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# Economic analysis of chromosome testing in couples with recurrent miscarriage to prevent handicapped offspring

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**ABSTRACT**

STUDY QUESTION Which strategy is least expensive to prevent the birth of a handicapped child in couples with recurrent miscarriage (RM); parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents, or amniocentesis in all ongoing pregnancies without the knowledge of parental carrier status?

SUMMARY ANSWER For virtually all couples with RM amniocentesis in all ongoing pregnancies without the knowledge of parental carrier status is less expensive in preventing the birth of a handicapped child than parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents.

WHAT IS KNOWN ALREADY One of the causes of RM is a balanced chromosome abnormality in one of the partners. If one of the partners is carrier of a balanced structural chromosomal abnormality, the risk of offspring with an unbalanced structural chromosome abnormality is increased. Like all couples, couples with RM also have an age-dependent risk for fetal aneuploidy, of which trisomy 21 is most common.

STUDY DESIGN, SIZE, DURATION Model-based economic analysis to compare costs and effects of two strategies in couples with RM to prevent the birth of a handicapped child in case of ongoing pregnancy.

PARTICIPANTS/MATERIALS, SETTING, METHODS Comparison of two strategies in women with RM: strategy (I) parental chromosome analysis

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followed by amniocentesis in pregnancy in case of carrier status of one of the parents and strategy (II) amniocentesis in all ongoing pregnancies without the knowledge of carrier status. No testing was the reference strategy. Data on probabilities and costs were derived from the literature. Incremental costs and effects were calculated [incremental cost-effectiveness ratio (ICER)]. Effectiveness was expressed as the number of prevented births of handicapped child equivalents compared with no testing. In these calculations, the birth of a handicapped child was valued 10 times worse than the loss of a viable pregnancy due to amniocentesis.

MAIN RESULTS AND THE ROLE OF CHANCE Depending on the risk for carrier status, the ICER for Strategy I (parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents) varied between €226 000 and €6 556 000 per prevented handicapped child equivalent. For Strategy II (amniocentesis in all ongoing pregnancies without the knowledge of carrier status), the ICER varied between €2000 and €233 000 per prevented handicapped child equivalent. Strategy I was less expensive than Strategy II only for a small subgroup of couples with maternal age <23 years, three or more previous miscarriages and a family history of RM.

LIMITATIONS, REASONS FOR CAUTION Our analysis is not a plea for amniocentesis in all women with RM. Individual risk assessment with serum markers and nuchal translucency is probably more effective at lower cost.

WIDER IMPLICATIONS OF THE FINDINGS This analysis can be used by clinicians to explain the chances of adverse pregnancy outcome in couples with RM, as well as by policy makers in health-care economics. Future guidelines on RM might be more restrictive from the perspective of the limited health-care resources that we have available.

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## INTRODUCTION

Recurrent miscarriage (RM) is a common problem in reproductive medicine. One of the causes of RM is a balanced chromosome abnormality in one of the partners. If either one of the partners is carrier of a balanced structural chromosomal abnormality, the risk of offspring with an unbalanced structural chromosome abnormality is increased. Products of conception with an unbalanced structural chromosome abnormality can lead to miscarriage, stillbirth or birth of a child with major congenital defects and severe mental handicaps (Hook et al., 1989; De Braekeleer and Dao, 1990; Franssen et al., 2005).

A balanced structural chromosome abnormality is found only in 2–6% of couples with RM (Hook et al., 1989; De Braekeleer and Dao, 1990; Franssen et al., 2005). The probability of a child with an unbalanced chromosomal abnormality in carrier couples with RM is estimated to be below 1% (Franssen et al., 2006; Barber et al., 2010).

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The European Society of Human Reproduction and Embryology (ESHRE) guideline for the management of RM recommends parental chromosome analysis in couples with RM to identify if one of the partners is a carrier of a balanced structural chromosome abnormality (Jauniaux et al., 2006; Franssen et al., 2007; NVOG, 2007). Selective parental chromosome analysis is advised, implying that parental chromosome analysis is offered only to couples at high risk of carrier status (≥2.2%). The risk of carrier status is estimated based on the 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 or in the parents of either partner (Franssen et al., 2005). Once a structural chromosome abnormality has been detected in a couple, invasive prenatal diagnosis (PND) is offered in subsequent pregnancies to diagnose possible unbalanced chromosomal abnormalities in the fetus. In case of such an unbalanced chromosomal abnormality, termination of pregnancy is an option. Parental chromosome analysis is laborious and contributes substantially to costs of the diagnostic work-up of RM.

Like all couples, couples with RM also have an age-dependent risk for fetal aneuploidy, of which trisomy 21 is most common. The probability of a pregnancy with a child with trisomy 21 varies between <0.1% in women between 20 and 25 years old and >2.2% in women over 42 years old (Wald et al., 1989).

There are two diagnostic strategies to reduce the risk of the birth of a handicapped child in couples with RM. The first and most frequently applied strategy is to perform parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents (Strategy I). The second strategy is to perform amniocentesis in all subsequent ongoing pregnancies (Strategy II). The aim of this study was to develop a theoretical economic model to compare costs and effects of these two strategies to assess which one is less expensive in the prevention of the birth of a handicapped child due to unbalanced structural chromosome abnormalities or fetal aneuploidy.

## METHODS

We developed a model to evaluate the costs and effects of two diagnostic strategies to prevent the birth of a handicapped child in couples with RM and a subsequent ongoing pregnancy. The strategies evaluated were as follows: Strategy (I) parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents and Strategy (II) amniocentesis in all ongoing pregnancies without the knowledge of carrier status.

The composite unfavourable outcome of pregnancy was defined as the birth of a handicapped child due to an unbalanced structural chromosomal abnormality or due to trisomy 21, induced abortion in case of a chromosomally abnormal offspring detected at invasive PND or the loss of a healthy and viable child/fetus due to amniocentesis.

Data on probabilities of carrier status in couples with RM were derived from the literature, as were data on the probability of the birth of a handicapped child conditional on carrier status of the parents (Franssen et al., 2006). The probability of carrier status depends on the maternal age at second miscarriage, number of miscarriage in the couple and family history of RM and varies between 0.5 and 10.2%. The probability of viable unbalanced offspring in carrier couples is 0.7% (Franssen et al., 2006).

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To calculate the probability of unbalanced viable offspring in couples with RM, we multiplied the probability of carrier status for the subgroups related to maternal age at second miscarriage, the number of miscarriages in the couple and family history of RM, with the probability of viable unbalanced offspring in these couples (0.7%). The probability of birth of a child with Down's syndrome was derived from published data, and reflects the risk of Down's syndrome in the general population (Wald et al., 1989).

The probability of an unfavourable outcome of pregnancy in couples with RM was calculated by combining the probabilities of carrier status with the probability of a pregnancy with trisomy 21, miscarriage due to amniocentesis and termination of pregnancy in case of viable unbalanced offspring.

The birth of a child with a handicap either due to an unbalanced translocation or due to trisomy 21 is often considered to yield more regret than loss of the pregnancy due to termination of pregnancy or an amniocentesis-related loss. To compare the impact of both poor outcomes in 1D, we introduced the regret ratio. The regret ratio has been developed to express the potential negative impact that the birth of a handicapped child may have on parents compared with loss of a pregnancy. The amount of regret caused by the birth of a handicapped child either due to an unbalanced translocation or due to trisomy 21 was assumed to be comparable. The initial regret ratio was set at 10, i.e. the birth of a handicapped child was supposed to create 10 times more regret than loss of a pregnancy, be it from termination of pregnancy or from an amniocentesis-related loss of an unaffected pregnancy (van der Meulen et al., 1999).

The formulas to assess the effectiveness of the two diagnostic strategies and the reference strategy in which no testing is performed are shown in the Appendices 1–3.

Costs were derived from the integral cost price index (2010) of an academic hospital in the Netherlands. The costs of parental chromosome analysis were estimated to be €1069 per couple (€946 for post-natal chromosomal analysis + €123 for genetic counselling). The costs of amniocentesis were €1188 [€866 (prenatal chromosome analysis) + €322 (appointment/intervention gynaecologist)].

We calculated incremental costs and effects of Strategy I and Strategy II. We combined the two outcomes in an incremental cost-effectiveness ratio (ICER). To calculate the ICER of both diagnostic strategies, we compared the two strategies to a strategy in which no testing was performed (reference strategy). The difference between the costs of parental chromosome analysis followed by amniocentesis in case of carrier status and no testing, as well as the difference between the costs of amniocentesis in all ongoing pregnancies without the knowledge of carrier status and no testing were divided by the reduction in probability of unfavourable outcome for the strategies compared with no testing.

Based on the maternal age at second miscarriage, the number of miscarriages in the couple and family history of RM, we made subgroups for which we calculated probabilities of an unfavourable outcome and costs. In a sensitivity analysis, we varied the regret ratio between 1 and 10. We varied the number of subsequent pregnancies between one pregnancy and three pregnancies.

## RESULTS

The probability of potentially viable offspring with an unbalanced chromosome abnormality in couples with RM that we used in our model is shown in Table I. This

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probability varied between 0.0035 and 0.0714% depending on the maternal age at second miscarriage, the number of miscarriages in the couple and family history of RM. Couples in which women were <23 years old at the second miscarriage, with three or more miscarriages, and a brother of sister and parents with RM were at highest risk of potentially viable offspring with an unbalanced chromosome abnormality (0.0714%). Couples in which women were ≥39 years old at the second miscarriage, who had two miscarriages without a family history of RM, had the lowest probability of potentially viable offspring with an unbalanced chromosome abnormality (0.0035%). Previous data show that the probability of potentially viable offspring with trisomy 21 (Supplementary data, Table SI) varies between 0.09 and 25%, depending on the maternal age.

**[TABLE I]**
Probability of potentially viable offspring with unbalanced chromosome abnormality, in couples with RM.
The probability of an unfavourable outcome of pregnancy for parental chromosome analysis plus amniocentesis (Strategy I) varied depending on the maternal age at second miscarriage, the number of miscarriages in the couple and family history of RM, and this probability was reduced compared with the strategy in which no tests were performed. The costs of this strategy were the costs of parental chromosome analysis added to the costs of amniocentesis in carrier couples. To prevent the birth of one handicapped child either caused by an unbalanced chromosomal abnormality or by trisomy 21, the incremental costs in case of one subsequent pregnancy varied between €226 000 and €2 178 000, depending on the maternal age at second miscarriage, the number of miscarriages in the couple and family history of RM.
The probability of an unfavourable outcome was lower with amniocentesis for all ongoing pregnancies than for no tests performed (Strategy II). The costs of the strategy were the costs of amniocentesis in all couples with RM. To prevent the birth of one handicapped child, the incremental costs in case of one subsequent pregnancy varied between €2000 and €235 000 for the various subgroups based on the maternal age at second miscarriage, the number of miscarriages in the couple and family history of RM.
In case of no testing (reference strategy), the probability of an unfavourable outcome of pregnancy was the probability of the birth of a handicapped child, and varied between 0.11% for couples in which women are 20 years old with two miscarriages and a family history of RM, and 7.15% for couples in which women are 46 years old, who were >39 years old at the second miscarriage, with three or more miscarriages and a family history of RM. There were no procedure-related costs for this strategy.
Only in couples with maternal age of 23 years, three or more previous miscarriages, a sibling with RM and parents with RM, was parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents the least expensive strategy to prevent the birth of a handicapped child. In all other couples amniocentesis in all ongoing pregnancies without the knowledge of carrier status was more effective and less expensive than parental chromosome analysis followed by amniocentesis. For example, for a couple with a maternal age of 34 years with two miscarriages, with a sibling with RM, and parents without a history of RM, the ICER was €426 000 for parental chromosomal analysis, whereas the ICER for amniocentesis in all ongoing pregnancies without the knowledge of carrier status was

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€50 000 to prevent the birth of one handicapped child. The ICERs calculated with our model are displayed in Table II (for two categories, broadly ranged, of current maternal age, for one subsequent pregnancy).

**[TABLE II]**
ICER for parental chromosome analysis and amniocentesis in couples with RM, maternal ages of 24 and 40 years old.

## DISCUSSION

In this study, by using a theoretical economic analysis, we showed that, in the vast majority of couples with RM, amniocentesis in all ongoing pregnancies without the knowledge of carrier status is less expensive than parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents in the prevention of handicapped offspring. This analysis can be used by clinicians to explain the chances of adverse pregnancy outcome in couples with RM, as well as by policy-makers in health-care economics to decide on the expenditure required, in view of declining resources.

There are no published data on the risk of Down's syndrome in women with RM with or without parental carrier status of balanced chromosome abnormalities. We assumed that the risk of aneuploidy leading to Down's syndrome in couples with RM was comparable with the risk of aneuploidy in the general population of women. If the risk of trisomy 21 would be different in couples with RM when compared with the risk of trisomy 21 in the general population, the ICERs would obviously change accordingly.

An alternative invasive PND to amniocentesis is chorionic villus sampling (CVS). It is estimated that amniocentesis is performed in 70% of all couples who undergo a PND procedure, compared with 30% CVS (Vansenne et al., 2010). For the analyses performed here, we did not distinguish between the two forms of invasive PND.

Nowadays, the ESHRE advises selective parental chromosome analysis in couples with RM (Jauniaux et al., 2006). In couples where the woman is less than 39 years old at the second miscarriage, parental chromosomal analysis is recommended, and in women who are over 39 years old at the second miscarriage parental chromosome analysis is not recommended, owing to the low probability of carrier status in these couples. This strategy reduces costs, as omitting parental chromosome analysis in women who are ≥39 years old at the second miscarriage partly reduces the costs of the parental chromosome analysis strategy. Our analysis shows that even this selective karyotyping is more expensive when compared with amniocentesis in all ongoing pregnancies of couples with RM without the knowledge of carrier status.

We compared the parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents, with amniocentesis in all ongoing pregnancies without the knowledge of carrier status in couples with RM. Obviously, a policy of amniocentesis in all women is not applicable to relatively young women (e.g. women <25 years old), whereas, in other women, amniocentesis is usually preceded by non-invasive risk estimation with nuchal translucency measurement and first trimester serum markers. Our analysis, therefore, is not a plea for amniocentesis in all women with RM, as individual risk assessment with serum markers and nuchal translucency is more effective at a lower cost. However, our analysis does demonstrate that parental chromosome analysis followed by amniocentesis in case of carrier status of

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one of the parents—which is a frequently applied strategy in daily practice—is more expensive than a general strategy of amniocentesis for all women. This information further contributes to the discussion to refrain from parental karyotyping in couples with RM without a previous child with an unbalanced karyotype.

In the present study, we considered the probability of the birth of a child with Down's syndrome and the probability of a child with an unbalanced chromosomal abnormality together as unfavourable outcome of pregnancy. Obviously, when the consequences of the birth of a child with an unbalanced chromosomal abnormality are valued much worse by parents than that of a child with Down's syndrome (in terms of difference in the regret ratio) or vice versa, the outcome of our analysis would change, as amniocentesis guided by parental karyotyping would then perhaps become less expensive when compared with amniocentesis for all women. Since we considered that the birth of a child with a handicap would yield 10 times more regret than termination of a pregnancy, we applied a regret ratio of 10 for the birth of a severely handicapped child compared with termination of a pregnancy. We considered the loss of pregnancy due to amniocentesis equal to the loss of pregnancy due to termination because of chromosome abnormalities. We realize that this regret ratio is arbitrary and is highly dependent on a couples' attitude towards having a handicapped child, the procedure-related risk of miscarriage and termination of pregnancy in case of a chromosomal abnormality. The regret ratio is, thus, determined by the ratio of the expected distress after the birth of a handicapped child to the expected distress after pregnancy loss (van der Meulen et al., 1999). The term ‘regret ratio’ is to be handled with care since the attitude of couples concerning the birth of a handicapped child will vary and children born with Down's syndrome or another chromosomal abnormality can become very special family members. No straightforward cost-effectiveness analysis can account for that. At this point, it is important that couples make their own decision after extensive non-directive counselling.

In the current analysis, we estimated costs of the diagnostic strategy to prevent the birth of a handicapped child. We did not account for long-term costs associated with the (health) care of a handicapped child. Health-care expenditures for infants and children with Down's syndrome are more than 10 times higher compared with children without the syndrome (Boulet et al., 2008). One could argue that any diagnostic strategy effective in reducing the risk of the birth of a handicapped child would save many long-term costs. From this perspective, even a more expensive diagnostic strategy (parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents) would reduce long-term costs. This does not change the fact that the strategy in which amniocentesis in all ongoing pregnancies without the knowledge of carrier status would still be less expensive.

In the case of more than one subsequent pregnancy, the ICER of parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents becomes somewhat more favourable compared with one subsequent pregnancy, but in the majority of the subgroups amniocentesis in all ongoing pregnancies without the knowledge of carrier status is still less expensive. In this theoretical model, we assumed a 100% uptake of invasive PND in couples that are confronted with abnormal test results. However, a recent study in a large sample of couples with RM showed that in carrier couples with the maternal age ≥36 years only 40% of the couples opted for invasive PND, whereas, in younger carrier couples, this

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was 60% (Vansenne et al., 2010). This low uptake of invasive PND will increase the costs of the strategy in which amniocentesis is guided by parental chromosome analysis even further. Possibly some of these couples do not opt for invasive diagnostics because of the risk of miscarriage associated with the procedure or the fact that they would not terminate the pregnancy in the case of a chromosomal abnormality. Indirectly, these couples prefer the risk of a handicapped child over the risk of termination of pregnancy. The regret ratio for these couples consequently would be <1. We performed a sensitivity analysis in which we varied the regret ratio between 0.1 and 10. For the vast majority of the subgroups, amniocentesis in all ongoing pregnancies without the knowledge of carrier status still was the least expensive strategy.

We assessed the costs and effects of parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents at the level of subgroups with a different risk profile, and not at the level of the general population. By doing so, we found that amniocentesis in case of carrier status of one of the parents in couples with RM was only less expensive than amniocentesis in all ongoing pregnancies without the knowledge of carrier status in those couples with a high risk of carrier status, that is, female age <23 years of age, with three or more previous miscarriages and a family history of RM. Consequently, we can conclude that, based on our model-based economic analysis, the criteria for selective karyotyping (i.e. parental karyotyping in high risk women, as advocated in recent European and national guidelines) are still too wide to make parental karyotyping cost-effective. Although such guidelines are a first step towards a more cost-effective management of couples with RM, future guidelines might even be more restrictive from the perspective of the limited health-care resources that we have available.

## SUPPLEMENTARY DATA

Supplementary data are available at http://humrep.oxfordjournals.org.proxy.library.uu.nl/.

## AUTHORS' ROLES

M.G., B.W.J.M., J.C.K. and F.v.d.V. were the principal investigators and designed the protocol. M.G. and B.W.J.M. were the coordinating investigators. M.L. and F.V. collected the data. B.W.J.M. and M.L. performed the statistical analysis. M.L. and F.V. wrote the initial draft and all authors took part in the further preparation of the paper. B.W.J.M. is the guarantor. All authors had access to all of the data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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## CONFLICT OF INTEREST

None declared.

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## APPENDIX 1

The probability of an unfavourable outcome of pregnancy if no testing is performed.

$$P_{\text{unfavourable outcome of pregnancy}} = (P_{OT} + P_D) \times RR$$

$P_{OT}$ probability of viable offspring with unbalanced chromosomal abnormality;

$P_D$ probability of birth of a child with Down's syndrome;

RR regret ratio (birth of handicapped child compared with pregnancy loss valued as '10').

## APPENDIX 2

The probability of an unfavourable outcome of pregnancy if parental chromosome analysis is performed in couples with RM with subsequent amniocentesis in carrier couples.

$$P_{\text{unfavourable outcome of pregnancy}} = P_{OT} + (P_{carrier} \times P_D) + (P_{carrier} \times P_{MA}) + (P_D \times RR)$$

$P_{OT}$ probability of viable offspring with unbalanced chromosomal abnormality, identified with parental chromosome analysis and subsequent amniocentesis followed by termination of pregnancy (loss of pregnancy);
$P_{carrier}$ probability of carrier status;
$P_{MA}$ probability of miscarriage due to amniocentesis (loss of pregnancy);
$P_D$ probability of birth of a child with Down's syndrome (assumed that Down's syndrome in carrier couples is detected by amniocentesis in these couples followed by termination of pregnancy);
RR regret ratio (birth of handicapped child compared with pregnancy loss valued as '10').

## APPENDIX 3

The probability of an unfavourable outcome of pregnancy if all women of couples with RM undergo amniocentesis.

$$P_{\text{unfavourable outcome of pregnancy}} = P_D + P_{MA} + (P_{OT} \times RR)$$

$P_D$ probability of fetus with trisomy 21, identified with amniocentesis followed by termination of pregnancy (pregnancy loss);
$P_{MA}$ probability of miscarriage due to amniocentesis (pregnancy loss);
$P_{OT}$ probability of birth of a child with an unbalanced chromosomal abnormality;
RR regret ratio (birth of handicapped child compared with pregnancy loss valued as '10').

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**Table I** Probability of potentially viable offspring with unbalanced chromosome abnormality, in couples with RM.

| Maternal age at second miscarriage (years) | $RM_{B/S}$ | $RM_{Parents}+$ | | $RM_{Parents}-$ | |
|---|---|---|---|---|---|
| | | ≥3 miscarriages | 2 miscarriages | ≥3 miscarriages | 2 miscarriages |
| <23 | + | 0.0714 | 0.0511 | 0.0511 | 0.0364 |
| | − | 0.0399 | 0.0280 | 0.0287 | 0.0196 |
| 23–33 | + | 0.0700 | 0.0504 | 0.0504 | 0.0357 |
| | − | 0.0399 | 0.0280 | 0.0280 | 0.0196 |
| 34–36 | + | 0.0406 | 0.0287 | 0.0287 | 0.0203 |
| | − | 0.0224 | 0.0154 | 0.0154 | 0.0112 |
| 37–38 | + | 0.0280 | 0.0196 | 0.0196 | 0.014 |
| | − | 0.0154 | 0.0105 | 0.0105 | 0.0077 |
| ≥39 | + | 0.0126 | 0.0084 | 0.0091 | 0.0063 |
| | − | 0.0070 | 0.0049 | 0.0049 | 0.0035 |

Values are percentages. RM, recurrent miscarriage; $RM_{B/S}$, history of ≥2 miscarriages in a brother or sister of either partner; $RM_{Parents}$, history of ≥2 miscarriages in parents of either partner; ≥3 miscarriages, history of ≥3 miscarriages in couples; 2 miscarriages, history of 2 miscarriages in couples. The probability of carrier status for the various subgroups was multiplied by the probability of the birth of a child with an unbalanced chromosome abnormality in carrier couples (Franssen *et al.*, 2005; Franssen *et al.*, 2006).

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**Table II** ICER for parental chromosome analysis and amniocentesis in couples with RM, maternal ages of 24 and 40 years old.

| Maternal age | | | $RM_{Parents}+$ | | | | $RM_{Parents}-$ | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Current age (years) | Age at second miscarriage (years) | | ≥3 miscarriages | | 2 miscarriages | | ≥3 miscarriages | | 2 miscarriages | |
| | | | PCA[a] | Amniocentesis[a] | PCA[a] | Amniocentesis[a] | PCA[a] | Amniocentesis[a] | PCA[a] | Amniocentesis[a] |
| 24 | <23 | $RM_{B/S}+$ | 226 | 198 | 308 | 198 | −19 | 198 | 404 | 198 |
| | | $RM_{B/S}-$ | 389 | 198 | 545 | 198 | −33 | 198 | 750 | 198 |
| 40 | 37–38 | $RM_{B/S}+$ | 684 | 10 | 967 | 10 | −32 | 10 | 1318 | 10 |
| | | $RM_{B/S}-$ | 1224 | 10 | 1783 | 10 | −46 | 10 | 2397 | 10 |
| | >39 | $RM_{B/S}+$ | 1490 | 10 | 2222 | 10 | −50 | 10 | 2929 | 10 |
| | | $RM_{B/S}-$ | 2661 | 10 | 3791 | 10 | −64 | 10 | 5272 | 10 |

ICER, (probability of unfavourable outcome in case of no testing−probability of unfavourable outcome in case of diagnostic strategy)/costs of diagnostic strategy. Negative ICER are the results of an increase in unfavourable outcome of pregnancy due to the applied diagnostic strategy; PCA, parental chromosome analysis followed by amniocentesis in case of carrier status of one of the parents; Amniocentesis, amniocentesis in all ongoing pregnancies without knowledge of carrier status; $RM_{B/S}$, history of ≥2 miscarriages in a brother or sister of either partner; $RM_{Parents}$, history of ≥2 miscarriages in parents of either partner; ≥3 miscarriages, history of ≥3 miscarriages in couples; 2 miscarriages, history of 2 miscarriages in couples; For example, in a couple with 2 miscarriages, the maternal age of 24 years, a positive family history of RM in brother or sister as well as with parents of the couple the ICER for parental chromosome analysis followed by amniocentesis in case of carrier status of one of the partners was €308 000. For the same couple, the ICER for amniocentesis in all ongoing pregnancies without the knowledge of carrier status was €198 000.

[a]ICER in 1000 Euro's per prevented the unfavourable outcome of pregnancy.