Miscarriage after a normal scan at 12 – 14 gestational weeks in women at low risk of carrying a fetus with chromosomal anomaly according to nuchal translucency screening

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Abstract

Objectives The aim was to estimate the risk of second trimester miscarriage in women with low risk of carrying a fetus with chromosomal abnormality according to nuchal translucency (NT) screening, and to determine if NT thickness or other factors affect the risk.

Methods The study population comprised 14 278 singleton pregnancies with a risk of Down's syndrome < 1:250 at NT scan, and where no fetal karyotyping was performed < 25 weeks. Risk factors for miscarriage were investigated by logistic regression.

Results The median risk of Down´s syndrome was 1:3138 (range 1:9651 – 1:251) and median NT was 1.7 mm (range 0.4 – 3.0). The miscarriage rate was 0.5% (77/14 278; 95% CI 0.4 – 0.6). After having controlled for maternal age we found the number of previous deliveries and miscarriages to independently predict miscarriage: odds ratio, OR, for each previous delivery 1.48, 95% CI 1.22 – 1.80, $p < 0.0001$; OR for each previous miscarriage 1.34, 95% CI 1.07 – 1.68, $p = 0.01$. Excluding women with any previous miscarriage and adjusting for parity we found a U-shaped relationship between maternal age and miscarriage ($p = 0.04$).

Conclusion In singleton pregnancies with estimated risk of Down's syndrome <1:250 according to NT screening at 12 – 14-weeks, the spontaneous fetal loss rate before 25 weeks is likely to be around 0.5%. NT thickness up to 3 mm does not seem to affect the risk of miscarriage in such pregnancies. Instead the risk seems to increase with number of previous miscarriages and deliveries, and possibly the risk is highest in the youngest and oldest women.

Introduction

First trimester nuchal translucency (NT) measurement is an established method of screening for fetal chromosomal abnormalities[1, 2, 3]. It has also been suggested that increased NT is associated with increased risk of fetal loss[4 – 13]. Because NT measurement at 12 – 14 weeks is now routinely offered at many centres, it is of interest to be able to estimate the risk of subsequent miscarriage and convey information on prognosis after having demonstrated an apparently normal fetus at the NT scan.

The primary aim of this study was to estimate the risk of second trimester miscarriage in women with a low risk of carrying a fetus with a chromosomal abnormality according to NT screening. A secondary aim was to determine if NT thickness or other factors affect the risk of subsequent miscarriage in these women.

Subjects and methods

Our study population is a subgroup of pregnant women derived from the '12-week arm' of the Swedish NUPP-trial (NUPP is an abbreviation for NackUPPklarning, which is Swedish for nuchal translucency). This national multi-centre trial has been described in detail in several publications[14 – 16]. Pregnant women who consented to take part in the trial were randomized to a single routine ultrasound examination either at 12 – 14 gestational weeks or at 18 – 20 weeks. Our study group comprises 14 278 pregnancies fulfilling the following criteria: singleton pregnancy with an apparently normal fetus at the 12-week routine scan, estimated risk of trisomy 21 < 1:250 with risk estimated on the basis of maternal age, fetal crown-rump length (CRL) and NT (but not biochemistry, e.g., PAPP-A or beta-hCG) using the software of the Fetal Medicine Foundation, (FMF)[17], and no amniocentesis, chorion villus sampling or cordocentesis < 25 weeks. A flow chart demonstrating the selection of our study group is shown in Figure 1.

The 12-week scans were performed transabdominally by 46 specially trained midwives with median 11 (interquartile range, 5 – 17) years' experience of mid-trimester routine ultrasound examinations. They included measurement of CRL and biparietal diameter (BPD), scrutiny of fetal anatomy following a predefined check-list, and measurement of NT in accordance with the technical guidelines published by the FMF[17]. The risk of trisomy 21 was calculated using the FMF software with risk calculation being done without biochemistry[17], see above. Any suspicion of fetal malformation at screening was confirmed or refuted by an obstetrician trained in obstetric ultrasound. Women with a risk of trisomy 21 ≥1:250 were offered fetal karyotyping and so were women with a history suggesting an increased risk of fetal chromosomal anomaly (e.g., a previous pregnancy where the fetus had a chromosomal

anomaly), and women carrying a fetus with a structural anomaly. For more details on study design we refer the reader to previous publications[14 – 16].

To facilitate follow-up, all women were given a questionnaire at their routine scan where they were asked to report pregnancy outcome (e.g., the name of the hospital where they had given birth). Information on pregnancy outcome was retrieved from patient records, from departments of neonatology, pediatric cardiology, pediatric surgery, neurosurgery, plastic surgery, genetics and pathology providing services to the hospitals involved, from the National Registry of Congenital Anomalies, and in some cases from personal contact with the women. For all pregnancies in the study group we had full information about the outcome of pregnancy with regard to the vital status of the fetus/child and the presence/absence of congenital malformations diagnosed before the baby was dismissed from postnatal care.

For statistical purposes fetuses and newborns with more than one malformation were assigned one main malformation diagnosis. Congenital heart malformations diagnosed within the first 12 months of life, and other types of malformation diagnosed (or suspected and later confirmed) before the baby was dismissed from postnatal care were included. Malformations were grouped into four categories according to their likely clinical consequences as described before[18]: 1) lethal malformations 2) severe malformations 3) malformations of intermediate severity 4) minor malformations. Minor malformations are not accounted for in this study.

Miscarriage was defined as spontaneous fetal loss <25 weeks of pregnancy. Perinatal death was defined as intrauterine death ≥25 weeks of pregnancy, intra-partum death, or death within 7 days of birth. In Sweden, termination of pregnancy is rarely allowed >22 weeks of pregnancy.

For the purpose of this study, gestational age was determined by fetal ultrasound biometry in all cases, also in *in vitro* fertilization pregnancies. We used the BPD formula of Selbing

and Kjessler[19] if the BPD was ≥21 mm; we used the CRL formula of Selbing and Fjällbrandt[20] if the fetal BPD had not been documented in the trial database or was <21 mm.

Maternal demographic background data, results of ultrasound examinations and pregnancy outcome were entered into a database via the internet using software specifically designed for the NUPP-trial (Medscinet, AB, Stockholm, Sweden). Information on maternal race, body mass index, tobacco use, obstetric history, maternal disease, or other possible risk factors for miscarriage was not recorded.

Statistical analysis

Two sets of statistical analyses were performed. First, putative risk factors for miscarriage within the study group were investigated. The risk factors evaluated were: maternal age (years), gestational age at the 12 – 14 week NT scan (days), nuchal translucency (mm), estimated risk of Down´s syndrome, previous spontaneous abortions (number), previous terminations of pregnancy (number), parity (number), and *in vitro* fertilization (yes/no). After visual inspection of the data, risk estimates were calculated using multiple logistic regression analyses (Gauss ™, Aptec Systems Inc., Maple Valley, WA, USA). The goodness of fit was assessed with the Hosmer and Lemeshow method[21]. If a first grade term and a second grade term of a variable were included in the same model, an F-test was performed in order to test the simultaneous effect of these two terms, i.e., the total effect of the variable. The number of investigated risk factors never exceeded 1/10 of the number of cases.

Second, analyses were performed to investigate whether our study group deviated from pregnant women not included in our study with regard to the possible risk factors for miscarriage investigated. To this end we compared parity, maternal age and number of previous miscarriages between the following three groups of women: declined randomization (group 1), randomized to an NT scan but excluded from the current study (group 2), randomized to NT scan and included in the current study (group 3). The association between

parity, number of previous miscarriages and age with inclusion in group 3 vs. in group 1 and 2 was explored using multivariate logistic regression analyses, where an interaction term between parity and number of previous miscarriages was also added. The same types of multiple logistic regression analyses were carried out to predict inclusion in group 3 versus in group 2. The possibility of parity affecting the estimation of risk of Down´s syndrome was evaluated by inspection of tabled data and by performing multivariate logistic regression analyses with parity and maternal age as predicting variables.

Two-tailed P-values < 0.05 were considered statistically significant.

Results

Demographic data and pregnancy outcome of the study group (14 278 women, 14 278 fetuses) and of the cases excluded after confirmation of the presence of at least one living fetus (3687 women, 3988 fetuses) are presented in Table 1. **Two hundred and sixty-six fetuses (1.9%) in the study group had a malformation of at least intermediate severity.** Main diagnoses of the malformed fetuses in our study group are presented in Table 2.

The miscarriage rate in our study group was 0.5% (77/14278; 95% CI 0.4 – 06). In 12 (16%) cases gestational age at miscarriage was unknown, 16 (21%) miscarriages were diagnosed at 12 – 15 weeks, 34 (44%) at 16 – 18 weeks and 15 (19%) at 22 – 24 weeks. Six of the 77 fetuses lost in miscarriage underwent both autopsy and post-abortem karyotyping. All six were normally formed and had normal karyotype. The remaining 71 fetuses underwent neither autopsy nor karyotyping.

Miscarriage rates in relation to the putative risk factors examined are presented in Tables 3 and 4, Table 3 showing descriptive statistics (numbers and percentages) and Table 4 presenting results for the uni-variate and multivariate logistic regression analyses. The risk of miscarriage increased with each previous delivery and with each previous spontaneous abortion. The odds ratio (OR) for parity changed only marginally when adjustments were made for maternal age, number of previous miscarriages and the other possible risk factors. Similarly, the association between number of previous miscarriages and miscarriage of the current pregnancy was independent of maternal age and parity. No interaction between parity and number of previous spontaneous abortions was found. When testing the simultaneous effect of maternal age as a linear and quadratic term, a highly significant U-shaped relationship between maternal age and risk of miscarriage was revealed. The U-shaped relationship persisted with borderline statistical significance ($p = 0.050$) after parity and number of previous spontaneous abortions had been added to the model including the two age

terms. The relation between maternal age and miscarriage is visualized in Figure 2. The figure shows odds ratios for miscarriage based on the ´best model´ presented in Table 4. The results from the 'best model' were also used to create graphs **(one graph for each maternal age)** illustrating the risk of miscarriage by parity and number of previous miscarriages. **Figure 3 shows the risk of miscarriage for 32-year-old women, 32-year old women offering a realistic example, because they may just as well be nulliparae as grand multiparae. To estimate the risk of miscarriage of a particular woman in a clinical situation, one would need one graph for each maternal age, alternatively a computer program to calculate the individual risk of miscarriage taking into account maternal age, parity and number of previous miscarriages.** Even in the subgroup of women with no previous spontaneous abortions parity was a risk factor for miscarriage (age-adjusted OR: 1.64; 95% CI: 1.31 – 2.05), and in this sub-set, the U-shaped relationship between miscarriage and maternal age was statistically significant (p = 0.04).

Our study group - a selected group of pregnant women at low risk of carrying a fetus with a chromosomal anomaly - deviated from pregnant women not included in our study (Table 5). Compared to women 25 - 29 years old, younger women (not significant), and older women were less likely to participate in the current study. Even though not statistically significant (p = 0.07), our results suggest a positive interaction between parity and the number of previous miscarriages for participation in the study, i.e., with increasing parity the likelihood of being included in the current study group increased with increasing number of previous miscarriages. In the group randomized to an NT scan, only maternal age predicted exclusion (group 2 vs. group 3, see above), those excluded being older. There was no association between parity (corrected for maternal age) and having a risk of trisomy 21 <1:250.

Discussion

To estimate the true miscarriage rate after a scan has revealed a living fetus at 12 – 14 gestational weeks is extremely difficult, because non-interventional observation after the scan is necessary. If scans have a clinical purpose, for instance when screening for trisomy 21 by NT measurement, non-intervention is possible only in apparently normal pregnancies, because most women at increased risk of trisomy 21 will undergo chorion villus sampling or amniocentesis, both of which increase the risk of miscarriage [22 – 24]. Moreover, if a chromosomal anomaly or a fetal malformation is revealed many women will terminate their pregnancy. This is why we decided to study a selected but well defined group of women with an apparently normal fetus at a 12-week scan and with a low risk of trisomy 21 and to include only those who did not undergo any invasive procedure before 25 gestational weeks. It is of clinical interest to be able to convey correct information on the prognosis to such ´low-risk´ women, because they constitute the vast majority (90 – 95%[15, 25]) of pregnant women. On the other hand, our results are applicable only to populations very similar to our own study population. The composition of any similar ´low-risk´ population will be determined by the ability of ultrasound examiners to detect fetal malformations at 12 –14 gestational weeks and by individual decisions, e.g., whether or not to undergo fetal karyotyping and whether or not to terminate the pregnancy for psychosocial or other reasons.

We found the risk of miscarriage to be 0.5% (95% CI of 0.4 – 0.6) after an apparently normal fetus with an estimated risk of Down´s <1:250 had been seen at a 12 – 14 week NT scan. This risk is lower than that reported (0.7%) among women < 35 years old with a living fetus seen at a scan at around 16 weeks[23]. One would have expected the miscarriage rate to be lower after confirmation of viability at 16 weeks than at 12 – 14 weeks. Probably, the study populations differed between the two studies. It is not meaningful to compare the miscarriage

rate in our study with that reported after a living fetus had been seen at a 12 –14 week scan in other published studies[4 – 13], because the other studies included only fetuses with increased NT [4, 6–8, 10, 12, 13], only high risk pregnancies where all women underwent fetal karyotyping [5, 9], or also fetuses with major malformations [5, 11]. As a result of this, miscarriage rates were much higher (0.9% - 13.2%) in these studies than in ours.

Even though it was not the aim of our study, it may be interesting to try to estimate the miscarriage rate in a total pregnant population – as opposed to in a selected population - from our data. To do this we need to study the outcome both of the pregnancies included in our study and those excluded. Among the pregnancies for which we know the outcome (n = 17870, see Table 1), there were 77 + 55 miscarriages and 134 pregnancy terminations (Table 1). The miscarriage rate in our total pregnant population can therefore be estimated to lie somewhere between 0.7% (77 + 55/ 17870) (95% CI 0.6 – 0.9) and 1.5% (77 + 55 + 134/17870) (95% CI 1.3–1.6). The highest figure should probably be slightly adjusted downwards, if we assume that some of the miscarriages among the women excluded were caused by amniocentesis or chorion villus sampling.

In our study population, the risk of miscarriage was not affected by gestational age or NT thickness, which are both 'generally accepted' risk factors for miscarriage. The absence of an association between NT thickness and miscarriage may be explained by no fetus in our study having NT >3mm; and the absence of an association between gestational age and miscarriage is likely to be explained by the narrow gestational age span at which the scans were performed (12 – 14 weeks). Our results confirm those of others that *in vitro* fertilization does not seem to be a risk factor for miscarriage.[26, 27, 28]. The only risk factors were parity and previous spontaneous abortions, both being independent risk factors. Our finding that the risk of miscarriage increased with the number of previous miscarriages agrees with those of others [29, 30, 31 – 34], while parity has not previously been reported to be a risk factor for either first or

second trimester miscarriage. Our results do not support that the association between parity and miscarriage risk was a result of bias, because the interaction between parity and number of previous miscarriages for participation in our study was not statistically significant, and parity was a highly significant risk factor for miscarriage even among women with no previous miscarriage. However, selection bias cannot be entirely excluded, because we have no information – and we have no possibility to obtain information retrospectively, our internet based database being anonymous – on previous stillbirths or preterm deliveries, which, theoretically, might be risk factors for miscarriage after 12 weeks[35, 36], or on other possible risk factors, e.g., increased body mass index[37], maternal smoking[38], maternal diabetes[39], anti-phospholipid syndrome[40], or bleeding early in the current pregnancy[41]. Therefore, we cannot determine if the presence of risk factors for miscarriage became more common with increasing parity because of unintended selection bias. If the latter were true, parity could simply be a confounder. We can only speculate about which mechanisms could explain a true association between parity and miscarriage. One possible mechanism is increasing ability with increasing parity to keep a fetus destined to die alive until the second trimester, another is unfavorable uterine environment for normal embryonic-fetal development in multipara. Uterine microcirculation/environment might change with each delivery so as to change the low-oxygen milieu necessary for normal embryonic development[42].

Both we and others have found a U-shaped relationship between maternal age and risk of miscarriage [43, 44]. Possibly, the increased risk in the oldest women in our study is to be explained by the risk of fetal aneuploidy increasing with maternal age[45, 46] (and fetal aneuploidy being a common cause of miscarriage) despite most fetuses with major chromosomal anomalies almost certainly having been excluded from our study group. It is a weakness of our study that only a few fetuses lost in miscarriage underwent autopsy and

karyotyping, a weakness that we probably share with most other studies reporting on miscarriage after a living fetus has been confirmed at a scan at 12 – 14 weeks[4, 5, 11, 13]. We can only make an approximate estimation of the true prevalence of fetal chromosomal anomalies in our study population. Among those women excluded who underwent fetal karyotyping because of pure worry, the prevalence of major chromosomal anomalies was 0.44% and that of clinically less important anomalies, e.g., Klinefelter's syndrome or balanced translocations, was 0.77% (Figure 1). If we assume that these prevalences were the same in our study population (indeed, an unlikely assumption, because median risk of trisomy 21 in our study population was 1: 3138, range 1:251 – 1: 9651 vs. 1:838, range 1:251 – 1:8302 among those women who underwent fetal karyotyping because of pure worry; Figure 1), then there could have been as many as 48 fetuses with major chromosomal anomalies (0.0044 x 14278 minus 15) among the 77 miscarriages (corresponding to 62%). Plausible explanations for an association between higher age and miscarriage could also be poorer health in older women, e.g., impaired function of the thyroid gland, which has been suggested to increase the risk of miscarriage[47] or uterine fibroids being more common in older women[48] and being a known risk factor for miscarriage[44]. The increased risk of miscarriage in the youngest women might be explained by specific obstetric risks among very young pregnant women. Women giving birth during their adolescence are at increased risk of adverse outcome both in terms of fetal loss[49, 50] and preterm birth[51 – 53]. Whether the risk of fetal chromosomal anomalies is increased in very young women is debatable[54, 55].

To sum up, in singleton pregnancies with an apparently normal fetus with estimated risk of Down's syndrome <1:250 according to NT screening at 12 – 14 weeks, the spontaneous fetal loss rate before 25 weeks is likely to be around 0.5%. NT thickness up to 3 mm does not seem to affect the risk of miscarriage in such pregnancies, but the risk seems to increase with

number of previous miscarriages and with parity, and possibly the risk is highest in the youngest and oldest mothers-to-be.

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Table 1. Demographic characteristics of the study cohort and of the cases excluded

	Study group (n=14 278)	Cases excluded * (3687 women, 3988 fetuses†)
Maternal age		
mean (±SD)	29.4 (± 4.4)	32.3 (± 5.6)
median (range)	30.0 (15 – 42)	33.0 (16 – 46)
35 years or older, %	12.3 (1754/14278)	41.6 (1535/3687)
Nullipara, %	52.0 (7421/14278)	41.9 (1546/3687)
Previous spontaneous abortion, %	19.8 (2833/14278)	33.4 (1231/3687)
Previous termination of pregnancy, %	23.6 (3368/14278)	37.4 (1380/3687)
In vitro fertilization pregnancy %	1.4 (196/14278)	1.8 (68/3687)
Previous pregnancy with chromosomal abnormality, %	0.07 (10/14 278)	0.4 (14/3687)
Previous pregnancy with malformed fetus	0.4 (60/14 278)	1.1 (41/3687)
Duplex pregnancy, %	0	8.0 (296/3687)
Triplex pregnancy, %	0	0.08 (3/3687)
Fetal crown rump length (mm) at scan		
mean (±SD)	69.1 (± 8.0)	69.5 (± 10.0)
median (range)	70.0 (38 – 84)	72.0 (38 – 84)
Fetal biparietal diameter (mm) at scan		
mean, (±SD)	23.3 (±2.4)	24.3 (±2.6)
median (range)	24.0 (15 – 34)	25.0 (17 – 34)
Nuchal translucency, mm		
mean, (±SD)	1.7 (±0.4)	2.1 (±1.2)
median (range)	1.7 (0.4 – 3.0)	1.9 (0.7 – 12.0)
≥2.5 mm, %	2.3 (323/14278)	8.3 (330/3988)
≥3 mm, %	0.03 (4/14278)	4.0% (160/3988)
Calculated risk of trisomy 21		
median (range)	1:3138 (1:9651– 1:251)	1:543 (1:9408 – 1:2)
Malformed fetus, %	1.9 (266/14 278)	2.8 (112/3893)
lethal or serious malformation, %	0.5 (78/14 278)	2.1 (83/3893)
malformation of intermediate severity, %	1.3 (188/14 278)	0.7 (29/3893)
malformation detected during pregnancy, %	0.1 (16‡/14 278)	1.5 (59/3893)
malformation detected at birth or abortion, %	1.8 (250§/ 14 278)	1.4 (53/3893)
Chromosomal abnormality, %	0.1 (15/14 278)	1.9 (75/3893)
trisomy 21, %	0.07 (10/14 278)	1.16 (45/3893)
trisomy 18, %	0.007 (1/14278)	0.18 (7/3893)
trisomy 13, %	0.007 (1/14278)	0.15 (6/3893)
Turner, %	0	0.13 (5/3893)
Other sex chromosome abnormalities, %	0	0.15 (6/3893)
Triploidy, %	0	0.08 (3/3893)
Other unbalanced autosomal anomlies, %	0.02 (3/14278)	0.08 (3/3893)
Live birth, %	99.0 (14130/14278)	88.5 (3448/3893)
Live birth < 25 weeks, %	0.08 (11/14278)	0.8 (33/3893)
Perinatal death, %	0.5 (71/14 278)	0.5 (19/3893)
Miscarriage, %	0.5 (77/14278)	1.4 (55/3893)
Termination of pregnancy, %	0	3.5 (134/3893)

Cont.

Table 1 continued

	Study group (n=14 278)	**Cases excluded [*] (3687 women, 3988 fetuses[†])**
Fetal karyotyping <25 weeks, %	0	39.6 (1540/3893)
Fetal karyotyping >25 + 0 weeks, %	0.1 (14[¶]/14278)	0.2 (8/3893)
Indication for fetal karyotyping >25+0 weeks		
Malformation, n	8	4
Intrauterine fetal death, n	4	4
Intrauterine growth restriction, n	1	
Polyhydramnion, n	1	

[*] Cases excluded after a living fetus had been confirmed at the 12-week scan

† Information on follow-up was available for 3893 of 3988 fetuses scanned.

‡Frontal encephalocele, n = 1; Hydrocephalus, n = 9; Skeletal dysplasia, n = 1; Common arterial trunc, n = 1; Hypoplastic left heart syndrome, n = 1; Tricuspid valve insufficiency, n = 1; Facial cleft, n = 1; Ovarian cyst, n = 1

§ Three fetuses had a lethal anomaly (bilateral renal agenesis, n=2; infantile polycystic kidney disease, n=1); 62 fetuses had a serious malformation, and 185 fetuses had a malformation of intermediate severity.

[¶]Amniocentesis, n = 12; chorion villus sampling, n = 1; cordocentesis, n = 1

Table 2. Main malformation diagnoses of malformed fetuses (n = 266)

	Number of fetuses
Lethal anomaly	**4**
Frontal encephalocele	1
Bilateral renal agenesis	1
Infantile polycystic kidney disease	2
Serious anomaly	**74**
Brain	5
Spina bifida	8
Eye/ear	6
Major heart malformation	22
Intestinal atresia	11
Renal dysplasia	2
Skeletal	11
Diaphragmatic hernia/malformation	3
Ectodermal anhidrotic dysplasia	1
Multiple malformations or syndrome	5
Anomalies of intermediate severity	**188**
Coloboma	3
Facial cleft	18
Choanal atresia	2
Non-major cardio-vascular anomalies	78
Uro-genital (including hypospadia and hydroneprosis)	41
Musculo-skeletal (including clubfoot and malformation of the sternocleidomastoid muscle)	46

Table 3. Miscarriage in relation to possible risk factors

	Miscarriage, n	Miscarriage, (%)	Total number of pregnancies
Maternal age, years			
20-24	9	(0.5)	1779
25-29	26	(0.5)	4906
30-34	20	(0.4)	5597
35-39	18	(1.1)	1667
≥40	2	(2.3)	87
Parity			
0	27	(0.4)	7425
1	24	(0.5)	4859
2	19	(1.2)	1540
≥3*	7	(1.5)	454
Gestational week at examination			
10	0	(0.0)	6
11	5	(0.8)	616
12	24	(0.6)	4087
13	46	(0.5)	8537
14	2	(0.2)	1029
15	0	(0.0)	3
Nuchal translucency, mm			
<.5	0	(0.0)	1
.5-.9	2	(0.9)	230
1-1.4	20	(0.6)	3450
1.5-1.9	37	(0.5)	6848
2.0-2.4	17	(0.5)	3426
2.5-2.9	1	(0.3)	319
3.0	0	(0.0)	4
Previous spontaneous abortion, number			
0	58	(0.5)	11453
1	10	(0.5)	2190
2	3	(0.6)	480
3	1	(1.0)	102
4	3	(7.7)	39
≥5	2	(14.3)	14
In vitro fertilization pregnancy			
No	76	(0.5)	14082
Yes	1	(0.5)	196
Previous termination of pregnancy, number			
0	53	(0.5)	10915
1	18	(0.7)	2592
2	4	(0.7)	615
3	1	(0.8)	118
4	1	(3.7)	27
≥5	0	(0.0)	11
Total	77	(0.5)	14278

***Of the seven women who had undergone 3 or more deliveries and had a miscarriage of the current pregnancy five were 3-para, one was 4-para and one was 8-para.**

Table 4. Results of uni-variate and multivariate logistic regression analyses demonstrating the effect of risk factors for miscarriage

	Uni-variate models		Model simultaneously including all displayed variables		Best model		
Evaluated Risk factor	**Odds Ratio***	**p-value**	**Odds Ratio***	**p-value**	**Odds Ratio***	**95 % CI**	**p-value**
Maternal age (years), linear term	1.04	0.13	0.60	0.01	0.61	0.42 – 0.91	0.015
Maternal age (years), quadratic term	1.00	0.07	1.01	0.01	1.01	1.00 – 1.02	0.015
Maternal age (years), simultaneous test[†]		0.002		0.06			0.050
Parity (number)	1.58	$<10^{-6}$	1.54	$<10^{-3}$	1.48	1.22 – 1.94	$<10^{-4}$
Previous spontaneous abortion (number)	1.48	$<10^{-4}$	1.35	0.009	1.34	1.07 – 1.68	0.010
Gestational age at examination (days)	0.97	0.33	0.97	0.36			
Nuchal translucency thickness (mm)	0.72	0.29	0.81	0.53			
Previous termination of pregnancy (number)	1.29	0.08	1.25	0.13			

* All estimates show the odds ratio for a one-step-increase, (e.g., if the OR for parity is 1.5, an increase in parity from 0 to 1 increases the odds of the outcome 1.5 times).
[†] Bi-variate model including age and age^2

Table 5. Results of multiple logistic regression analysis demonstrating the effect of age, parity and number of previous miscarriages on the likelihood of being included in our study group compared to having declined participation or having been excluded

	Odds ratio		p-value
	Estimate†	95%CI	
Maternal age, years*			
<20	0.63	0.17 – 2.36	0.50
20-24	0.59	0.28 – 1.26	0.17
30-34	0.65	0.47 – 0.91	0.01
35-39	0.78	0.62 – 0.99	0.04
≥40	0.61	0.51 – 0.74	$<10^{-6}$
Previous miscarriage	1.00	0.96 – 1.04	0.94
Parity	0.88	0.86 – 0.91	$<10^{-6}$

CI, confidence interval
*Maternal age was divided into classes as shown, the reference group being women 25 - 29 years old.
†The estimates show the odds ratios for a one-step - increase (e.g., if the OR for parity is 1.5, an increase in parity from 0 to 1 increases the odds of the outcome 1.5 times).

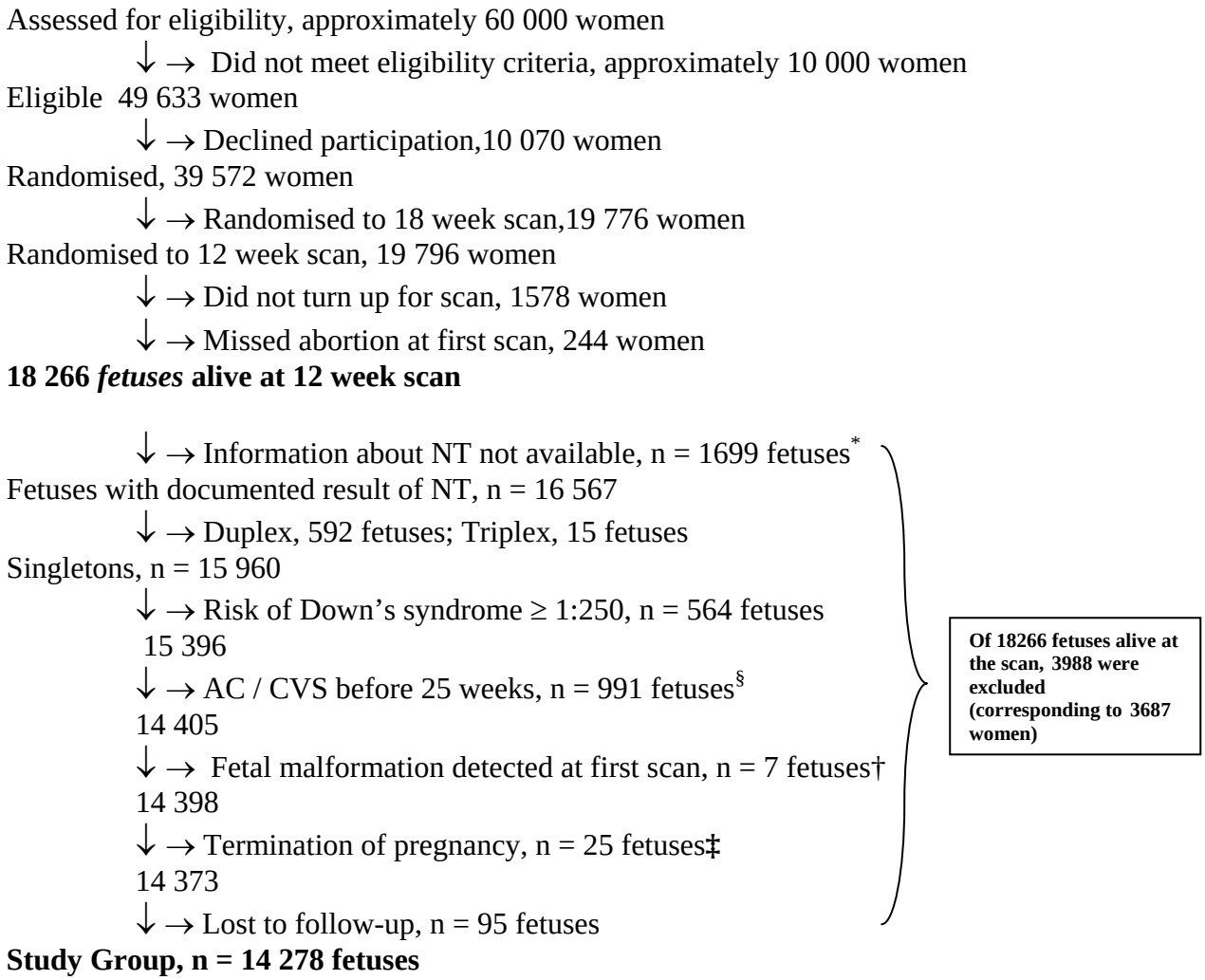
Legends

Figure 1. Flow chart demonstrating the selection of our study group.

Figure 2. Change in odds of miscarriage **with maternal age.** The unbroken line shows the odds ratios, OR, with 95 % confidence intervals. **These** were obtained from the estimates for the linear and quadratic term for maternal age shown in Table 4 (´best´ model).

Figure 3. The risk (in percentage) of miscarriage by parity and number of previous miscarriages for 32-year-old women The illustration is based on the risk estimates obtained by the ´best´ model, shown in Table 4 **(the mathematical formula used to calculate the risk is available from the authors on request).**

Figure 1



AC, amniocentesis; CVS, chorion villus sampling

* Missing information about nuchal translucency (NT) is explained by the woman being too advanced in her pregnancy for NT measurement to be possible (crown rump length > 84 mm), difficulties with measuring NT, failure to document the NT measurement in the trial database, or obvious lethal malformations, e.g., anencephaly

§ Indications for fetal karyotyping: worry, 905 (90.5%); abnormal ultrasound finding, 24 (2.4%); previous fetus with chromosomal abnormality, 20 (2%); increased risk according to second trimester serum screening, 15 (1.5%); increased risk according to family history, 9 (0.9%); previous child with structural malformation, 8 (0.8%); other, 10 (1%). Of the 905 women who underwent fetal karyotyping because of pure worry (median risk of Down´s syndrome 1:883, range 1:8302 – 1:251), four (0.44%) carried a fetus with a major chromosomal anomaly (trisomy 21, three cases; lethal deletion, one case), and seven (0.77%) carried a fetus with a less serious chromosomal anomaly (47xxy, two cases; 47xxx, one case; structurally normal X0, one case; balanced translocation, two cases; marker chromosome, one case).

† Gastroshisis, n = 2; Anencephaly, n = 1; Holoprosencephaly, n = 1; Spina bifida, n = 1; Skeletal dysplasia, n = 1; Posterior urethral valve, n = 1 (six of the seven pregnancies were terminated, one pregnancy where the fetus had gastroschisis continued)

‡ Reason for termination of pregnancy: Cytomegalus virus infection, n = 1; Oligohydramnion, n = 1; Maternal malignant ovarian tumor, n = 1; Psychosocial reason, n = 12; Unknown reason, n = 10

Figure 2

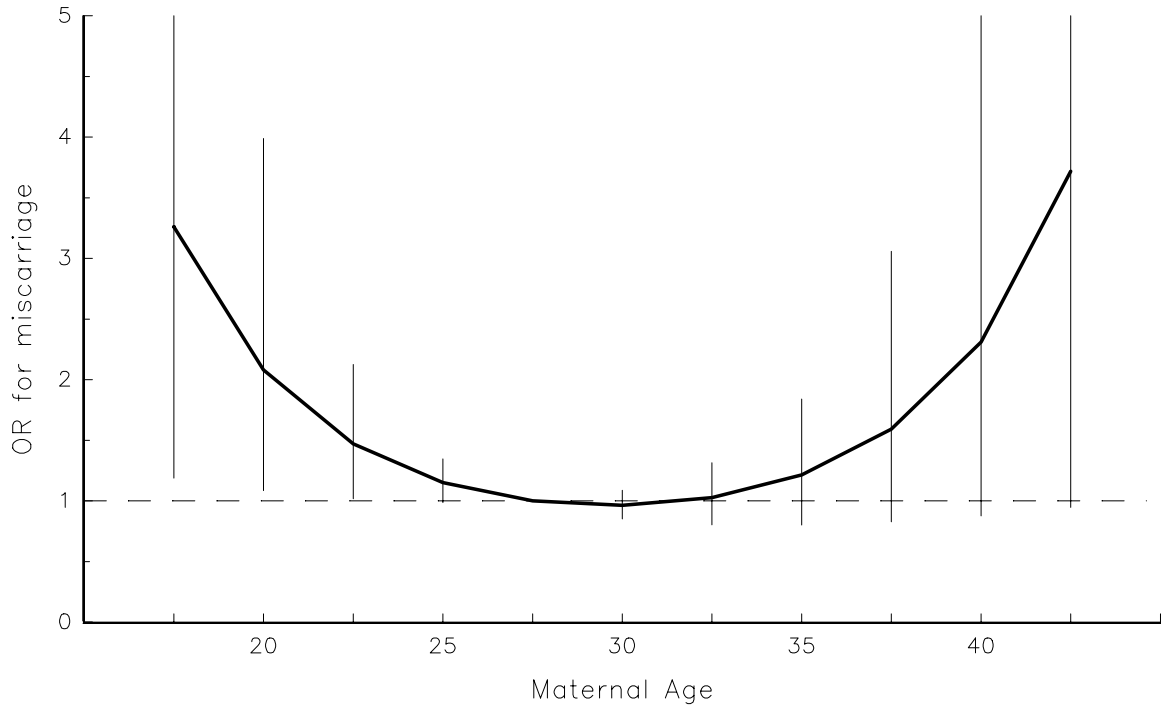
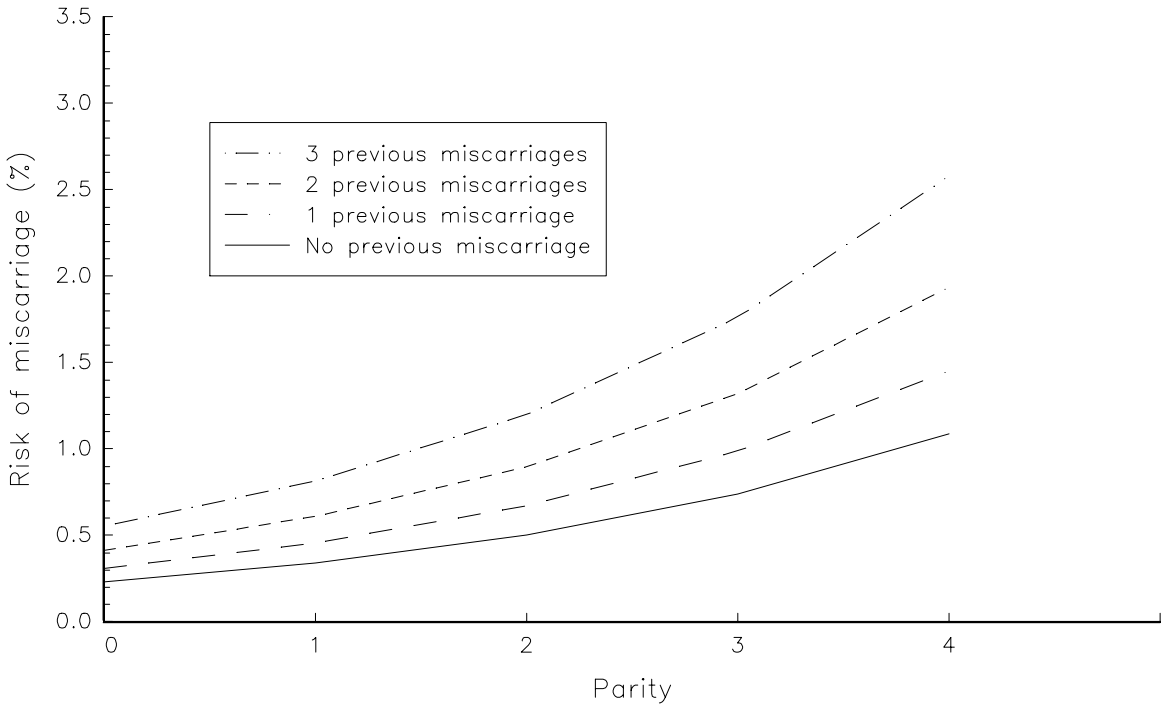


Figure 3.


3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Risk of miscarriage (%)
3 previous miscarriages
2 previous miscarriages
1 previous miscarriage
No previous miscarriage
0
1
2
3
4
Parity