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Outcomes of monoamniotic twin pregnancies managed primarily in outpatient care—A Danish multicenter study

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Conflict of interest

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ABSTRACT

Introduction: Monoamniotic twin pregnancies are high-risk pregnancies, and management by inpatient or frequent outpatient care is recommended. We report the outcomes of a national cohort of monoamniotic twin pregnancies managed primarily as outpatients**. Material and methods:** We analyzed prospectively recorded data from the Danish Fetal Medicine Database, local databases, and medical records of all monoamniotic twin pregnancies diagnosed at the first trimester scan or later, and managed at the six major fetal medicine centers in Denmark over a 10 year period. **Results:** Sixty-one monoamniotic twin pregnancies were included. Thirteen pregnancies were terminated early. Of the remaining 48 pregnancies with a normal first trimester scan, there were 36 fetal losses (25 spontaneous miscarriages <22+0 weeks, three late terminations and eight intrauterine deaths >22 weeks) and 60 live-born children (62.5%), all of whom were delivered by cesarean delivery at a median gestational age of 33+0 weeks. Three children had minor malformations and there was one pregnancy with twin-to-twin-transfusion-syndrome. After 26+0 weeks, 78.8% were managed as outpatients. Intrauterine death occurred in 3.8% of outpatients and in 28.6% of inpatients (admitted due to complications). At weeks 32, 33, and 34, the prospective risk of intrauterine death was 6.9%, 4.2%, and 5.9%, respectively. **Conclusion:** In this nationwide, unselected population, only

62.5% of fetuses with a normal first trimester scan were born alive. In contrast, the mortality was 3.8% after 26 weeks among the 78.8% of the cohort that was managed as outpatients. More knowledge is still needed to predict which pregnancies are at the highest risk of intrauterine death.

Keywords:

monoamniotic twin pregnancy, twin-to-twin-transfusion syndrome, pregnancy, twins, monozygotic, fetal mortality, intrauterine fetal death, prenatal care, gestational age, ultrasonography,

Abbreviations:

GA: gestational age

IUFD: intrauterine fetal death

MA: monoamniotic

TTTS: twin-to-twin-transfusion syndrome

Key message:

Management of monoamniotic twin pregnancies by inpatient or frequent outpatient care has been recommended. Relatively infrequent outpatient controls seems possible and safe in the majority of cases, with 3.8% mortality after 26 weeks.

INTRODUCTION

Monoamniotic (MA) twin pregnancies are at high risk of a range of severe complications, including increased risk of miscarriage (1, 2), fetal malformations (2-5), intrauterine or neonatal death (2, 4-6), and mortality rates as high as 70% (6, 7). Cord entanglement is considered one of the key reasons for the increased risk of sudden intrauterine fetal death (IUFD), and obstetric management by frequent outpatient (surveillance several times a week) or inpatient (sometimes by continuous fetal surveillance) management has been recommended (8), and most studies recommend considering preterm delivery by cesarean delivery at or before 33 weeks (1, 5, 7). Recently, a French center

published data supporting frequent outpatient care, continuing the pregnancy beyond 32 weeks, and vaginal delivery (9). These data suggest that management protocols—and likely counseling—of this high-risk group varies considerably between centers (10).

The aim of our study was to assess MA pregnancy outcomes by using population-based data that included all MA pregnancies in Denmark over a 10-year period. All pregnant women were offered the same prenatal screening program and managed by the same obstetric management protocol, which included infrequent outpatient management.

MATERIAL AND METHODS

This study included all MA twin pregnancies in Denmark, with at least one ultrasound scan during pregnancy, from January 2004 to December 2013. We excluded conjoined twins, pregnancies with higher-order multiples that included MA twin pairs, and pregnancies that initially were diagnosed as MA, but were later confirmed as diamniotic.

In 2004, a free national prenatal screening program was introduced in Denmark that offered all pregnant women a first trimester (11–13 weeks) ultrasound scan including assessment of amniochorionicity in pregnancies with more than one fetus and risk of chromosomal anomalies based on nuchal translucency, maternal age, and biochemical factors, as well as a second trimester anomaly scan at 18–21 weeks (11). All Danish obstetric departments use the same fetal medicine database software (Astraia GMBH, Munich, Germany) for prospective registration of data from prenatal screening and diagnosis, and data from the national Danish Fetal Medicine Database are derived from these local Astraia databases (12). The identification of monoamnionicity was based on the first trimester ultrasound scan if it revealed a single placenta and the absence of a dividing amniotic membrane. All pregnancies were dated using the crown–rump length of the largest twin.

We retrieved detailed information on all MA twin pregnancies by integration of data from three sources: 1) local (Astraia) databases from all six major fetal medicine centers covering the entire Danish population with respect to management of MA twin pregnancies; 2) The Danish Fetal Medicine Database; and 3) local medical records for the mother. The personal identification number assigned to all citizens residing in Denmark allows unambiguous individual-level record linkage of all Danish registers and linkage between a mother and her children (13). Data included gestational age (GA) at time of MA diagnosis, prenatally

diagnosed malformations or complications including twin-to-twin transfusion syndrome (TTTS), pregnancy outcome and delivery mode, GA at delivery, birth weight, and malformations diagnosed at birth. Medical records were reviewed in cases of missing database data, and in all pregnancies continuing beyond 24+0 weeks to register antenatal admissions, reason for admission, monitoring during admission, maternal and/or fetal complications, and indication for delivery. Monoamnionicity was diagnosed from the ultrasound scan and was confirmed by visual examination of the placenta and membranes at delivery or after termination.

Since TTTS in MA pregnancies cannot be classified according to Quintero stages, assessment of possible TTTS complications were based on polyhydramnios, large/small bladder and flow patterns.

In Denmark, there is no tradition for routine inpatient monitoring of MA pregnancies and women with a MA pregnancy are hospitalized only for delivery or if they are at risk of complications during the pregnancy. Uncomplicated MA twin pregnancies were managed in accordance with national guidelines, which were not changed during the study period. These guidelines included outpatient surveillance at a major center with ultrasound assessment of fetal growth, umbilical and middle cerebral artery flow, and signs of TTTS every second week from diagnosis until 28 weeks; and subsequent weekly surveillance by either ultrasound alone or alternating ultrasound and cardiotocography. MA twin pregnancies were considered uncomplicated if there was no evidence of intrauterine growth restriction, TTTS, or ultrasound signs of anemia or obstetric conditions that required admission (e.g. preeclampsia or risk of preterm birth) (14). Antenatal corticosteroid was administrated to induce lung maturation before or at 34+0 weeks or before delivery prior to 34 weeks. In the absence of other indications, delivery by elective cesarean delivery was recommended at 32–34 weeks. Indications for delivery before 32–34 weeks followed standard recommendations for monochorionic diamniotic twin pregnancies, including maternal and/or fetal indications such as preeclampsia, intrauterine growth restriction, and nonreassuring antenatal testing.

Statistical analyses

All statistical analyses were performed using Stata version 14 (Stata Corp., College Station, TX, USA). Fisher's exact test was used to identify differences in outcomes of the two phases. Survival was illustrated with a Kaplan-Meier curve. The prospective risk of IUFD was calculated as the number of IUFDs occurring after a certain GA divided by the number of live fetuses at this GA.

Ethical approval

The study was approved by the Danish Data Protection Agency (j.nr. 1-16-02-426-14).

RESULTS

During the study period, there were 610,894 deliveries in Denmark, of which 13,316 were twin deliveries. The rate of MA pregnancies was 0.10/1,000 deliveries, and 0.47/100 twin deliveries.

Sixty-four MA twin pregnancies were included. One pregnancy was excluded because of missing outcome date due to emigration. Two pregnancies were excluded due to late diagnosis after 17 weeks of gestation. The final study cohort included 61 MA pregnancies (122 fetuses) (Figure 1). The median GA at the time of diagnosis was 12+5 weeks (range, 9+2 to 16+5 weeks).

Early terminations (before week 18+0)

Twenty-six fetuses (13 pregnancies; 21.3%) were terminated because of the MA diagnosis itself, early signs of fetal malformations, or on maternal indication at a median GA of 13+3 weeks (range, 11+6 to 16+5 weeks).

Spontaneous miscarriage (before 22 weeks)

Twenty-five fetuses were lost spontaneously (26%). Eighteen of these fetuses in nine pregnancies (14.3%) were lost before 18 weeks. Seven fetuses in four pregnancies were lost between 18+0 and 22+0 weeks. One of these fetuses was lost at 19+0 weeks, one week after selective feticide (clamping) of the co-twin because of twin reversed arterial perfusion sequence. The median GA at the time of miscarriage was 15+3 weeks (range, 12+0 to 21+3 weeks).

After a normal first trimester scan, there was a 62.5% chance of live births of MA twins and an overall risk of adverse outcome of 37.5%, of which spontaneous miscarriage accounted for 25/36 (69.4%).

Late terminations (weeks 18+0 to 22+0)

Of the ongoing 71 fetuses, three (4.2%) were terminated after the second trimester scan: Two fetuses in one pregnancy were terminated at 22+0 weeks because of severe TTTS, and one fetus underwent clamping of the umbilical cord at week 18+0 because of twin reversed arterial perfusion sequence.

Outcome after second trimester anomaly scan

Of the 68 fetuses in 34 pregnancies reaching week 22+0, there were eight double IUFDs (four pregnancies) (11.8%) and 60 live-born children (88.2%) (Table 1). All live-born children were delivered by cesarean delivery. The timing of IUFD is shown in figure 2.

Outcomes according to management protocol (Figure 1*)*

In the study cohort 78.8% of pregnancies (52 fetuses in 26 pregnancies) were managed as outpatients, and the women were hospitalized only for delivery at a mean GA of 33+1 weeks (range, 28+5 to 36+2 weeks). In this group, there was one double IUFD at week 31+2 (3.8%). Among the 21.2% who were treated as inpatients (because of complications), six of seven women were admitted because of typical obstetric causes (Table 1). In the inpatient group, there were two double IUFDs (28.6%), one at week 26+1 and the other at week 34+1, and the mean GA at delivery was 32+2 weeks (range, 28+0 to 34+1 weeks). As expected, the risk of IUFD was higher in the inpatient group than in the outpatient group (2/7 = 28.6% vs. 1/28=3.8%, p=0.59).

IUFD after 22 weeks

Case 3 (in Table 1): IUFD at 24+0 weeks. Pregnancy was uncomplicated with a normal ultrasound scan at 23+3 weeks. This IUFD was considered not to have been preventable. Case 10: While hospitalized for regulation of pregestational noninsulin-dependent diabetes, the mother developed insulin-dependent diabetes following glucocorticoid administration at 24+1

weeks. A double fetal IUFD was found at 26+1 weeks. We were not able to conclude about the cause of IUFD from the medical records. This IUFD case was likely to have been not preventable. Case 32: IUFD at 34+1 weeks. The mother was admitted at 33+3 weeks because of mild preeclampsia with slightly increased blood pressure and proteinuria. She was monitored daily with cardiotocography and flow assessment, which were normal, until elective cesarean delivery at 34+1 weeks, where a double IUFD was found. Autopsy of the children, both with a weight close to the 50th percentile, showed no malformations. This case of IUFD was considered to have been potentially preventable. Case 33: IUFD at 31+2 weeks. The pregnancy received increased outpatient surveillance because of a period of intermittent variable flow patterns, but returned to standard outpatient care after normal findings. It was not possible to classify the potential preventability of this case.

The total prospective risk of IUFD according to GA (Figure 3) reached a nadir at 33 weeks (4.2%) and thereafter increased with increasing GA. The median GA at the time of delivery of live-born children was 33+0 weeks (range, 28+0 to 36+2 weeks) in this cohort. The median birth weight was 1908 g (range 860 g to 2750 g). There were no neonatal deaths.

Admissions during pregnancy

Seven MA pregnant women were hospitalized at some time after the second trimester scan (Table 1). Two of these women were admitted twice (median admission duration of 20.5 days). The median admission duration for the remaining five cases was 5 days.

Complications and indications for delivery (Table 1)

Fetal and/or maternal complications were found in 15 cases (44.1%) that continued after 26 weeks of gestation. The delivery indications were primarily elective (23/34) according to the national guidelines. Other indications were IUFD (4/34), abnormal fetal flow patterns on ultrasound (1/34), preeclampsia (1/34), and delivery because of suspicion of acute cord compression (1/34), but cord compression was not confirmed at delivery. In four women, delivery was initiated because of preterm premature rupture of the membranes or spontaneous preterm contractions. Seven women were delivered before the recommended 32-34 weeks because of complications.

Malformations

Three children in three pregnancies were born with minor malformations (3/60, 5.0%): two children with talipes and one child with hypospadia.

DISCUSSION

In this unselected cohort of all MA pregnancies in Denmark over a 10 year period, we found an overall mortality of 37.5% following a normal first trimester scan, which corroborates the high risk of adverse outcomes associated with MA twin pregnancies found by others (7). A lower overall risk reported in some studies might partly reflect the inclusion or exclusion of subgroups of outcomes, such as the prospective risk of 19% reported by Hack et al. (13) who did not include miscarriages before 20 weeks. Counselling about prospective risks should be given at the time of diagnosis of monoamnionicity, which in many countries is at the first trimester scan.

We found that spontaneous miscarriages between the first trimester scan and 22 weeks occurred in 26% of cases, which is similar to the 21% reported by Murata et al. (14). In this study, mortality was 11.8% after the second trimester scan, and all were IUFDs. The literature on mortality risk is conflicting. Dias (3) and Murata (14) reported lower risks, 5.9% (2/34) and 1.7% (1/60) after 20 and 22 weeks, respectively, whereas Hack (17%) (13), Heyborne (15.4%) (4) and Demaria (32%) (15) reported higher perinatal mortality rates after 20 weeks. Our findings regarding mortality are consistent with the results reported by Morikawa (10%) (16) and Allen (13.9%) (2), and by the review by Rossi (11.4%) (17) after 22 weeks. Selection bias and differences in malformation rates might partly explain these differences, but some of these adverse outcomes are considered to be unpreventable. The focus in the recent literature has been on management of MA pregnancies especially from the time of viability and on preventable fetal deaths.

Publications on the outcomes and associated recommendations for MA twin pregnancy management represent a wide spectrum from elective inpatient care from 26 weeks with continuous surveillance or several times daily (6, 8), to outpatient care by biweekly surveillance from 28 weeks (9) and up to four times weekly from 26-28 weeks of gestation (5). In a recent review, Post and Heyborne (6) compared outcomes after contemporary inpatient and

frequent outpatient management, and found that elective inpatient care was associated with a fetal death rate of 0.8%, which was significantly lower than 8.1% in the outpatient group. They concluded that contemporary management of MA twin pregnancies should include elective inpatient care from around week 26, depending on the GA limit where the parents would find intervention or delivery to be an option. By contrast, in the hitherto largest study, which was published in 2015 and included a retrospective review of 193 MA twin pregnancies, Van Mieghem and colleagues (5) found that IUFD did not differ between the outpatient (4.7% (5/106)) and elective inpatient (1.4% (2/142)) groups. In that study, they compared a group of outpatients followed after 28+6 weeks, a group of elective inpatients hospitalized before 29+0 weeks, and a group of complicated inpatient, who were admitted acutely before 29+0 weeks. As an international, multicenter study that included eight centers, the management protocols were not identical: in four centers, patients were primarily elective inpatients from 26–28 weeks and two centers used primarily outpatient care. Outpatient management included surveillance with ultrasound scans once or twice a week and, on average, four cardiotocograms weekly, and 57% of the outpatients were hospitalized.

Our study is the first population-based study to include all MA twin pregnancies in a single country over a 10 year period. In our cohort, 78.8% of pregnancies (26/33) with two viable fetuses at 26 weeks were managed as outpatients and the women were hospitalized only for delivery. With one double IUFD in our outpatient group, the fetal death rate was 3.8% and did not differ significantly from the fetal death rates for inpatients and outpatients reported by Van Mieghem et al. and Post et al. (6). Although our sample size was small, we found that the risk of IUFD was higher in the complicated inpatient group than in the outpatient group (28.6% vs 3.8%). This difference is as expected and reflects the severity of the underlying condition, and no inference about the difference in safety for low-risk patients can be deduced from this comparison. Among the seven pregnant women that were admitted during pregnancy, one of the two IUFD cases was considered to have been potentially preventable.

Unfortunately, we did not have access to information about severe neonatal respiratory or nonrespiratory complications, but there were no neonatal deaths in our study. The prospective risk of IUFD for each gestational week decreased from 11.8% in week 24 to a nadir of 4.2% at week 33 (see figure 3). These data are consistent with those reported by Van Mieghem and colleagues and by Hack et al. (15), who found a prospective risk of 3% to 4% after 32 weeks (15). These rates support the common clinical practice of delivering MA twins between 32 and 34 weeks. Since prematurity is a consequence for almost all MA twin babies, the accompanying increased risk of long-term neurodevelopmental delay, especially in case of very

preterm babies (in our cohort 14 children were born before 32 weeks), should be included when counseling about outcome in MA pregnancies.

Hospitalization of a pregnant woman can have a severe negative effect on her family and social life, and is associated with a high degree of loneliness, boredom, and powerlessness (20). Prolonged hospitalization because of obstetric high-risk indications is associated with a >40% risk of depression and anxiety among mentally healthy women (21, 22). These severe consequences should be considered in the counseling and management of MA twin pregnancies.

The source of data in this study and the access to detailed information on obstetric management and complications ensure the completeness and quality of data in our study. Denmark has a long history of use of national obstetric guidelines and recommendations regarding prenatal diagnostics, which minimize variability in management between hospitals.

The register design of the study carries a risk of registration errors, but this risk has been reduced by the review of medical records. Another limitation is the lack of more detailed information about neonatal outcome. A further limitation is the small sample size, which is to be expected because MA twin pregnancy is a rare condition, and our study was not sufficiently powered to detect the optimal time for delivery.

CONCLUSION

This study presents data from an unselected cohort of MA pregnancies in a single country over a 10 year period. Mortality was 37.5% after a normal first trimester scan. In accordance with evidence based guidelines, more than ¾ of the study population were managed as outpatients after 26 weeks. Mortality among outpatients was 3.8% after 26 weeks. Whilst 10 times higher than singletons, the mortality is not higher than other reported risks in MA pregnancies, and we believe the results of the study support this management protocol. MA pregnancies are associated with high risk and still more knowledge is needed to be able to predict which pregnancies are at the highest risk of IUFD.

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Legends of Tables and Figures:

Table 1: Ongoing monoamniotic pregnancies after second trimester scan.

Figure 1: Flowchart of the study group.

Figure 2: Kaplan–Meier curve of intrauterine fetal death by gestational age.

Figure 3: Prospective risk of intrauterine fetal death.

Table 1: Ongoing MA pregnancies after second trimester scan

Case	Outcome	GA at outcome	Delivery indication	Admissions during pregnancy (GA, duration)	Cause of admission	Complications (maternal and fetal)	Birth weight (g)
1	Liveborn twins	33+6	Elective	No	-	SGA in one fetus	2030/1800
2	Liveborn twins	33+2	Elective	No	-	SGA in one fetus	1950/1690
3	Double IUFD	24+0	-	No	-	-	
4	Liveborn twins	32+6	Elective	No	-	SGA in one fetus	1710/1660
5	Liveborn twins	34+0	Elective	No	-	SGA in one fetus	1830/1750
6	Liveborn twins	34+0	Elective	No	-	-	2140/2060
7	Liveborn twins	33+6	Elective	No	-	-	2333/2370
8	Liveborn twins	31+6	Elective	No	-	-	1640/1670
9	Liveborn twins	32+3	Subacute cesarean due to abnormal flow patterns	No	-		1710/1880
10	Double IUFD	26+1	-	Yes, for two weeks from 24+1 weeks until IUFD diagnosis	Dysregulated diabetes	Dysregulated diabetes	

11	Liveborn twins	36+2	Elective	No	-	-	2750/2630
12	Liveborn twins	35+4	Elective	No	-	-	2620/2270
13	Liveborn twins	35+2	Elective	No	-	-	2345/2440
14	Liveborn twins	32+2	Elective	No	-	Mild preeclampsia	1935/1975
15	Liveborn twins	29+4	Spontaneous preterm delivery	No	-	Cervix insufficiency	1626/1600
16	Liveborn twins	34+6	Subacute cesarean due to suspicion of cord compression (none found)	No	-	-	2250/2195
17	Liveborn twins	34+1	Elective	No	-	No	2119/2048
18	Liveborn twins	34+0	Elective	Yes. From 28+3 to 29+0 weeks	Cord entanglement seen on ULS	No	2290/2230
19	Liveborn twins	31+4	Spontaneous preterm delivery (PPROM)	Yes. From 23+6 to 26+6 weeks, and from 29+1 to 34+1 weeks	Cervix insufficiency	Cervix insufficiency	1684/1780
20	Liveborn twins	32+3	Elective	No	-	No	1670/1714
21	Liveborn twins	28+5	Spontaneous preterm delivery (PPROM)	No	-	One fetus with IUGR	1100/930

22	Liveborn twins	34+0	Elective	Yes, one day from 29+3 weeks	Suspicion of preterm labor	No	2165/2100
23	Liveborn twins	31+5	Elective	No	-	No	1500/1760
24	Liveborn twins	32+3	Elective	No	-	No	1860/1905
25	Liveborn twins	28+0	Preeclampsia	Yes, from 26+0 to 26+2 weeks and from week 26+6 until delivery	Preeclampsia, IUGR	IUGR in both fetuses, preeclampsia	860/880
26	Liveborn twins	32+0	Elective	No	-	One fetus with IUGR	1410/1550
27	Liveborn twins	33+5	Elective	No	-	One fetus with SGA, cervix insufficiency	2030/2020
28	Liveborn twins	32+1	Elective	No	-	No	2075/2295
29	Liveborn twins	34+1	Spontaneous preterm delivery	Yes, from 34+0 weeks until delivery	Cervix insufficiency	Cervix insufficiency	2140/1840
30	Liveborn twins	31+6	Elective	No	-	No	1674/1521
31	Liveborn twins	35+5	Elective	No	-	No	2345/2425
32	Double IUFD	34+1	-	Yes, from week 33+3	Preeclampsia	Preeclampsia	

33	Double IUFD	31+2	-	No	-	One fetus with SGA. Transient abnormal flow patterns that normalized	
34	Liveborn twins	33+5	Elective	No	-	No	1915/1820

Abbreviations:

IUFD: IntraUterine Fetal Death

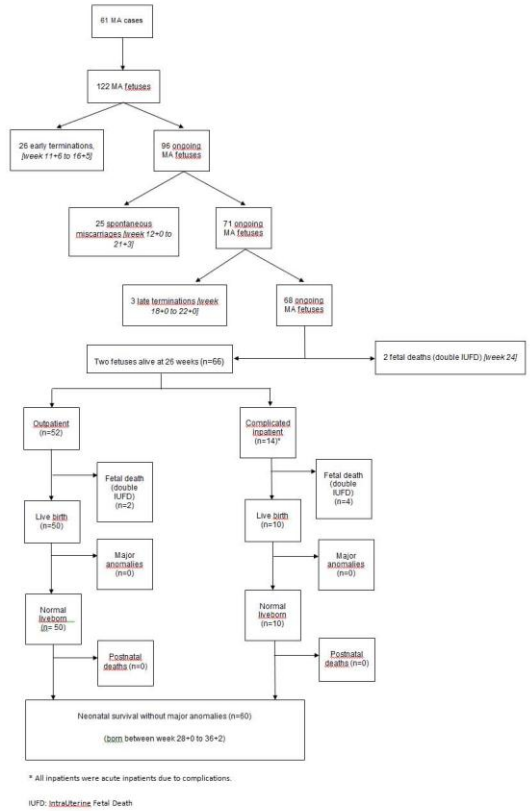
GA: Gestational Age

PPROM: Preterm Premature Rupture Of Membranes

SGA: Small-for-Gestational Age

ULS: ULtrasound Scan

Figure 1: Flowchart of the study group



* All inpatients were acute inpatients due to complications.

IUFD: Intrauterine Fetal Death

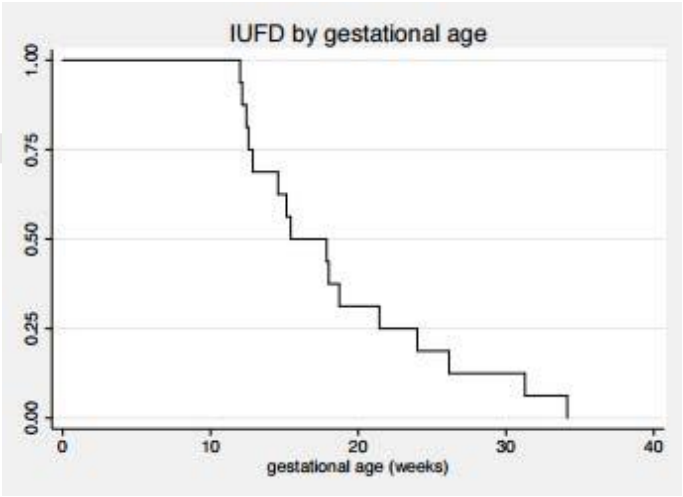


Figure 3: Prospective risk of intrauterine fetal death