| | |
|---|---|
| Postprint Version | 1.0 |
| Journal website | http://humrep.oxfordjournals.org/content/25/6/1411.long |
| Pubmed link | http://www.ncbi.nlm.nih.gov/pubmed/20382970 |
| DOI | 10.1093/humrep/deq089 |




# Consecutive or non-consecutive recurrent miscarriage: is there any difference in carrier status?

E. VAN DEN BOOGAARD[1,*], S.P. KAANDORP[1], M.T.M. FRANSSEN[1], B.W.J. MOL[1,2], N.J. ESCHOT[3], C.H. WOUTERS[4], F. VAN DER VEEN[1], J.C. KOREVAAR [2] AND M. GODDIJN[1]

[1]Department of Obstetrics and Gynaecology, Academic Medical Center, Centre for Reproductive Medicine, H4-205, PO Box 22660, 1100 DD Amsterdam, The Netherlands
[2]Department of Clinical Epidemiology and Biostatistics and Bioinformatics, Academic Medical Center, Amsterdam, The Netherlands
[3]Department of Clinical Genetics, Academic Medical Center, Amsterdam, The Netherlands
[4]Department of Clinical Genetics, Erasmus Medical Centre, Rotterdam, The Netherlands

**ABSTRACT**

BACKGROUND Carrier status of a structural balanced chromosome abnormality is associated with recurrent miscarriage. There is, at present, no evidence of the impact of the sequence of preceding pregnancies on the probability of carrier status. The aim of our study was therefore to examine whether the history of consecutive versus non-consecutive miscarriages in couples with two or more miscarriages has any impact on the probability of carrying a chromosome abnormality.

METHODS A nested case–control study was performed in six centres for clinical genetics in the Netherlands. Couples referred for chromosome analysis after two or more miscarriages were included: 279 couples with a carrier of a structural chromosomal abnormality and 428 non-carrier couples who served as controls. Univariable and multivariable logistic regression analyses, corrected for known risk factors for carrier status, were performed. The main outcome measure was the probability of carrier status.

RESULTS Two hundred and fifty-six of 279 (92%) carrier couples and 381 of 428 (89%) non-carrier couples had experienced consecutive miscarriages (P = 0.21). A history of two or three consecutive miscarriages did not alter the probability of carrier status when compared with two [odds ratio (OR) 0.90, 95% confidence interval (CI) 0.48–1.7] or three (OR 0.71, 95% CI 0.39–1.3) non-consecutive miscarriages.

CONCLUSIONS The sequence of preceding pregnancies is not a risk factor for carrier status. Therefore, couples with miscarriages interspersed with healthy child(ren) should be managed the same as couples with consecutive miscarriages regarding chromosome diagnosis.

## INTRODUCTION

Good clinical practice starts with a clear definition of the clinical problem. Currently, no consensus exists on the definition of recurrent miscarriage (Stirrat, 1990; Farquharson et al., 2005). Several national and international guidelines have been published on this topic, but their definitions vary with regard to the number of preceding miscarriages as well as the sequence of previous pregnancies (ACOG, 2002; RCOG, 2003; Jauniaux et al. (ESHRE), 2006). To date, the American College of Obstetrics and Gynaecology (ACOG) defines recurrent miscarriage as two or more consecutive miscarriages and the European Society of Human Reproduction and Embryology (ESHRE) defines recurrent miscarriage as three or more consecutive miscarriages (ACOG, 2002; ESHRE, 2006). In contrast to these guidelines, the definitions from the Royal College of Obstetricians and Gynaecologists (RCOG), 'three or more miscarriages', and the Dutch Society of Obstetrics and Gynaecology (NVOG), 'two or more miscarriages', do not contain the word consecutive (RCOG, 2003; NVOG, 2007). As a result of this discrepancy, it is unclear in daily clinical practice which couples should be diagnosed with recurrent miscarriage and when to start the diagnostic work-up.

In all guidelines, it is advised to include at least karyotyping of the couple at high risk of a structural chromosome abnormality in the diagnostic work-up, as carrier status of a structural chromosome abnormality is strongly associated with recurrent miscarriage (de Braekeleer and Dao, 1990; Christiansen et al., 2005; Franssen et al., 2005). The addition of the word consecutive suggests an essential role for the sequence of preceding miscarriages, but the relation between this sequence and the risk of carrier status is still unknown.

To examine these relations, we investigated the influence of consecutive versus non-consecutive preceding miscarriages on the probability of carrier status in couples with a history of two or more, not necessarily consecutive, miscarriages.

## MATERIALS AND METHODS

A nested case–control study was performed in six centres for Clinical Genetics in the Netherlands between January 1992 and January 2001, with follow-up until 2003. From a cohort previously described to identify independent risk factors for carrier status, all couples referred for chromosome analysis after recurrent miscarriage during this period were identified (Franssen et al., 2005, 2006). Only couples with a history of two or more clinically proven miscarriages that occurred at a gestational age up to 20 weeks were included. Couples in which one of the partners was found to be a carrier of a structural chromosome abnormality were marked as cases. Two control couples were randomly selected for each carrier couple, by including the couples tested immediately before and after the carrier couples. The sequence of preceding miscarriages could be consecutive or non-consecutive. Consecutive was defined as at least two preceding miscarriages in a row, not interspersed with any other pregnancy.

Data on obstetric history were obtained from medical records of the department of clinical genetics and medical records of the referring physician, and from questionnaires filled out by both partners. The main outcome measure was the probability of carrier status.

### Statistical analysis

First, we determined the association between the sequence of preceding pregnancies and parental chromosomal abnormalities by univariable logistic regression analysis. Secondly, we performed multivariable logistic regression analysis. In the multivariable analysis, we included the four risk factors identified previously: maternal age at the time of the second miscarriage, number of preceding miscarriages, history of two or more miscarriages in a brother or sister and history of two or more miscarriages in the parents of either partner (Franssen et al., 2005). Subgroup analyses were performed on patients with at least three preceding consecutive and non-consecutive miscarriages.

## 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. A total of 1148 couples were invited to participate in the study: all 382 carrier couples and 766 non-carrier couples. After the invitation, 707 couples were included in the study, 279 carrier couples and 428 non-carrier couples. Baseline characteristics of carriers and non-carriers are summarized in Table I. In carrier couples, the mean maternal age was significantly lower and the mean number of miscarriages was significantly higher than in non-carrier couples (P = 0.016 and 0.004). There were 256 of 279 (92%) carrier couples and 381 of 428 (89%) non-carrier couples who had experienced consecutive miscarriages (P = 0.21).

**[TABLE 1]**

**[TABLE 2]**

Univariable regression analysis showed no significant difference in carrier status between couples with at least two consecutive and couples with at least two non-consecutive miscarriages [odds ratio (OR) 1.4, 95% confidence interval (CI) 0.83–2.4]. After multivariable logistic regression analysis, corrected for known risk factors, a history of at least two consecutive miscarriages (OR 0.90, 95% CI 0.48–1.7) was not retained as an independent risk factor influencing the probability of carrier status. In women with at least three miscarriages, univariable regression analysis showed no difference in carrier status between couples with at least three consecutive and couples with at least three non-consecutive miscarriages (OR 0.99, 95% CI 0.60–1.6). A history of three consecutive miscarriages also turned out not to be an independent risk factor for carrier status after multivariable logistic regression analysis (OR 0.71, 95% CI 0.39–1.3).

## DISCUSSION

The results of this study show that a history of consecutive versus non-consecutive miscarriages in couples with two or more miscarriages is not a risk factor for carrier status of a structural chromosome abnormality.

Thus, by offering karyotyping only to couples with consecutive miscarriages as is current practice, couples with non-consecutive miscarriages who are also potentially at high risk for carrying a structural chromosome abnormality are incorrectly excluded from a relevant diagnostic test and appropriate counselling.

Possible limitations of this data collection have been described by Franssen et al. A recall bias cannot be ruled out completely, i.e. carrier couples might be more aware of their family history and personal obstetric history (Franssen et al., 2005). Other causes of recurrent miscarriage are possibly not documented completely in our database. Although we registered other identified causes, antiphospholipid antibody screening was not performed by all physicians at that time.

Carrier couples are likely to experience more future miscarriages than non-carrier couples and they have an increased risk of viable unbalanced offspring, but the long-term chances of a healthy child are similar for carrier couples and non-carrier couples (Franssen et al., 2006). Preimplantation genetic diagnosis (PGD) might be a possibility in carrier couples, with the rationale that relatively more live births will be achieved and that the number of miscarriages will be reduced. However, chances of pregnancy are relatively low and no outcomes are known of RCTs which determine the effectiveness of PGD in couples with recurrent miscarriage (Thornhill et al., 2005; Harper et al., 2006) Therefore, we recommend that PGD should so far not be the standard care in carrier couples.

By adopting the selective screening strategy for parental chromosome analysis in the guidelines, ESHRE has made an important step towards more efficiency in chromosome

testing (Franssen et al., 2005; ESHRE, 2006). Our results show that the sequence of preceding miscarriages does not influence the risk of carrier status and should thus not play a role in management.

It is difficult to identify the origin of the word consecutive in the definition of recurrent miscarriage. Most likely, it dates from a study on miscarriage sequences published in 1938, which has been cited frequently (Malpas, 1938). In recent publications on the topic of recurrent miscarriage, the majority of authors include the word consecutive in their definition (Clark et al., 2001; Farquharson et al., 2005; BMJ Publishing Group, 2005; Rai and Regan, 2006; Christiansen et al., 2008; Haas and Ramsey, 2008). With regard to carrier status, the sequence of pregnancies seems to be a matter of chance. We cannot find any arguments why to offer karyotyping in a woman with, for example, a healthy child followed by three consecutive miscarriages and withhold the same diagnostics in a woman with a history of one miscarriage followed by the birth of a healthy child and then two more miscarriages. The role of consecutive versus non-consecutive miscarriages in couples with other underlying causes, e.g. antiphospholipid antibody syndrome, remains a topic for future research, as does the reproductive outcome in relation to the sequence of preceding pregnancies.

Apart from the issue of miscarriages being consecutive or not, there are several more issues to be considered regarding the definition of recurrent miscarriage, such as the number of preceding miscarriages and the upper gestational age. For the upper gestational age, it has been stated that consensus is urgently needed (Christiansen et al., 2005). The same could be stated for the lower gestational age, since it is unclear whether biochemical pregnancies should be included in the definition. An appropriate diagnosis is important and is the basis for an evidence-based diagnostics, treatment and future research. If the definition requires at least three miscarriages, couples with a history of two miscarriages might well be harmed if denied proper diagnosis (Franssen et al., 2005).

According to our opinion, good clinical practice in recurrent miscarriage moves from employing a fixed definition towards risk assessment in an individual patient, applying evidence-based risk factors to assess chances of underlying abnormalities and adverse future pregnancy outcome. The definition should indicate when to consider diagnostic work-up and should therefore be broad.

In conclusion, we did not find any influence of consecutive versus non-consecutive miscarriages on the probability of carrier status. Therefore, couples with miscarriages interspersed with healthy child(ren) should be managed in the same way as couples with consecutive miscarriages and according to the ESHRE guidelines. Future research should focus on the relationship between other underlying risk factors and the sequence of pregnancies, to further specify the definition of recurrent miscarriage.

## FUNDING

The study was supported by ZonMW, the Netherlands Organisation for Health Research and Development (ZonMW) (Grant no. 945-02-032). The researchers are independent from the funder.

## ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Review Board (IRB), Academic Medical Centre, University of Amsterdam.

## REFERENCES

American College of Obstetricians and Gynecologists (ACOG). Management of recurrent early pregnancy loss. ACOG practice bulletin. Int J Gynaecol Obstet 2002;78:179–190.

BMJ Publishing Group. Recurrent miscarriage. Clin Evid 2005;14:1–10.

Christiansen OB, Nybo Andersen AM, Bosch E, Daya S, Delves PJ, Hviid TV, Kutteh WH, Laird SM, Li TC, van der Ven K. Evidence-based investigations and treatments of recurrent pregnancy loss. Fertil Steril 2005;83:821–839.

Christiansen OB, Steffensen R, Nielsen HS, Varming K. Multifactorial etiology of recurrent miscarriage and its scientific and clinical implications. Gynecol Obstet Invest 2008;66:257–267.

Clark DA, Coulam CB, Daya S, Chaouat G. Unexplained sporadic and recurrent miscarriage in the new millennium: a critical analysis of immune mechanisms and treatments. Hum Reprod Update 2001;7:501–511.

De Braekeleer M, Dao TN. Cytogenetic studies in couples experiencing repeated pregnancy losses. Hum Reprod 1990;5:519–528.

Dutch Society of Obstetrics and Gynaecology (NVOG). Guideline: Recurrent Miscarriage. Utrecht, The Netherlands, 2007.

Farquharson RG, Jauniaux E, Exalto N. Updated and revised nomenclature for description of early pregnancy events. Hum Reprod 2005;20:3008–3011.

Franssen MT, Korevaar JC, Leschot NJ, Bossuyt PMM, Knegt AC, Gerssen-Schoorl KB, Wouters CH, Hansson KB, Hochstenbach R, Madan K et al. Selective chromosome analysis in couples with two or more miscarriages: case-control study. BMJ 2005;331:137–141.

Franssen MT, Korevaar JC, van der Veen F, Leschot NJ, Bossuyt PMM, Goddijn M. Reproductive outcome after chromosome analysis in couples with two or more miscarriages: index [corrected]-control study. BMJ 2006;332:759–763.

Haas DM, Ramsey PS. Progestogen for preventing miscarriage. Cochrane Database Syst Rev 2008;CD003511.

Harper JC, Boelart K, Geraedts JPM, Harton G, Kearns WG, Moutou C, Muntjewerff N, Repping S, SenGupta S, Scriven PN et al. ESHRE PGD Consortium data collection V: Cycles from January to December 2002 with pregnancy follow-up to October 2003. Hum Reprod 2006; 21:3–21.

Jauniaux E, Farquharson RG, Christiansen OB, Exalto NE, (ESHRE). Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod 2006;21:2216–2222.

Malpas P. A study of abortion sequences. J Obstet Gynaecol Br Empire 1938; 45:932–949.

Rai R, Regan L. Recurrent miscarriage. Lancet 2006;368:601–611.

Royal College of Obstetricians and Gynaecologists (RCOG). The Investigation and Treatment of Couples with Recurrent Miscarriage. London, UK, 2003.

Stirrat GM. Recurrent miscarriage. Lancet 1990;336:673–675.

Thornhill AR, de Die-Smulders CE, Geraedts JP, Harper JC, Harton GL, Lavery SA, Moutou C, Robinson MD, Schmutzler AG, Scriven PN et al. ESHRE PGD Consortium Best practice guidelines for clinical preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS). Hum Reprod 2005;20:35–48.

## TABLES

### Table 1 and Table 2

**Table I** Baseline characteristics at the time of chromosome analysis, for patients with two or more miscarriages.

| ≥2 miscarriages (*n* = 707) | Carriers (*n* = 279) | Non-carriers (*n* = 428) | *P*-value |
|---|---|---|---|
| Maternal age in years at the time of chromosome analysis | 31.8 (4.3) | 32.7 (5.0) | 0.012[a] |
| Maternal age in years at second miscarriage | 30.5 (4.2) | 31.6 (4.9) | 0.002[a] |
| Number of preceding miscarriages before chromosome analysis | 3.0 (1.2) | 2.8 (1.1) | 0.004[a] |
| Number of preceding live births, median (min–max) | 0.0 (0–6) | 1.0 (0–5) | 0.029[b] |
| Consecutive miscarriages, number (%) | 256 (92) | 381 (89) | 0.2[c] |

Values are means (SD) unless indicated otherwise.
[a]Student's *t*-test.
[b]Non-parametric test.
[c]$\chi^2$ test.

**Table II** Baseline characteristics at the time of chromosome analysis, for patients with three or more miscarriages.

| ≥3 miscarriages (*n* = 386) | Carriers (*n* = 170) | Non-carriers (*n* = 216) | *P*-value |
|---|---|---|---|
| Maternal age in years at the time of chromosome analysis | 31.7 (4.3) | 32.6 (5.3) | 0.07[a] |
| Maternal age in years at second miscarriage | 29.9 (4.2) | 30.8 (5.1) | 0.06[a] |
| Number of preceding miscarriages before chromosome analysis | 3.7 (1.2) | 3.5 (1.0) | 0.20[a] |
| Number of preceding live births, median (min–max) | 1.0 (0–6) | 1.0 (0–5) | 0.14[b] |
| Consecutive miscarriages, number (%) | 132 (78) | 168 (78) | 0.98[c] |

Values are means (SD) unless indicated otherwise.
[a]Student's *t*-test.
[b]Non-parametric test.
[c]$\chi^2$ test.