

Reproductive outcome after chromosome analysis in couples with two or more miscarriages: case-control study

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Abstract

Objective To compare reproductive outcomes in couples carrying a structural chromosome abnormality and non-carrier couples referred for chromosome analysis after two or more miscarriages.

Design Case-control study.

Setting Six centres for clinical genetics in the Netherlands.

Participants 278 carrier couples and 427 non-carrier couples referred for chromosome analysis between 1992 and 2000 after two or more miscarriages before 20 weeks of gestation. Couples were followed up for at least 24 months after chromosome analysis.

Main outcome measures The birth of at least one healthy child, at least one more miscarriage, and viable offspring with unbalanced chromosomal abnormalities after parental chromosome analysis.

Results Mean follow-up after chromosome analysis was 5.8 years. 120 of 247 (49%) carrier couples had one miscarriage or more after chromosome analysis compared with 122 of 409 (30%) non-carrier couples (difference 19%, 95% confidence interval 11% to 26%; $P < 0.01$). The percentage of couples with at least one healthy child was not significantly different in carrier couples (83%) and non-carrier couples (84%) (difference -1%, -7% to 5%). Among 550 pregnancies in carrier couples, two viable unbalanced chromosomal abnormalities were detected at prenatal diagnosis (0.4%) and the fetuses aborted and two children with an unbalanced karyotype were born (0.4%).

Conclusions Couples whose carrier status was ascertained after two or more miscarriages have a low risk of viable offspring with unbalanced chromosomal abnormalities. Their chances of having a healthy child are as high as non-carrier couples, despite a higher risk of miscarriage.

Introduction

Balanced structural chromosome abnormalities (abnormalities that involve the rearrangement of genetic material but no overall gain or loss, such as inversions and translocations) in parents can cause recurrent miscarriage. In couples with two or more miscarriages the incidence of these abnormalities varies between 3% and 6%. In carrier couples the products of conception can have a normal karyotype, the same balanced structural chromosome abnormality as the carrier, or an unbalanced structural chromosome abnormality. The last scenario can lead to a miscarriage, a stillborn child, or a child born with major congenital defects and severe mental handicap. Current guidelines for the management of recurrent miscarriage recommend chromosome analysis in both partners.¹⁻³ Once a structural chromosome abnormal-

ity has been detected, prenatal diagnosis in subsequent pregnancies and termination of pregnancy in the case of an unbalanced fetal karyotype is available.

To counsel carrier couples about their risk of viable offspring with unbalanced chromosomal abnormalities and their chances of having a healthy child or miscarriage we need to know the outcome in a population with similar abnormalities. Reports of reproductive outcome in carrier couples whose carrier status was ascertained after recurrent miscarriage provide information on only the first pregnancy after chromosome analysis or on the results of prenatal diagnosis in subsequent pregnancies, or they lack detailed information on reproductive outcome.⁴⁻⁹ In most studies a control group was not investigated, and they all studied small numbers of carrier couples.⁴⁻⁹

We aimed to investigate the long term reproductive outcome in carrier couples whose carrier status was ascertained after two or more miscarriages and compare this outcome with that in non-carrier couples with two or more miscarriages.

Methods

Study design

We used the databases of six centres for clinical genetics in the Netherlands to identify all couples presenting for parental chromosome analysis between January 1992 and January 2001, after two or more miscarriages. When one partner was found to carry a structural chromosome abnormality we identified the couple as a carrier couple. We selected a random subset of two non-carrier couples per carrier couple by identifying the non-carrier couples tested immediately before and after the carrier couple. We selected couples with at least two verified miscarriages before 20 weeks of gestation. Exclusion criteria were fewer than two miscarriages verified by a pregnancy test or ultrasonography, or if the couple did not speak Dutch, and the presence of genetic diseases in the couple that might cause chromosomal abnormalities in the fetus.

We examined the couples' medical records and asked both partners to complete a questionnaire. We collected additional information from telephone interviews and the referral medical records. Reproductive outcome was recorded for at least 24 months after chromosome analysis. The main outcome measure was a successful reproductive outcome, defined as the birth of one or more healthy (phenotypically normal) children. Other outcome measures were miscarriages and other adverse reproductive outcomes, including stillbirths, viable offspring with unbalanced chromosomal abnormalities, and viable offspring with other

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Table 1 Baseline characteristics of couples carrying a structural chromosome abnormality and non-carrier couples referred for parental chromosome analysis after two or more miscarriages. Values are numbers (percentages) of couples unless otherwise indicated

	Carrier couples (n=278)	Non-carrier couples (n=427)	P value
Maternal age (years):			
Mean (SD)	31.8 (4.3)	32.7 (5.0)	
Median (interquartile range)	32 (29-35)	32 (29-37)	0.02
Pregnant	73 (26)	111 (26)	0.56
Number of previous miscarriages:			
2	108 (39)	212 (50)	
3	111 (40)	152 (36)	
≥4	59 (21)	63 (15)	0.01
Mean	3.0	2.8	<0.01
Number of healthy children:			
0	154 (55)	207 (49)	
1	98 (35)	156 (37)	
≥2	26 (9)	64 (15)	0.05
Mean	0.6	0.7	0.04
Number of handicapped, stillborn, or diseased children:			
No previous abnormal offspring	252 (91)	384 (90)	
≥1 abnormal offspring	26 (9)	43 (10)	0.75

chromosomal or congenital abnormalities, detected either prenatally or after birth. See bmj.com for details of cytogenetic analysis and statistical analysis.

Results

Baseline characteristics

Between January 1992 and January 2001, 11 971 couples were referred for parental chromosome analysis after two or more miscarriages. A structural chromosome abnormality was found in 382 couples (3.2%). We invited 1148 couples to participate in our study: all 382 carrier couples and 766 non-carrier couples. Of those invited, 61% were eligible for inclusion: 278 couples with a balanced structural chromosome abnormality (73%) and 427 couples with normal parental karyotypes (56%).

We found significant differences in baseline characteristics between carrier couples and non-carrier couples (table 1). Women who were carriers were younger, had experienced more miscarriages, and had a lower mean number of healthy children.

The 278 recorded structural chromosome abnormalities consisted of 177 reciprocal translocations

(64%), 43 robertsonian translocations (15%), 21 pericentric inversions (8%), 21 paracentric inversions (8%), and 16 other structural chromosome abnormalities (6%). The sex distribution of carriers was unequal: 176 (63%) carriers were women.

Follow-up

After the results of chromosome analysis became available, 49 couples decided not to conceive (31 carrier couples (15%) and 18 non-carrier couples (6%)). See bmj.com.

Pregnancy occurred at least once after chromosome analysis in 239 carrier couples and 390 non-carrier couples (table 2). A significantly greater proportion of carrier couples than non-carrier couples had one miscarriage or more after the analysis.

The success rate—defined as the birth of at least one healthy child—was lower in carrier couples than in non-carrier couples for both the first pregnancy and second pregnancy after parental chromosome analysis (table 3). After the second pregnancy the success rate was not significantly different in the two groups. At least one healthy child was born to 83% of the carrier couples and 84% of the non-carrier couples (difference - 1%, - 7% to 5%; P = 0.047%), and adverse pregnancy outcomes were similar in the two sets of couples.

Among the carrier couples, proportions giving birth to one healthy child or more during the follow-up period were similar in the various types of structural chromosome abnormality: 83% (131 of 157) for reciprocal translocations, 82% (31 of 38) for robertsonian translocations, 78% (29 of 37) for inversions, and 93% (14 of 15) for other abnormalities.

See bmj.com for full details of reproductive outcomes of carrier couples: terminations, stillbirths, and handicap. Six pregnancies were terminated: three for social reasons; one because of trisomy 21; and two because of an unbalanced karyotype resulting from a structural chromosome abnormality in the carrier. Three stillbirths occurred after carrier status had been established. None had had prenatal diagnosis. In total, we found four unbalanced karyotypes: two were detected at prenatal diagnosis and followed by induced abortion, one was detected at prenatal diagnosis but not followed by pregnancy termination, and one was found in a severely handicapped child. All four unbalanced karyotypes resulted from a reciprocal translocation in one of the parents: three resulted from a translocation in the mother and one in the father.

Discussion

The risk of viable offspring with chromosomal abnormalities was low in carrier couples whose carrier status was ascertained after two or more miscarriages. Their chances of having a healthy child were as high as non-carrier couples, despite a higher risk of a subsequent miscarriage.

Comparison with related research

The incidence of structural chromosome abnormalities in our study (3.2%) was at the low end of the range of incidences found in previous studies (3-6%). This might be because we used restrictive selection criteria for structural chromosome abnormalities, as recommended.¹⁰ We did not include individuals with a chromosomal polymorphism (such as inversion 9), low

Table 2 Reproductive outcome after parental chromosome analysis in couples with recurrent miscarriage.* Values are numbers (percentages) of couples unless otherwise indicated

Reproductive outcome	Carrier couples (n=247)	Non-carrier couples (n=409)	Difference in % (95% CI)§	P value
Failure to conceive	8 (3.2)	19 (4.6)	-1.4 (-4.4 to 2.0)	0.38
One or more miscarriages	120 (48.6)	122 (29.8)	18.8 (11.1 to 26.3)	<0.01
One or more terminated pregnancies	6 (2.4)	8 (2.0)	0.5 (-1.8 to 3.4)	0.69
One or more ectopic pregnancies	3 (1.2)	13 (3.2)	-2.0 (-4.3 to 0.7)	0.11
One or more stillbirths	3 (1.2)	6 (1.5)	-0.3 (-2.1 to 2.2)	0.79
One or more children who died postpartum	1 (0.4)	4 (1.0)†	-0.6 (-2.1 to 1.4)	0.41
One or more ill or handicapped children	2 (0.8)	11 (2.7)‡	-1.9 (-4.0 to 0.5)	0.09
One or more healthy children	205 (83.0)	344 (84.1)	-1.1 (-7.2 to 4.6)	0.71

*Limited to couples who still wanted to conceive after chromosome analysis and those pregnant at the time of chromosome analysis.

†One couple with two children who died after birth.

‡One couple with two ill or handicapped children.

§Calculated difference might be different from the crude percentages owing to rounding off of numbers.

Table 3 Successful reproductive outcome after parental chromosome analysis in couples with two or more miscarriages.* Values are numbers (percentages) of couples unless otherwise indicated

	Success rate per pregnancy†				Cumulative success rate‡			
	Carriers (n=239)	Non-carriers (n=390)	Difference in % (95% CI)	P value	Carriers (n=247)	Non-carriers (n=409)	Difference in % (95% CI)§	P value
Pregnancy after chromosome analysis:								
1st	148/239 (62)	280/390 (72)	-10 (-18 to -2)	0.01	148 (60)	280 (68)	-9 (-16 to -1)	<0.01
2nd	66/151 (44)	119/215 (55)	-12 (-22 to -1)	0.03	173 (70)	324 (79)	-9 (-16 to -2)	<0.01
3rd	45/85 (53)	35/87 (40)	13 (-2 to 27)	0.12	194 (79)	332 (81)	-3 (-9 to 4)	0.41
4th	14/40 (35)	18/48 (38)	-3 (-22 to 17)	0.63	200 (81)	339 (83)	-2 (-8 to 4)	0.54
5th	10/23 (43)	6/23 (26)	17 (-10 to 41)	0.22	205 (83)	342 (84)	-1 (-7 to 5)	0.84
6th	2/12 (17)	4/16 (25)	-8 (-36 to 24)	0.60	205 (83)	342 (84)	-1 (-7 to 5)	0.84
Total follow-up	—	—	—	—	205 (83)	344 (84)	-1 (-7 to 5)	0.71

*Success rate defined as the birth of at least one healthy child.

†Limited to couples with at least one pregnancy after chromosome analysis.

‡Limited to couples pregnant during chromosome analysis or who still wanted to conceive after the analysis, or both (including couples with failure to conceive after chromosome analysis).

§Calculated difference might be different from the crude percentages owing to rounding off of numbers.

level mosaicism, or sex chromosome aneuploidy, abnormalities that are included in many other series describing the incidence of structural chromosome abnormalities in couples with recurrent miscarriage.

In agreement with two recent studies,^{4,5} we found that the birth of a healthy child at first pregnancy after chromosome analysis was lower in carrier couples (59%) than non-carrier couples (72%).

Limitations

Out of a total of 550 pregnancies after parental chromosome analysis in couples whose carrier status was ascertained after recurrent miscarriage, only two cases of viable offspring with chromosomal abnormalities were detected at prenatal diagnosis (0.4%). In two other cases severely handicapped children with an unbalanced structural chromosome abnormality were born (0.4%). Even though the response rate among carrier couples was good (73%), a selection bias could have occurred: couples with viable offspring with unbalanced chromosome abnormalities may have been more likely to refuse to participate in our study, thus leading to an under-representation of such abnormalities.

Implications

Two earlier studies had small numbers of carrier couples and limited their observations to the pregnancy immediately after parental chromosome analysis.^{4,5} We recorded successive pregnancy outcomes during a long follow-up period. In our cohort, 83% of the carrier couples and 84% of the non-carrier couples gave birth to at least one healthy child after chromosome analysis; this finding could have implications for the counselling of couples with recurrent miscarriage due to chromosome abnormalities. However, a subgroup of women who repeatedly miscarry (four or more miscarriages) may have a worse prognosis because other factors might contribute to their miscarriages.

Currently, counselling couples about their risk of having a child with an unbalanced karyotype is based mainly on empirical risk estimates or databases that lack exact data on reproductive history or outcome, or both. In general, carrier couples ascertained after the birth of an affected child are at the highest risk of having viable offspring with chromosomal abnormalities (20-22%), whereas couples ascertained after recurrent miscarriage have an estimated risk of 2-5% (derived

from data obtained by prenatal diagnosis after parental chromosome analysis).

In our cohort, less than 2% of carrier couples had viable offspring with unbalanced chromosomal abnormalities. Structural chromosome abnormalities more commonly resulted in miscarriage rather than viable offspring with unbalanced chromosomal abnormalities. However, more than 10% of carrier couples decided not to conceive after parental chromosome analysis, so there may be a case for changing the guidance to these couples.

Conclusion

The risk of viable offspring with chromosomal abnormalities is low in carrier couples whose carrier status was ascertained after two or more miscarriages. Their chances of having a healthy child are as high as non-carrier couples, despite a higher risk of a subsequent miscarriage. The more accurate risk information provided by our study should help carrier couples when deliberating between the risk of another miscarriage, a handicapped child, and the chance of a healthy child.

What is already known on this topic

Couples who carry structural chromosome abnormalities, whose carrier status is ascertained after recurrent miscarriage, are at risk of having a child with severe congenital abnormalities

What this study adds

The risk of viable offspring with chromosomal abnormalities is low in carrier couples whose carrier status is ascertained after two or more miscarriages

Their chances of having a healthy child are as high as for non-carrier couples (over 80%), but they have a higher risk of a subsequent miscarriage

The more accurate risk information provided by our study should help carrier couples when deliberating between the risk of another miscarriage, a handicapped child, and the chance of a healthy child

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“We were treated like adults”—development of a pre-medicine summer school for 16 year olds from deprived socioeconomic backgrounds: action research study

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Abstract

Objective To develop a one week widening access summer school for 16 year old pupils from non-traditional backgrounds who are considering applying to medical school, and to identify its short term impact and key success factors.

Design Action research with partnership schools in deprived inner-city areas in five overlapping phases: schools liaison, recruitment of pupils and assessment of needs, programme design, programme delivery, and evaluation. The design phase incorporated findings from one-to-one interviews with every pupil, and workshops and focus groups for pupils, parents, teachers, medical student assistants, NHS staff, and other stakeholders. An in-depth process evaluation of the summer school was undertaken from the perspective of multiple stakeholders using questionnaires, interviews, focus groups, and observation.

Participants 40 pupils aged 16 years from socioeconomically deprived and under-represented ethnic minority groups.


Results The summer school was popular with pupils, parents, teachers, and staff. It substantially raised pupils' confidence and motivation to apply to medical school. Critical success factors were identified as an atmosphere of “respect”; a focus on hands-on work in small groups; the input of medical students as role models; and vision and leadership from senior staff. A particularly popular and effective aspect of the course was a grand round held on the last day, in which pupils gave group presentations of real cases.


Conclusion An action research format allowed us to draw the different stakeholders into a collaborative endeavour characterised by enthusiasm, interpersonal support, and mutual respect. The input from pupils to the programme design ensured high engagement and low drop-out rates. Hands-on activities in small groups and social drama of preparing and giving a grand round presentation were particularly important.

Introduction

“Widening access” programmes designed to increase applications to medical school from “non-traditional” pupils (that is, those from lower socioeconomic backgrounds, certain ethnic minority groups, and those whose parents did not attend university) have had mixed success.^{1 2} The failure of such pupils to apply to medical school, and to stay the course once accepted, is mainly to do with lack of confidence, lack of support, low motivation, unrealistic images of medicine and medical school, and thinking of themselves as “not a university type.”^{3 4}

We developed a widening access summer school for pupils from under-represented groups to encourage application to medical school and measured its

 Details of using the IMS score, suggestions for improving the scheme, and quotes from pupils are on bmj.com

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