Predicting IVF outcome

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Predictive factors in in vitro fertilization (IVF): a systematic review and meta-analysis

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ABSTRACT

Background Various models have been developed for the prediction of pregnancy after IVF. These models differ from one another in the predictors they include. We performed a systematic review and meta-analysis to identify the most relevant predictors for success in IVF.

Methods We systematically searched MEDLINE and EMBASE for studies evaluating IVF/ICSI outcome. Studies were included if they reported an unconditional odds ratio or whenever one could be calculated for one or more of the following factors: age, type of infertility, indication, duration of infertility, basal FSH, number of oocytes, fertilization method, number of embryos transferred and embryo quality.

Results Fourteen studies were identified. A summary OR could be calculated for 5 factors. We found negative associations between pregnancy and female age (OR: 0.95, 95% CI: 0.94 to 0.96), duration of subfertility (OR: 0.99, 95% CI: 0.98 to 1.00) and basal FSH (OR: 0.94, 95% CI: 0.88 to 1.00). We found a positive association with number of oocytes (OR 1.04, 95% CI: 1.02 to 1.07). Better embryo quality was associated with higher pregnancy chances. No significant association was found for type of infertility and fertilization method. A summary OR for IVF indication and number of embryos transferred could not be calculated, because studies reporting on these used different reference categories.

Conclusions Female age, duration of subfertility, bFSH and number of oocytes, all reflecting ovarian function, are predictors of pregnancy after IVF. Better quality studies are necessary, especially studies that focus on embryo factors that are predictive of success in IVF.
INTRODUCTION

The first birth after in vitro fertilization (IVF) and embryo transfer was reported in 1978 (1). Initially, IVF was used to bypass infertility in women with bilateral tubal occlusion (2). In later years, IVF was also initiated in couples with unexplained subfertility, male subfertility, cervical factor, failed ovulation induction, endometriosis, or unilateral tubal pathology (3-5). In contrast to women with bilateral tubal occlusion, these women are not completely sterile but still have a chance of natural conception. To prevent overtreatment in these women it is important to balance the probability of achieving a pregnancy after IVF against the probability of achieving a pregnancy through natural conception.

Several cohort studies have identified factors that are possibly predictive of success after IVF, such as the diagnosis after the fertility workup, the number of previous unsuccessful IVF attempts and a previous pregnancy, with and without IVF (6-12). A useful prediction model for IVF success should include all relevant predictive factors, if these are available at a reasonable cost. Unfortunately, the putative predictive factors identified by these studies varied per study, and not all studies arrived at similar conclusions about factors predictive of IVF success.

To answer the question which factors can help in predicting pregnancy after IVF and should be included in an IVF prediction model, we performed a systematic review of the factors female age, parity, basal FSH, duration of subfertility, indication for subfertility, number of oocytes retrieved, method of fertilization, number of embryos transferred, and embryo quality to predict pregnancy after IVF, and to obtain pooled estimates of their predictive value through meta-analysis. These nine putative factors were chosen since they are routinely obtained in daily practice as part of standard patient care.

MATERIAL AND METHODS

Criteria for considering studies for this review

Articles were eligible if they evaluated the association between one or more of the pre-identified predictive factors and pregnancy after IVF/ICSI treatment in an unselected patient group. Articles were selected if the target population were subfertile women undergoing ovarian stimulation with gonatrophins in fresh autologous IVF and ICSI procedures. The outcome measures were clinical pregnancy, defined as gestational sac confirmed by ultrasound at 6 weeks gestation, and ongoing pregnancy, defined as a pregnancy with heartbeat of one or more fetuses confirmed by ultrasound at 12 weeks gestation.
Search strategy for the identification of studies

The searches were performed by a medical librarian (J.L.) experienced in conducting searches for systematic reviews. Literature searches were conducted in the bibliographic databases OVID MEDLINE and OVID EMBASE, from 1978 till August 2009, using both free-text words and index terms specific to each database (MeSH, SH). No language or any other restriction was applied. The search included an iterative process to refine the search strategy through adding search terms as new relevant citations were identified. We downloaded all references identified into Reference Manager® software (version 11.0).

To safeguard against missing relevant studies, we did not search for each of the nine individual factors separately (which might not be mentioned as such in title and abstract), but we searched for all prognostic studies on IVF or ICSI, using the following approach. A broad search for IVF/ICSI was combined with terms for pregnancy or pregnancy outcome (i.e. live birth). Next, this search was combined with two filters: [1] a broad search filter for prognostic methodology (based on terms as regression analysis, logistic models, multivariate or univariate or odds) and, separately [2], a broad search filter for prognostic/predictive factors (i.e. prognostic factor*, predictive factor*, independent* variable*). To check whether this search captured all relevant articles, we run a separate search for three individual factors (female age, basal FSH, number of embryos) without the abovementioned filters. This yielded no additional relevant articles. For details of the MEDLINE and EMBASE search see appendix I and II.

In and exclusion criteria

Articles were included if they reported on one or more studies that had evaluated associations between one or more predictive factors and pregnancy after IVF, if the study group consisted of subfertile women undergoing a fresh autologous IVF/ICSI cycle, and if a stimulation protocol with down regulation had been used.

Articles were excluded if they reported on a specific patient group within the subfertile IVF/ICSI population or if an unconditional odds ratio for the association between the putative predictive factor(s) and pregnancy was not reported and could not be calculated from the data presented.

Identification

The abstracts of all articles identified through the search were read by one researcher (L.L.), who selected all articles that were potentially eligible. In the next step, two researchers (L.L. and M.W.) carefully read and evaluated potentially eligible articles and decided on inclusion. In case of disagreement, the decision of a third reviewer (F.V.) was final. The reference list of every selected article was carefully checked to identify other potentially eligible studies.
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Methods of review
The following information was extracted from each included article: study characteristics, (specified as consecutive or randomized study, prospectively or retrospectively, inclusion and exclusion criteria), predictors, outcome measures and their specific definitions (biochemical pregnancy defined as a positive pregnancy test, clinical pregnancy defined as ultrasonographic confirmation of an intrauterine gestation sac with fetal viability) and whether missing data were reported and/or imputed. If necessary, and whenever possible, we contacted the authors for missing data.

Statistical analyses
We extracted, calculated or recalculated the odds ratios for each predictor in each of the included articles, based on the data presented. We evaluated statistical heterogeneity graphically by drawing forest plots and by calculating the I² statistic. We then obtained summary estimates of the association by calculating the pooled unconditional odd ratio, using random effects modelling. The ORs of individual studies and summary odds ratios with corresponding confidence intervals were calculated using the Comprehensive Meta-Analysis software package (version 2).

RESULTS

Results of search
Our search retrieved 1,397 articles. The process of paper selection is summarized in Fig. 1. After screening titles and abstracts we selected 58 articles for further reading. Forty three articles did not meet our inclusion criteria, in particular in terms of reporting an unconditional odds ratio or allowing calculation of an odds ratio from the data presented (7;9;11-51). One article did not report on pregnancy or live birth as an outcome (52). A final number of 14 studies reporting on one or more of the predictive factors was included in the review.

Methodological quality of included studies
The characteristics of the 14 included studies are summarized in Table I. The number of evaluated predictors varied from 1 to 16. An overview of critical features of the included studies is shown in Fig. 2. Patient selection was consecutive in five (36%) studies. Only three studies (21%) had collected their data prospectively. Nine studies described their treatment protocol in sufficient detail. In 12 articles pregnancy was clearly defined. Only four studies reported on missing data. None of the studies used imputation for missing data.
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Figure 1 | Process from initial search to final inclusion for papers on predictive factors in IVF/ICSI

Potentially relevant papers on predictive factors and IVF/ICSI
\( n = 1397 \)

\[ \text{Citations excluded after screening title and abstract} \quad n = 1339 \]

Primary papers retrieved for full-text evaluation
\( n = 58 \)

\[ \text{Papers retrieved from cross references} \quad n = 0 \]

Primary papers retrieved for full-text evaluation
\( n = 58 \)

\[ \text{Papers excluded after reading full-text paper} \quad n = 44 \]

Reasons for exclusion:
- No unconditional odds ratio reported or could not be calculated \( n = 43 \)
- No outcome of pregnancy or live birth \( n = 1 \)

Primary papers included
\( n = 14 \)
- Age 13
- Primary or secondary subfertility 3
- Duration of subfertility 3
- Indication for IVF 4
- bFSH 7
- Number of oocytes retrieved 7
- Fertilization method 2
- Number of embryos transferred 2
- Embryo quality 3
### Table I | Characteristics of the selected studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Inclusion and exclusion criteria</th>
<th>n</th>
<th>Study design</th>
<th>Outcome</th>
<th>Agonist/antagonist</th>
<th>Variables reported on</th>
</tr>
</thead>
</table>
| Ebbesen et al.  | Women undergoing their first IVF-treatment cycle at a university fertility clinic | Inclusion:  
- First IVF cycle  
- No previous attempts with IVF-treatment  
- Ability to read and understand Danish  
Exclusion:  
- Preimplantation Genetic Diagnosis  
- Unplanned change of treatment type | 837 ptn² | pros. CH¹ | Clinical pregnancy | Agonist | Age  
Smoking habits  
Daily coffee  
Stress measures  
BMI  
bFSH  
Method of fertilization  
Number of oocytes |
| Sabatini et al. | Women undergoing their first IVF cycles | Inclusion:  
- Regular cycle in the previous 6 months  
Exclusion:  
- Woman’s age > 45 years | 1589 ptn | ret. CH | Live birth | Agonist | Age | bFSH |
| Wang et al.     | Data from all fertility centres in Australia and New Zealand on women undergoing their first autologous fresh IVF/ICSI cycle | Inclusion:  
- Age woman ≥ 18 years  
- First autologous fresh cycle  
Exclusion:  
- Mixed fresh-thaw cycles  
- Gamete intrafallopian transfer cycles  
- Natural cycles  
- Surrogacy cycles | 36412 ptn | ret. CH | Live birth/clinical pregnancy | NA ⁴ | Age |
| Ottosen et al.  | IVF and ICSI treatment cycles from a public fertility clinic | Exclusion:  
- Cryo embryo transfer  
- Single embryo transfer | 2193 cycl | ret. CH | Clinical pregnancy | Agonist or antagonist | Age  
Duration of infertility  
BMI  
bFSH  
Indication for IVF  
Method of fertilization  
Number of oocytes  
Number of fertilized oocytes  
Fertilization rate  
Score of best/second best embryo |
Continuation of table I

<table>
<thead>
<tr>
<th>Author</th>
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<th>Agonist/antagonist</th>
<th>Variables reported on</th>
</tr>
</thead>
</table>
| Ferlitsch et al. (2004) | Women referred for IVF to a university hospital | Inclusion:  
- Weight and height known  
Exclusion:  
- severe endometriosis  
- a single ovary with possible normal ovarian response  
- any ovarian cyst measuring > 10 mm in diameter on baseline day | 171 ptn | ret. CH      | Clinical pregnancy                 | Agonist or antagonist | BMI, LH, FSH, E2, Prolactin, TSH, Endometrium thickness, Protocol |
| Hauzman et al. (2004) | Women who conceived after IVF/ICSI | Inclusion:  
- Frozen archived serum sample for inhibin A measurement  
- Only first pregnancy | 151 ptn | ret. CH | Ongoing/clinical pregnancy | Agonist | Age, Number of oocytes, Number of embryos transferred, Day 11 hCG, level, Mean inhibin A level |
| Hunault et al. (2002) | Patients from a university hospital in their first IVF cycle | Inclusion:  
- Transfer of two embryos  
Exclusion:  
- ICSI treatment  
- Oocyte donation  
- Cryo preserved embryos | 642 ptn | ret. CH | Ongoing pregnancy | Agonist | Age, Duration of infertility, Type of infertility, Indication for IVF, Total number of sperm cells, Progressive motile sperm cells, Estrogen level, Number of preovulatory follicles, Number of oocytes retrieved, Proportion of oocytes fertilized, Day of ET, No of embryos suitable for transfer, Stage development best and second best embryo, Morphology score of the best and second best embryo |
| Sharma et al. (2002) | Women undergoing IVF at an academic fertility centre | Exclusion:  
- Cryo embryo transfers  
- ICSI treatment | 2056 ptn | ret. CH | Clinical pregnancy | Agonist | Age, Number of oocytes, Number of embryos transferred |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Participants</th>
<th>Outcome</th>
<th>Variables Reported on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maugey-Laulom et al. (2002)</td>
<td>Women undergoing IVF or ICSI</td>
<td>Exclusion: - Women age ≥ 38 years and FSH &gt;10 UI/ml</td>
<td>144 ptn pros. CH</td>
<td>Ongoing pregnancy</td>
<td>Age, Endometrium thickness, Endometrium morphology, Pulsatility index, Protodiastole notch, Sub- and intra endometrial vascular signals</td>
</tr>
<tr>
<td>Hart et al. (2001)</td>
<td>All women undergoing their first IVF or ICSI</td>
<td>Inclusion: - Fibroids ≤ 5 cm Exclusion: - Cryo embryo transfers - Donated oocytes</td>
<td>434 ptn pros. CC</td>
<td>Biochemical pregnancy</td>
<td>Age, bFSH, Number of ampoules FSH, Number of oocytes, Number of available embryos, Intramural fibroid ≤ 5 cm in size</td>
</tr>
<tr>
<td>Bansci et al. (2000)</td>
<td>Women undergoing their first stimulated IVF cycle at an academic fertility centre</td>
<td>Inclusion: - Regular menstrual cycle - bFSH level on day 1-4 Exclusion: - Endocrine disorder - Oocyte donation - Unstimulated cycles</td>
<td>435 ret. CH</td>
<td>Ongoing pregnancy</td>
<td>Age, Type of infertility, Indication for IVF, Duration of infertility, bFSH</td>
</tr>
<tr>
<td>Strandell et al. (2000)</td>
<td>Women undergoing IVF/ICSI</td>
<td>Inclusion: - Transfers with two embryos Exclusion: - Woman's age &gt; 40 years - Cryo embryo transfers</td>
<td>1441 ptn ret. CH</td>
<td>Birth</td>
<td>Age, Previous pregnancy, Previous childbirth, Indication for IVF, FSH initial daily dose, Duration of ovarian stimulation, FSH total dose, Number of oocytes, Number of fertilized oocytes, Proportion of fertilized oocytes, Day of embryo transfer, Number of good quality embryos available, Number of good quality embryos transferred, No of embryos suitable for freezing</td>
</tr>
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<table>
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<tr>
<th>Author</th>
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<th>Outcome</th>
<th>Agonist/antagonist</th>
<th>Variables reported on</th>
</tr>
</thead>
</table>
| Syrop et al. (1999) | Women undergoing their first IVF cycle        | Inclusion:  
- Complete data available from first treatment cycle following determination of day 3 FSH/estradiol and ovarian volume  
- Ovarian volume was determined by 1 of 2 physicians  
- Both ovaries were sonographically visualized  
- FSH/estradiol determinations performed by same laboratory  
Exclusion:  
- Anovulatory patients | 261 ptn | ret. CH | Clinical pregnancy | Agonist | Age  
Smoking (current/former)  
bFSH  
E2  
Smallest ovarian size |
| Stolwijk et al. (1997) | Women undergoing their first IVF or donor treatment in an academic fertility centre | Inclusion:  
- Normal uterine cavity  
Exclusion:  
- ICSI treatment  
- When there was no male partner | 277 ptn | ret. CH | Ongoing/Clinical/Biochemical | Agonist | Age |

¹ ICSI = intracytoplasmatic sperm injection  
² ptm = patients; cycl = cycles  
³ Study design: pros. CH = prospective cohort study; pros. CC = prospective case control study; ret CH = retrospective cohort study  
⁴ NA = information not available  
⁵ bFSH = basal FSH  
⁶ E2 = estradiol
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Figure 2 | Summary of study quality. Numbers indicate the number of studies.

<table>
<thead>
<tr>
<th>Predictor: age</th>
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<tr>
<td>Thirteen studies evaluated the association between female age and pregnancy after IVF (53-65). The characteristics of these studies are listed in Table I. The number of included patients varied from 144 to 36,412.</td>
</tr>
</tbody>
</table>

Three studies categorised age and data from these studies could not be pooled. One of these studies dichotomised age in two categories, ≤ 35 or > 35 years (61). Women aged 35 years or older had significantly lower pregnancy chances compared to women who were younger than 35 years. The second study categorized the patients into four categories, i.e. <30, 30-34, 35-38 and 39-45 years (60). Women in the age categories <30 and 30-34 years had 3.2 and 2.8 higher chances of a pregnancy compared to women in the age category 39-45 years. The third study showed that women aged 30 years or older compared to women in the age category 25 to 29 had lower pregnancy chances (65). |

Figure 3 | Forest plot presenting the effect of age on pregnancy after IVF/ICSI
Age was reported as a continuous variable in the remaining 10 studies. Visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity across the studies (Fig. 3). The summary odds ratio for pregnancy and female age was 0.95 (95% CI: 0.94 to 0.96) indicating that increasing female age was associated with lower pregnancy chances in IVF.

**Predictor: duration of subfertility**

Three studies evaluated the association between duration of subfertility and pregnancy (53;57;59). One study subdivided duration of subfertility in six categories (59). The authors from that study reported that women with a duration of subfertility exceeding 12 months had lower pregnancy chances compared to women with a duration of subfertility of less than 12 months. In two studies duration of subfertility was taken as a continuous measurement and data could be pooled. Visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity across the studies (Fig. 4). The ongoing pregnancy rate per woman was lower with increasing duration of subfertility. The summary odds ratio of the two studies, reporting on 1,077 patients, was 0.99, (95% CI: 0.98 to 1.00).

**Figure 4** | Forest plot presenting the effect of duration of subfertility on pregnancy after IVF/ICSI

**Predictor: type of subfertility**

Three studies reported associations between type of subfertility (primary versus secondary subfertility) and pregnancy (53;57;63). One study reported that women with a previous clinical pregnancy had lower pregnancy chances after IVF, but women who previously had given birth had higher pregnancy chances after IVF. Neither of these associations was significant (63). Since this study did not report a 95% confidence interval, it could not be included in the meta analysis.

The data from two studies, including 1,077 cycles, could be pooled (53;57). Visual examination of the forest plot and the I² statistic (0%) suggested no heterogeneity between the studies (Fig. 5). The summary OR was 1.04 (95% CI: 0.65 to 1.43).
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Figure 5 | Forest plot presenting the effect of type of subfertility on pregnancy after IVF/ICSI

<table>
<thead>
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<th>Predictor: indication for IVF</th>
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| Four studies reported the association between indication for IVF and pregnancy (53;57;59;63). One study evaluated this predictor using three categories: unexplained infertility, male infertility and tuboperitoneal disease. Unexplained infertility was used as the reference category. Women with male subfertility or tuboperitoneal disease had lower pregnancy chances compared to those with unexplained subfertility (53). A second study reported that women with either male subfertility, tubal subfertility or subfertility caused by endometriosis had lower pregnancy chances compared to women with unexplained infertility (59).

In a third study the predictor “indication for IVF” was classified using four categories, with tubal subfertility as the reference category. Couples with male subfertility or with unexplained subfertility had lower pregnancy chances after IVF compared to couples with a tubal factor (57). The fourth study reported on each predictor separately. Women with tubal subfertility had significantly lower pregnancy chances after IVF and women with the indication endometriosis, male subfertility, unexplained subfertility and hormonal factors had higher pregnancy chances though not significant (63). Because of the use of different reference categories, we were not able to obtain a summary estimate of the odds ratio.

Predictor: basal FSH

Seven studies reported the association between basal FSH and pregnancy after IVF (53-55;59;60;64;66). Two of these studies (59;60) dichotomised basal FSH into the categories 0 to 10 IU and >10 IU. In both studies pregnancy chances were significantly higher in women with FSH <10 IU than in women with FSH concentrations of > 10 IU. The data of the remaining five studies could be pooled. The I² statistic (2%) suggested mild heterogeneity (Fig. 6). The summary OR confirmed that increasing bFSH values were associated with lower pregnancy rates after IVF (OR 0.94; 95% CI: 0.88 to 1.00).
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Figure 6 | Forest plot presenting the effect of basal FSH on pregnancy after IVF/ICSI

Predictor: number of oocytes retrieved
Six studies reported on the association between number of oocytes retrieved and pregnancy (55;57;59;61;63). Two studies had categorised the data. One study dichotomised number of oocytes in ≤ 5 and >5 oocytes retrieved (61). The other study used three categories: 1 to 5 oocytes, 6 to 10 and 11 or more oocytes (59). Both studies found that women with more oocytes had higher pregnancy chances.

The data of four studies could be pooled. Visual examination of the forest plot and the $I^2$ statistic (0%) suggested no heterogeneity across the studies (Fig. 7). We found a positive association between increasing number of oocytes retrieved and pregnancy chances after IVF, with a summary OR of 1.04 (95% CI: 1.02 to 1.07).

Figure 7 | Forest plot presenting the effect of number of oocytes retrieved on pregnancy after IVF/ICSI

Predictor: method of fertilization (IVF or ICSI)
Two studies reported on the association of method of fertilization and pregnancy chances after IVF (59;63). One study reported lower pregnancy chances with ICSI compared to IVF (OR 0.95, 95% CI: 0.79 to 1.14), though not significant (59). The other study showed no difference. This study did not report a 95% CI interval (63).
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Predictor: number of embryos transferred
Two studies reported on the number of embryos transferred and IVF success (56;61). One study dichotomised the number into the categories more than 2 and 2 or less embryos transferred. Women where more than two embryos were transferred had significantly higher pregnancy chances (61). The second study showed higher, though not statistically significant, pregnancy chances when transferring more embryos (56). No summary OR could be calculated.

Predictor: embryo quality
Three studies evaluated the association between embryo quality and pregnancy after IVF (57;59;63). One study classified embryo quality using two separate factors, evaluating the best and the second best embryo in terms of stage of development and morphology score (57). The stage of development was described using 3 categories: delayed, appropriate and advanced stage. Advanced stage was used as the reference category. Women in whom either the best or second best embryo had a delayed or appropriate development stage had lower pregnancy chances compared to women where either the best or second best embryo had an advanced development stage. Lower morphology scores were also associated with lower pregnancy chances.

The second study reported that women with embryos with higher development stage and morphology scores, combined into one predictor, had higher pregnancy chances, compared to women with lower development stage and morphology score (59). The third study used three other predictors for embryo quality: number of good quality embryos available, number of good quality embryos transferred, and number of embryos suitable for freezing (63). All three predictors were associated with higher pregnancy chances after IVF. In all studies better embryo quality was associated with higher pregnancy chances, but, since these studies used different factors or combinations of embryo factors to report embryo quality, it was not possible to pool the data and calculate a summary OR.

DISCUSSION
Predicting pregnancy chances after an IVF cycle can help to prevent overtreatment and to balance the probability of achieving a pregnancy after IVF against the probability of achieving a pregnancy through natural conception. Although many studies reported on potential predictors of pregnancy chances after IVF, there is no consensus to pinpoint which predictors are clinically most relevant and on what factors one should base the decision to start treatment or not. In this systematic review and meta-analysis we evaluated nine putative predictive factors that could help in predicting pregnancy chances after IVF. Based on the available evidence we conclude that female age, duration of subfertility, basal FSH and number of oocytes are predictive of IVF success. Unfortunately we could not perform a meta-analysis on the factors indication for IVF, number of embryos transferred
and embryo quality, since there was no uniform method of reporting these variables. No meta-analysis was performed on the method of fertilization either, since only one study reported an OR and 95% confidence interval.

This meta-analysis provides robust evidence for female age being one of the strongest factors in predicting pregnancy chances after IVF. Our study not only shows that age is a significant predictor, it also shows that this predictor is identified by nearly every one of the included studies as an important predictor. So based on these findings, female age should not only be considered as a candidate predictor when developing a prognostic model for success in IVF, but the summary estimate from our meta-analysis could also be used as a prior estimate in a new prognostic model.

The biological explanation for the declining chances to conceive with increasing female age most likely lies in the diminished ovarian reserve, the decrease in both quantity and quality of oocytes, which is clinically relevant in women from their mid-30s. Diminished ovarian reserve generally leads to a poor response to gonadotropin therapy, and limits the possibility of a successful pregnancy. In our society many couples delay childbearing, which is illustrated by the mean age of women who become mothers for the first time; their age has increased over the last 17 years from 24.3 to 26.0 years.

The other factors we found to be associated with pregnancy chances, bFSH, duration of infertility and number of oocytes, are also age related. An older woman is likely to have a longer duration of subfertility, bFSH rises with increasing age and the number of oocytes declines with age. Unfortunately in this meta-analysis we were not able to perform a multivariable analysis and thus we do not known whether age in itself overrides these factors.

Although we could only include two studies reporting on the predictive value of number of embryos transferred and could not calculate a summary OR, there are several randomized controlled trials comparing fresh single embryo transfer to fresh double embryo transfer that clearly showed that double embryo transfer doubles the chance of pregnancy but also increases the risk of multiple pregnancy. These trials included ‘good prognosis’ women i.e. younger women without a history of multiple failed IVF cycles and with a certain number of good quality embryos available for transfer. However even in an unselected patient population the same results were found i.e. increased pregnancy chance but higher multiple pregnancy rate after double embryo transfer. The number of embryos transferred are thus not only predictive for pregnancy, but also for multiple pregnancy.

In addition to number of embryos, several studies have reported multivariable analyses that show that embryo quality in itself is a predictor of pregnancy chances in IVF, next to age. Our review shows that these studies did not use a uniform method
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for reporting embryo quality. This made it impossible to perform a meta-analysis and to evaluate which embryo factor is most important. Since there are differences between studies on how they report embryo quality and differences in their selection criteria, it remains unclear which embryo factor is most predictive of pregnancy. Therefore studies on the relation between embryo quality and pregnancy need to use a standardised way of assessing embryo quality.

Several studies also showed that indication for IVF is a predictor for pregnancy (8;9;12). Since studies use different reference categories and different number of categories it was not possible to perform a meta-analysis. For future studies it would be useful to report every indication for IVF as a separate variable instead of combining all indications into one factor, to be able to compare all studies.

Our review of the literature on the nine predictors revealed that a remarkably few number of articles reported unconditional odds ratios, leaving only a few articles for inclusion. Maybe more data could be gathered, resulting in more precise summary estimates, in future IPD meta-analysis.

In summary, our systematic review shows that female age, duration of subfertility, basal FSH and number of oocytes are predictive for pregnancy chances after IVF. As a consequence these factors should be considered when making a decision to start treatment or not and the summary estimates could be used as a prior estimate in a new prognostic model. On the predictors indication for IVF, method of fertilization, number of embryos transferred and embryo quality we were not able perform a meta-analysis. Better quality studies are necessary, especially studies that focus on embryo factors that are predictive of success in IVF.
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Appendix I | Search Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
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<tr>
<td>1</td>
<td>Fertilization in Vitro/ or Sperm Injections, Intracytoplasmic/</td>
</tr>
<tr>
<td>2</td>
<td>(Fertilat* adj2 in Vitro).ti,ab.</td>
</tr>
<tr>
<td>3</td>
<td>(ivf or icsi or ic-si).ti,ab.</td>
</tr>
<tr>
<td>4</td>
<td>(intracytoplas* adj5 sperm*).ti,ab.</td>
</tr>
<tr>
<td>5</td>
<td>embryo transfer/</td>
</tr>
<tr>
<td>6</td>
<td>(embryo adj2 (transfer* or implant*)).ti,ab.</td>
</tr>
<tr>
<td>7</td>
<td>reproductive techniques/ or reproductive techniques, assisted/</td>
</tr>
<tr>
<td>8</td>
<td>or/1-7</td>
</tr>
<tr>
<td>9</td>
<td>exp pregnancy/</td>
</tr>
<tr>
<td>10</td>
<td>Birth Rate/ or live birth/</td>
</tr>
<tr>
<td>11</td>
<td>exp Pregnancy Rate/</td>
</tr>
<tr>
<td>12</td>
<td>pregnan*.ti,ab.</td>
</tr>
<tr>
<td>13</td>
<td>(livebirth* or childbirth*).ti,ab.</td>
</tr>
<tr>
<td>14</td>
<td>((live or rate<em>1) adj1 birth</em>1).ti,ab.</td>
</tr>
<tr>
<td>15</td>
<td>(birth<em>1 adj2 (rate</em>1 or live or child*)).ti,ab.</td>
</tr>
<tr>
<td>16</td>
<td>((newborn<em>1 or child</em>) adj2 (live or born)).ti,ab.</td>
</tr>
<tr>
<td>17</td>
<td>(succes* adj (rate<em>1 or outcome</em>1)).ti,ab.</td>
</tr>
<tr>
<td>18</td>
<td>((gestation or reproducti<em>2) adj2 (achiev</em>2 or succes* or outcome*1)).ti,ab.</td>
</tr>
<tr>
<td>19</td>
<td>or/9-18</td>
</tr>
<tr>
<td>20</td>
<td>8 and 19</td>
</tr>
<tr>
<td>21</td>
<td>letter/ or case reports/ or randomized controlled trial/ or editorial/ or (animals/ not (animals/ and humans/))</td>
</tr>
<tr>
<td>22</td>
<td>20 not 21</td>
</tr>
<tr>
<td>23</td>
<td>regression analysis/ or logistic models/ or linear models/ or Multivariate Analysis/ or Odds ratio/</td>
</tr>
<tr>
<td>24</td>
<td>(multivaria* or univaria*).ti,ab.</td>
</tr>
<tr>
<td>25</td>
<td>odds.ti,ab.</td>
</tr>
<tr>
<td>26</td>
<td>(Crude adj (association* or relative risk*)).ti,ab.</td>
</tr>
<tr>
<td>27</td>
<td>((logistic* or log or coefficient) adj3 (regression* or model* or analy*)).ti,ab.</td>
</tr>
<tr>
<td>28</td>
<td>(multiple adj3 regression*).ti,ab.</td>
</tr>
<tr>
<td>29</td>
<td>(regression adj3 model*).ti,ab.</td>
</tr>
<tr>
<td>30</td>
<td>((linear or analy*) adj1 regression).ti,ab.</td>
</tr>
<tr>
<td>31</td>
<td>or/23-30</td>
</tr>
<tr>
<td>32</td>
<td>22 and 31</td>
</tr>
<tr>
<td>33</td>
<td>prognosticat*.ti,ab.</td>
</tr>
<tr>
<td>34</td>
<td>(prognos* adj2 value*).ti,ab. not (test* or assay* or imaging or ultrasonograph*).ti.</td>
</tr>
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</table>
Continuation of appendix I

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
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<tbody>
<tr>
<td>35</td>
<td>(prognostic adj6 (factor* or variable or parameter* or indicator* or importance or index)).ti,ab.</td>
</tr>
<tr>
<td>36</td>
<td>(predict* adj2 factor*).ti,ab.</td>
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<tr>
<td>37</td>
<td>(predicting adj2 variable*).ti,ab.</td>
</tr>
<tr>
<td>38</td>
<td>((significat* or positive* or negat*) adj (predict? or predictor*)).ti,ab.</td>
</tr>
<tr>
<td>39</td>
<td>(predict* adj3 (ongoing pregnanc* or pregnancy rate*)).ti,ab.</td>
</tr>
<tr>
<td>40</td>
<td>((independent* or dependent*) adj4 (factor* or variable* or predictor* or associat* or marker*)).ti,ab.</td>
</tr>
<tr>
<td>41</td>
<td>or/33-40</td>
</tr>
<tr>
<td>42</td>
<td>22 and 41</td>
</tr>
</tbody>
</table>

Appendix II | Search Embase

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
<td>fertilization in vitro/ or intracytoplasmic sperm injection/</td>
</tr>
<tr>
<td>3</td>
<td>(ivf or icsi or ic-si).tw.</td>
</tr>
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<td>(intracytoplasm* adj5 sperm*).tw.</td>
</tr>
<tr>
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<td>embryo transfer/</td>
</tr>
<tr>
<td>6</td>
<td>(embryo adj2 (transfer* or implant*)).tw.</td>
</tr>
<tr>
<td>7</td>
<td>infertility therapy/</td>
</tr>
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<td>8</td>
<td>or/1-7</td>
</tr>
<tr>
<td>9</td>
<td>exp pregnancy/</td>
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</tr>
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<td>pregnan*.tw.</td>
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<td>((live or rate<em>1) adj1 birth</em>).tw.</td>
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<td>(birth<em>1 adj2 (rate</em>1 or live or child*)).tw.</td>
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<td>((newborn<em>1 or child</em>) adj2 (live or born)).tw.</td>
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<td>letter/ or case report/ or randomized controlled trial/ or editorial/ or ((animal or nonhuman) not human).hw.</td>
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# Searches

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>23</td>
<td>linear regression analysis/ or multivariate logistic regression analysis/ or exp multivariate analysis/ or statistical model/</td>
</tr>
<tr>
<td>24</td>
<td>(multivaria* or univaria*).tw.</td>
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