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Association of late second trimester miscarriages with placental histology and autopsy findings

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ABSTRACT

Objectives: To describe the placental histology and autopsy findings in pregnancies where fetal demise occurred before a gestational age of 22 weeks.

Study design: This study was a subset of a larger study where the effect of alcohol exposure during pregnancy on stillbirths was studied. In a prospective cohort, 7,010 singleton pregnancies were followed from the first antenatal visit until infant one year of age visit. Gestational age was assessed by ultrasound, preferably at the first antenatal visit. All pregnancy losses were identified and when the fetuses delivered at or after a gestation of 20 weeks, the mother or parents were approached for consent for autopsy. This study describes the placental pathology and findings at autopsy in losses before 22 weeks gestation (late second trimester miscarriages).

Results: Fourteen cases were identified in which 13 had an autopsy and 12 had a histological examination of the placenta. The most prevalent histological abnormality was placental abruption which was seen in 6 miscarriages, occasionally on its own, or in combination with maternal vascular malperfusion or acute chorioamnionitis. The second most frequent finding was maternal vascular malperfusion, as found in five placentas, alone or in combination with other pathology. The third most frequent pathology was acute chorioamnionitis, found in four placentas, in combination or alone. Other causes were diffuse chronic villitis due to cytomegalovirus infection and early amnion rupture with anhydramnios and cord obstruction.

Conclusions: Causes of fetal demise at the end of the second trimester differ little from causes of stillbirth. There is value in using placental histology in late second trimester miscarriages to try to identify the cause of demise.

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Introduction

There is very little information on rates and common causes of spontaneous second trimester miscarriage, possibly due to the global lack of reporting systems. In the United States, fetal mortality from the National Vital Statistics System is presented only for fetal deaths at 20 weeks gestation or more [1]. In the United Kingdom (UK) the cut-off point is 24 weeks [2] while 22 weeks is recommended by the World Health Organization [3]. Although the miscarriage rate in human conception is very high in early pregnancy, it improves to less than 10% after six weeks [4]. In the UK, fetal loss at 12–24 weeks

gestational age is defined as a late miscarriage [5,6]; and the prevalence rates vary between 0.7 and 3%. After a gestation of 16 weeks, the likelihood of losing a viable pregnancy is only 1%. Simpson et al found a spontaneous miscarriage rate of only 0.4% between 15 and 21 weeks in 264,653 pregnancies [7]. Little is known about the underlying causes of second trimester miscarriage as 51% are classified as idiopathic [6].

There is usually no community based information on perinatal mortality rates based on gestational age at demise rather than birthweight in many countries. Gestational age is preferable to birthweight, as the lower cut off points for

birthweight may exclude growth restricted fetuses born at, or shortly after, a gestational age of 22 or 28 weeks depending on the definition used [8].

As the aetiology of second trimester miscarriages and early stillbirths may be similar, information on the causes and rates of

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miscarriage may provide valuable information in the effort to reduce stillbirths. In addition, it is necessary to analyse stillbirth and perinatal mortality rates regularly to project whether the millennium goals for 2030 will be reached. [8] Although there has been a 25.5% decline in global stillbirth rates from 2000 to 2016, the slow improvement in sub-Saharan Africa is a cause for concern [9]. Every opportunity should therefore be used to obtain additional information regarding stillbirth.

A unique opportunity was afforded South Africa when the Safe Passage Study, undertaken in three populations, chose the low-income population in Cape Town as one of the clinical sites. The primary and secondary hypotheses, design and the schedule of evaluations and events have been described [10]. Precise information on all pregnancies, from the first antenatal visit until the infant one year of age visit, allowed accurate documentation of pregnancy losses and death in the first year of life. As a gestational age of 20 weeks or more was one of the inclusion criteria, in contrast to the 22 week lower limit for the definition of stillbirth in South Africa [11], valuable information became available as autopsies were done in stillbirths from 20 weeks onwards. In the subsequent analyses of these stillbirths, the high prevalence of mid-trimester miscarriage became apparent, precipitating this study.

Methods

After approval of the Health Research Ethics Committee of Stellenbosch University, 7060 pregnant women were recruited at the antenatal clinics in Bishop Lavis from August 2007 to January 2015. From this cohort, 7010 singleton pregnancies were selected for this study (Fig. 1). At the recruitment visit, participants

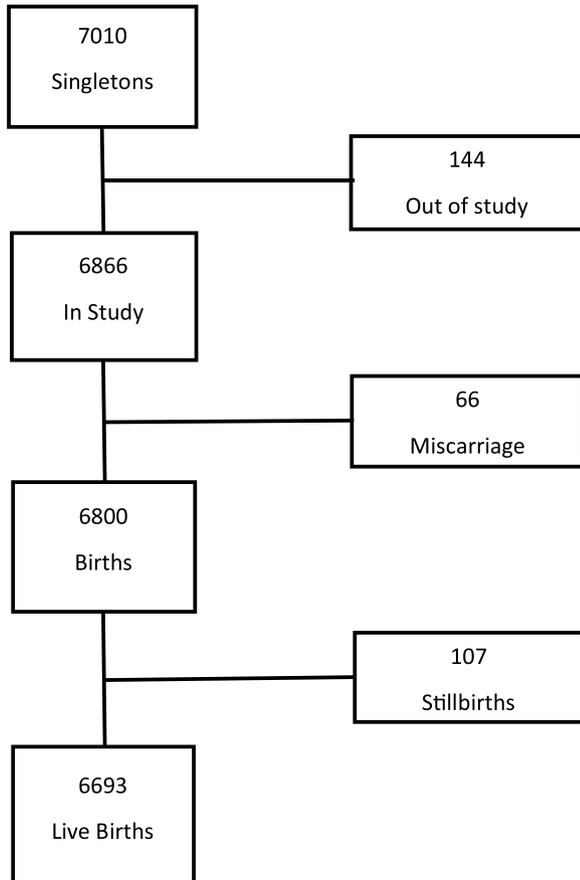


Fig. 1. The study profile of singleton pregnancies.

provided informed consent which included collection of the placenta for histological examination after delivery. With a fetal demise, a separate informed consent was obtained for autopsy [12]. Research midwives checked labor ward admissions and deliveries daily to determine if a study participant had delivered. In women with fetal demise the designated social worker and/or senior personnel of the study were alerted to provide support and counselling and, at an appropriate time, discussed consent for autopsy. Examination of the placenta and the autopsy were done according to a standard protocol [13].

All demises were presented and discussed at weekly perinatal mortality meetings which were attended by obstetricians, neonatologists, pathologists, and geneticists. The primary cause of death was then determined according to the Perinatal Problem Identification Programme (PPIP) [14] and all deliveries from 22 weeks and later were excluded from the present study. During the discussions at the perinatal meetings it became apparent that in certain women, fetal demise had occurred prior to 22 weeks but the fetus delivered at or after 22 weeks. The gestational age at demise was determined in different ways: i) early ultrasound examination, ii) gestational age when fetus was known to be alive i.e. fetal heart rate monitored or fetal heart activity observed on ultrasound, iii) measurement of the foot length at autopsy /assessment gestational age by the pathologist using organ weights and degree of maceration [15]. The participant was included in the present study only when it was certain that demise had occurred prior to 22 weeks according to the first ultrasound examination unless there was a great discrepancy between the ultrasound derived gestational age and gestational age according to foot length or birthweight. It therefore means that the study consisted of second trimester miscarriages only. As a dual control, the list of fetal demises beyond 20 weeks gestation was verified. Any case where the fetal heart rate was recorded at or after 22 weeks, was regarded as a stillbirth and therefore not included. Terminations of pregnancy were included in the study as the primary obstetric reason for the termination was taken into account.

Results

There were initially 7010 singleton pregnancies, but after a loss of 136 voluntary withdrawals and 8 lost to follow-up at delivery, 6866 pregnancies (97.9%) remained in the study. (Fig. 1). Spontaneous miscarriages occurred in 66 (rate 0.96%) singleton pregnancies of which 19 occurred before 12 weeks and 47 at gestational age 12⁰ to 24⁴ weeks (rate 0.69%). Most of the miscarriages occurred at a gestational age of 16^{0/7} to 19^{6/7} weeks (Table 1). Autopsies were done on 13 fetuses where the gestational age at delivery varied between 20^{6/7} and 24^{4/7} weeks. In the 4 pregnancies where the gestational age at delivery was 22 weeks or more, the gestational age calculated according to foot length was less than this (Table 2). Therefore, these 4 were also regarded as second trimester miscarriages. The ultrasound derived gestational ages were done between 8^{1/7} and 17^{3/7} weeks. Associated complications in these 14 cases were suspected urinary tract infection in 2, pregnancy induced hypertension in 1, previous miscarriages in 2, and a

Table 1
Gestational age at delivery/demise.

Gestational age	Number	%
<12 weeks	19	28.8
12 ^{0/7} – 13 ^{6/7}	5	7.6
14 ^{0/7} – 15 ^{6/7}	5	7.6
16 ^{0/7} – 17 ^{6/7}	13	19.7
18 ^{0/7} – 19 ^{6/7}	16	24.2
20 ^{0/7} – 21 ^{6/7}	8	12.1
Total	66	100

Table 2
Placental histology and cause of death in late second trimester miscarriages (demise before 22 weeks' gestation).

Placental Histology	Autopsy	Maternal age	Gravidy	Parity	GA at delivery	GA according to FL	Birth weight (g)	Placental weight (g)	Histological Findings
Yes	Yes	17	1	0	21w2d	21w6d	408	154	Acute chorioamnionitis, abruption
Yes	Yes	26	2	1	22w0d	16w3d	60	42	Maternal vascular malperfusion
Yes	Yes	17	1	0	22w6d	16w6d	160	140	Chronic villitis with OFV, CMV
Yes	Yes	20	2	1	24w4d	17w5d	148	70	Early amnion rupture with anhydramnios, cord obstruction
Yes	Yes	25	2	1	21w3d	14w3d	50	41	Maternal vascular malperfusion
No	Yes	36	1	0	21w1d	23w1d	450	N/A	N/A
Yes	Yes	32	2	1	21w6d	22w6d	410	104	Acute chorioamnionitis, abruption
Yes	Yes	17	1	0	20w6d	20w2d	331*	82	Acute chorioamnionitis
Yes	Yes	23	2	0	20w6d	14w4d	103*	49	Termination of pregnancy for Turner syndrome
Yes	No	32	2	3	19w3d	N/A	N/A	282	Acute chorioamnionitis, abruption, maternal vascular malperfusion
Yes	Yes	31	4	3	21w2d	22w1d	336*	132	Abruption
Yes	Yes	29	2	1	22w3d	15w2d	62*	31	Maternal vascular malperfusion, abruption
No	Yes	22	2	1	21w1d	16w3d	71*	N/A	N/A
Yes	Yes	23	3	0	21w4d	22w4d	400	131	Maternal vascular malperfusion, abruption

OFV = Obliterative fetal vasculopathy.

* No birth weight available, only autopsy weight; CMV = cytomegalo virus; GA = gestational age; FL = foot length; N/A = not available.

previous termination of pregnancy in 1. Seven cases presented with vaginal hemorrhage and one with loss of fetal movements, after which the fetal demise was diagnosed by ultrasound. In five women, fetal demise was diagnosed at a scheduled ultrasound examination and in the remaining one when she presented during labor. Histology of the placenta was available for 12 women (Table 2). The most prevalent histological abnormality was placental abruption which was seen in 6 miscarriages, occasionally on its own, or in combination with maternal vascular malperfusion or acute chorioamnionitis (inflammatory abruption). The second most frequent finding was maternal vascular malperfusion, alone or in combination with other pathology. The third most frequent pathology was acute chorioamnionitis, in combination or alone. Other abnormalities were more rarely seen (Table 2).

Discussion

The survival probability of early human conceptions is very low. At least 73% of natural single conceptions have no real chance of surviving six weeks of gestation [16]. After very early gestation, survival rates improve rapidly, as 90% of the remainder will survive to term. The rate of mid-trimester or late miscarriage (to use the terminology of the authors) is usually given as between 0.72% to 2.9% of pregnancies [5,6,17]. This is very similar to the 1% to 2.9% in different methods of artificial reproduction [18]. After 16 weeks the rate is reduced to around 1% [8,7]. In our study a rate of 0.96% was found, but it does not truly reflect the rate from a gestational age of 12 weeks onwards, as not all pregnancies were followed up from a gestational age of 12 weeks since the mean gestational age at booking for the study was 20 weeks 6 days and 30% of participants booked after 24 weeks (unpublished data, Safe Passage Study). The real prevalence rate of second trimester miscarriage in our population is therefore probably much higher.

Several researchers have examined possible underlying causes of second trimester miscarriage. Anderson et al. [19] examined the serum of 1676 pregnant women, donated in early pregnancy, before a gestation of 22 weeks, for soluble FMS-like kinase and placental growth factor. Spontaneous abortion occurred in 59 women (3.5%). Increasing continuous concentrations of both FMS-like kinase and placental growth factor were significantly associated with a decreased hazard ratio for spontaneous abortion. Ball et al. [20] examined whether late miscarriage was associated with reduced trophoblast invasion and spiral artery transformation. Compared to normal pregnancy, myometrial spiral arteries in late miscarriage showed reduced endovascular and intramural

trophoblast. In an examination on the association of mutations in coagulation factors in women with unexplained fetal loss, both the factor V and the prothrombin mutations were associated with an approximate tripling of the risk of late miscarriages [21]. The authors postulated that placental thrombosis may be the underlying pathogenic mechanism. In another study, of 351 of miscarriages between 12 and 24 weeks of gestation, 51% were classified as idiopathic [6]. Other causes were antiphospholipid syndrome (33%), cervical weakness (7%), uterine anomaly (4%), bacterial vaginosis (3%) and hypothyroidism (1%) as causes of mid trimester pregnancy losses. However, the authors did not refer to abruption or maternal vascular malperfusion.

Heller et al. [22] reviewed medical records and pathologic material of spontaneous second trimester pregnancy losses. From the 67 placentas available, 38 (56.7%) showed histologic acute chorioamnionitis. Another study tried to establish the cause of death in spontaneous abortion in 422 consecutive second trimester abortions [23]. Different degrees of maceration were found which probably indicated different mechanisms. The largest group was the one without maceration in which an explanation was found in 85%. Ascending infection (acute chorioamnionitis) was found although membranes were not ruptured. Another study reported on placental histology in 118 women with second trimester abortions, stillbirths and perinatal deaths, and the highest infection rate (58.2%) was found in second trimester abortions where infection was also the most frequent cause of death (45.5%) [24].

Although gestational age was determined by ultrasound between 8¹ and 17³ weeks, there were major differences between the ultrasound derived gestational age and gestational age according to foot length or birthweight. This probably indicates a severe degree of fetal growth restriction at the time of the first ultrasound examination. These findings also demonstrate how difficult it may be to determine the exact gestational age in growth restricted fetuses when ultrasound examinations are done in the second trimester. From the abovementioned studies, it is clear that placental pathology plays a major role in the etiology of spontaneous second trimester miscarriages. This is also the main finding in our study. Interestingly, placental disease was also the leading cause of antepartum stillbirths (26%) in the 633 stillbirths examined by the Stillbirth Network. However, they did not differentiate between the different placental conditions such as maternal vascular malperfusion or acute chorioamnionitis [25]. In the Dutch Cohort of 750 antepartum stillbirths, 65% were due to placental disease but intrauterine infection was found in only 1.8% of stillbirths [26].

The etiology of second trimester miscarriages in our population is therefore very similar to that of fetal death. More attention should therefore be given to national statistics on second trimester miscarriages and placental histology should be requested in all cases of spontaneous mid-trimester miscarriage as this may assist in establishing the etiology, thereby possibly preventing mid-trimester miscarriages and even more significantly perhaps stillbirths and preterm delivery and adverse pregnancy outcome.

Declaration of Competing Interest

The authors have no conflict of interest to report

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