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

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BACKGROUND: Various models have been developed for the prediction of pregnancy after *in vitro* fertilization (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) 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 five factors. We found negative associations between pregnancy and female age [OR: 0.95, 95% confidence interval (CI): 0.94–0.96], duration of subfertility (OR: 0.99, 95% CI: 0.98–1.00) and basal FSH (OR: 0.94, 95% CI: 0.88–1.00). We found a positive association with number of oocytes (OR 1.04, 95% CI: 1.02–1.07). Better embryo quality was associated with higher pregnancy chances. No significant association was found for the 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.

Key words: *in vitro* fertilization / IVF / pregnancy / predictive factors / meta-analysis

Introduction

The first birth after *in vitro* fertilization (IVF) and embryo transfer was reported in 1978 (Steptoe and Edwards, 1978). Initially, IVF was used to bypass infertility in women with bilateral tubal occlusion (Edwards, 1965). In later years, IVF was also initiated in couples with unexplained subfertility, male subfertility, cervical factor, failed ovulation induction, endometriosis or unilateral tubal pathology (Hull *et al.*, 1985; Hamberger *et al.*, 1998; National Collaborating Centre for Women's and Children's Health, 2004). 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 (Hughes *et al.*, 1989; Nayudu *et al.*, 1989; Haan *et al.*, 1991; Stolwijk *et al.*, 1996; Templeton *et al.*, 1996; Minaretzis *et al.*, 1998; Lintsen *et al.*, 2007). 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.

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: (i) a broad search filter for prognostic methodology (based on terms as regression analysis, logistic models, multivariate or univariate or odds) and, separately (ii) 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 and number of embryos) without the above-mentioned filters. This yielded no additional relevant articles. For details of the MEDLINE and EMBASE search, see Supplementary data, Tables SI and SII.

Inclusion 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 (OR) 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.

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 foetal 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 ORs 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 I^2 statistic. We then obtained summary estimates of the association by calculating the pooled unconditional OR, using random effects modeling. The ORs of individual studies and summary ORs with corresponding confidence intervals (CIs) were calculated using the comprehensive meta-analysis software package (version 2).

Results

Results of search

Our search retrieved 1397 articles. The process of paper selection is summarized in Fig. 1. After screening titles and abstracts, we selected 58 articles for further reading. A total of 43 articles did not meet our inclusion criteria, in particular in terms of reporting an unconditional OR or allowing calculation of an OR from the data presented (Baeten *et al*., 1988; Hughes *et al*., 1989; Piette *et al*., 1990; Erenus *et al*., 1991; Toner *et al*., 1991; Baeten *et al*., 1993; Chan *et al*., 1993; Logerot-Lebrun *et al*., 1993; Bouckaert *et al*., 1994; Roseboom *et al*., 1995; Stolwijk *et al*., 1996; Templeton *et al*., 1996; Duleba *et al*., 1997; Commenges-Ducos *et al*., 1998; Joesbury *et al*., 1998; Minaretzis *et al*., 1998; Sharif *et al*., 1998; Templeton and Morris, 1998; Wheeler *et al*., 1998; Homan *et al*., 2000; Lundin *et al*., 2001; Terriou *et al*., 2001; Akande *et al*., 2002; Tomas *et al*., 2002; Chuang *et al*., 2003; Kupka *et al*., 2003; Van Montfoort *et al*., 2004; Anderheim *et al*., 2005; Anguas *et al*., 2005; Lintsen *et al*., 2005; Qublan *et al*., 2005; Rhodes *et al*., 2005; Srouji *et al*., 2005; Tersoglio *et al*., 2005; Kolibianakis *et al*., 2006; Lane *et al*., 2006; Lee *et al*., 2006; Carrera-Rotllan *et al*., 2007; Roberts, 2007; Terriou *et al*., 2007; Alvarez *et al*., 2008; Shapiro *et al*., 2008; Roberts *et al*., 2009). One article did not report on pregnancy or a live birth as an outcome (Bancsi *et al*., 2004). A total of 14 studies, reporting on one or more of the predictive factors, were 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.

Predictor: age

A total of 13 studies evaluated the association between female age and pregnancy after IVF (Stolwijk *et al*., 1997; Syrop *et al*., 1999; Bancsi *et al*., 2000; Strandell *et al*., 2000; Hart *et al*., 2001; Hunault *et al*., 2002; Maugey-Laulom *et al*., 2002; Sharma *et al*., 2002; Hauzman *et al*., 2004; Ottosen *et al*., 2007; Sabatini *et al*., 2008; Wang *et al*., 2008; Ebbesen *et al*., 2009). The characteristics of these studies are listed in Table I. The number of included patients varied from 144 to 36 412.

Three studies categorized age and data from these studies that could not be pooled. One of these studies dichotomized age into two categories, $\leq$35 or $>$35 years (Sharma *et al*., 2002). Women aged 35 years or older had significantly lower pregnancy chances compared with 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 (Sabatini *et al*., 2008). Women in the age categories $<$30 and 30–34 years had 3.2 and 2.8 higher chances of a pregnancy compared with women in the age categories 39–45 years. The third study showed that women aged 30 years or older compared with women in the age categories 25–29 had lower chances of pregnancy (Wang *et al*., 2008).

Age was reported as a continuous variable in the remaining 10 studies. Visual examination of the forest plot and the I^2 statistic (0%) suggested no heterogeneity across the studies (Fig. 3). The summary OR for pregnancy and female age was 0.95 (95% CI: 0.94–0.96) 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 (Bancsi *et al*., 2000; Hunault *et al*., 2002; Ottosen *et al*., 2007). One study subdivided duration of subfertility in six categories (Ottosen *et al*., 2007). The authors from that study reported that women with a duration of subfertility exceeding 12 months had lower pregnancy chances compared with women with a duration of subfertility of $<$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 I^2 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 OR of the two studies, reporting on 1077 patients, was 0.99, (95% CI: 0.98–1.00).

Predictor: type of subfertility

Three studies reported associations between type of subfertility (primary versus secondary subfertility) and pregnancy (Bancsi *et al*., 2000; Strandell *et al*., 2000; Hunault *et al*., 2002). 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

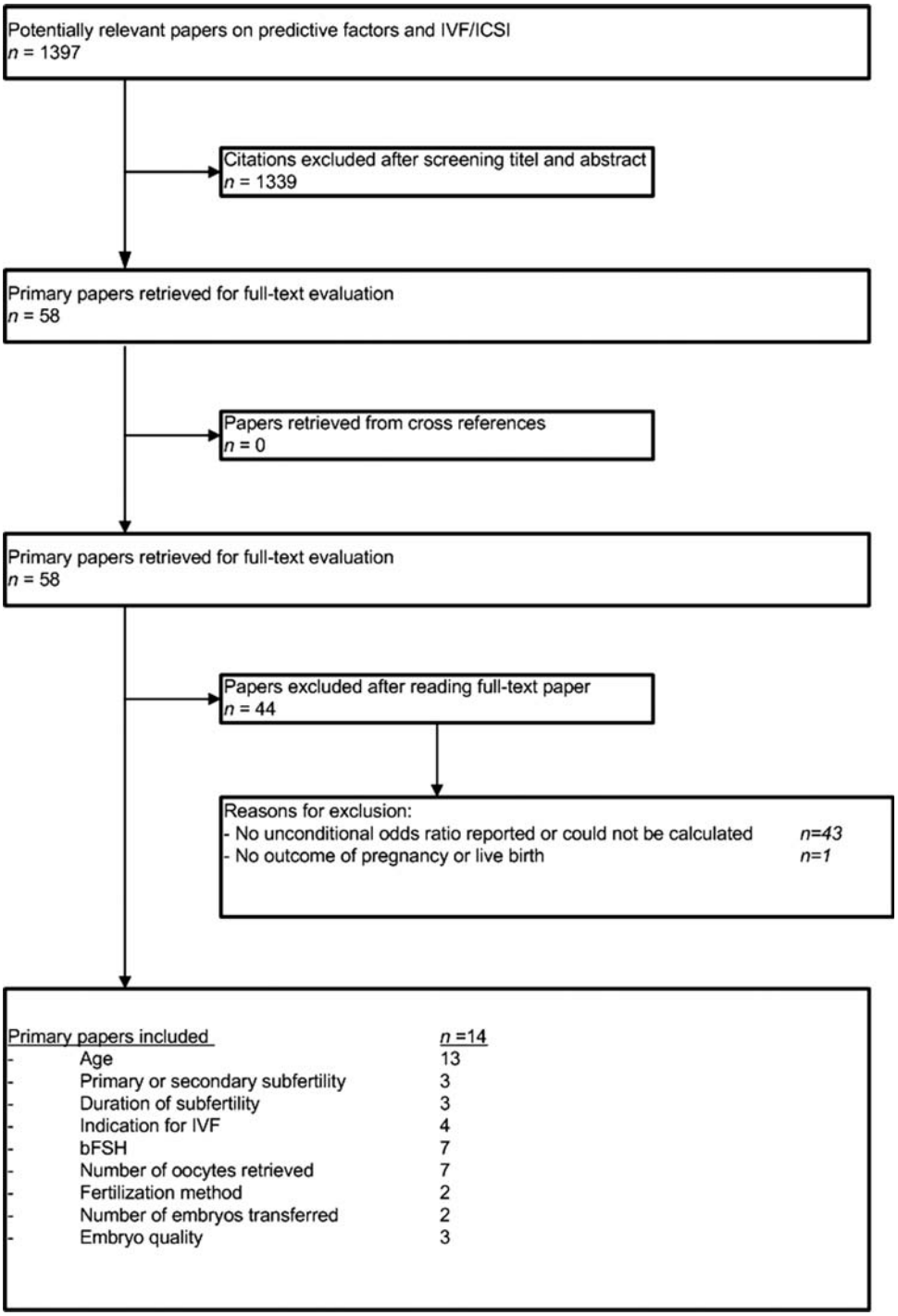

Figure 1 Process from initial search to final inclusion for papers on predictive factors in IVF/ICSI.

was significant (Strandell *et al.*, 2000). Since this study did not report a 95% CI, it could not be included in the meta-analysis.

The data from two studies, including 1077 cycles, could be pooled (Bancsi *et al.*, 2000; Hunault *et al.*, 2002). Visual examination of the forest plot and the I^2 statistic (0%) suggested no heterogeneity between the studies (Fig. 5). The summary OR was 1.04 (95% CI: 0.65–1.43).

Predictor: indication for IVF

Four studies reported the association between indication for IVF and pregnancy (Bancsi *et al.*, 2000; Strandell *et al.*, 2000; Hunault *et al.*, 2002; Ottosen *et al.*, 2007). One study evaluated this predictor using three categories: unexplained infertility, male infertility and tubo-peritoneal disease. Unexplained infertility was used as the reference category. Women with male subfertility or tuboperitoneal disease

Table I Characteristics of the selected studies

Author	Patients	Inclusion and exclusion criteria	*n*	Study design	Outcome	Agonist/ antagonist	Variables reported on
Ebbesen *et al.* (2009)	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 ptn[2]	pros. CH[3]	Clinical pregnancy	Agonist	Age Smoking habits Daily coffee Stress measures BMI bFSH[5] Method of fertilization Number of oocytes
Sabatini *et al.* (2008)	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.* (2008)	Data from all fertility centres in Australia and New Zealand on women undergoing their first autologous fresh IVF/ICSI[1] cycle	Inclusion: • Age woman ≥18 years • First autologous fresh cycle Exclusion: • Mixed fresh-thaw cycles • Gamete intrafallopian transfer cycles • Natural cycles • Surrogacy cycles	36 412 ptn	ret. CH	Live birth /clinical pregnancy	NA[4]	Age
Ottosen *et al.* (2007)	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

Continued

Table I *Continued*

Author	Patients	Inclusion and exclusion criteria	*n*	Study design	Outcome	Agonist/ antagonist	Variables reported on
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 bFSH $E2^6$ 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 fist 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 pre-ovulatory follicles Number of oocytes retrieved Proportion of ooctyes fertilized Day of embryo transfer 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

Maugey-Laulom *et al.* (2002)	Women undergoing IVF or ICSI	Exclusion: • Women age ≥38 years and FSH >10 IU/ml	144 ptn	pros. CH	Ongoing pregnancy	Agonist	Age Endometrium thickness Endometrium morphology Pulsatility index Protodiastole notch Sub- and intra endometrial vascular signals
Hart *et al.* (2001)	All women undergoing their first IVF or ICSI	Inclusion: • Fibroids ≤5 cm Exclusion: • Cryo embryo transfers • Donated oocytes	434 ptn	pros. CC	Biochemical pregnancy	Agonist	Age bFSH Number of ampoules FSH Number of oocytes Number of available embryos Intramural fibroid ≤5 cm in size
Bancsi *et al.* (2000)	Women undergoing their first stimulated IVF cycle at an academic fertility centre	Inclusion: • Regular menstrual cycle. • bFSH level on day 1–4 Exclusions: • Endocrine disorder • Oocyte donation • Unstimulated cycles	435	ret. CH	Ongoing pregnancy	Agonist	Age Type of infertility Indication for IVF Duration of infertility bFSH
Strandell *et al.* (2000)	Women undergoing IVF/ICSI	Inclusion: • Transfers with two embryos Exclusion: • Woman's age >40 years. Cryo embryo transfers	1441 ptn	ret. CH	Birth	Agonist	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

Continued

Table I *Continued*

Author	Patients	Inclusion and exclusion criteria	*n*	Study design	Outcome	Agonist/ antagonist	Variables reported on
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 one of two 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

ICSI, intracytoplasmatic sperm injection; ptn, patients; cycl, cycles; pros. CH, prospective cohort study; pros. CC, prospective case control study; ret CH, retrospective cohort study; NA, information not available; bFSH, basal FSH; E2, estradiol.

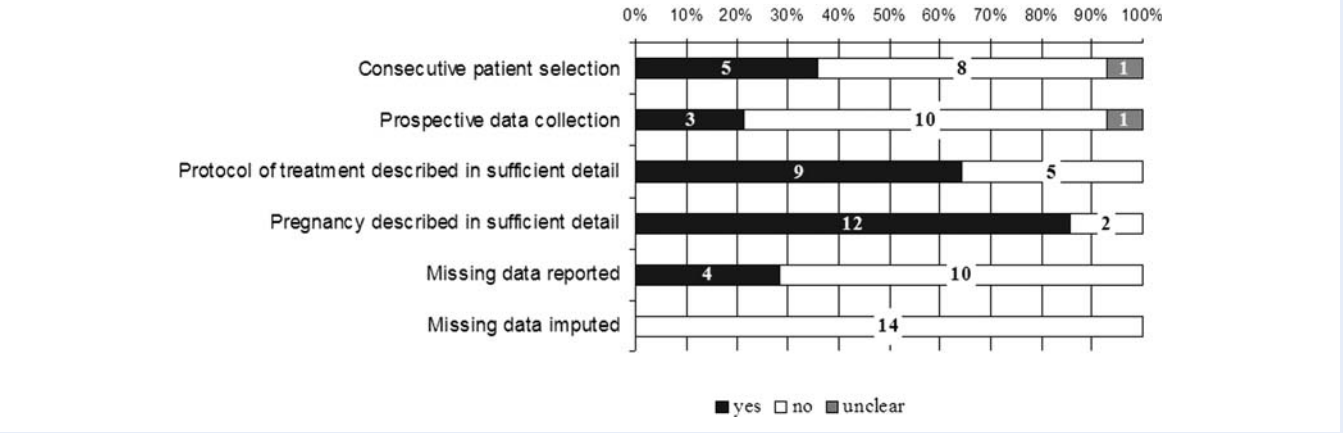

Figure 2 Summary of study quality. Numbers indicate the number of studies.

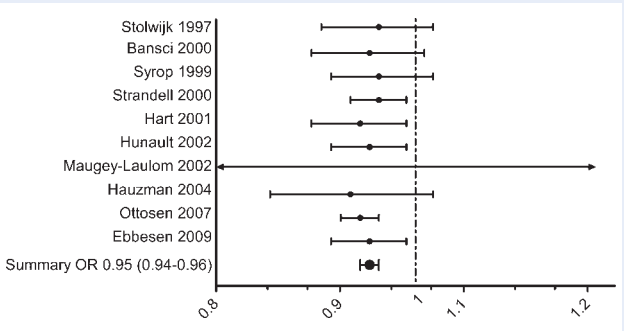

Figure 3 Forest plot presenting the effect of age on pregnancy after IVF/ICSI.

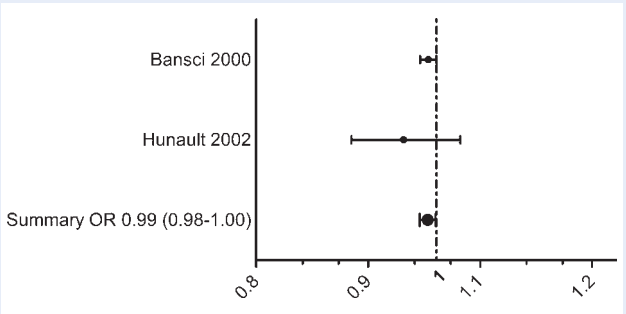

Figure 4 Forest plot presenting the effect of duration of subfertility on pregnancy after IVF/ICSI.

had lower pregnancy chances compared with those with unexplained subinfertility (Bancsi *et al.*, 2000). A second study reported that women with either male subfertility, tubal subfertility or subfertility caused by endometriosis had lower pregnancy chances compared with women with unexplained infertility (Ottosen *et al.*, 2007).

In the 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 with couples with a tubal factor (Hunault *et al.*, 2002). 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 (Strandell *et al.*, 2000). Because of the use of different reference categories, we were unable to obtain a summary estimate of the OR.

Predictor: basal FSH

Seven studies reported the association between basal FSH and pregnancy after IVF (Syrop *et al.*, 1999; Bancsi *et al.*, 2000; Hart *et al.*, 2001; Ferlitsch *et al.*, 2004; Ottosen *et al.*, 2007; Sabatini *et al.*, 2008; Ebbesen *et al.*, 2009). Two of these studies (Ottosen *et al.*, 2007; Sabatini *et al.*, 2008) dichotomized basal FSH into the categories 0–10 IU and >10 IU. In both studies, the chances of pregnancy 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 I^2 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: 0.88–1.00).

Predictor: number of oocytes retrieved

Six studies reported on the association between the number of oocytes retrieved and pregnancy (Strandell *et al.*, 2000; Hart *et al.*, 2001; Hunault *et al.*, 2002; Sharma *et al.*, 2002; Ottosen *et al.*, 2007). Two studies had categorized the data. One study dichotomized number of oocytes in ≤5 and >5 oocytes retrieved (Sharma *et al.*, 2002). The other study used three categories: 1–5 oocytes, 6–10 and 11 or more oocytes (Ottosen *et al.*, 2007). Both studies found that women with more oocytes had higher chances of pregnancy .

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: 1.02–1.07).

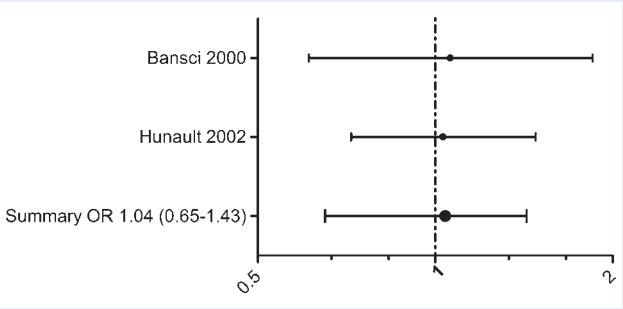

Figure 5 Forest plot presenting the effect of type of subfertility on pregnancy after IVF/ICSI.

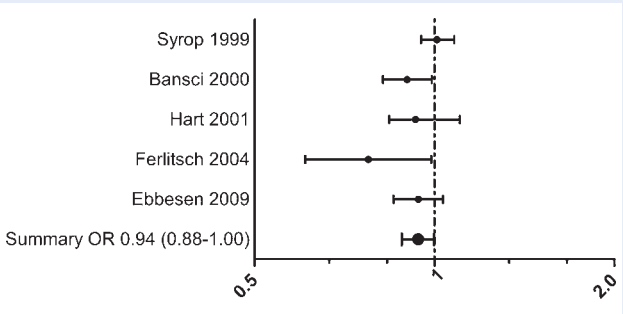

Figure 6 Forest plot presenting the effect of basal FSH on pregnancy after IVF/ICSI.

Predictor: method of fertilization (IVF or ICSI)

Two studies reported on the association of method of fertilization and chances of pregnancy after IVF (Strandell *et al.*, 2000; Ottosen *et al.*, 2007). One study reported lower pregnancy chances with ICSI compared with IVF (OR 0.95, 95% CI: 0.79–1.14), though not significant (Ottosen *et al.*, 2007). The other study showed no difference. This study did not report a 95% CI (Strandell *et al.*, 2000).

Predictor: number of embryos transferred

Two studies reported on the number of embryos transferred and IVF success (Sharma *et al.*, 2002; Hauzman *et al.*, 2004).One study dichotomized the number into the categories more than two and two or less embryos transferred. Women where more than two embryos were transferred had significantly higher pregnancy chances.(Sharma *et al.*, 2002) The second study showed higher, though not statistically significant, chances of pregnancy when transferring more embryos (Hauzman *et al.*, 2004). No summary OR could be calculated.

Predictor: embryo quality

Three studies evaluated the association between embryo quality and pregnancy after IVF (Hunault *et al.*, 2002; Strandell *et al.*, 2000; Ottosen *et al.*, 2007). 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 (Hunault *et al.*, 2002). The stage of development was described using three 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 with 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 with women with lower development stage and morphology score (Ottosen *et al.*, 2007). 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 (Strandell *et al.*, 2000). All three predictors were associated with higher pregnancy chances after IVF. In all studies better embryo quality was associated with higher chances of pregnancy, but as 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.

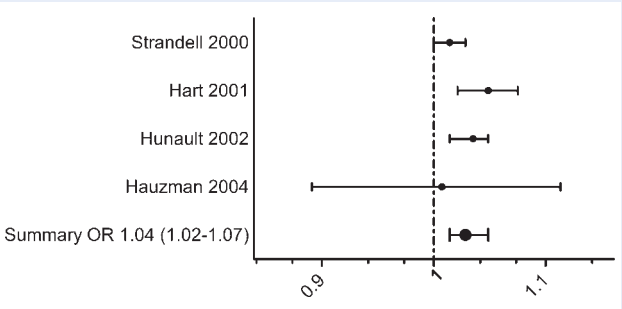

Figure 7 Forest plot presenting the effect of number of oocytes retrieved on pregnancy after IVF/ICSI.

Discussion

Predicting chances of pregnancy 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. On the basis of 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% CI.

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 is also shown 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 of conceiving 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 (Broekmans *et al*., 2007). Diminished ovarian reserve generally leads to a poor response to gonadotrophin therapy, and limits the possibility of a successful pregnancy (Ulug *et al*., 2003). 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.(UNECE, 2005).

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 (Lenton *et al*., 1988; MacNaughton *et al*., 1992) and the number of oocytes declines with age (Baird *et al*., 2005). Unfortunately, in this meta-analysis, we were not able to perform a multivariable analysis and thus we do not know whether age in itself overrides these factors.

Although we could only include two studies (Sharma *et al*., 2002; Hauzman *et al*., 2004) 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 (Gerris *et al*., 1999; Martikainen *et al*., 2001; Thurin *et al*., 2004; Lukassen *et al*., 2005). 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 (Van Montfoort *et al*., 2006). The number of embryos transferred is 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 (Minaretzis *et al*., 1998; Lundin *et al*., 2001; Terriou *et al*., 2001; Terriou *et al*., 2007). Our review shows that these studies did not use a uniform method 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 standardized way of assessing embryo quality.

Several studies also showed that indication for IVF is a predictor for pregnancy (Templeton *et al*., 1996; Minaretzis *et al*., 1998; Lintsen *et al*., 2007). 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 remarkably few articles reported unconditional ORs, leaving only a few articles for inclusion. Maybe more data could be gathered, resulting in more precise summary estimates, in future individual patient data 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 were unable to perform a meta-analysis. Better quality studies are necessary, especially studies that focus on embryo factors that are predictive of success in IVF.

Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

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