Female reproductive ageing

Haadsma, Maaike Laura

Chapter 5

Miscarriage risk for IVF pregnancies in poor responders to ovarian hyperstimulation

M.L. Haadsma, H. Groen, T.M. Mooij, C.W. Burger, F.J.M. Broekmans, C.B. Lambalk, F.E. van Leeuwen, A. Hoek on behalf of the OMEGA project group

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ABSTRACT

The increase in miscarriage rate with advancing female age is attributed to a decline in oocyte quality. A poor response to ovarian hyperstimulation is often an expression of a decrease in oocyte quantity. Although oocyte quality and quantity both decrease as a result of ovarian ageing, it is unclear whether these two processes are related to each other. To investigate the relation between oocyte quantity and quality, miscarriage rates were compared between IVF-treated women with a poor and normal response, respectively. Data were studied from a retrospective nationwide cohort of Dutch women undergoing IVF treatment from 1983-1995. Women achieving an ongoing pregnancy after their first complete IVF cycle (N=1468) were compared with those experiencing miscarriage (N=357) with respect to their ovarian response. Logistic regression analysis showed a statistically significant association between poor response (<4 retrieved oocytes) and miscarriage (P=0.001). Due to interaction, this association became stronger with increasing female age. Among women <36 years, miscarriage rates between poor and normal responders did not differ, whereas among women ≥36 years poor responders had a statistically significant increased miscarriage rate compared with normal responders (P=0.001). These results support the hypothesis of a relationship between quantitative ovarian reserve and oocyte quality.

INTRODUCTION

The process of female reproductive ageing is attributed to a decline in both the quantity and the quality of the remaining oocytes[8]. The age-related decrease in oocyte number, which eventually leads to menopause, has been recorded and quantified in various histological studies[15;19;22;174]. Years before menopause, fertility is already severely impaired: the chance to conceive gradually declines, whereas the chance of a chromosomally abnormal conception and miscarriage increases[117]. This phenomenon is attributed to a decrease in oocyte quality, most notably the increasing occurrence of aneuploidy in the oocyte[7;230;231]. Clinically, the size of the remaining oocyte pool can be estimated by endocrine and sonographic ovarian reserve tests or by ovarian response to hyperstimulation during IVF treatment. No clinical non-invasive tests are available to assess oocyte quality.

The nature of the relationship between oocyte quantity and oocyte quality as the two components determining reproductive capacity is as yet unclear[53;232]. On the one hand, follicle loss and quality loss could progress independently of each other. The number of follicles present in the ovaries at any moment is most likely determined by the size of the endowed fetal follicle pool and the atresia rate of these follicles. Oocyte quality may be determined by biological damage accumulating over the course of the years. This hypothesis is supported by the fact that after correction for female age, ovarian reserve tests have no evident additional predictive value for either the chance to conceive or the chance of miscarriage, both in general subfertile populations and in IVF-treated patients[72;134;136;138;146;150;151;223;233]. On the other hand, various hypotheses do support a possible relationship between oocyte quality and quantity. It has been postulated that oocyte quality is mainly determined during fetal life; subsequently the best oocytes are selected for ovulation first, leaving the oocytes of lesser quality for later years[62;69]. The 'limited pool hypothesis' states that the process of oocyte selection might become impaired if the number of oocytes to select from is decreased[63]. Furthermore, as the number of follicles declines, the endocrine environment of the remaining oocytes may hypothetically harm their quality, for example by increased levels of FSH[64;65]. In support of a direct relationship between oocyte quantity and quality is the fact that a poor response in IVF treatment is predictive of low pregnancy chances, independent of female age[112;139;140;234]. In line with these findings one would expect a relationship between poor response and increased miscarriage rates, but data on this subject are scarce[152-154].

Examination of the association between poor response (as marker of oocyte quantity) and miscarriage (as marker of oocyte quality) is hampered by the fact that poor responders have low pregnancy chances; as a result a large IVF population is needed. Therefore this issue was addressed in a nationwide retrospective cohort of Dutch IVF patients. The aim of the study was to evaluate whether women who conceive after a poor response at their first complete IVF cycle have an increased risk of miscarriage.

MATERIALS AND METHODS

Study design

The present study is part of the so-called OMEGA project, a large retrospective cohort study in the Netherlands, originally designed to assess the effects of ovarian stimulation in IVF treatment on the risk of hormone-related cancers. The study population, study procedures and data collection methods have been described in detail elsewhere[109;235]. In brief, all subfertile women starting at least one IVF cycle in the Netherlands between 1 January, 1983 (the national start of IVF treatment) and 1 January, 1995 were included in the cohort (N=19,840). An extensive questionnaire on risk factors was sent to all women who could be traced, including detailed questions on reproductive history and lifestyle (response rate of 73%). In addition, trained research assistants retrieved data on medical and reproductive history, subfertility characteristics and course and outcome of treatment from the medical files. Due to limited project funding data collection could only be completed for 75% of all women who gave permission to do so. Cases with non-conventional first IVF cycles (N=894), i.e. gamete or zygote intra-Fallopian transfer, intracytoplasmic sperm injection and oocyte or embryo-donated cycles, and cases without detailed information on the first IVF cycle (N=589), were excluded. Complete data from both questionnaire and medical file were available for 8,457 women[144]. The OMEGA database was considered to be suitable for the present research question despite the fact that IVF practice has changed considerably since its inception. Although medication protocols and laboratory procedures have improved, poor response remains one of the chief challenges in today's reproductive medicine[236].

Selection for analysis

For the present analysis the 8,457 women with complete data on their first conventional IVF treatment were identified (see Figure 1). Cycles with complicated oocyte retrievals were excluded, since the oocyte yield at retrieval was not representative of the actual number of oocytes available. Complicated oocyte retrievals included prematurely terminated follicle aspirations, mainly due to excessive pain, and ovulation during the oocyte retrieval. In 810 cases the first IVF cycle was cancelled before oocyte retrieval. Excluding these cases would cause selection bias, since the main reasons for cycle cancellation were anticipated poor response and hyper-response. Therefore, in all cases of cycle cancellation the consecutive IVF cycle –if performed- was selected for analysis, provided this second cycle included an uncomplicated oocyte retrieval. Pregnancies documented in the questionnaires were compared to the outcome of IVF treatment as retrieved from the medical files. If conflicting results emerged, the medical file was checked again; in unresolved cases the outcome of the IVF treatment was considered unknown. The women whose first complete IVF cycle ended in either a miscarriage (N=357) or ongoing pregnancy (N=1468) were selected for analysis.

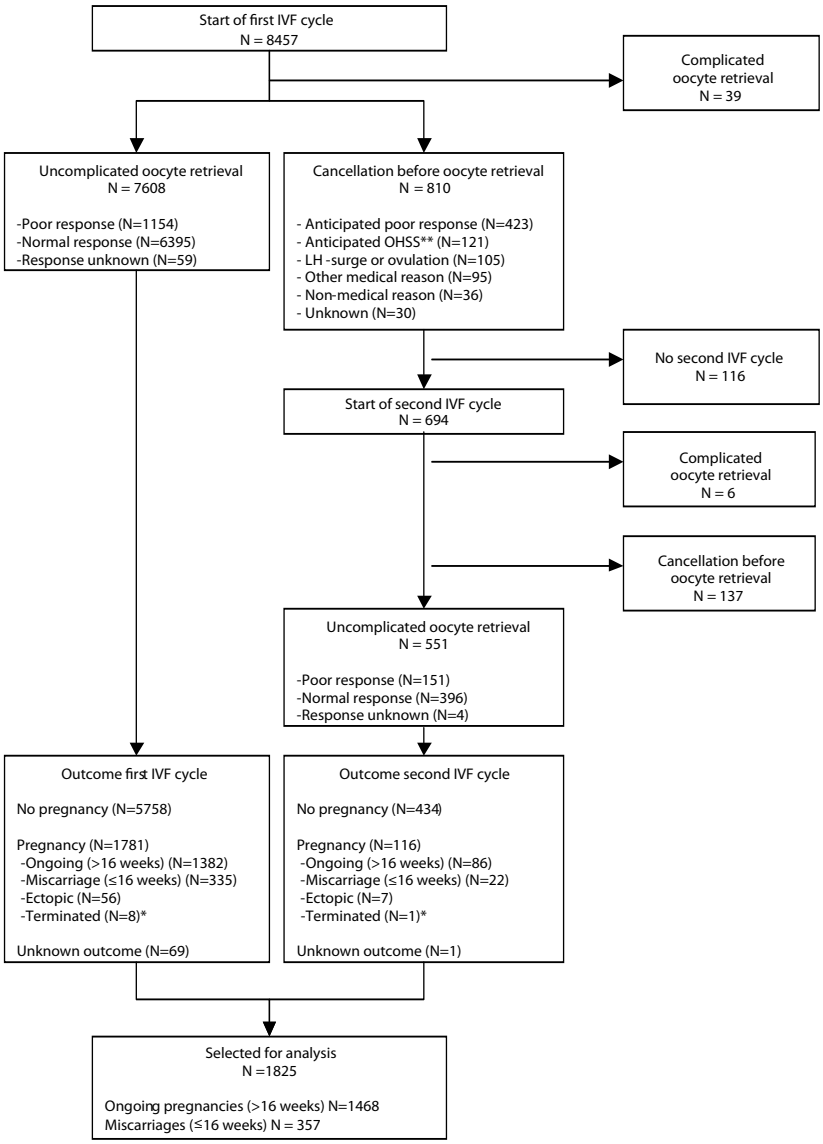

Figure 1. Flow chart of eligible patients
*Reasons for artificial termination of pregnancy: trisomy 21 (N=4) and triploidy (N=1) detected with prenatal diagnosis, congenital malformations on ultrasound with normal karyotype (N=3), and reason unknown (N=1); OHSS = ovarian hyperstimulation syndrome.

Definitions

A poor response was defined as an oocyte yield at oocyte retrieval of ≤ 3 oocytes; a normal response was defined as an oocyte yield of 4 oocytes or more. This frequently used cut-off value was chosen, since previous analyses of the relationship between poor response and oocyte quantity showed that women with an oocyte yield of less than 4 oocytes during IVF treatment have an increased

risk of early menopause[109;110]. Moreover, clinically a minimum of four oocytes is needed to have an average of two embryos available for transfer, given a mean fertilization rate of 50-60% in IVF[237]. In the present analysis, in all cases at least one oocyte was retrieved, since only women who conceived after IVF were eligible.

Miscarriage was defined as pregnancy loss between 4 and 16 weeks of pregnancy, with the exception of confirmed extra-uterine pregnancies or artificially terminated pregnancies. Multiple gestations that partially ended before and partially after 16 weeks were regarded as ongoing pregnancies. Karyotype of miscarriage tissue was not available.

Ongoing pregnancy was defined as a viable intra-uterine pregnancy of at least 16 weeks gestation. Of the 1468 ongoing pregnancies analyzed, 1406 (96%) resulted in a live birth. The main reason for not achieving a live birth in this group was immature birth due to multiple pregnancy.

For patient characteristics, such as female age and smoking habit, values were documented at the start of IVF treatment. Smoking was defined as smoking at least one cigarette a day for at least one year.

Statistical analysis

To assess the association between (poor) response and miscarriage, women achieving an ongoing pregnancy after their first complete IVF cycle were compared with those experiencing miscarriage with respect to their ovarian response. In addition, potential confounders including female age and other patient characteristics were compared between the groups with ongoing pregnancy and miscarriage and between the groups with poor and normal response, respectively. For these univariate analyses chi-squared test, Mann-Whitney U test and Student's T-test were used when applicable. Logistic regression analysis was used to calculate the odds ratio (OR) for miscarriage associated with poor response. Potential confounders were evaluated by adding each potential confounder separately into the logistic model. If this resulted in a change in OR of 10% or more, the confounder was included in the model[238]. This process was repeated until no other confounders were identified. The presence of interaction between ovarian response and other potential risk factors for miscarriage was assessed using product terms. Potential confounders included all patient characteristics available, except the variables regarding previous pregnancies. It is well known that women with a history of miscarriage have an increased risk to miscarry again[239]. Since it was postulated that poor responders have an increased chance to miscarry based on lower oocyte quality, this also affects the chance of having experienced previous miscarriage and, conversely, previous ongoing pregnancy. Correction for these presumed confounders would underestimate the true relation between poor response and miscarriage. In addition to the assessment of the relationship between poor response and miscarriage, the relationship between number of retrieved oocytes (as a continuous variable and in categories) and miscarriage was examined using the same statistical approach. A *P*-value <0.05 was considered statistically significant. Data were analysed with Statistical Package for Social Sciences (SPSS) 14.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the differences between the women with ongoing pregnancy and miscarriage. Poor response was strongly associated with miscarriage (*P*=0.001). In addition, higher female age, smoking, primary subfertility, previous miscarriage, longer duration of subfertility and the number of ampoules of medication used were statistically significantly associated with miscarriage (P<0.001, P=0.01, P=0.03, P<0.01, P=0.04 and P<0.001 respectively).

Table 1. Patient characteristics according to pregnancy outcome after first complete IVF cycle

	Ongoing pregnancy *Total N = 1468*		Miscarriage *Total N = 357*		
	Data available *N*	No. (%) or median* (10^{th} -90^{th} percentile)	Data available *N*	No. (%) or median* (10^{th} -90^{th} percentile)	*P*-value
Poor response	1455	96 (6.6%)	350	41 (11.7%)	0.001[a]
Age (years)*	1464	32.4 (27.4 – 37.1)	356	33.4 (28.0 – 38.4)	<0.001[b]
Body mass index (kg/m^2)*	1428	21.7 (18.9 – 26.2)	341	21.6 (19.1 – 26.0)	NS[c]
Smoking	1452	529 (36.4%)	354	155 (43.8%)	0.01[a]
Primary subfertility	1446	959 (66.3%)	332	199 (59.9%)	0.03[a]
Miscarriage before first IVF	1415	182 (12.9%)	323	62 (19.2%)	<0.01[a]
Ongoing pregnancy before first IVF	1415	264 (18.7%)	323	67 (20.7%)	NS[a]
Duration of subfertility (years)*	1277	4.5 (2.3 – 8.7)	311	4.8 (2.6 – 9.4)	0.04[c]
Main cause of subfertility	1315		323		NS[a]
Tubal factor		506 (38.5%)		136 (42.1%)	
Male factor		324 (24.6%)		66 (20.4%)	
Unknown origin		370 (28.1%)		86 (26.6%)	
Other		115 (8.7%)		35 (10.8%)	
DES-exposure in utero	1318	33 (2.5%)	319	10 (3.1%)	NS[a]
Ovarian surgery before start of IVF	1468	135 (9.2%)	357	44 (12.3%)	NS[a]
Use of clomiphene citrate	1468	46 (3.1%)	357	14 (3.9%)	NS[a]
Total no. of ampoules HMG or rFSH*[d]	1235	21 (14 – 33)	302	24 (15 – 36)	<0.001[c]
Number of transferred embryos*	1468	3 (2 – 4)	357	3 (2 – 4)	NS[c]
Number of multiple births	1468	418 (28.5%)	-	-	-

a. Chi-square test; b. Student's T-test; c. Mann-Whitney U test; d. For this calculation women using clomiphene citrate were excluded. DES = diethylstilbestrol; HMG = human menopausal gonadotrophin; NS = not statistically significant; rFSH = recombinant FSH

The differences between the women with poor and normal response are shown in Table 2. The number of retrieved oocytes was unknown for 20 women. Among the poor responders 29.9% miscarried, compared with 18.5% of the normal responders. Higher female age, higher body mass index, primary subfertility, longer duration of subfertility and both prior miscarriage and ongoing pregnancy all had a statistically significant association with poor response (P<0.001, P=0.01, P=0.02, P=0.03, P=0.02 and P=0.04 respectively). Furthermore, in normal responders more embryos were transferred and a higher proportion of ongoing pregnancies led to the birth of a multiple compared with poor responders (both P<0.001).

Table 2. Patient characteristics according to ovarian response after first complete IVF cycle

	Poor response *Total N = 137*		Normal response *Total N = 1668*		
	Data available *N*	No. (%) or median* (10^{th} -90^{th} percentile)	Data available *N*	No. (%) or median* (10^{th} -90^{th} percentile)	*P*-value
Miscarriage	137	41 (29.9%)	1668	309 (18.5%)	0.001[a]
Age (years)*	137	34.2 (27.8 – 39.1)	1668	32.4 (27.6 – 37.1)	<0.001[b]
Body mass index (kg/m^2)*	133	22.1 (19.5 – 29.2)	1616	21.6 (18.9 – 26.0)	0.01[c]
Smoking	135	58 (43.0%)	1653	616 (37.3%)	NS[a]
Primary subfertility	132	74 (56.1%)	1629	1077 (66.1%)	0.02[a]
Miscarriage before first IVF	132	27 (20.5%)	1591	211 (13.3%)	0.02[a]
Ongoing pregnancy before first IVF	132	34 (25.8%)	1591	292 (18.4%)	0.04[a]
Duration of subfertility (years)*	110	5.3 (2.5 – 10.6)	1467	4.5 (2.4 – 8.6)	0.03[c]
Main cause of subfertility	124		1501		NS[a]
Tubal factor		50 (40.3%)		584 (38.9%)	
Male factor		26 (21.0%)		363 (24.2%)	
Unknown origin		33 (26.6%)		421 (28.0%)	
Other		15 (12.1%)		133 (8.9%)	
DES-exposure in utero	117	3 (2.7%)	1501	40 (2.7%)	NS[a]
Ovarian surgery before start IVF	137	18 (13.1%)	1668	159 (9.5%)	NS[a]
Use of clomiphene citrate	137	6 (4.4%)	1668	52 (3.1%)	NS[a]
Total no. of ampoules HMG or rFSH*[d]	104	23 (14 – 42)	1430	22 (14 – 33)	NS[c]
Number of transferred embryos*	137	2 (1 – 3)	1668	3 (2 – 4)	<0.001[c]
Number of multiple births[e]	96	11 (11.5%)	1359	402 (29.6%)	<0.001[a]

a. Chi-square test; b. Student's T-test; c. Mann-Whitney U test; d. For this calculation women using clomiphene citrate were excluded; e. Proportion of multiple pregnancies / ongoing pregnancies. DES = diethylstilbestrol; HMG = human menopausal gonadotrophin; NS = not statistically significant; rFSH = recombinant FSH

Logistic regression analysis showed an OR for miscarriage associated with poor response of 1.9 (95% confidence interval 1.3-2.8; *P*-value = 0.001). None of the potential confounders changed the OR more than 10%, although female age was very close (9.6% change in OR, from 1.88 to 1.70). In addition, an interaction was found between female age and poor response: the association of poor response with miscarriage became stronger with increasing female age. The other potential confounders did not interact with the type of response. Table 3 shows the ORs for miscarriage associated with poor response in different age categories; within these different age categories female age was not identified as a confounder. To illustrate the interaction between poor response and female age, miscarriage rates were calculated according to age category and ovarian response (Figure 2). For women below 36 years of age, miscarriage rates between poor and normal responders did not differ [20% (17 of 86) vs. 17% (237 of 1380)] while among women of 36 years and older poor responders had a statistically significant increased miscarriage rate compared to their peers with normal response [47% (24 of 51) vs. 25% (72 of 288);P=0.001].

The OR for miscarriage associated with the number of oocytes as a continuous variable was 0.98 (95% confidence interval 0.96-1.0), implying that for each extra oocyte retrieved, the risk of miscarriage decreased by 2%. Next, the number of oocytes was divided into categories. The categories of one and two oocytes were combined, since in only ten women one oocyte was harvested. Table 4 shows the ORs for miscarriage associated with the different oocyte number categories. A statistically significant trend of increasing miscarriage risk with a lower category of oocyte number (*P*-value= 0.004). None of the potential confounders, including female age, affected the ORs substantially and no interaction was found between any of the potential confounders and oocyte number.

Table 3. Odds ratios for miscarriage associated with poor response according to age category

	N (%)	Odds ratio	95% CI	*P*-value
≤ 30 years	640 (35.5%)	0.9	0.3 – 2.4	NS
31-35 years	826 (45.8%)	1.4	0.7 – 2.7	NS
≥ 36 years	339 (18.8%)	2.7	1.5 – 4.9	0.002
All ages	1805 (100%)	1.9	1.3 – 2.8	0.001

CI = confidence interval; NS = not statistically significant

Table 4. Odds ratios for miscarriage associated with number of retrieved oocytes

	N (%)	Odds ratio	95% CI	*P*-value
1-2 oocytes	52 (2.9%)	2.6	1.4 - 4.6	0.001
3 oocytes	85 (4.7%)	1.6	0.9 - 2.6	NS
4 oocytes	121 (6.7%)	1.2	0.7 - 1.8	NS
≥ 5 oocytes (reference)	1547 (85.7%)	1	-	-

Chi-square test showed a statistically significant trend of increasing miscarriage risk with a lower category of oocyte number (*P*-value= 0.004)

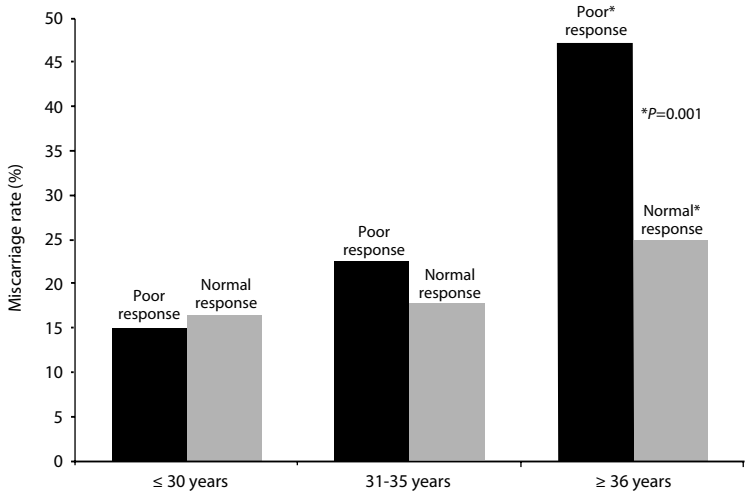

Figure 2. Miscarriage rates according to age category and ovarian response

In total, 254 (13.9%) of the 1825 cycles analysed, were started before 1990. When these cycles were excluded from the analyses, similar results were found. Likewise, similar results were found when women treated with clomiphene citrate were excluded.

DISCUSSION

This study shows that poor responders to IVF treatment have an increased risk of miscarriage with increasing female age compared with normal responders. Also, the risk of miscarriage increases with a lower number of retrieved oocytes. These results support the hypothesis that oocyte quantity and oocyte quality are indeed related.

The association between poor response and oocyte quantity has already been demonstrated by the increased risk of early menopause for poor responders to IVF treatment[109;110]. The number of oocytes collected per oocyte retrieval shows substantial intraindividual variation across IVF cycles. Thus, a poor response does not always reflect decreased oocyte quantity but may also be due to chance or under dosing of medication. Since the incidence of reduced ovarian reserve increases with female age, the chance that a poor response indeed reflects decreased oocyte quantity is higher in older women. The finding in the present study that the association between poor response and miscarriage becomes stronger with increasing female age is in line with this phenomenon. The same is true for the fact that young poor responders appear to have better chances of a live birth than their older counterparts[139;140;225]. An additional explanation for the fact that young poor responders have better prospects is that biological damage accumulated over time may harm oocyte quality. This phenomenon may include direct effects on the oocyte itself such as oxidative stress, as well

as ageing processes in its surroundings, resulting in defective microcirculation or granulosa cell function[61;63;67;68]. Following this line of reasoning, oocyte quality is determined both by the number of oocytes left *and* female age.

The present study demonstrates that the lower the number of oocytes retrieved, the stronger the association with miscarriage (Table 4). Within the group of poor responders (≤ 3 oocytes) the same tendency was found, although numbers were too small to reveal significant differences: in women with an oocyte yield of one or two oocytes the OR for miscarriage was 2.6 (95% CI 1.4 – 4.6) compared to an OR of 1.6 (95% CI 0.9 – 2.6) in the group with three oocytes.

The number of ampoules of medication used (either human menopausal gonadotrophin or recombinant FSH) was higher in the miscarriage group than in the women with ongoing pregnancies. This difference decreased after correction for female age, but was still statistically significant (P=0.004). Possibly, a higher medication dose harms oocyte quality or negatively influences implantation environment. However, absolute differences in the number of ampoules were small.

Poor responders did not use more ampoules of medication than normal responders and the association between medication dose and miscarriage was not influenced by the number of oocytes retrieved. This finding was expected, since only first complete IVF cycles were assessed; treatment protocol adjustments usually result from the outcome of previous cycles.

Since the 1980s and 1990s, the period when the study cohort underwent treatment, stimulation protocols and oocyte retrieval techniques have improved considerably. It can be assumed that in our study population a proportion of the women had a low response due to imperfect treatment (according to present knowledge) and would nowadays be normal responders. It is remarkable that despite the assumed presence of these 'accidental' poor responders statistically significant relationships were found, probably facilitated by the cohort size. Despite all improvements, to date 'true' poor responders still have low chances in IVF treatment[240]. As is stated by Tarlatzis and colleagues in their review of management of poor responders, 'the ideal stimulation protocol still remains a challenge as the diminished oocyte cohort and oocyte quality cannot be reversed within the limits of our present capabilities'[236]. Even the wide scale application of ICSI has not proved to be a solution this far[241]. Poor response is one of the chief challenges in today's reproductive medicine, showing that despite the age of the cohort, the results are of current interest.

The fact that poor responders have an increased risk of miscarriage in our study may also be explained by the lack of embryo selection in poor responders. Generally, in normal responders multiple embryos are available and the morphologically best-looking embryos are selected for transfer. In poor responders, embryo selection is usually not possible since the number of embryos available is too low. Even if the proportion of good quality oocytes and thus good quality embryos is the same in poor and normal responders, the absolute number of good quality embryos available

will be lower in poor responders. Embryos of lesser quality will thus be transferred more often, possibly leading to an increased miscarriage rate. This explanation is supported by Winter and colleagues, who performed a large retrospective study on risk factors for miscarriage after assisted reproductive technology[154]. They found that women with a non-elective embryo transfer had an increased risk of miscarriage compared with their peers with an elective embryo transfer, also after correction for female age and ovarian response. In line with these findings from an infertile study population, in fertile couples recurrent miscarriage has also been associated with an inadequate selection mechanism allowing abnormal embryos to implant more easily[242].

Another possible explanation for the increased miscarriage rate in poor responders is the fact that they are less prone to multiple pregnancies. Generally, in multiple gestations the chance that the whole pregnancy is lost is smaller than in singleton pregnancies. In the present study data on early ultrasound measurement were not available; therefore multiple gestations that eventually resulted in the birth of a singleton were counted as an ongoing pregnancy. Moreover, it has been shown that pregnancy loss per gestational sac is lower in double than in single implantations[243;244]. Lambers and colleagues hypothesize that this may be explained by an optimal implantation environment and/or interaction between the fetuses, but may also result from higher embryo quality in twin pregnancies in terms of genetic and developmental potential. The fact that poor responders have a lower chance of (twin) pregnancy and an increased risk of miscarriage would than be explained by the same phenomenon. In the present study, no relationship was found between the numbers of embryos transferred and miscarriage rate, not in the total study population nor within the groups of poor responders and normal responders separately.

Next to the study of Winter and colleagues, two other large retrospective studies found no association between poor response and miscarriage[152;153]. In both studies a poor response was defined as an oocyte yield of 4 oocytes or less, whereas the definition of 3 oocytes or less was used in this study. This difference in definitions may account for our different findings, since in the present study women with 4 retrieved oocytes had no increased risk of miscarriage compared with the women with 5 retrieved oocytes or more. Including this category of 4 retrieved oocytes in the poor response group may blur the association between poor response and miscarriage. In addition, Kumbak and colleagues only selected pregnancies for their analysis if a gestational sac had been identified by transvaginal ultrasound examination, performed 3-4 weeks after embryo transfer. This means that early pregnancy losses before ultrasound examination were not included. It has been demonstrated that the shorter the duration of pregnancy before miscarriage, the larger the chance that the loss is caused by aneuploidy[51;119;122]. Since aneuploidy is the main acknowledged manifestation of decreased oocyte quality, excluding (very) early pregnancy losses may lead to underestimation of the relationship between oocyte quantity and quality.
Karyotype of miscarriage tissue to confirm aneuploidy as the cause of the pregnancy loss was not

available in our study. Nasseri *et al*. did assess the fetal karyotype of women with a miscarriage and found increased levels of FSH and/or oestradiol in women with an aneuploid fetal karyotype compared with women with a euploid foetal karyotype (161). However, Massie *et al*. and Havryliuk *et al.* could not confirm these findings[162;163].

A number of studies assessed the relationship between ovarian reserve tests, such as FSH and antral follicle count (AFC), and miscarriage in IVF and non-IVF populations. Three small retrospective studies showed an increased miscarriage rate among women with abnormal test results, but these findings could not be confirmed in a number of other studies, including two with prospective design[146-151;233]. The reason that ovarian reserve tests apparently have no evident predictive value for miscarriage could be that these tests do not reflect oocyte quantity accurately enough. For instance, raised FSH concentrations may originate from a variety of causes apart from decreased ovarian reserve and AFC is thought to overestimate quantitative ovarian reserve in older women, since a larger proportion of the remaining follicle pool is recruited for development with age[19;76;77;107;226]. On this subject the study of Sabatini *et al.* is of interest[245]. They found that increased FSH concentrations have predictive value for live birth in an IVF population, but only in women over 35 years of age. Possibly this is caused by the fact that in women of advanced age increased FSH concentrations are more likely to represent diminished ovarian reserve, whereas in younger women other causes are more likely. The oocyte yield after ovarian hyperstimulation may be the (dynamic) ovarian reserve test that most accurately approaches the true ovarian reserve.

In conclusion, the present study demonstrates that poor responders, specifically above the age of 35 years, have an increased chance of miscarriage compared with their peers with normal response. This is in line with the findings that poor responders have decreased pregnancy chances after IVF treatment. Women in their late thirties and early forties with a poor response in IVF treatment should not only be informed about their low pregnancy chances, but also about their increased risk of miscarriage.

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