 22 weeks gestation between 1999 and 2009

were referred for evaluation and counseling to the stillbirth clinic. They were offered prenatal care and follow-up in the following pregnancy. Women with a documented subsequent pregnancy were included in this observational study.

A detailed medical and obstetric history was obtained. Emphasis was placed on placenta-associated pregnancy complications; placental abruption, early-onset preeclampsia / HELLP syndrome, intrauterine growth restriction (IUGR), recurrent fetal loss and stillbirth. Autopsy or placental pathology results were obtained, when available. A detailed thrombophilia screen [factor V Leiden, prothrombin 20210A mutation, methyl tetrahydrofolate reductase genotype (MTHFR), protein C, protein S, antithrombin, lupus anticoagulant, anticardiolipin and β-2 glycoprotein1 antibodies] was carried out on all women after the stillbirth event on peripheral blood samples collected for this purpose (details available from authors upon request).

Data on the subsequent pregnancy was prospectively collected, including the intrepregnancy interval, evidence of growth restriction, placental and cord abnormalities, infection (toxoplasma, rubella, cytomegalovirus, herpes virus, hepatitis and parvovirus), associated maternal risk factors (as outlined above), fetal gender, anatomical and chromosomal abnormalities (where available). Pregnancy outcome was recorded, including fetal loss, repeat stillbirth, placental abruption, gestational age and birth weight at delivery, induction of labor and mode of delivery, as well as medication taken during pregnancy.

Placental stillbirth was defined when fetal death was associated with placental abruption, IUGR and/or large or multiple infarcts, and fetal structural abnormalities were not found. A subgroup analysis was performed comparing pregnancy outcome in the subsequent pregnancy between women with and without prior placental stillbirth.

IUGR was defined as birth weight less than the 10th percentile adjusted for gestational age and gender according to locally derived tables [5].

We utilized as controls all women (n=10,370) who gave birth at Sheba Medical Center between January 1st, 2007 and December 31st, 2007. Data was extracted from a computerized database. The information in this database is entered prospectively by the obstetrician or midwife responsible for the laboring woman's medical care, and includes maternal demographics, obstetrical history, labor and delivery events and immediate neonatal outcome. Institutional research ethics board approval was obtained.

Statistical analysis was performed with SigmaStat 1.0 software (Jandel Engineering Ltd, Linslade, UK). Categorical data were compared using the Pearson chi-square test and Fisher exact test, as appropriate. Relative risks (RR) and 95% confidence intervals (CI) were calculated when appropriate and considered significant if the confidence interval excluded unity. Continuous variables were compared using the Student *t*-test when data were normally distributed and the Mann-Whitney rank sum test when not normally distributed. A P-value <0.05 was considered statistically significant.

Results

From 1999 to 2009, 347 women gave birth to stillborn infants at Sheba Medical Center, with a stillbirth rate of 3.17 cases per 1000 live births. Seventy-three women with a subsequent pregnancy after the stillbirth event were identified and composed the study group. Etiologies for the index stillbirth event were 24/73 (32.9%) placental (i.e., placental abruption, severe growth restriction, large/multiple placental infarcts), 7/73 (9.6%) maternal (i.e., hypertensive complications, uncontrolled diabetes mellitus), 8/73 (11%) cord accidents, 8/73 (11%) fetal causes (fetal anomaly/hydrops), 3/73 (4.1%) infection, and 23/73 cases (31.5%) were unexplained. Mean maternal age was 29.2±5.0 years at the time of the subsequent pregnancy, and this was, on average, 1.4±1.4 years after the initial stillbirth event. Median gravidity was 3 (range 2–9) while median parity was 2 (range 1–8). Thirty-four of 73 women (46.6%) had no liveborn children at the time of this pregnancy, although several (14/73) had previous miscarriages. During pregnancy, medication was prescribed at the discretion of the attending physician. Thirty-five women were treated with low molecular weight heparin (LMWH), 23 received low dose aspirin, six required antihypertensive medication and three women received insulin for the treatment of diabetes in pregnancy. Several women were treated with more than one medication.

Our control group consisted of 10,370 women who gave birth at Sheba Medical Center during 2007. Mean maternal age was 30.2±5.2, similar to the study group.

Study group women gave birth earlier, had an increased rate of induction of labor and their newborns had lower birth weights compared with controls (Table 1).

Table 1 Demographic and obstetric data in study group (subsequent pregnancy after prior stillbirth) and control group.

Characteristics	Study group (n=73)	Control group (n=10,370)	P-value
Maternal age (years±SD)	29.2±5.0	30.2±5.2	NS
Gestational age (weeks±SD)	36.9±3.2	38.8±2.0	<0.0001
Birth weight (g±SD)	2848±678	3214±528	<0.0001
Induction of labor (n/number of live born) (%)	35/56 (62.5)	2744/10338 (26.5)	<0.0001
C/S (n/number of live born) (%)	18/56 (32.1)	2567/10338 (24.8)	NS

C/S=cesarean Section, NS=not significant.

Women after stillbirth in our cohort had an increased risk of hypertensive pregnancy complications, diabetes mellitus and placental abruption compared with controls (Table 2). However, the rates of IUGR were quite similar between study and control groups.

Five repeat stillbirth events occurred among our 73 study group women, therefore, the risk of stillbirth was 22 times higher for study group women, compared with controls (6.8% vs. 0.3%, RR 22.2, 95% CI 8.9–55.4, P<0.0001). Three out of five women with repeat stillbirth events received prophylactic dose enoxaparin (40–60 mg/d) from the beginning of their prenatal care follow-up, two women received low dose aspirin in addition, and three women received other medications (Table 3). In addition to the above, one women suffered immediate neonatal death of an extremely premature infant born at 23 weeks after preterm ruptured membranes, and nine more study group women (12.3%) had pregnancies that ended with first trimester spontaneous miscarriage. There was also one case of ectopic pregnancy and one case of termination of pregnancy due to Trisomy 21. Therefore, the overall rate of take-home babies for the immediate subsequent pregnancy after stillbirth in our study group was 76.7% (56/73). Unfortunately, reliable information on the rates of miscarriage in our control population is not available, therefore, a comparison of fetal loss rates was not possible.

We defined placental stillbirth when fetal death was associated with placental abruption, IUGR and/or large or multiple infarcts on histological evaluation, and fetal structural abnormalities were not found. Twenty-nine of 73 women consented to pathological evaluation of fetus and/or placenta. Thirty women (41%) had evidence of prior placental stillbirth. Forty-three had prior non-placental stillbirth, of which 20 cases were unexplained. The frequencies of preterm delivery of <37 weeks' gestation and fetal loss rates were similar between women with prior placental and prior non-placental stillbirth. However, the risk of IUGR in the subsequent pregnancy after stillbirth was 10.5 times higher, and thrombophilic abnormalities were also more frequent in the prior placental stillbirth subgroup compared with the prior non-placental stillbirth subgroup (Table 4).

Results of thrombophilia screening were available for all study group women. Forty-two women (57.5%) had a positive thrombophilia screen, of which 12 were combined thrombophilias. The most prevalent thrombophilias were antiphospholipid antibodies (15/73 women, 20.5%), Factor V Leiden and Prothrombin G20210A mutations (12/73 women, 16.4%, each).

Table 2 Comparison of pregnancy complications and outcomes in subsequent pregnancy after prior stillbirth and control group.

Characteristics	Study group (n=73) (%)	Controls (n=10,370) (%)	P-value	Relative risk (95% confidence interval)
Hypertensive disorders	10 (13.7)	357 (3.4)	<0.0001	3.98 (2.2; 7.1)
Diabetes mellitus	10 (13.7)	719 (6.9)	0.042	1.97 (1.1; 3.5)
Placental abruption	2 (2.7)	41 (0.4)	0.028	6.93 (1.7; 28.1)
IUGR	7 (9.6)	926 (8.9)	NS	1.07 (0.53; 2.18)
Repeat stillbirth	5 (6.8)	32 (0.3)	<0.0001	22.2 (8.9; 55.4)

IUGR=intrauterine growth restriction, NS=not significant. Birth weight less that 10th percentile for gestational age.

Table 3 Repeat stillbirth in women with prior stillbirth.

Number	Medical background	Gestational age of 1st stillbirth	Assumed cause of 1st stillbirth	Treatment during subsequent pregnancy	Gestational age of 2nd stillbirth	Assumed cause of 2nd stillbirth
1	cHTN, FII heterozygous	26 weeks	Severe Preeclampsia	Anti HTN	22 weeks	Unexplained
2	FII homozygous, APLA	26 weeks	IUGR, Parvovirus infection	LMWH	24 weeks	IUGR
3	MTHFR+/+	30 weeks	Unexplained	LMWH, LDA, folic acid	28 weeks	Unexplained
4	cHTN, APLA	36 weeks	Cord accident	Anti HTN	35 weeks	Placental abruption
5	APLA	35 weeks	Placental abruption	LMWH, LDA	41 weeks	Placental abruption

Treatment outline: Women who received LMWH treatment were treated by prophylactic doses (40–60 mg/d) of enoxaparin started as soon as pregnancy was diagnosed. No anti-Xa monitoring was undertaken. LDA was given as aspirin 100 mg/d. Antihypertensive treatment was undertaken with alph-methydopa 3–4 times daily, titrated according to blood pressure.
cHTN=chronic hypertension, FII=prothrombin G20210A mutation, anti-HTN=antihypertensive medication, APLA=antiphospholipid antibodies, IUGR=intrauterine growth restriction, MTHFR +/+=homozygocity for the MTHFR C677G polymorphism, LMWH=low molecular weight heparin, LDA=low dose aspirin.

Table 4 Pregnancy outcomes in the subsequent pregnancy following a prior placental compared with non-placental stillbirth.

Characteristics	Prior placental stillbirth (n=30)	Prior non-placental stillbirth (n=43)	P-value	Odds ratio (95% confidence interval)
Preterm delivery (<37 weeks gestation)	7 (23.3%)	14 (32.5%)	0.39	0.63 (0.19; 2.04)
Repeat stillbirth	2 (6.6%)	3 (6.9%)	0.66	0.95 (0.1; 7.7)
IUGR	6 (20.0%)	1 (2.3%)	0.016	10.5 (1.12; 245.6)
Liveborn AGA	17 (56.6%)	33 (76.7%)	0.069	0.4 (0.13; 1.22)
Thrombophilia	22 (73.3%)	20 (46.5%)	0.022	3.16 (1.04; 9.85)

Placental stillbirth is non-anomalous stillbirth associated with one or more of the following: placental abruption, intrauterine growth restriction and large/multiple placental infarcts. Thrombophilia, evidence for at least one thrombophilic abnormality as outlined in the Materials and methods section. IUGR=intrauterine growth restriction, AGA=appropriate for gestational age.

All five recurrent stillbirth cases occurred in women with thrombophilia, three of which had evidence of antiphospholipid antibodies. Therefore, the risk of repeat stillbirth was seven times higher for women with evidence of antiphospholipid antibodies, compared with those without (OR 7.0, 95% CI 1.05; 46.6, P=0.055). In four out of five recurrent stillbirth cases the repeat event occurred earlier than the initial event. The details of the five repeat stillbirth cases are outlined in Table 3.

Discussion

Scant evidence currently exists in the literature regarding pregnancy outcome after a stillbirth pregnancy. In the present study, we show that overall, women after a stillbirth event can be assured of a subsequent encouraging outcome, as almost 77% of them take home a liveborn baby in the pregnancy immediately following the stillbirth event. Nevertheless, the frequency of obstetric complications among these parturients was very high when compared with the general population. Women after stillbirth suffered twice as often from diabetes mellitus in pregnancy; hypertensive complications were four times more prevalent; while placental abruption was nearly seven times more frequent than in the control group. This significant association between previous perinatal mortality and maternal obstetric complication in the following pregnancy has also been observed by other authors [12, 16, 20, 24].

Placental dysfunction may be related to several broad categories of stillbirth, including restricted fetal growth and placental abruption. Risk factors for placental complications can persist into the next pregnancy. Freeman et al. [6] have already demonstrated over two decades ago, the increased risk for the birth of a small for gestational age (SGA) infant in the subsequent pregnancy after an SGA stillborn. Among women in our study group, a significantly higher rate of growth restriction (RR 10.5) was observed in the subgroup of women with prior placental stillbirth. The interdependency between growth restriction and fetal demise was also demonstrated in another study [24], in which the delivery of a previous preterm SGA infant was an important predictor of the subsequent risk of stillbirth.

A repeat stillbirth is probably the most dreaded outcome for women with prior stillbirth. Several authors found a 3.5–10 fold greater risk for recurrent intrauterine fetal death in the subsequent pregnancy [9, 10, 21], while others did not report increased recurrence risks for women with prior stillbirth [3, 12, 14, 16]. In our study, we found a much higher risk (RR 22) for recurrent fetal demise than previously reported. Some of the difference may result from the study population of women referred to a high-risk clinic (referral bias), and possibly due to a high prevalence of prothrombotic risk factors among the investigated population. The exact prevalence of prothrombotic risk factors among our control population is not available. Nevertheless, a recent study by Salomon et al. [19] investigated healthy primiparous Israeli women without a history of thrombosis for prothrombotic factors. In that study, factor V Leiden, prothrombin mutation, MTHFR homozygocity and lupus anticoagulant were evaluated in 637 women with a normal ultrasound scan at 14–16 weeks. An overall 30% prevalence of prothrombotic factors was found, with 25.4% of women harboring at least one prothrombotic factor and 4.6% having two or more. The prevalence of factor V Leiden was 3.8%, prothrombin G20210A mutation was 4.2%, MTHFR 677T homozygocity 12.7% and lupus anticoagulant 4.7% in that unselected population. In the present study, we found a higher rate of overall thrombophilias, with 42/73 (57.5%) women presenting with at least one prothrombotic factor and 16.4% having two or more. The prevalence of factor V Leiden was 16.4% in our post-stillbirth population, prothrombin

G20210A 16.4%, MTHFR 677T 9.6%, and antiphospholipid antibodies were present in 20.5% of women. As the study population is relatively small, it is difficult to distinguish whether this increased incidence directly contributed to the occurrence of stillbirth, or is associated with it due to the selected nature of the referred population.

All but one case of repeat stillbirth happened before 37 weeks' gestation and earlier than the first event. We have previously shown, as have others, that preterm stillbirth is more likely to be associated with growth restriction and placental dysfunction than term stillbirth, while term stillbirth is more attributed to other causes [8, 22, 23]. Moreover, in all recurrent stillbirth cases the initial fetal demise was also preterm (Table 3). Samueloff et al. [20] also found that the gestational age of stillborn infants was significantly lower in the recurrent-stillbirth group, while Surkan et al. [24] found that a history of a previous stillbirth almost quadrupled the risk of preterm stillbirth in the subsequent delivery, but not of term stillbirth.

Thrombophilic mutations are common, a fact which has been an obvious impediment to clarifying their specific role in pregnancy complications such as recurrent pregnancy loss, preecplampsia, IUGR and intrauterine fetal death. The association between maternal thrombophilia and adverse pregnancy outcome is extremely controversial [1, 10, 11, 15, 18, 25]. In a recent study, we demonstrated a very high proportion of maternal thrombophilia in a cohort of women with stillbirth, especially placental stillbirth [22]. In the present study, despite a high rate of thromboprophylaxis, pregnancy complications were still frequent, especially among women with prior placental stillbirth. This highlights the problematic association between thromboprophylaxis and prevention of pregnancy complications.

Newborns in our study group were born earlier and with lower birth weight. This is partially explained by the very high rate of labor induction in the study group. Possibly, the higher rates of labor induction result not only from actual pregnancy complications necessitating earlier delivery but also from physician and patient anxiety. A possible management bias regarding treatment of women in the subsequent pregnancy after unexplained stillbirth was also found by Robson et al. [17]. In that study, 93% of participating Australian obstetricians declared they would recommend an elective induction of labor in the subsequent pregnancy after an unexplained stillbirth, even in the absence of any other obstetric indication.

Nearly all repeat stillbirth cases (4/5) in our study cohort occurred before 37 weeks' gestation. This questioned the usefulness of a policy of earlier induced labor, as those repeat cases occurred at gestational ages when elective induction is still unjustified, and therefore, not a practical approach.

In summary, despite an overall encouraging prognosis for pregnant women after a stillbirth event, we show an increased risk of obstetric complications, and highlight the need to further differentiate between women with placental stillbirth and those with non-placental stillbirth. Further study is needed in order to define women at increased risk for placental pregnancy complications, as well as means of prevention and salvage.

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