

Selective chromosome analysis in couples with two or more miscarriages: case-control study

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Abstract

Objective To identify additional factors, such as maternal age or factors related to previous reproductive outcome or family history, and the corresponding probability of carrying a chromosome abnormality in couples with two or more miscarriages.

Design Nested case-control study.

Setting Six centres for clinical genetics in the Netherlands.

Participants Couples referred for chromosome analysis after two or more miscarriages in 1992-2000; 279 carrier couples were marked as cases, and 428 non-carrier couples served as controls.

Main outcome measures Independent factors influencing the probability of carrier status and the corresponding probability of carrier status.

Results Four factors influencing the probability of carrier status could be identified: maternal age at second miscarriage, a history of three or more miscarriages, a history of two or more miscarriages in a brother or sister of either partner, and a history of two or more miscarriages in the parents of either partner. The calculated probability of carrier status in couples referred for chromosome analysis after two or more miscarriages varied between 0.5% and 10.2%.

Conclusions The probability of carrier status in couples with two or more miscarriages is modified by additional factors. Selective chromosome analysis would result in a more appropriate referral policy, could decrease the annual number of chromosome analyses, and could therefore lower the costs.

Introduction

Couples who have had two or more miscarriages are at increased risk of either of the partners carrying a structural chromosome abnormality. The incidence of carrier status increases from approximately 0.7% in the general population to 2.2% after one miscarriage, 4.8% after two miscarriages, and 5.2% after three miscarriages.^{1,2} No consensus exists about the management of recurrent miscarriage as to whether chromosome analysis should be offered after two or three miscarriages.³⁻⁵

Whether the probability of carrier status is also modified by maternal age or by factors related to previous reproductive outcome or family history is not known. If it is, the possibility of withholding chromosome analysis from couples with a low probability of carrier status could be considered. We aimed to identify additional factors influencing the probability of carrier status in couples with two or more miscarriages and to calculate the associated

probability of carrier status for every combination of these factors.

Methods

Patients—We used the databases of six centres for clinical genetics in the Netherlands to identify all couples referred for chromosome analysis after two or more miscarriages between 1 January 1992 and 1 January 2001. Cases were all couples in which one of the partners was found to be a carrier of a structural chromosome abnormality. As controls, we selected a random subset of non-carrier couples by identifying the last couple tested before the carrier couple and the first couple tested after the carrier couple in each centre. We included only couples with at least two miscarriages with a gestational age up to 20 weeks and verified by a pregnancy test or ultrasonography.

Data collection—We examined the medical records of the relevant department of clinical genetics, and both partners filled out a questionnaire. We collected additional information from telephone interviews and referral medical records.

Statistical analysis—We used logistic regression analysis to identify factors influencing the probability of carrier status and to calculate the corresponding probability of carrier status. We divided variables into five subgroups: general history; maternal age at chromosome analysis, at first miscarriage, and at second miscarriage; number of miscarriages; obstetric history; and family history. We first did univariate logistic regression analysis with all variables. We retained variables with $P \leq 0.2$ in the univariate analysis for subsequent steps. We then did multivariate logistic regression analysis, adding variables to the model by subgroup. We retained only variables with $P \leq 0.1$ in the model. (See bmj.com for details.) As this was a nested case-control study, we had to adjust the model for the relative proportions of cases and controls in the total population of couples referred for chromosome analysis after two or more miscarriages. We then calculated the probability of carrier status from the final model for every combination of variables.

Results

Between 1 January 1992 and 1 January 2001, 11 971 couples had been referred to the participating centres for chromosome analysis after two or more miscarriages. We invited 1148 couples to participate in the study. We included 62% of the invited couples—279 (73%) carrier couples and 428 (56%) non-carrier couples.



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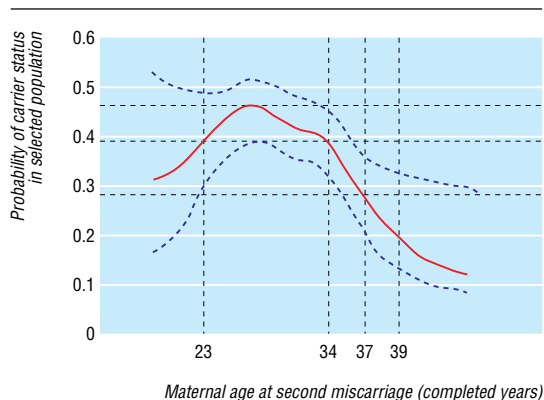
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Splines analysis: probability of carrier status in different categories of maternal age at second miscarriage, with 95% confidence intervals. Probability of carrier status is based on selected population of included couples (279 carrier couples; 428 non-carrier couples); numbers of carrier couples and non-carrier couples need to be adjusted to determine probability of carrier status in total screening population

At the time of chromosome analysis, differences existed between carrier couples and non-carrier couples (see bmj.com). The mean maternal age was significantly lower and the mean number of miscarriages was significantly higher in carrier couples than in non-carrier couples.

The structural chromosome abnormalities recorded consisted of 174 (62%) reciprocal transloca-

tions, 44 (16%) Robertsonian translocations, 3 (1%) (Y;22) translocations, 21 (8%) pericentric inversions, 21 (8%) paracentric inversions, 7 (3%) marker chromosomes, and 9 (3%) other structural chromosome abnormalities. Male and female carriers were not distributed equally: 177 (63%) carriers were women and 102 (37%) carriers were men.

A non-linear relation existed between maternal age and the log odds of carrier status. We decided to divide maternal age at second miscarriage into five categories—<23 years, 23-33 years, 34-36 years, 37-38 years, and ≥39 years—on the basis of the results of splines analysis (fig).

After multivariate logistic regression analysis, four factors influencing the probability of carrier status were retained in the final model (table 1). We calculated the probability of carrier status for every combination of variables in the final model (table 2). We found a probability of carrier status of 10.2% in couples with a maternal age <23 years at the second miscarriage, referred after three or more miscarriages, and with a brother or sister as well as parents with a history of two or more miscarriages. At lowest risk (0.5%) were couples with a maternal age ≥39 years at the second miscarriage, referred after two miscarriages, and without a brother or sister or parents with a history of two or more miscarriages. Couples with a probability of carrier status below 2.2%, which is the reported incidence in couples with only one miscarriage, are noted in table 2.

As the multivariate model can be used only if all variables are known, which may not always be the case, we also built a model with maternal age at second miscarriage as the only variable. According to this model, couples with a maternal age of ≥37 years have a probability of carrier status below 2.2%.

If chromosome analysis had been withheld from couples with a probability of carrier status below 2.2%, the number of chromosome analyses would be reduced by 18% according to the multivariate model. If the model based on maternal age at the second miscarriage was applied, the reduction would be 10% (table 3).

Table 1 Factors influencing probability of carrier status after multivariate logistic regression analysis (P<0.10)*

Covariates	Odds ratio (95% CI)	P value
Maternal age (years) at second miscarriage:		
<23	6.2 (1.1 to 34.3)	0.04
23-33	6.1 (1.3 to 27.7)	0.02
34-36	3.3 (0.7 to 16.1)	0.13
37-38	2.3 (0.4 to 12.0)	0.33
≥39	1.0	–
3 v ≥2 miscarriages	1.4 (1.0 to 2.1)	0.05
≥2 miscarriages in a brother or sister	1.9 (1.1 to 3.2)	0.02
≥2 miscarriages in parents	1.4 (0.9 to 2.2)	0.10

*Limited to 528 couples with complete data.

Table 2 Probability of carrier status in couples with two or more miscarriages, according to multivariate logistic regression model*. Values are percentages

Maternal age (years) at second miscarriage	(RM _{bs})	(RM _{parents}) +		(RM _{parents}) –	
		≥3 misc	2 misc	≥3 misc	2 misc
<23	+	10.2	7.3	7.3	5.2
	–	5.7	4.0	4.1	2.8
23-33	+	10.0	7.2	7.2	5.1
	–	5.7	4.0	4.0	2.8
34-36	+	5.8	4.1	4.1	2.9
	–	3.2	2.2	2.2	1.6†
37-38	+	4.0	2.8	2.8	2.0†
	–	2.2	1.5†	1.5†	1.1†
≥39	+	1.8†	1.2†	1.3†	0.9†
	–	1.0†	0.7†	0.7†	0.5†

RM_{bs}=history of ≥2 miscarriages in a brother or sister of either partner; RM_{parents}=history of ≥2 miscarriages in parents of either partner; ≥3 misc=history of ≥3 miscarriages in couple; 2 misc=history of ≥2 miscarriages in couple.

*Limited to 528 couples with complete data.

†Couples with probability of carrier status <2.2%. Intercept based on the total population = –5.388.

Discussion

In couples with two or more miscarriages, more factors than just the number of miscarriages influence the probability of carrier status. Low maternal age at second miscarriage, a history of three or more miscarriages, a history of two or more miscarriages in a brother or sister of either partner, and a history of two or more miscarriages in the parents of either partner all increase the probability of carrier status. The efficiency of parental chromosome analysis could be increased by withholding the test from couples with a low probability of carrier status.

The response rate among carrier couples was higher than that among non-carrier couples. This might be explained by a better understanding of the condition among carrier couples. A difference may also exist in the accuracy of data obtained by questionnaires between carrier couples and non-carrier couples. The existence of such a “recall bias” cannot be ruled out entirely.

Table 3 Couples with chromosome analysis, and percentage reduction compared with current policy in period 1992-2001

Screening strategy	Couples analysed*		Reduction†		Total reduction (%; 95% CI)‡
	Carriers	Non-carriers	Carriers (%; 95% CI)	Non-carriers (%; 95% CI)	
Current policy	382	11 589	–	–	–
Restricted policy based on four predictive factors‡	351	9 503	31 (8, 6 to 11)	2086 (18, 17 to 19)	2117 (18, 17 to 18)
Restricted policy based on maternal age at second miscarriage	359	10 812	23 (6, 4 to 9)	1159 (10, 9 to 10)	1182 (10, 9 to 10)

*Numbers of analysed couples adjusted to numbers of carrier couples and non-carrier couples in total population.

†Reduction if chromosome analysis withheld from couples with probability of carrier status <2.2%.

‡Maternal age at second miscarriage; ≥3 miscarriages; history of ≥2 miscarriages in a brother or sister of either partner; history of ≥2 miscarriages in parents of either partner.

The reported incidence of carrier status in couples with recurrent miscarriage varies between 3.6% and 5.8%.^{2 6 7} In this study, the incidence of carrier status was relatively low at 3.2%. This might be explained by our use of more restrictive selection criteria for structural chromosome abnormalities.

Calculating the probability of carrier status by using a multivariate model has not been described previously. We found that maternal age at second miscarriage was the most influential factor. The recurrence of miscarriage in women in their late 30s or older is probably more often due to age related chromosome abnormalities than to structural chromosome abnormalities.

The literature is divided as to whether the incidence of carrier status is higher after three miscarriages than after two miscarriages. Some studies have reported no significant difference, whereas others have reported a significant increase in the incidence of carrier status after three miscarriages.⁸⁻¹⁰ Unlike our study, these studies all described series of patients without controls. We have shown an independent influence of a history of three or more miscarriages, compared with two miscarriages, on the probability of carrier status. This influence was less evident in the multivariate analysis than in the univariate analysis, because the number of miscarriages was, to some extent, correlated with the maternal age at the time of the miscarriages.

We have shown that a history of two or more miscarriages in a brother or sister of either partner or a history of two or more miscarriages in the parents

of either partner influences the probability of carrier status in couples with two or more miscarriages. This finding is supported by the fact that structural chromosome abnormalities can exist within families.^{11 12}

Conclusions

Selective chromosome analysis in couples with two or more miscarriages—that is, withholding chromosome analysis from couples with a low probability of carrier status—would result in a more appropriate referral policy, could decrease the annual number of chromosome analyses, and could therefore reduce the costs to the healthcare system.

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What is already known on this topic

The incidence of structural chromosome abnormalities is increased in couples with recurrent miscarriage

Currently, chromosome analysis is offered to both partners after two or three miscarriages

What this paper adds

Low maternal age at second miscarriage, a history of three or more miscarriages, a history of two or more miscarriages in a brother or sister, and a history of two or more miscarriages in the parents of either partner all increase the probability of carrier status

Selective chromosome analysis could reduce the number of chromosome analyses by 18%

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