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CLINICAL ARTICLE

Outcome of pregnancy following second- or third-trimester intrauterine fetal death

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ABSTRACT

Objective: To investigate the outcomes of a pregnancy after a second- or third-trimester intrauterine fetal death (IUFD). **Methods:** A prospective observational study was conducted at Trousseau Hospital (Paris, France) between 1996 and 2011. The first ongoing pregnancy in women who had had a previous IUFD was monitored. Management of their treatment was according to a standardized protocol. Recurrence of fetal death was the main outcome criterion. **Results:** The subsequent pregnancies of 87 women who had experienced at least one previous IUFD were followed up. The cause of previous IUFD was placental in 50 (57%) women, unknown in 19 (22%), adnexal in 12 (14%), metabolic in 2 (2%), and malformative in 4 (5%). Three (3%) participants had another stillbirth. Overall, obstetric complications occurred in 34 (39%) pregnancies (including 22 [25%] preterm births, 5 [6%] small for gestational age, and 6 [7%] maternal vascular complications). Obstetric complications were significantly more common among women whose previous stillbirth had been due to placental causes than among those affected by other causes ($P = 0.02$). **Conclusion:** Most pregnancies after IUFD resulted in a live birth; however, adverse obstetric outcomes were more common when the previous stillbirth was due to placental causes.

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1. Introduction

Between five and seven stillbirths occur in every 1000 pregnancies [1,2]. This dramatic event engenders a high degree of anxiety about the next pregnancy for women, their partners, and caregivers. However, according to published data [3–9], the risk of another stillbirth ranges from nil to a 20-fold increase compared with that for primigravidas.

Although some studies have shown an increase in the incidence of stillbirth and obstetric complications (e.g. placental abruption, preterm delivery, and low birth weight) in women who have had a previous stillbirth [10,11], others have found that the risk of stillbirth in these women is no higher than that in the general population [12]. Moreover, the definition of fetal loss is particularly heterogeneous in the literature, including late spontaneous abortions as well as intrapartum stillbirths. Finally, many studies are population-based, lacking information about the etiology of stillbirth and details of the follow-up [8,12,13].

Because of the conflicting evidence in the literature about stillbirth recurrence rates, the objective of the present study was to conduct an investigation of a cohort of pregnancies after a second- or third-trimester stillbirth at one healthcare center, using a standardized protocol for the etiologic investigations, and where the management of the next pregnancy involved only a limited number of obstetricians. The

main aim of the study was to investigate the occurrence of subsequent intrauterine fetal death (IUFD), preterm birth, small for gestational age (SGA) neonates, and any vascular complication of pregnancy (pre-eclampsia, HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count], and placental abruption) in women with a history of IUFD. The secondary objective was to determine whether the cause of fetal death in the index pregnancy affected the occurrence of complications during a subsequent pregnancy.

2. Materials and methods

A prospective observational study was conducted at Trousseau Hospital (Paris, France) between January 1, 1996, and December 31, 2011. Eligible women had their first ongoing pregnancy (past 12 weeks) after a previous second- or third-trimester stillbirth. Only women followed up for the whole pregnancy and who went on to deliver at Trousseau Hospital were included. The study was approved by the National Ethics Committee for Research in Obstetrics and Gynecology. Informed consent was obtained from all study participants.

Stillbirth was defined as an intrauterine death after 15 weeks of gestation. A systematic work-up to try to identify the cause of the intrauterine death was done after the IUFD if it occurred at Trousseau Hospital, or when a woman subsequently presented to the hospital for the first time (while planning a pregnancy or when already pregnant again). The work-up involved a systematic examination of the fetal autopsy, the macroscopic and microscopic placental conditions,

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fetal karyotyping, and laboratory testing (blood type; Rhesus factor; Kleihauer–Betke test; serologic screening for recent toxoplasma, rubella, cytomegalovirus, and parvovirus B19; and bacteriologic, hematologic, and biochemical screening). The cause of death was classified into five possible categories according to the local classification system, which was devised in agreement with obstetricians and fetopathologists: (1) placental [14] when at least one of a list of problems was identified (pre-eclampsia, HELLP syndrome, placental abruption, intrauterine growth retardation, uterine artery Doppler anomalies, or histologic evidence of placental vascular dysfunction); (2) malformative when severe structural anomalies were identified by ultrasound or fetal autopsy; (3) adnexal in case of cord accidents, fetal maternal hemorrhage confirmed by positive Kleihauer–Betke test, or red-blood-cell alloimmunization; (4) metabolic in the case of diabetes mellitus or an obstetric cholestasis; or (5) unknown when, despite all the investigations or because of a lack of information, no cause was identified. If the cause of the stillbirth appeared to be placental or remained unexplained, further investigations were undertaken to determine whether the stillbirth could have been due to inherited thrombophilias (deficiencies of proteins C or S, factor V Leiden mutation, prothrombin G20210A gene mutation, antithrombin III deficiency, or hyperhomocysteinemia), circulating antiphospholipid antibodies (anticardiolipin antibodies, anti β 2GPI1, and lupus anticoagulant), or antinuclear factor if there was clinical evidence of lupus. If the stillbirth had occurred in another hospital, efforts were made to obtain all prenatal care records.

The standardized protocol of management for these patients included: first-trimester ultrasonography with uterine artery Doppler; monthly ultrasonography with uterine and umbilical artery Dopplers, fetal weight estimation, and screening for fetal malformations in the second or third trimester; prenatal care visits at least once a month; and weekly monitoring of blood pressure, proteinuria, and fetal heart rate during the third trimester. A psychological follow-up was offered to all women during pregnancy as part of standard management; however, these data are not included in the present study.

Some aspects of the protocol were slightly modified according to the cause and the timing of the stillbirth. In women whose previous stillbirth was due to placental causes, specific treatments were prescribed to prevent the recurrence of placental vascular pathology. From early diagnosis of pregnancy to 35–36 weeks, the patients received a daily dose of 100–160 mg aspirin. Aspirin was also given to women whose previous stillbirth was not obviously due to a placental cause but in whom uterine artery Doppler at 12 weeks of pregnancy showed elevated resistance indices and bilateral notches. If the screening for thrombophilia was positive, a daily prophylactic dose of 4000 IU enoxaparin—a low-molecular-weight heparin—was prescribed as soon as the pregnancy test was positive until 6 weeks after delivery, with an interruption of treatment during labor and until 12 hours postpartum [15]. Women whose stillbirth had been due to placental causes but in whom screening for thrombophilia was negative were also given a low-molecular-weight heparin if the first-trimester uterine artery Doppler was highly pathologic (i.e. bilateral resistance index > 80% and/or bilateral notches). Women with hyperhomocysteinemia were supplemented with daily doses of 10 mg vitamin B9 and 0.25 mg vitamin B12, and were checked for normal homocysteine rates under treatment.

In the case of an uneventful pregnancy, labor was usually induced at the beginning of the ninth month (i.e. 37–38 weeks of pregnancy) according to the cause of the first stillbirth, the gestational age at the time that it occurred, and the medical history of the patient.

The main outcome criteria were: a recurrence of IUFD and the occurrence of pregnancy complications such as preterm birth (<37 weeks); a SGA fetus or neonate (birthweight <10th percentile using Leroy–Lefort birth weight curves); vascular complications of pregnancy such as pre-eclampsia, placental abruption, or HELLP syndrome; and a composite outcome called “any complication”, which included any of the aforementioned obstetric outcomes.

Statistical analyses were performed using Medcalc version 12 (Ostend, Belgium; <http://www.medcalc.org>). Categorical data were compared using the Pearson χ^2 test and the Fisher exact test, as appropriate. Continuous variables were compared using the Student *t* test. $P < 0.05$ was considered statistically significant.

3. Results

The subsequent pregnancies of 87 patients who had experienced at least one prior IUFD were followed up. The characteristics of the patients at the time of the previous stillbirth are shown in Table 1. The mean age of the patients was 31 ± 5 years. At the time of the previous IUFD, 58 (67%) women had been nulliparous.

The cause of stillbirth was classified as placental for 50 (57%) patients (Table 2), of whom 27 (54%) were found to have a positive result when screened for thrombophilia (Table 3). More than half of these 27 women had antiphospholipid syndrome (Table 3). Of the 12 IUFDs with adnexal causes, seven were due to cord accidents, two to fetal–maternal hemorrhage, one to amniotic bonds, one to extrachorial placenta, and one to red-blood-cell alloimmunization. Of the four stillbirths that were due to malformative causes, one was due to hydrocephalus, one to diaphragmatic hernia, and two to polymalformative syndromes. Both stillbirths due to metabolic causes involved obstetric cholestasis. Fifty-six (64%) stillbirths occurred during the third trimester, among which 28 (50%) occurred during the last month of the pregnancy (between 37 and 42 weeks).

The mean age of the participants at the time of their next pregnancy was 33 ± 5 years, median gravidity was three (range 2–9), and median parity was two (range 0–6). Fifty-four (62%) women had had no live births at the time of this pregnancy.

Among 69 (79%) participants given at least low doses of aspirin, the cause of previous IUFD had been placental in 49 (71%). Among the 37 patients whose previous stillbirth was not due to placental causes, 20 (54%) received treatment with aspirin. These patients either had severe anomalies of uterine artery Doppler at the first-trimester ultrasound, mild fetal growth retardation, or multiple previous stillbirths. Six participants were given aspirin before the results of the complete etiologic work-up were obtained, but were then stopped when no placental cause was found.

Among the cohort, 84 (97%) went on to have a live birth. The obstetric complications, according to the etiology of the index IUFD, are shown in Table 4, and the obstetric outcomes among women whose previous stillbirth had been due to placental causes (the placental group) and

Table 1
Characteristics of the patients at the time of the index IUFD.

Characteristic	Median (range)
Age, y	31 (21–43) ^a
Gravidity	2 (1–8)
Parity	1 (0–5)
Number of previous live births	0 (0–3)
Number of previous IUFDs	0 (0–2)

Abbreviation: IUFD, intrauterine fetal death.

^a Mean (range).

Table 2
Cause of index intrauterine fetal death (n = 87).

Cause	No. (%)
Placental	50 (57)
Malformative	4 (5)
Metabolic	2 (2)
Adnexal	12 (14)
Unexplained	19 (22)

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